Volume 21, Supplement 2
October 2021

CLINICAL LYMPHOMA, MYELOMA & LEUKEMIA

A Peer-Reviewed, Monthly Journal

ISI Impact Factor 3.231

Included in Index Medicus/ MEDLINE/PUBMED

ISSN 2152-2650

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Official Journal of the International Myeloma Society and the Society of Hematologic Oncology

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CLINICAL LYMPHOMA, MYELOMA & LEUKEMIA

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Clinical Lymphoma, Myeloma & Leukemia (ISSN 2152-2650) is published monthly by Elsevier, 230 Park Avenue, Suite 800, New York, NY 10169. POSTMASTER: Send address changes to *Clinical Lymphoma, Myeloma & Leukemia*, Elsevier Customer Service Department, 3251 Riverport Lane, Maryland Heights, MO 63043, USA.

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CLINICAL LYMPHOMA, MYELOMA & LEUKEMIA

Volume 21, Supplement 2
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Abstracts of the 18th International Myeloma Workshop

Vienna, Austria
September 8–11, 2021

About the 18th IMW

The 18th International Myeloma Workshop, under the auspices of the International Myeloma Society (IMS), is devoted to fostering scientific and clinical exchange on the latest breakthroughs in multiple myeloma and related plasma cell disorders. Scientific programming at the 18th IMW will cover the latest genomic advances, new drug targets and agents, immunotherapeutic approaches including Car T-cell therapies, COVID-19 in multiple myeloma, and more.

This book compiles the abstracts from oral and poster session presentations at the 18th IMW held at the Messe Wien Exhibition & Congress Center in Vienna, Austria from September 8–11, 2021. The abstracts are reproduced as submitted by the author and accepted by the Scientific Program Committee. They appear in order of abstract code and track.

About the International Myeloma Society

The International Myeloma Society (IMS) is a professional, scientific, and medical society established to bring together clinical and experimental scientists involved in the study of myeloma. The purpose of this society is to promote research, education, clinical studies (including diagnosis and treatment), workshops, conferences, and symposia on all aspects of multiple myeloma worldwide.

The IMS is a membership organization comprised of basic research scientists, and clinical investigators in the field along with physicians and other healthcare practitioners. IMS is governed by a Board of Directors representing practices from around the world, and encourages and promotes the study of this expanding field through its annual International Myeloma Workshop.

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Publication of this abstract supplement is supported by the International Myeloma Society

Abstracts of the 18th International Myeloma Workshop

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ORAL PRESENTATIONS

OAB-001

Overall survival and progression-free survival by treatment duration with Daratumumab + Lenalidomide/Dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: phase 3 MAIA study

Philippe Moreau[1], Thierry Facon[2], Shaji Kumar[3], Torben Plesner[4], Robert Z. Orlowski[5], Nizar Bahlis[6], Supratik Basu[7], Hareth Nahi[8], Cyrille Hulin[9], Hang Quach[10], Hartmut Goldschmidt[11], Michael O'Dwyer[12], Aurore Perrot[13], Christopher Venner[14], Katja Weisel[15], Joseph R. Mace[16], Noopur Raje[17], Mourad Tiab[18], Margaret Macro[19], Laurent Frenzel[20], Xavier Leleu[21], Huiling Pei[22], Brenda Tromp[23], Maria Delioukina[24], Saad Z. Usmani[25]

[1]University Hospital Hôtel-Dieu; [2]University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France; [3]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [4]Vejle Hospital and University of Southern Denmark, Vejle, Denmark; [5]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada; [7]The Royal Wolverhampton Hospitals NHS Trust and University of Wolverhampton, Wolverhampton, United Kingdom; [8]Karolinska Institute, Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden; [9]Department of Hematology, Hôpital Haut Lévêque, University Hospital, Pessac, France; [10]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [11]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT); [12]Department of Medicine/Haematology, NUI, Galway, Republic of Ireland; [13]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [14]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [15]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [16]Florida Cancer Specialists, St. Petersburg, FL, USA; [17]Massachusetts General Hospital Cancer Center; [18]CHD Vendée, La Roche sur Yon, France; [19]Centre Hospitalier Universitaire (CHU) de Caen, Caen, France; [20]Department of Clinical Haematology, Hopital Necker-Enfants Malades, Paris, France; [21]Service d'Hématologie et Thérapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France; [22]Janssen Research & Development, LLC, Titusville, NJ, USA; [23]Janssen Research & Development, LLC, Leiden, The Netherlands; [24]Janssen Research & Development, LLC, Spring House, PA, USA; [25]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA*

Introduction: In the primary analysis of MAIA, daratumumab (DARA) plus lenalidomide and dexamethasone (D-Rd) reduced the risk of disease progression or death by 44% vs lenalidomide and dexamethasone (Rd) in transplant-ineligible patients (pts) with newly diagnosed multiple myeloma (NDMM). Here, we report the updated efficacy and safety of D-Rd vs Rd after almost 5 years of median follow-up from the prespecified interim overall survival (OS) analysis of MAIA (NCT02252172). **Methods:** Pts with NDMM ineligible for high-dose chemotherapy and autologous stem cell transplantation due to age ≥65 years or comorbidities were randomized 1:1 to D-Rd or Rd. All pts received 28-day cycles of Rd (R: 25 mg PO once daily on Days 1-21; d: 40 mg PO on Days 1, 8, 15, 22) ± DARA (16 mg/kg IV QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W thereafter). All pts were treated until disease progression/unacceptable safety events. The primary endpoint was progression-free survival (PFS). **Results:** 737 pts (D-Rd, 368; Rd, 369) enrolled and baseline characteristics were well balanced. Median age was 73 (range, 45-90) years. At a 56.2-month median follow-up, a significant 32% reduction in the risk of death was observed with D-Rd vs Rd. Median OS was not reached (NR) in either arm (HR, 0.68; 95% CI, 0.53-0.86; P=0.0013 [crossing the prespecified stopping boundary of P=0.0414]); estimated 5-year OS rates were 66.3% with D-Rd and 53.1% with Rd. The updated median PFS was NR with D-Rd vs 34.4 months with Rd (HR, 0.53; 95% CI, 0.43-0.66; PPP=0.2480); a PFS benefit was not observed with D-Rd vs Rd in pts who received P=0.3579). No new safety concerns were identified with longer follow-up. The most common grade 3/4 treatment-emergent adverse event was neutropenia (D-Rd, 54.1%; Rd, 37.0%). **Conclusions:** After ~5 years of follow-up, D-Rd vs Rd showed a significant and clinically meaningful PFS and OS improvement in transplant-ineligible pts with NDMM. Additionally, D-Rd showed a greater PFS benefit vs Rd among pts treated for ≥18 months than among pts treated for shorter durations. Taken together with real-world data indicating that many transplant-ineligible pts do not receive a second line of therapy, the favorable benefit-risk profile observed in MAIA supports the frontline use of D-Rd in transplant-ineligible pts with NDMM.

OAB-002

Daratumumab improves depth of response and progression free survival in transplant-ineligible, high-risk, newly diagnosed multiple myeloma (NDMM)

Andrzej Jakubowiak[1], Shaji Kumar[2], Rohan Medhekar[3], Huiling Pei[4], Patrick Lefebvre[5], Shuchita Kaila[3], Jianming He[3], Marie-Helene Lafeuille[5], Annelore Cortoos[9], Anil Londhe[7], Panagiotis Mavros[3], Thomas Lin[6], Saad Z. Usmani[8]

[1]University of Chicago, Chicago, IL, USA; [2]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [3]Janssen Scientific Affairs, LLC; [4]Janssen Research & Development, LLC, Titusville, NJ, USA; [5]Analysis Group, Inc; [6]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [7]Janssen R&D US; [8]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA

Introduction: Patients with high-risk NDMM who are ineligible for autologous stem cell transplant (ASCT) have limited first-line treatment options, and new regimens to improve their outcomes are needed. Daratumumab (Dara) is approved in combination with lenalidomide and dexamethasone (D-Rd) and in combination with bortezomib, melphalan, and prednisone (D-VMP) in ASCT-ineligible NDMM patients, based on the randomized clinical trials (RCTs), MAIA and ALCYONE, respectively. A recent meta-analysis of data from these two RCTs along with ASCT-eligible patients from the CASSIOPEIA RCT demonstrated that incorporation of Dara was associated with improved progression free survival (PFS) in high-risk NDMM patients. The current study builds upon these findings by focusing on the more homogenous population of ASCT-ineligible high-risk patients from MAIA and ALCYONE RCTs, using longer follow-up data, adjusting for patient-level imbalances in baseline characteristics, and evaluating additional efficacy endpoints. **Methods:** A stratified pooled analysis of patient-level data for ASCT-ineligible NDMM patients with high cytogenetic risk [i.e., del(17p), t(4;14), or t(14;16)] from MAIA and ALCYONE RCTs was conducted, adjusting for cytogenetic abnormality subtype, baseline performance status, International Staging System stage, type of multiple myeloma, and renal impairment. The impact of Dara on PFS and rates of complete response or better (≥CR), minimal residual disease (MRD)-negative CR, very good partial response or better (≥VGPR), and overall response (ORR), compared to control treatment, was assessed using the study identifier as the stratification factor. **Results:** There were 101 patients in Dara and 89 patients in the control cohort. Median follow-up was 43.7 months. In the adjusted analysis, the risk of progression or death was reduced by 41% in the Dara cohort vs control (hazard ratio [95% confidence interval (CI)] = 0.59 [0.41-0.85]). At 36 months, the proportion of patients who did not progress and were still alive was 41.3% in the Dara and 19.9% in the control cohort. Deeper response was observed in the Dara cohort with higher rates, and adjusted odd ratios (95% CI) for ≥CR (41.6% vs. 22.5%; 2.63 [1.34-5.16]), MRD-negative CR (24.8% vs. 5.6%; 5.50 [1.97-15.34]), ≥VGPR (75.3% vs. 46.1%; 4.03 [2.09-7.78]), and ORR (92.1% vs. 74.2%; 4.88 [1.94-12.27]) compared to control. **Conclusion:** Addition of Dara to backbone regimens resulted in 41% reduction in risk of progression or death among ASCT-ineligible high-risk NDMM patients. Additionally, patients in the Dara cohort had a two-fold higher likelihood of achieving ≥CR and a five-fold higher likelihood of achieving MRD-negative CR relative to control. This study provides additional evidence that the use of Dara based first-line treatment benefits high-risk NDMM patients.

OAB-003

CARDAMON:Carfilzomib (K) maintenance following Autologous Stem Cell Transplant (ASCT) or carfilzomib-cyclophosphamide-dexamethasone (KCd) consolidation for newly diagnosed (NDTE) multiple myeloma (MM)

Rakesh Popat[1], William Wilson[2], Marquita Camilleri[2], Ruth De Tute[3], Gavin Pang[2], Richard Jenner[2], Tushhar Dadaga[2], Sumaiya Kamora[2], Matthew Streetly[4], Karthik Ramasamy[5], Elizabeth Phillips[6], Mike Chapman[7], Ceri Bygrave[8], James Cavenagh[9], Jonathan Sive[2], Reuben Benjamin[10], Lydia Eccersley[9], Sandra Hassan[11], Fenella Willis[12], Laura Clifton-Hadley[13], Roger Owen[14], Kwee Yong[2]

[1]University College London Hospitals NHS Foundation Trust; [2]Cancer Research UK and UCL Cancer Trials Centre, University College London; [3]HMDS, St James Hospital Leeds, UK; [4]Guys and St Thomas' NHS Trust; [5]Oxford University Hospitals NHS Trust; [6]Christie NHS Foundation Trust; [7]Cambridge Institute for Medical Research; [8]University Hospital of Wales; [9]Barts Health NHS Trust; [10]Kings College Hospital; [11]Queens Hospital; [12]St George's NHS Trust; [13]Cancer Research UK and UCL Cancer Trials Centre, University College London; [14]St James' Institute of Oncology

Background: The role of upfront ASCT for NDTE MM remains under evaluation with high MRD rates following novel induction and consolidation (cons) strategies. K maintenance represents an alternative strategy to lenalidomide maintenance. The CARDAMON trial investigated K maintenance following KCd induction plus either ASCT or KCd cons. **Methods:** NDTE pts received 4 x KCd induction (K 20/56 mg/m2 biweekly, C 500 mg D 1,8,15, d 40mg weekly) before 1:1 randomisation to ASCT or 4 x KCd cons followed by 18 cycles K maintenance (56mg/m^2 D1,8,15). Flow cytometric MRD (10-5) was assessed post induction, pre-maintenance and at 6 months maintenance. Primary endpoints were ≥VGPR post induction and 2-year PFS from randomisation. Secondary endpoints included improvements in disease response and MRD conversion following ASCT/ cons and maintenance. **Results:** 281 patients were registered, with 218 randomised to either ASCT or cons. The median PFS for ASCT was not yet reached vs 3.4 years for cons, with cons failing to show non-inferiority (difference in 2-year PFS 6.5%, 70% CI 1.0% to 11.1%). 196 patients received

K maintenance (99 ASCT, 97 cons), 17 remain on treatment. A median of 16 cycles (1-18) were given over a median of 15.9 months (0-21.5). COVID-19 led to maintenance treatment interruptions in 41 (8 ASCT, 6 Cons) and treatment discontinuation in 15 (9 ASCT, 6 Cons). The median K dose given was 50.6mg/m2 and was similar across both arms (51.2 vs 49.4mg/m2, p=0.03). K maintenance was discontinued for PD in 14.1% (ASCT) vs 22.7% (cons), and for adverse events (AEs) in 7.1% (ASCT) vs 4.1% (cons). Most common AEs were hypertension and infections and more ≥G3 AEs were noted in ASCT vs cons (p=0.01). Patient/ clinician withdrawals from maintenance were low but occurred more in the ASCT arm (9.1% vs 1%). MRD neg patients post ASCT/ Cons had a longer PFS than MRD pos (p=0.002); with a higher MRD neg rate in the ASCT arm (53.6% vs 35.1% in Cons, p=0.01). MRD neg patients at 6 months post maintenance also had longer PFS (p=0.004 cf MRD pos patients); again with higher MRD neg rates in the ASCT arm (58.1% ASCT vs 40.5% Cons, p=0.02). There was no difference in PFS for MRD neg patients according to treatment arm from PBSCH, post-ASCT/ Cons or 6 months maintenance timepoints. Overall, 27.8% of MRD pos patients converted to MRD neg post ASCT/ Cons with more converting with ASCT (39.1% ASCT vs 16.1%, p=0.004). 23.5% of MRD pos patients converted to neg during maintenance (30.6% ASCT, 17.8%: p=0.2). Maintenance of MRD negativity over the first 6 months was similar between ASCT and Cons arms (p=0.3). There was no evidence that the timing of achievement of MRD negativity impacted PFS. **Conclusions:** K maintenance at 56mg/m2 weekly was deliverable and tolerable, with continued higher MRD neg rates at 6 months post-ASCT compared to post-Cons. However more ≥G3 AEs and discontinuations for AEs/ patient choice were noted for K maintenance after ASCT.

OAB-004

Carfilzomib-based induction/ consolidation with or without autologous transplant and Lenalidomide (R) or Carfilzomib-Lenalidomide (KR) maintenance: efficacy in high-risk patients of the FORTE study

Roberto Mina[1], Elena Zamagni[1], Delia Rota-Scalabrini[1], Paolo Corradini[1], Mariella Grasso[1], Stelvio Ballanti[1], Nicola Giuliani[1], Luca De Rosa[1], Claudia Cellini[1], Iolanda Donatella Vincelli[1], Cristina Velluti[1], Andrea Capra[1], Anna Maria Cafro[1], Alessandro Gozzetti[1], Massimo Gentile[1], Sara Aquino[1], Angelo Palmas[1], Antonio Ledda[1], Maria Teresa Petrucci[1], Pellegrino Musto[1], Mario Boccadoro[1], Francesca Gay[1]

[1]European Myeloma Network, Italy

Introduction: Multiple myeloma (MM) patients (pts) with high-risk cytogenetic abnormalities (CA) have a shorter survival as compared to the standard-risk ones. In the FORTE study, carfilzomib-lenalidomide-dexamethasone induction/consolidation with ASCT (KRd-ASCT) significantly improved progression-free survival (PFS) vs KRd without ASCT (KRd12) or carfilzomib-cyclophosphamide-dexamethasone (KCd) plus ASCT (KCd-ASCT). KR maintenance also prolonged PFS vs R. The primary aim of this analysis was to evaluate the impact of treatment on PFS and 1-year sustained MRD negativity (1y-MRD neg) rates according to pt cytogenetic risk. **Methods:** Pts were randomized to KRd-ASCT vs KCd-ASCT vs KRd12 and, thereafter, to KR vs R maintenance. High risk (HiR) was defined as the presence of ≥1 HiR CA [del17p, t(4;14), t(14;16), del1p and 1q gain (3 copies) or amp1q (≥4 copies)], double hit (DH) as the presence of ≥2 HiR CA, standard risk (SR) as the absence of all evaluated HiR CA. **Results:** 396 out of 474 enrolled pts with complete fluorescence in situ hybridization (FISH) data were included in the analysis: 243 HiR, 105 DH and 153 SR pts. Among HiR pts, 60 had del17p, 65 t(4;14), 20 t(14;16), 44 del1p, 126 1q gain and 49 amp1q. SR pts benefited from intensification with KRd-ASCT vs KRd12 (HR 0.47, p=0.05) and KCd-ASCT (HR 0.38, p=0.01), with a 4-year PFS of 80%, 67% and 57%, respectively. In HiR pts, KRd-ASCT improved PFS vs KRd12 (HR 0.6, p=0.04) and KCd-ASCT (HR 0.57, p=0.01), with a 4-year PFS of 62%, 45% and 45%, respectively. The advantage with KRd-ASCT vs KRd12 (HR 0.53, p=0.07) and KCd-ASCT (HR 0.49; p=0.03) was also observed in DH pts (4-year PFS 55%, 31% and 33%, respectively). Despite the limited number of patients in each subgroup, a trend towards a PFS benefit from KRd-ASCT vs KRd12 was observed in pts with del17p (HR 0.61, p=0.3), t(4;14) (HR 0.59, p=0.2) and 1q gain (HR 0.45, p=0.02). In pts with del1p, KRd-ASCT (HR 0.24, p=0.06) and KRd12 (HR 0.33, p=0.09) showed superiority over KCd-ASCT, while amp1q pts had the worst outcome regardless of treatment (KRd-ASCT vs KCd-ASCT, HR 1.16, p=0.73; KRd12 vs KCd-ASCT, HR 1.34, p=0.45). KR improved PFS vs R in SR (3-year PFS 90% vs 73%, HR 0.42, p=0.06), HiR (3-year PFS 69% vs 56%, HR 0.6, p=0.04) and DH pts (3-year PFS 67% vs 42%, HR 0.53, p=0.1). Despite the small subgroups, a beneficial trend with KR vs R was observed in pts with del17p (HR 0.59, p=0.37), t(4;14) (HR 0.59, p=0.3), 1q gain (HR 0.54, p=0.07) and del1p (HR 0.23, p=0.08), while amp1q pts showed the worst outcome and no benefit from KR vs R (HR 0.83, p=0.7). **Conclusion:** KRd-ASCT and KR maintenance are highly effective in SR and also in HiR and DH pts, with impressive 4-year PFS from diagnosis (KRd-ASCT: HiR 62%, DH 55%) and 3-year PFS from maintenance (KR: HiR 69%, DH 67%), thus providing an effective option in HiR pts, who still represent an unmet medical need.

OAB-005

Update of safety and efficacy of Isatuximab short-duration fixed-volume infusion plus Bortezomib, Lenalidomide, and Dexamethasone combined therapy for NDMM ineligible/with no immediate intent for ASCT

Enrique Ocio[1], Aurore Perrot[2], Pierre Bories[3], Jesús F. San-Miguel[4], Igor W. Blau[5], Lionel Karlin[6], Joaquín Martínez-López[7], Wolfram Pönisch[8],

Sara Bringhen[9], Magda Marcatti[10], María-Victoria Mateos[11], Paula Rodríguez-Otero[4], Nadia Le Roux[12], Yvonne Dong[13], Sandrine Macé[14], Thomas Fitzmaurice[12], Philippe Moreau[15]

[1]University of Cantabria; [2]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [3]Réseau Régional de Cancérologie Onco-Occitanie; [4]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA; [5]Medical Clinic, Charité University Medicine Berlin, Berlin, Germany; [6]Service d'Hématologie Clinique, Centre Hospitalier Lyon Sud, Pierre-Bénite, France; [7]Departamento de Hematología, Hospital 12 de Octubre, Complutense University, CNIO, Madrid, Spain; [8]University of Leipzig; [9]Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; [10]Vita-Salute San Raffaele University; [11]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca; [12]Sanofi; [13]Sanofi R&D, Beijing, China; [14]Sanofi, Vitry-sur-Seine, France; [15]University Hospital Hôtel-Dieu

Introduction: One standard-of-care treatment for patients with newly diagnosed multiple myeloma (NDMM) not eligible for autologous stem cell transplant (ASCT) is the combination of bortezomib (V), lenalidomide (R), and dexamethasone (d). Isatuximab (Isa), a monoclonal antibody targeting a specific epitope of CD38, is approved in combination with pomalidomide/carfilzomib plus d for the treatment of adults with relapsed/refractory multiple myeloma. The objective of this study was to evaluate the efficacy and safety of the approved short-duration fixed-volume infusion of Isa, combined with VRd (Isa-VRd) in patients with NDMM ineligible/with no immediate intent for ASCT. **Methods:** In Part A of this Phase 1b study (NCT02513186), a weight-based infusion of Isa-VRd was effective and well tolerated (median infusion duration at first infusion, 3.7 hours). Here, we present results from Part B, where Isa (10 mg/kg) was administered as a fixed-volume infusion of 250 mL with standard doses of VRd (Ocio Blood 2020). The primary endpoint is the complete response (CR) rate of Isa-VRd. **Results:** Of 46 patients in Part B, 30 (65.2%) were receiving study treatment at data cutoff (March 17, 2021). Median patient age was 70.0 years (range, 49–87), and 8 (17.4%) had high-risk cytogenetics. There were 13 (28.3%) patients eligible, but with no immediate intent, for ASCT; of these, 7 (53.8%) proceeded to mobilization and 6 (46.2%) performed apheresis (median 8.1×10^6 CD34+ cells/kg collected). The median duration of Isa infusion decreased to 1.3 hours from the third infusion onward. The overall response rate was 97.8%, including a CR/stringent CR (sCR) rate of 35.6% and very good partial response rate of 55.6%. After implementation of the SEBIA Hydrashift Isa immunofixation assay assessing serum M-protein without Isa interference, the adjusted CR/sCR rate increased to 53.3%. Investigation of minimal residual disease (MRD) negativity by combined next-generation flow cytometry or sequencing methods at a threshold of 10-5 revealed 23/45 (51.1%) of response-evaluable patients with MRD negativity. All patients experienced ≥1 treatment-emergent adverse event (TEAE), 32 (69.6%) had Grade ≥3 TEAEs, 20 (43.5%) had serious TEAEs, and 6 (13.0%) had TEAEs leading to death. Infusion reactions were observed in 13 (28.3%) of patients; none were of Grade ≥3. The most frequently reported TEAEs were constipation (69.6%), asthenia (67.4%), diarrhea (56.5%), and peripheral sensory neuropathy (50.0%). The most common Grade ≥3 hematologic abnormalities were lymphopenia (76.1%) and neutropenia (41.3%). **Conclusions:** These results confirm the feasibility, efficacy, and safety of the approved short-duration fixed-volume infusion method of Isa in combination with VRd in patients with NDMM ineligible/with no immediate intent for ASCT. Isa-VRd is under investigation in ongoing Phase 3 studies. **Funding:** Sanofi.

OAB-006

A novel algorithm to identify, characterize and define the prognostic impact of complex catastrophic events in Multiple Myeloma

Vincenza Solli[1], Andrea Poletti[1], Enrica Borsi[1], Marina Martello[1], Lucia Pantani[2], Silvia Armuzzi[1], Ilaria Vigliotta[3], Elena Zamagni[4], Paola Tacchetti[3], Serena Rocchi[1], Katia Mancuso[1], Gaia Mazzocchetti[1], Barbara Taurisano[1], Ignazia Pistis[3], Michele Cavo[1], Carolina Terragna[3]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" - Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [2]University of Bologna DIMES department / IRCCS Azienda Ospedaliero Universitaria di Bologna Istituto di Ematologia "Seràgnoli"; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [4]European Myeloma Network, Italy

Introduction: Multiple Myeloma (MM) is a genetically complex disease, characterized by the recurrence of several chromosomal aberrations, which impair the disease prognosis. The use of genome-wide technologies has recently highlighted the existence of Complex Chromosomal Events (CCEs), caused by distinct phenomenons: Chromothripsis (CT), caused by single-step genomic events, and Stepwise Events (SE), consequence of multiple, small and sequential genomic events, occurring throughout subsequent cell cycles. The prognostic impact of CT in MM has not yet been fully elucidated. Aims of our study were: (1) to detect CCEs in MM, with a focus on CT, by using an original and reliable bio-informatic algorithm, (2) to characterize the genetic and genomic context of CT and (3) to correlate the presence of CTwith pts prognosis. **Methods:** A total of 488 newly diagnosed MM patients (pts) have been included in the study. Genomic data have been obtained by SNPs arrays on bone marrow (BM) aspirates CD138+ enriched cell fractions; data were analysed by Affymetrix's programs and R-scripts. **Results:** An original algorithm able to discriminate among the 2 different CCEs (CT and SE),was set up and tested, by implementing the most commonly reported guidelines for CCEs identification with knowledges on MM-specific highly heterogeneous genomic context. CCEs were detected in 174 pts (36% with at least one CCE): in particular, 46/174 pts (26%) carried CT. CT can affect any chromosome, yet showing significant associations with the following genomic regions: chr1p (p=8.37E-15), chr2q (p=4.27E-8), chr11q (p=6.99E-5) and chr22q (p=5.15E-7). Pts carrying CT were more likely to carry

also IgH translocations associated to bad prognosis (p=0.002, HR 3.4) and TP53 deletions (p=1.16E-5, HR=6.26). The presence of any CT event conferred hazard ratio of 1.52 (p=0.019) and 1.68 (p=0.019) to pts' progression-free (PFS) and overall survival (OS), respectively, independently from the presence of both TP53 deletion and translocation t(4;14), as evaluated in a multivariated model. An association between CT events and XBP1 gene deletion was observed; since XBP1 expression has been correlated to an effective proteasome inhibitor (PI) therapy response, CT events particularly impacted survival expectancies of PI-treated pts, whose PFS and OS were significanlty worse than those of other pts (p=0.0098 and =0.023, respecitvely). Finally, the same CT events acquired at diagnosis were observed in those 4/55 pts, whose BM aspirates were analysed also at relapse, thus suggesting that, once occurred, CT might have a driver role for disease progression. **Conclusion:** Our results showed that CT impact MM pts prognosis, independently from the genomic region affected and the pts' genomic backgroung.
Acknowledgment: AIRC_IG2014, RF-2016.

OAB-007

Single-cell multiomic analysis identifies regulatory programs in relapsed/refractory multiple myeloma

Alexandra Poos[1], Moritz Przybilla[2], Nina Prokoph[3], Jan-Philipp Malllm[4], Stephan Tirier[5], Simon Steiger[5], Isabelle Lander[5], Nicola Giesen[6], Lukas John[7], Katharina Bauer[8], Anja Baumann[9], Stefanie Huhn[1], Anna Grab[1], Carsten Müller-Tidow[10], Hartmut Goldschmidt[11], Oliver Stegle[12], Marc Raab[13], Karsten Rippe[5], Niels Weinhold[7]

[1]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; [2]Division Computational Genomics and Systems Genetics, German Cancer Research Center (DKFZ) Heidelberg; Genome Biology Unit, European Molecular Biology Laboratory (EMBL) Heidelberg and Wellcome Sanger Institute, Cambridge; [3]Department of Internal Medicine V, University Hospital Heidelberg; [4]Open Lab for Single Cell Sequencing (scOpenLab), German Cancer Research Center (DKFZ) and BioQuant, Heidelberg; [5]Division of Chromatin Networks, German Cancer Research Center (DKFZ) and BioQuant, Heidelberg; [6]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; [7]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [8]Open Lab for Single Cell Sequencing (scOpenLab), German Cancer Research Center (DKFZ) and BioQuant, Heidelberg; [9]Clinical Cooperation Unit (CCU) Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg; [10]Heidelberg University Hospital; [11]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT); [12]Division Computational Genomics and Systems Genetics, German Cancer Research Center (DKFZ) Heidelberg; Genome Biology Unit, European Molecular Biology Laboratory (EMBL) Heidelberg and Wellcome Sanger Institute, Cambridge; [13]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Introduction: Despite new treatment approaches, in most patients with multiple myeloma (MM) resistant subclones expand, finally resulting in the development of relapsed/refractory disease (RRMM). Recent single-cell transcriptomic (scRNA-seq) studies have improved our understanding of tumor heterogeneity in MM, but our knowledge about the regulatory processes and gene expression signatures in resistant subclones is still limited. Thus, we performed single-cell assay for transposase-accessible chromatin using sequencing (scATAC-seq) as well as scRNA-seq from the same MM patient samples and developed a new approach for the analysis of the transcriptome and epigenome of competing subclones. **Methods:** CD138+ bone marrow cells of 11 RRMM patients were longitudinally collected and profiled using 10X Genomics scRNA- and scATAC-seq platform. Pre-processing was performed with CellRanger and downstream analysis using Seurat and ArchR. To determine clones based on copy number variations (CNVs), we leveraged inferCNV for scRNA-seq and developed a sliding window approach adapted from a previously published method by Satpathy et al. for scATAC-seq data. Whole genome sequencing was available to confirm the identified CNV clones. **Results:** We obtained chromatin accessibility profiles of >43000 cells after quality control, establishing the first epigenetic map of RRMM with clearly separated clusters for each patient. Samples from distinct MM subgroups, particularly t(4;14) and t(11;14), clustered together in a pseudo-bulk analysis based on transcription factor activity scores from scATAC. To investigate treatment-induced clonal dynamics we aligned sc chromatin accessibility profiles to clones inferred in scRNA-seq based on CNVs enabling us to track individual tumor subclones over time. An example for clonal adaptation is a patient with two subclones that both responded differently to pomalidomide plus anti-CD38 treatment: while clone 1 showed a higher activity for members of IRF family, ZEB1 and KLF family members were more active in clone 2. Branching evolution was e.g. observed in a patient treated with a MEK/BRAF inhibitor. This patient showed two subclones before treatment, achieved a complete remission and relapsed with one dominant clone. One of the initial subclones could be identified as the precursor of this dominant clone with both showing high activity of NFKB family members, while higher activity of SOX10/15 was only observed upon MEK/BRAF inhibition. An example for combined clonal adaptation and selection was observed in a patient with bi-allelic inactivation of TP53 in one of the two subclones before MCL1 inhibition. Interestingly, this clone was depleted at relapse. **Conclusions:** In summary, our new approach to track individual tumor subclones over time indicates clonal adaptation or selection in virtually all RRMM patients and reveals new insights into regulatory mechanisms underlying treatment-resistance, opening potential avenues for new therapies.

OAB-008

Identification of high-risk Multiple Myeloma with a plasma cell Leukemia-like transcriptomic profile

Davine Hofste op Bruinink[1], Rowan Kuiper[1], Mark van Duin[2], Tom Cupedo[1], Vincent H.J. van der Velden[2], Remco Hoogenboezem[1], Bronno van der Holt[1], H. Berna Beverloo[2], Erik T. Valent[3], Michael Vermeulen[2], Francesca Gay[4], Annemiek Broijl[2], Hervé Avet-Loiseau[5], Nikhil C. Munshi[6], Pellegrino Musto[7], Philippe Moreau[8], Sonja Zweegman[9], Niels W.C.J. van de Donk[10], Pieter Sonneveld[1]

[1]Erasmus MC Cancer Institute; [2]Erasmus MC; [3]SkylineDx; [4]European Myeloma Network, Italy; [5]CRCT-Toulouse; [6]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System; [7]"Aldo Moro" University School of Medicine, Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico; [8]University Hospital Hôtel-Dieu; [9]Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands; [10]Amsterdam University Medical Center, VU Amsterdam, Department of Hematology, Cancer Center Amsterdam

Background: Primary plasma cell leukemia (pPCL) is an aggressive subtype of multiple myeloma that is characterized by ≥20% circulating tumor cells (CTCs), whereas CTC levels in newly diagnosed multiple myeloma (NDMM) are <20%. Currently, there is no molecular marker for pPCL. It therefore remains to be elucidated if certain NDMM tumors molecularly resemble pPCL and if this has any prognostic significance in the context of conventional high-risk (HR) markers in NDMM. Aims: (1) To construct and validate a transcriptomic classifier for PCL-like disease. (2) To test its value as independent prognostic marker in NDMM. **Methods:** Transcriptomic data were generated of CD138-enriched bone marrow (BM) plasma cells from both NDMM patients enrolled in the Cassiopeia (NCT02541383) and HO143 (EudraCT 2016-002600-90) trials and pPCL patients from the EMN12/HO129 (EudraCT 2013-005157-75) trial. NDMM CTC levels were determined with the EuroFlow NGF protocol. HR FISH was defined as the presence of either t(4;14), t(14;16) or del17p.154 NDMM and 29 pPCL patients were divided into a discovery and validation cohort to construct and test a classifier for PCL-like disease. Subsequently, data from 8 additional NDMM cohorts were used to assess the association of PCL-like status with progression-free survival (PFS) and overall survival (OS) in Cox proportional hazards (PH) models including conventional HR markers. **Results:** Baseline CTC levels were determined in 297 NDMM and 51 pPCL patients. CTCs could be detected in 87% of NDMM patients, with a limit of detection <10-5. CTC levels were positively associated with tumor burden (BM plasmacytosis). In the discovery cohort, 1700 genes correlated with high CTC levels (FDR <0.05), independently of tumor burden. These included genes involved in cell adhesion, cell migration and proliferation. After optimization by leave-one-out cross-validation, a classifier for PCL-like disease was built with a selection of 54 genes. This showed a sensitivity of 93% to identify pPCL in the validation cohort, but also classified 10% of NDMM tumors as PCL-like. In a cohort of 2139 NDMM patients, Cox PH regression analyses confirmed a significant and independent association of PCL-like status with PFS and OS, in the context of either R-ISS stage, ISS stage, HR FISH, SKY92 HR or UAMS70 HR status. PCL-like status in combination with R-ISS, age and treatment status showed a hazard ratio of 1.64 (95% CI, 1.30-2.07, p<0.0001) for PFS and 1.89 (95% CI, 1.42-2.50, p<0.0001) for OS. PCL-like status conferred a median OS of only 13.2 months among NDMM patients with R-ISS III. **Conclusions:** (1) pPCL cannot only be identified clinically, but also molecularly. (2) PCL-like status is a novel marker for HR disease in NDMM that identifies patients with a tumor transcriptome similar to pPCL and has independent prognostic value in the context of conventional HR markers. (3) PCL-like status could help detect NDMM patients with early stage or borderline pPCL.

OAB-009

Genome-wide CRISPR interference screen identifies RNA Regulator of Lipogenesis (RROL) as a leading LncRNA dependency in Multiple Myeloma

Eugenio Morelli[1], Mariateresa Fulciniti[1], Mehmet K. Samur[2], Caroline Ribeiro[3], Leon Wert-Lamas[4], Jon Henninger[5], Annamaria Gulla[1], Anil Aktas-Samur[2], Katia Todoerti[6], Srikanth Talluri[4], Woojun D. Park[7], Nicola Amodio[8], Giada Bianchi[9], Charles Lin[7], Yu-Tzu Tai[1], Antonino Neri[10], Dharminder Chauhan[4], Teru Hideshima[2], Masood Shammas[11], Pierfrancesco Tassone[8], Rick Young[12], Kenneth Anderson[1], Carl Novina[4], Massimo Loda[3], Nikhil C. Munshi[13]

[1]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Dana-Farber Cancer Institute, Boston, USA; [3]Cornell University; [4]Dana-Farber Cancer Institute & Harvard Medical School; [5]Whitehead Institute of Biomedical Research; [6]Fondazione Cà Granda IRCCS Policlinico; [7]Baylor college of medicine; [8]Magna Graecia University, Catanzaro, Italy; [9]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [10]University of Milan; [11]Dana Farber Cancer Institute and VA Boston Healthcare System, Boston, MA, USA; [12]MIT Department of Biology; [13]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Introduction: Long noncoding RNAs (lncRNAs) are profoundly dysregulated in multiple myeloma (MM), yet their tumor-promoting features remain to be defined. Here, we have coupled extensive transcriptomic profiling of patient samples (n=360) with a genome-wide CRISPR interference (CRISPRi) viability

screen (4 cell lines) to generate a map of lncRNA "dependencies" in MM; moreover, we describe the molecular and functional role – as well as its therapeutic potential – of the screen top hit RNA Regulator of Lipogenesis (RROL), a nuclear-retained lncRNA generated by alternative splicing of MIR17HG. **Methods:** Loss-of-function (LOF) studies using antisense oligonucleotides (ASO) confirmed the RROL dependency in a large panel of MM cell lines and CD138+ patient cells, in vitro and in vivo in animal models. This effect was not antagonized in DROSHA KO MM cells or by ectopic expression of MIR17HG-derived miR-17-92, indicating a microRNA-independent role of RROL. **Results:** Transcriptomic analysis after RROL depletion indicated a significant impact on the de novo lipogenesis (DNL) gene networks. RROL occupancy at DNL gene loci was detected by chromatin isolation by RNA precipitation followed by qRT-PCR (ChIRP-qPCR) and confirmed by DUAL RNA FISH analysis. At functional level, we demonstrated that RROL depletion reduces DNL in MM cells using an unbiased lipidomic profiling as well as by measuring the incorporation of C14-radiolabeled glucose into lipids. Importantly, we also proved that exogenous palmitate, the downstream product of DNL pathway, can significantly rescue the growth inhibitory effect of RROL depletion in MM cells; thus implicating a role for DNL in the growth promoting effect of this lncRNA. RNA-Protein Pull Down (RPPD) and in vivo RNA yeast three-hybrid (Y3H) assays led to identify c-MYC (MYC) as a relevant protein interactor of RROL; a finding validated by RIP-qPCR. Coupling RNA FISH with immunofluorescence, we co-detected RROL and MYC at the ACC1 promoter. Importantly, neither RROL or MYC could occupy ACC1 promoter and exert regulatory control in the absence of the other factor. Moreover, using in vitro (Co-IP/MS) and in vivo (BioID) assays, we identified WDR82 as an RROL-dependent MYC partner implicated in the transcriptional control of ACC1 expression. Finally, to therapeutically antagonize RROL, we have screened >100 ASOs and provided the basis to develop a first-in-class RROL inhibitor. This inhibitor has shown a very strong anti-MM activity in vitro (IC50<5nM) while sparing non-malignant cells; the in vivo activity is currently under investigation and will be presented. **Conclusion:** In conclusion, we here report a unique regulatory function of a novel lncRNA supporting MM cell growth via its control of the lipogenic metabolic axis. The ongoing development of RROL inhibitors may allow clinical application of this unique targeted therapy in MM.

OAB-010

Gain(1q) promotes mitochondrial oxidative phosphorylation and suppresses interferon response and tumor immunity in multiple myeloma and other human cancers

Rodger Tiedemann[1], Ali Mahdipour-Shirayeh[1], Natalie Erdmann[1], Ines Tagoug[1]

[1]Princess Margaret Cancer Centre, University Health Network

Introduction: Gain of chromosome 1q is a recurrent genomic feature of many human tumors and is present in 33-48% of newly diagnosed MMs (NDMM). Analogous to deletion of 17p, +1q can occur as a secondary genetic event in all MM subtypes, and is associated with poor prognosis. Although uncommon in precursor stages such as monoclonal gammopathy of undetermined significance (MGUS), the prevalence of +1q rises significantly in symptomatic MM, and at relapse, suggesting roles in malignant transformation and treatment escape. The molecular mechanisms underlying these associations remain poorly understood. Here, we report an analysis of the transcriptional consequences of +1q in single MM cells and in bulk tumor samples. **Methods:** To define the molecular consequences of +1q at a cellular level, we performed single cell RNA-sequencing (scRNA-seq) and single-cell inferred CNV (sciCNV) analysis of primary MM bone marrow samples. This provided paired DNA/RNA omics information within single cells. From MM samples containing intra-clonal populations with and without +1q we directly examined the effects of +1q on gene expression. The effects of +1q were delineated using intra-clonal isogenic sibling cells lacking +1q as controls. We validated our findings using 10 tumor cohorts, including 2 MM cohorts representing >1300 NDMM patients and 8 non-MM cohorts representing 3,915 patients with other malignancies. **Results:** From these studies we show that primary MM cells with +1q significantly upregulate mitochondrial oxidative phosphorylation (OXPHOS), causing increased reactive oxygen species and reduced energy stress, compared with isogenic sibling cells without +1q. Despite increased OXPHOS, +1q cells do not appear to experience increased hypoxia nor reduced glycolysis, suggesting that they continue to benefit from aerobic glycolysis (Warburg metabolism). At the same time +1q MM cells overexpress ADAR and suppress IFN type 1 and 2 responses, repressing tumor immunity. Overexpression of CD46, CFH, CFHR1, CHFR5, ARPC5 and SELL from +1q further suppress pathways involved in tumor immune recognition, particularly by complement and antibodies. MM tumors overexpressing MYC are enriched amongst +1q samples, with MYC co-operating with MCL1 to promote mitochondrial oxidative phosphorylation, leading to apparent enrichment of a MYC gene expression signature in +1q samples, though MYC itself is not increased by +1q. From MM registry data, +1q cooperates with MYC to promote OXPHOS, and OXPHOS strongly predicts patient survival, particularly in high-risk t(4;14) and del(17p) subtypes. Examination of 8 non-MM tumor cohorts reveals that other human cancers with +1q similarly upregulate OXPHOS and MYC programs and/or suppress tumor immunity (IFN-g and -a responses, complement pathways and allograft rejection). **Conclusion:** Overall, from these multi-omic analyses we identify critical reprogramming events in MM and other human cancers that arise from +1q and that predict patient survival.

OAB-011

Clonal phylogeny and evolution of critical cytogenetic aberrations in multiple myeloma at single cell level

Yuting Yan[1], Xiaoqi Qin[2], Jiahui Liu[2], Huishou Fan[2], Zhen Yu[3], Wei Liu[2], Mu Hao[3], Lugui Qiu[4], Gang An[5]

[1]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union; [2]Chinese Academy of Medical Sciences and Peking Union Medical College; [3]State

Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin; [4]Institute of Hematology and Blood Diseases Hospital; [5]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Introduction: Single-cell analysis is of significant importance in delineate the exact phylogeny of subclonal population and in discovering subtle diversification. So far studies of intratumor heterogeneity and clonal evolution in multiple myeloma (MM) were largely focused at the bulk tumor population level. **Methods:** Here, we performed quantitative multi-gene fluorescence in situ hybridization (QM-FISH) in 129 longitudinal samples of 57 MM patients. All the patients had newly-diagnosed and relapsed paired samples. An expanded cohort of 188 MM patients underwent conventional FISH (cFISH) to validate the cytogenetic evolution in bulk tumor level. 43 of 57 patients (75.4%) harbored three or four cytogenetic clones at diagnosis. We delineated the phylogeny of subclonal tumor population and derived the evolutionary architecture in each patient. **Results:** Patients with clonal stabilization had a significantly improved OS than those with other evolutionary patterns (median OS, 71.2 vs. 39.7 vs. 35.2 vs. 25.5 months, for stable, differential, branching and linear patterns, respectively, p=0.001). Besides, a high degree of consistency and complementarity across cFISH and QM-FISH was observed in evaluation of cytogenetic evolution pattern in MM. **Conclusion:** Survival after relapse were greater influenced by the presence of high-risk aberrations at relapse (hazard ratio =2.07) rather than present at diagnosis (hazard ratio=1.55). This study shows that QM-FISH is a valuable tool to elucidate the clonal architecture at single cell level. Clonal evolution pattern is of prognostic significance, highlighting the need for repeated cytogenetic evaluation in relapsed MM.

OAB-012

Depth of response and MRD in newly diagnosed ultra high-risk myeloma and plasma cell leukemia treated with Dara-CVRd and V-MEL ASCT: results of the molecularly stratified UK OPTIMUM/MUKnine trial

Martin Kaiser[1], Andrew Hall[2], Katrina Walker[2], Ruth De Tute[3], Sadie Roberts[2], Emma Ingleson[2], Kristian Bowles[4], Mamta Garg[5], Anand Lokare[6], Christina Messiou[7], Graham Jackson[8], Guy Pratt[6], Gordon Cook[9], Mark Drayson[10], Roger Owen[3], Sarah Brown[2], Matthew Jenner[11]

[1]The Institute of Cancer Research; [2]Leeds Institute of Clinical Trials Research, Leeds University, UK; [3]HMDS, St James Hospital Leeds, UK; [4]Norfolk and Norwich University Hospitals; [5]Leicester Royal Infirmary, UK; [6]University Hospitals Birmingham NHS Foundation Trust, UK; [7]The Royal Marsden Hospital; [8]Newcastle Hospitals NHS Trust; [9]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK; [10]Institute of Immunology and Immunotherapy, University of Birmingham, Edgbaston, Birmingham, UK; [11]Southampton University Hospital, UK

Background: Outcome for patients with ultra high-risk (UHiR) newly diagnosed multiple myeloma (NDMM) or plasma cell leukemia (PCL) continues to be adverse, and UHiR patients are underrepresented in clinical trials. Recently, deepened responses have been reported for anti-CD38 monoclonal antibody combination therapy in NDMM. We report here protocol defined endpoints for the risk-stratified OPTIMUM/MUKnine (NCT03188172) trial for UHiR NDMM and PCL. Patients received daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone (Dara-CVRd) induction and bortezomib-augmented HDMEL and ASCT. Early endpoints response and MRD from induction to day 100 post ASCT are reported. **Methods:** Between Sep 2017 and Jul 2019, 472 patients with suspected NDMM from 39 UK hospitals were centrally molecularly screened. Of these, 107 patients were identified as having UHiR NDMM by trial genetic (≥2 high-risk lesions (double-hit): t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p)) or gene expression SKY92 (SkylineDx) profiling, or with PCL (circulating plasmablasts >20%) and enrolled in OPTIMUM. Induction consisted of 6 cycles of Dara-CVRd, HDMEL and ASCT augmented with bortezomib, followed by Dara-VR(d) consolidation for 18 cycles and Dara-R maintenance. Primary trial endpoints are minimal residual disease (MRD) status post ASCT and progression-free survival. Secondary endpoints include response, safety and quality of life. **Results:** Median follow-up for the 107 patients in the safety population was 22.2 months (95% CI: 20.6 – 23.9). At baseline, 27% of patients were ISS stage I, 40% stage II and 32% stage 3 with 1.0% missing data and patient median age was 60 (range 35 to 78) years. 53% of patient tumors carried double-hit genetics and 77% a SKY92 high-risk signature. Two patients died early during induction due to myeloma-related infection. Bone marrow aspirates suitable for MRD assessment by flow (10-5 sensitivity) were available for 81% of patients at end of induction and 78% at D100 post ASCT. Responses in the ITT population at end of induction were 94% ORR with 22% CR, 58% VGPR, 15% PR, 1% PD, 5% timepoint not reached (TNR; withdrew, became ineligible or died) and at D100 post ASCT 83% ORR with 47% CR, 32% VGPR, 5% PR, 7% PD, 10% TNR. For PCL patients, response post ASCT was lower with 22% CR, 22% VGPR, 22% PR and 22% PD, 11% TNR. MRD status was 41% MRD-neg, 40% MRD-pos and 19% not evaluable post induction and 64% MRD-neg, 14% MRD-pos and 22% not evaluable at D100 post ASCT. Most frequent induction grade 3/4 AEs were neutropenia (21%), thrombocytopenia (12%) and infection (12%). **Conclusions:** We report here high response and MRD-negativity rates with Dara-CVRd quintuplet induction and augmented ASCT in difficult-to-treat UHiR NDMM and PCL patients, with good tolerability and all-oral/subcutaneous deliverability. However, some early progressors highlight the ongoing need for innovation in UHiR MM and PCL.

OAB-013

Iberdomide (IBER) in combination with dexamethasone (DEX) and daratumumab (DARA), bortezomib (BORT), or carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM)

Sagar Lonial[1], Paul G. Richardson[2], Rakesh Popat[3], Edward A. Stadtmauer[4], Jeremy T. Larsen[5], A. Oriol[6], Stefan Knop[7], Sundar Jagannath[8], Gordon Cook[9], Ashraf Z. Badros[10], Paula Rodríguez-Otero[11], David S. Siegel[12], Tuong Vi Nguyen[13], Antonia Di Micco[14], Alpesh Amin[13], Min Chen[13], Elisabeth Kueenburg[14], Niels W.C.J. van de Donk[15]

[1]Winship Cancer Institute, Emory University; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]University College London Hospitals NHS Foundation Trust; [4]University of Pennsylvania, Philadelphia, PA, USA; [5]Mayo Clinic, Scottsdale, AZ, USA; [6]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol; [7]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; [8]The Mount Sinai Hospital; [9]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK; [10]The University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland Medical Center, Baltimore, MD, USA; [11]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [12]John Theurer Cancer Center, Hackensack University Medical Center; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [15]Amsterdam University Medical Center, VU Amsterdam, Department of Hematology, Cancer Center Amsterdam*

Background: CC-220-MM-001 (NCT02773030) is an ongoing phase 1/2 study evaluating the maximum tolerated dose, recommended phase 2 dose (RP2D), safety, and preliminary efficacy of IBER, an oral, novel cereblon E3 ligase modulator (CELMoD®) compound, with different treatment combinations in independent cohorts, in pts with MM. Here we report results from the IBER+DARA+DEX (IberDd), IBER+BORT+DEX (IberVd), and IBER+CFZ+DEX (IberKd) cohorts in RRMM. **Methods:** Eligible pts received ≥2 (IberDd and IberKd cohorts) or ≥1 prior regimens (IberVd cohort), containing lenalidomide or pomalidomide, and a proteasome inhibitor. All pts had progressed ≤60 days from last therapy. Escalating oral doses of IBER were given on day (D)1–21 of each 28-D cycle in the IberDd cohort and in the IberKd cohort with weekly CFZ, and on D1–14 of each 21-D cycle in the IberVd cohort. DEX was given weekly in all 3 cohorts. **Results:** As of April 8, 2021, 43 pts had received IberDd, 25 IberVd, and 9 IberKd. Median age was 67, 64, and 61 years, and median time since diagnosis was 7.35, 7.1, and 6.7 years in the IberDd, IberVd, and IberKd cohorts, respectively. Extramedullary plasmacytomas were present in 7 (16%), 4 (16%), and 2 (22%) pts in the IberDd, IberVd, and IberKd cohorts, respectively. Exposure to prior regimens was heterogeneous; all pts were refractory to their last prior regimen and ≥33% pts in the 3 cohorts were triple-class refractory. IBER doses ranged from 1.0 to 1.6 mg. Median follow-up was 4.17, 4.86, and 5.03 months, 22 (51%), 6 (24%), and 5 (56%) pts continue on treatment, and median cycles received were 4, 6, and 5 with IberDd, IberVd, and IberKd, respectively. Hematologic grade (G) 3–4 treatment-emergent adverse events (TEAEs) of interest included neutropenia (67%), leukopenia (23%), anemia (21%), and febrile neutropenia (5%) with IberDd; neutropenia (28%) and thrombocytopenia (24%) with IberVd; and lymphopenia (44%) and neutropenia (33%) with IberKd. Neutropenia was manageable with G-CSF. Occurrence of non-hematologic TEAEs was low, with very few G3–4 fatigue, rash, and gastrointestinal disorders. The overall response rate was 46% with IberDd, 56% with IberVd, and 50% with IberKd, including a VGPR or better of 24%, 28%, and 38%, respectively. Median time to response was 4.1 (4.0–12.0), 3.6 (3.0–13.1), and 4.1 (4.1–8.1) weeks, in the IberDd, IberVd, and IberKd cohorts, respectively. Median duration of response is 35.7 weeks in the IberVd cohort (not reached in the other cohorts). RP2D was determined at 1.6 mg in the IberDd cohort; dose evaluation continues in the other cohorts. **Conclusions:** In pts with heavily pretreated RRMM, IberDd, IberVd, and IberKd showed a tolerable safety profile and promising efficacy. These results support further development of IBER-based regimens in MM, including the initiation of phase 3 combination studies. Previously published in Lonial S, et al. HemaSphere 2021;5(S2):49.

OAB-014

Newly diagnosed Multiple Myeloma patients with high levels of circulating tumor cells are distinguished by increased bone marrow plasma cell proliferation

A. Cathelijne Fokkema[1], Madelon de Jong[1], Sabrin Tahri[1], Zoltán Kellermayer[1], Chelsea den Hollander[1], Michael Vermeulen[1], Natalie Papazian[1], Mark van Duin[1], Annemiek Broijl[1], Pieter Sonneveld[1], Tom Cupedo[1]

[1]Erasmus MC Cancer Institute

Background: Circulating tumor cells (CTCs) are present in the blood of all patients with (precursor)stages of Multiple Myeloma (MM). The levels of CTCs vary widely between patients, yet the biology behind this variability is unknown. Importantly, MM patients with a higher percentage of CTCs have an inferior prognosis independent of high-risk cytogenetics, suggesting that CTC numbers are a relevant reflection of tumor cell biology. Here, we set out to identify differences in CTCs and paired bone marrow plasma cells (BM PCs). Additionally, we compared BM PCs from patients with high and low levels of CTCs with the goal of identifying mechanistic drivers of high-risk disease. **Methods:** We isolated PCs from viably frozen mononuclear cells of peripheral blood and bone marrow aspirates of newly diagnosed MM patients. Common high-risk mutations were present in both groups. We performed single cell RNA sequencing of paired CTCs and BM PCs from five patients with a high percentage of CTCs (0.5%-8%). In addition, we generated

single cell transcriptomes of BM PCs of eight patients with a high percentage of CTCs (2-22%) and 13 patients with low percentage of CTCs (0.004%-0.08%) **Results:** Single cell transcriptomes were generated from 44,779 CTCs and 35,697 bone marrow PCs. When paired CTCs and BM PCs were integrated, we identified 9 common clusters, no cell specific cluster for either source was detected. Moreover, only 25 genes were significantly differentially expressed between CTCs and BM PCs. The absence of unique clusters in either CTCs or BM PCs, and the transcriptional overlap between these two sources indicate that CTC levels are not driven by the emergence of a transcriptionally different migratory clone, but are likely a reflection of altered BM PC biology. To identify such alterations, we compared bone marrow PCs from patients with high and low percentages of CTCs. Single cell transcriptomes were generated from 74,830 bone marrow PCs. Integration of all patients lead to the identification of 8 distinct PC clusters, one of which was characterized by active proliferation as defined by transcription of STMN1 and MKI67. Interestingly, this proliferative cluster was larger in patients with a high percentage of CTCs. Furthermore, cell cycle analyses based on canonical G2M and S phase markers revealed that actively cycling PCs were more frequent in the BM of patients with a high percentage of CTCs (64% versus 30%, p<0.001), irrespective of the cluster in which these cells were contained. **Conclusions:** Through single cell transcriptomic analyses we reveal that CTCs and MM cells from BM are transcriptionally similar. Importantly, we identify increased BM PC proliferation as a significant difference between patients with high and low levels of CTCs, implicating an increased entry into the cell cycle as one of the mechanisms driving CTC levels and MM disease pathobiology.

OAB-015

Minimal residual disease following autologous stem cell transplant for myeloma patients in the Myeloma XI trial: prognostic significance and the impact of lenalidomide maintenance and molecular risk

Ruth De Tute[1], Charlotte Pawlyn[2], David Cairns[3], Faith Davies[4], Andy Rawstron[5], John Jones[2], Anna Hockaday[6], Tom Menzies[6], Rowena Henderson[6], Gordon Cook[7], Mark Drayson[8], Matthew Jenner[9], Martin Kaiser[2], Walter Gregory[6], Gareth Morgan[4], Graham Jackson[10], Roger Owen[11]

[1]HMDS, St James Hospital Leeds, UK; [2]The Institute of Cancer Research; [3]Leeds Institute of Clinical Trials Research, University of Leeds; [4]The Myeloma Institute; [5]Leeds Teaching Hospitals Trust; [6]Clinical Trials Research Unit; [7]University of Leeds; [8]Institute of Immunology and Immunotherapy, University of Birmingham, Edgbaston, Birmingham, UK; [9]Southampton University Hospital, UK; [10]Newcastle Hospitals NHS Trust; [11]St James' Institute of Oncology

Background: Minimal residual disease (MRD) status after autologous stem cell transplant (ASCT) predicts progression-free and overall survival outcomes in patients with multiple myeloma. The prognostic impact of MRD when assessed at serial time points in the context of maintenance therapy and the interaction between MRD and molecular risk are less well defined. **Methods:** In the phase III Myeloma XI trial eligible patients were randomly assigned to lenalidomide maintenance or no maintenance at 3 months following ASCT. MRD status was assessed by flow cytometry prior to maintenance randomization (ASCT+3) and 6 months after maintenance randomization (ASCT+9). The relationship between MRD status and progression-free survival (PFS) and overall survival (OS) was examined. PFS is landmarked as the time from the date of ASCT+3/ASCT+9 to the date of progression or death from any cause. OS is landmarked as the time from the date of ASCT+3/ASCT+9 to the date of death from any cause. Participants who had not met the endpoint were censored at the date last known to have not met the endpoint. Adverse molecular risk abnormalities were defined as gain(1q), del(17p), t(4;14), t(14;16) or t(14;20). **Results:** At ASCT+3, of 750 patients with informative samples, 475 (63.3%) were MRD negative and 275 (36.6%) were MRD positive. MRD negative status at ASCT+3 was associated with a 57% reduction in PFS events (HR=0.43, 95% CI 0.34-0.55; P<0.001) and a 47% reduction in the risk of death (HR=0.53, 95% CI 0.36-0.78; P=0.0011). At ASCT+9, of 326 patients with informative samples, 214 (65.6%) were MRD negative and 112 (34.4%) were MRD positive. MRD negative status was associated with a 79% reduction in PFS events (HR=0.21, 95% CI 0.13-0.34; P<0.0001) and a 67% reduction in the risk of death (HR=0.33, 95% CI 0.15–0.75; P=0.0077). Regardless of MRD status, at both time points, maintenance lenalidomide was associated with a significant improvement in PFS compared with observation. Sustained MRD negativity from ASCT+3 to ASCT+9 or the conversion to MRD negativity by ASCT+9 were associated with the longest PFS and OS. Patients randomized to lenalidomide maintenance were more likely to convert from being MRD-positive before maintenance randomization to MRD-negative 6 months later (lenalidomide 30%, observation 17%). High-risk molecular features had an adverse effect on PFS and OS for patients both MRD-negative and MRD-positive at both ASCT+3 and ASCT+9. On multivariable analysis MRD status, maintenance therapy and molecular risk maintained prognostic impact at both ASCT+3 and ASCT+9. **Conclusions:** In patients with multiple myeloma, MRD status at both ASCT+3 and ASCT+9 is a powerful predictor of PFS and OS. At both time points, regardless of MRD status, lenalidomide maintenance was associated with improved PFS and OS, whilst high-risk molecular features were associated with adverse outcomes.

OAB-016

Treatment pathways for patients with multiple myeloma: a real-life study based on the French National Claim database from 2014 to 2019

Aurore Perrot[1], Vincent Augusto[2], Marie Pierres[3], Matthieu Javelot[3], Caroline Guilmet[3], Martin Prodel[4], Ludovic Lamarsalle[4], Marie Laurent[4], Isabelle Borget[5], Cyrille Touzeau[6]

[1]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [2]Center for Biomedical and Healthcare Engineering Mines; [3]JANSSEN Cilag France; [4]HEVA; [5]Institut Gustave Roussy; [6]Centre Hospitalier Universitaire de Nantes

Background: Multiple Myeloma (MM) disease course is a succession of remissions and relapses, which define lines of treatment. For each line, several regimens can be used. This study provides a comprehensive overview of the evolution through treatment lines of MM patients, based on the nationwide French National Health Insurance (NHI) databases, called SNDS ("Système National des Données de Santé"). These databases include hospital records, primary and secondary care, and death records of 66 million people. **Methods:** This is a retrospective observational cohort study including all cases of multiple myeloma from 2014 to 2019 identified through the French NHI databases (SNDS). Cases were detected using a validated algorithm which was expanded to consider recent evolution of MM therapeutic management. Incident patients of 2014 and 2015 were extracted and followed up until December 31st, 2019. Treatment lines were reconstructed from 2014 to 2019 through ATLAS, an artificial intelligence algorithm adapted from the Smith-Waterman alignment sequence. Time To Next Treatment (TTNT) for each line has been estimated with a Kaplan Meier method. **Results:** 40,747 prevalent treated patients with MM were identified in the SNDS from 2014 to 2019. This analysis involved more specifically 7,118 of these patients, including 3,557 incident patients from 2014 and 3,561 from 2015. Patients were followed until December 31st, 2019, or death. For the frontline treatment, 76% [N=5,409] had a frontline without transplant (L1 NTE) and 24% [N=1,709] had a frontline with transplant (L1 TE). Among patients with L1 NTE (resp. TE), 15% [N=827] (resp. 33% [N=560]) stayed in frontline until the end of the follow-up, 31% [N=1,682] (resp. 4% [N=71]) died after their frontline, and 54% [N=2,900] (resp. 63% [N=1,078]) switched to L2. Among patients with a L1 NTE (resp. TE) and a L2, 26% [N=764] (resp. 35% [N=378]) stayed in L2 until the end of the follow-up, 29% [N=841] (resp. 12% [N=124]) died after their L2, and 45% [N=1,295] (resp. 53% [N=576]) switched to L3. Among patients with a L1 NTE (resp. TE) and a L3, 24% [N=316] (resp. 28% [N=159]) stayed in L3 until the end of the follow-up, 28% [N=367] (resp. 19% [N=111]) died after their L3, and 47% [N=612] (resp. 53% [N=306]) switched to L4. The median TTNT for L1 NTE (resp. TE) was 2.4 (resp. 3.3) years. The overall survival rate at 5 years for patients with a L1 NTE (resp. TE) was 41% (resp. 75%). Regarding treatment sequencing, the main course of patients was as follows: frontline: V-based regimen (VMP for NTE, VTd for TE); L2: Rd; L3: Pom-dex; L4: Dara mono. **Conclusions:** This study shows the flow of patients from frontline to L4+ and their survival rates. The study also showed that real-world data are a powerful tool to study treatment lines at a national scale and lead the way to more precise analyses of optimal therapeutic sequences, including their impact on the overall survival.

OAB-017

Attenuation of T cell cytotoxicity mediated by CD200 expression on multiple myeloma cells

Pooja Shah[1], Thorsten Stühmer[1], Daniela Brünnert[1], Umair Munawar[1], Ellen Leich[1], Sabrina Kraus[1], Manik Chatterjee[1], Andreas Schlosser[1], Ralf C. Bargou[1], Hermann Einsele[1], Friederike Berberich-Siebelt[1], Torsten Steinbrunn[1]

[1]University Hospital of Würzburg

Background: The CD200/CD200 receptor (CD200R) axis is known to entail an immunoregulatory function in myeloid derived cells. The ligand, CD200, is implicated in solid and hematological malignancies to be associated with poor prognosis. Multiple myeloma (MM), a plasma cell malignancy, shows strong expression of CD200 in the majority of patient derived primary cells. However, the downstream mechanism upon CD200 ligand binding to the CD200R in T cells is not well understood. In this study, we evaluate the role of CD200 as a potential immune checkpoint in MM and seek to unravel the mechanism of immune escape mediated by CD200. **Methods:** CD200 expression on patient-derived primary MM cells and MM cell lines was tested using flow cytometry. A Sleeping Beauty Transposon vector system was used to overexpress CD200 on MM cell lines. CD3/CD28-activated healthy donor T cells were co-cultured with CD200+/- MM cell lines L363, U266 and MM.1s. Using flow cytometry or luciferase assay, the co-culture was analyzed to assess cytotoxicity. To study downstream signaling effects of CD200R activation, CD3/CD28-activated T cells were treated with recombinant human CD200 (rhCD200) and/or anti-CD200 blocking antibody. Western blotting was performed to analyze potential downstream effector signaling. **Results:** Approximately three-quarters of patient-derived primary MM cells (n=120) expressed CD200. In MM cell lines (n=9), no surface or cytoplasmic expression of CD200 was observed. Hence, we stably expressed CD200 on MM cell lines using a Sleeping Beauty transposon vector system. In both, flow cytometric analysis and luciferase assay, we observed up to 50% decrease in CD3+ T cell-mediated cytotoxicity in the presence of CD200-expressing MM cells. Possible differences in proliferation rates of MM cell lines due to CD200 overexpression were ruled out by performing an Alamar blue assay. In myeloid derived cells, docking protein-2 (DOK2) is known to directly interact with CD200R. DOK2 was phosphorylated upon CD200 binding in activated T cells when treated with rhCD200 in a time and concentration-dependent manner. This effect could be reversed with an anti-CD200 blocking antibody, providing a mechanistic explanation for the observed attenuation of T cell function. **Conclusions:** CD200 expression on MM cell lines leads to attenuated cytotoxicity from primary healthy donor CD3+ T cells. Here, we provide evidence that this inhibitory mechanism in CD3+ T cells is mediated via DOK2.

OAB-018

A BCL2L1 armoured BCMA-targeting CAR T cells to overcome exhaustion and enhance persistence in multiple myeloma

Ranjan Maity[1], Sacha Benaoudia[1], Holly Lee[1], Elie Barakat[1], Noemie Leblay[1], Sungwoo Ahn[1], Franz Zemp[1], Douglas Mahoney[1], Paola Neri[1], Nizar Bahlis[1]

[1]Arnie Charbonneau Cancer Research Institute, University of Calgary

Background: Chimeric antigen receptor (CAR) T cells targeting BCMA have resulted in deep responses in patients with relapsed MM however most remissions are not sustained. While cellular and molecular mediators of relapse post CAR T therapy are not fully delineated, current data suggest three possible mechanisms including the lack of persistence of the CAR T cell product, acquired exhaustion and less commonly loss of BCMA expression. **Methods:** Using CITE-seq we measured the expansion of variable T cell subsets, T cell specific activation and inhibitor markers and their functional states in serial blood and marrow samples (n=10) collected from patients treated with anti BCMA CAR T cells. **Results:** CAR T cells were identified by the expression of the chimeric CAR T cell transcript. With the exception of one patient where biallelic loss of BCMA was identified at relapse, CAR T cells of resistant patients were enriched with terminally exhausted CD45RA+ cells with loss of CD28, low BCL2L1 (gene encoding BclxL) expression, high CD57 with co-expression of checkpoint inhibitors (LAG3, TIGIT and PD1). The lack of persistence of the CAR T cells product was notable in all relapsing patients consistent with an activation induced cells death (AICD). **Conclusions:** Cognizant of the role BclxL plays in T cells survival in response to CD28 co-stimulatory signaling, we postulated that increasing BclxL expression is a feasible strategy to enhance CAR T cell resistant to AICD, improve their persistence and anti-BCMA reactivity. To this goal, we designed a 2nd generation lentiviral CAR construct where the anti-BCAM scFV-41BBz CAR and the BCL2L1 cDNA were linked with self-cleaving 2A sequence. The efficiency in eradicating MM cells of this BclxL armored CAR (BCL2L1_CAR) was compared to that of non-unarmored CAR (BCMA_CAR) in vitro and in vivo studies. While BCL2L1_CAR and BCMA_CAR were equally cytotoxic to OPM2 MM cells, in MM cell lines expressing the FAS death receptor ligand FASLG (MM1S, OCMY5 and H929) BCL2L1_CAR viability and cytotoxic activity was significantly superior to that of unarmored BCMA_CAR. Of note, the expression of FASLG was upregulated in H929 cells when co-cultured with CAR T cells. Importantly, under chronic antigenic stimulation conditions, where CAR T cells were stimulated every 2 days over a 28 days period with irradiated OPM2 cells, we found no phenotypic difference between BCL2L1_CAR and BCMA_CAR with respect to the composition of Tem cells (CCR7–CD45RO+CD45RA–) or Tcm cells (CCR7+CD45RO+CD45RA–). However, under these chronic antigenic stimulation conditions, the CAR T cells viability, proliferation and anti-MM cytotoxic activities of the BCMA_CAR were dramatically reduced compared to that of the BCL2L1 armored CAR. Therefore BCL2L1 blockade of AICD not only enhanced the viability and cytotoxicity of CAR-T cells but surprisingly also reduced their functional exhaustion. Our findings provide a novel approach for CAR-T optimization and overcoming relapse resulting from lack of persistence.

OAB-019

CRISPR screens with single-cell transcriptome readout reveal potential mechanisms of response to natural killer cell treatment in multiple myeloma

Sara Gandolfi[1], Olli Dufva[1], Jani Huuhtanen[1], Olga Dashevsky[2], Jay Klievink[1], Jonas Bouhlal[1], Michal Scheffer[2], Matti Kankainen[1], Ricardo De Matos Simoes[2], Constantine Mitsiades[2], Satu Mustjoki[1]

[1]University of Helsinki; [2]Dana Farber Cancer Institute, Boston, MA

Background: Natural killer (NK) cell-based therapy is a promising approach to improve treatment responses in multiple myeloma (MM), which remains incurable. However, genetic determinants and mechanisms of sensitivity or resistance to NK cells in MM are incompletely understood. Here, we investigated the transcriptional impact of genes identified as regulators of sensitivity to NK cells in genome-wide CRISPR screens and integrated the findings with patient-derived data. **Methods:** To systematically dissect the mechanisms by which select genes identified in our previous genome-wide studies influence MM cell response to NK cells, we performed pooled CRISPR screens with a single-cell (sc) transcriptome readout using the CROP-seq platform. Based on genome-wide screen ranking and biological relevance, 31 genes were selected. Pools of MM1.S and LP1 expressing sgRNAs targeting select hits were co-cultured with NK cells for 24 h or left untreated, followed by scRNA-seq and sgRNA detection and assignment to cells, followed by differential gene-expression analysis and patient data correlation. **Results:** The analysis of the transcriptomic responses in MM cells upon NK cell exposure revealed that engagement by NK cells resulted in activation of IFNy-JAK-STAT signaling and upregulation of HLA class I genes, including the inhibitory NKG2A ligand HLA-E, as well as HLA class II. We then evaluated the impact of each sgRNA perturbation on gene expression in each condition, compared to the untreated control. Silencing of IFNy signaling mediators (JAK1, JAK2, STAT1, IFNGR2) prevented the induction of the IFNy response upon NK cell exposure, providing a mechanism for the observed sensitization to NK cells via reduced expression of HLA I genes. Disruption of TRAF2, NFKBIA, or NFKBIB, which also sensitized MM1.S to NK cells, induced NF-kB signaling. The induced NF-kB signature included increased expression of the death receptor FAS, pivotal for susceptibility to NK cells in the MM1.S CRISPR screen. We then correlated the findings with patient data from the CoMMpass dataset. Mutations in the NF-kB negative regulators TRAF2 and NFKBIA were associated with increased expression of NF-kB target genes also identified experimentally by CROP-seq. Also, NFKBIA mutations were linked to reduced

HLA-E expression in both MM patients and CROP-seq, suggesting a potential explanation for the NK-sensitizing effect of NFKBIA disruption. Interestingly, patients with NLRC5 mutations had lower HLA-E expression consistent with CROP-seq data, indicating that although rare, NLRC5 mutations may predispose MM cells to higher NK-sensitivity. **Conclusions:** Our data shed light on mechanisms of response to NK cells in MM and identify potential therapeutic targets for combination treatment. Furthermore, patient data correlation highlights subgroups that might have an increased susceptibility to NK cell treatment, highlighting the potential of such studies in the identification of predictive biomarkers.

OAB-020

The role of checkpoint inhibitor PD-1H/VISTA in Multiple Myeloma bone disease

Jing Fu[1], Shirong Li[1], Huihui Ma[1], Jun Yang[2], Gabriel Pagnotti[3], Stephen Weiss[4], Markus Mapara[1], Suzanne Lentzsch[1]

[1]Columbia University; [2]Columbia University Medical Center; [3]University of Texas - MD Anderson Cancer Center; [4]Life Sciences Institute, University of Michigan

Background: Multiple myeloma (MM) bone disease remains one of the most devastating complications of this incurable cancer, causing bone fractures, pain, mobility issues, and neurological deficits. MM cells secret pro-osteoclastogenic factors which lead to osteoclast (OCL) activation. Our previous work showed that matrix metalloproteinase 13 (MMP-13) is a critical osteoclastogenic factor highly secreted by MM cells and induces OCL fusion and bone resorption independently of its proteolytic activity (JCI 2016). We recently reported that MMP-13 binds to checkpoint inhibitor programmed death-1 homolog (PD-1H/VISTA), a surface receptor that is expressed on OCLs and mediates MMP-13 induced OCL fusion and bone resorption activity (ASH 2019). Bone resorption activity is significantly impaired in Pd-1h-/- OCLs in vitro. However, the function of PD-1H in MM bone disease has not been defined. **Methods:** The role of PD-1H in MM bone disease was investigated using the intratibial 5TGM1 Rag2-/- MM bone disease mice model. Pd-1h-/-Rag2-/- mice were generated by crossbreeding Pd-1h-/- with Rag2-/- mice. Firefly luciferase-expressing 5TGM1 cells were intratibially injected into age and sex-paired Rag2-/- or Pd-1h-/-Rag2-/- mice (N=10). 3 weeks later, tibiae were harvested for quantitative micro-CT followed by histological analysis. **Results:** Morphological analyses of trabecular and cortical bones confirmed that Pd-1h-/- recipient mice exhibited significantly less 5TGM1-induced bone loss ($P<0.05$). In trabecular bone, 5TGM1 induced 40.0% decrease of bone volume fraction in Rag2-/- mice vs 12.5% in Pd-1h-/-Rag2-/- mice, 7.3% decrease of trabecular bone numbers in Rag2-/- mice vs 0.6% in Pd-1h-/-Rag2-/- mice, 12.1% decrease of trabecular bone thickness in Rag2-/- mice vs 4.2% in Pd-1h-/-Rag2-/- mice, 8.1% increase of trabecular bone spacing in Rag2-/- mice vs 0.6% in Pd-1h-/-Rag2-/- mice, and 22.2% increase of specific bone surface in Rag2-/- mice vs 5.5% in Pd-1h-/-Rag2-/- mice. Similar effects were observed in cortical bone. 5TGM1 induced 18.9% decrease of cortical bone thickness in Rag2-/- mice vs 1.6% in Pd-1h-/-Rag2-/- mice, 7.28% decrease of cortical bone area fraction in Rag2-/- mice vs 2.7% in Pd-1h-/-Rag2-/- mice, and 8.19% decrease of cortical tissue mineral density in Rag2-/- mice vs 1.7% in Pd-1h-/-Rag2-/- mice. **Conclusions:** Taken together, our study, for the first time, reveals that checkpoint inhibitor PD-1H/VISTA is the critical receptor for MMP-13 in osteoclasts, thereby mediating MMP-13-induced osteoclast fusion, activation, and bone resorption. MM-induced trabecular bone loss was significantly lower in Pd-1h-/- mice, demonstrating that PD-1H/VISTA plays a critical role in MMP-13-induced MM bone disease. Given the checkpoint role of PD-1H/VISTA in cancer immunosuppression, we further posit that targeting the interaction of MMP-13 and PD-1H may represent a novel therapeutic strategy to treat MM bone disease and modulate the MM immune environment.

OAB-021

BCMA-specific ADC MEDI2228 and Daratumumab induce synergistic myeloma cytotoxicity via enhanced IFN-driven innate immune responses and expression of CD38 and NKG2D ligands

Lijie Xing[1], Su Wang[2], Jiye Liu[3], Tengteng Yu[3], Hailin Chen[3], Kenneth Wen[3], Phillip Hsieh[3], Shih-Feng Cho[4], Gang An[5], Lugui Qiu[6], Nikhil C. Munshi[7], Kenneth Anderson[8], Yu-Tzu Tai[8]

[1]Shandong Provincial Hospital Affiliated to Shandong First Medical University; [2]Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA.; [3]Dana-Farber Cancer Institute; [4]Faculty of Medicine, College of Medicine, Kaohsiung Medical University; [5]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [6]Institute of Hematology and Blood Diseases Hospital; [7]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System; [8]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Background: Efforts are required to improve potency and durability of CD38- and BCMA-based immunotherapies in human multiple myeloma (MM). **Methods:** We here delineated the molecular and cellular mechanisms underlying novel immunomodulatory effects triggered by BCMA pyrrolobenzodiazepine (PBD) antibody drug conjugate MEDI2228 which may augment efficacy of these immunotherapies. RNA sequencing followed by gene set enrichment analysis showed that MEDI2228 significantly enriched IFN I-signaling and induced type I interferon (IFN I)-stimulated genes (ISGs) in MM cell lines. The most MEDI2228-enhanced IFN-driven genes include chemokines/cytokines and receptors (i.e., CXCL9/10, CCL4L1/2, CCL22, CCL1/3/4/5, CCL3L1/3, TNFSF9/10, CSF2 (GM-CSF),

CCR7), RSAD2, CASP1, ISGs (i.e., XAF1, TRIMs, IFITs, ISG15, GBP2/3, OAS1/2/L, RNASEL, MX1/2, FAS), RUNX3, GZMB, IKBKE, IRF1/6/7/9, STAT1/2/4/6, MB21D1(CGAS), TMEM173 (STING), IFIT1/2/3/5, and SOCS1/2/3. **Results:** Regardless of genetic heterogeneity and resistance to current anti-MM therapies, MEDI2228 induced dose- and time-dependent DNA damage-ATM/ATR-CHK1/2 pathways, activation of cGAS-STING-TBK1-IRF3 and STAT1-IRF1-signaling cascades, as well as increased CD38 expression. It overcame CD38 downregulation triggered by IL6 and bone marrow stromal cell culture supernatant (BMSC-sup), via activation of STAT1-IRF1 without phosphorylation of STAT3 in immunomodulatory drugs (IMiDs)- and bortezomib-resistant MM cell lines. In contrast, MEDI2228 did not change CD38 expression and survival in BCMA-negative NK effector cells. Significantly, MEDI2228 with anti-CD38 monoclonal antibody Daratumumab (Dara) synergistically induced NK-mediated lysis of MM cell lines and autologous resistant patient MM cells, even in the presence of BMSC-sup and BMSCs. In parallel, MEDI2228 increased membrane expression of NKG2D ligands (NKG2DLs), i.e., MICA/B and ULBPs, in all MM cells tested, including Dara-resistant patient cells, correlating with enhanced MM cell susceptibility to NK cell killing. Since MEDI2228, but not its MMAF-ADC homolog M3 even used at >1-log higher concentrations enhanced surface expression of CD38 and NKG2DLs on MM cells, the potent DDR-mediated immunomodulation triggered by MEDI2228 vs M3 is critical in rendering MM cells more susceptible to Dara-induced NK cell killing. Importantly, M2 still activated STAT1/IRF1 signaling to induce CD38 and MICA/B expression in MM tumors grown in mice. All MM1S tumor-bearing NSG mice reconstituted with human NK cells became tumor-free following a single low dose M2 with Dara treatment, with 100% host survival. **Conclusions:** Taken together, our data showed that MEDI2228 restored MM sensitivity to CD38 targeting by Dara without depleting NK cells and potentiated immunogenic cell death of MM cells. These results therefore provide the mechanistic rationale for clinical evaluation of combination CD38- and BCMA-directed immunotherapies to further improve patient outcome in MM.

OAB-022

Monoallelic deletion of BCMA locus is a frequent feature in MM and is associated with increased genomic loss

Mehmet K Samur[1], Anil Aktas-Samur[1], Romain Lannes[2], Jill Corre[3], Kenneth Anderson[4], Hervé Avet-Loiseau[5], Nikhil C. Munshi[6]

[1]Dana-Farber Cancer Institute, Boston, USA; [2]IUCT Oncopole; [3]Institut Universitaire du Cancer de Toulouse-Oncopole; [4]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [56]CRCT-Toulouse; [6]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: Immunotherapies in MM targeting BCMA, have shown remarkable clinical benefits.However, two recent reports highlighted that biallelic loss of BCMA cause resistance to anti-BCMA therapy.In both studies BCMA locus was deleted bringing in focus importance of del16p.We have evaluated 2883 MM patients at diagnosis and relapse to understand frequency of BCMA targeting events and characteristics of MM patients with BCMA deletion. **Methods:** We observed del16p in 8.58% (7.6% to14.6% in individual studies) of newly-diagnosed patients (n=2458).Frequency of 16p loss in both HMM and NHMM were similar, suggesting its independence from MM subtypes.Overall CN loss was significantly higher in patients with BCMA loss compared to rest of the MM patients.High risk deletion events such as del1p and del17p were more likely to be observed in patients with loss of BCMA locus (OR [95% CI] 19.3(13.1-25.8), FDR = 1.5e-65; and 8.8(6.3-12.1), FDR = 5.5E-39, respectively)]. MM patients with loss of BCMA locus have increased mutational load (8202 with 95% HDI 6921 and 9535) compared to those without BCMA locus loss (6975 with 95% HDI 6626 – 7343); probability of difference greater than 0 was 96.8% and difference of the means were 1222 [95% CI 112-2589]. To understand the risk profile of patients with loss of BCMA locus, we next focused on the observation that BCMA loss frequently co-occurs with other deletions. **Results:** We observed that when BCMA and TP53 or BCMA and del1p loss are present in the same patient, they are likely to have same clonality.These data suggested a possibility of co-occurrence of these events in same cell. To further investigate this observation, we used single cell DNA sequencing data from patients with sub clonal and clonal BCMA locus loss.Interestingly, almost all cells with BCMA loss also had p53 loss, while not all p53 loss cells had BCMA loss suggesting that the chronology of this copy number alternation may suggest first p53 loss followed by BCMA loss. Our data from a patient with BCMA targeting therapy also indicated that BCMA loss tend to co-occur with TP53 deletions (OR=5.67 [95% CI 4.12-7.84], p value < 0.0001).Moreover, we found that TP53 mutations were more frequent for patients with del16p and del17p, compared to patients who only had del16p. **Conclusions:** Our data from large scale copy number profiles showed that even without treatment pressure, monoallelic BCMA deletions are frequent events.Moreover, patients with these events show increased genomic loss.Such behavior potentially make these cells vulnerable for biallelic loss of other genes.Our results highlight that by looking at mRNA or protein expressions at bulk sample would not directly indicate the presence or absence of cells with target loss and therefore evaluating single cell level data are necessary.These results suggest the need to study del16p in patients being targeted for BCMA-directed therapy and its association with del17p raises question about the role of BCMA targeted therapy in high-risk myeloma.

OAB-023

Efficacy and safety of ciltacabtagene autoleucel, a BCMA-directed CAR-T cell therapy, in patients with progressive multiple myeloma after 1–3 prior lines of therapy: Initial results from CARTITUDE-2

Adam Cohen[1], Mounzer Agha[2], Deepu Madduri[3], Yael Cohen[4], Michel Delforge[5], Jens Hillengass[6], Hartmut Goldschmidt[7], Katja Weisel[8], Marc-Steffen Raab[9], Christoph Scheid[10], Jordan M. Schecter[11], Kevin C. De Braganca[11], Helen Varsos[11], Liwei Wang[11], Martin Vogel[11], Marlene Carrasco-Alfonso[12], Muhammad Akram[12], Xiaoling Wu[12], Tonia Nesheiwat[12], Hermann Einsele[13]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [2]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]Tel- Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [5]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT); [8]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [9]University Hospital Heidelberg, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/ Oncology, German Cancer Research Center, Heidelberg, Germany; [10]Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany; [11]Janssen R&D, Raritan, NJ, USA; [12]Legend Biotech USA, Inc, Piscataway, NJ, USA; [13]University Hospital of Würzburg

Background: Ciltacabtagene autoleucel (cilta-cel) is a CAR-T cell therapy expressing two B-cell maturation antigen (BCMA)-targeting, single-domain antibodies. The multicohort, phase 2 CARTITUDE-2 study (NCT04133636) is evaluating the safety and efficacy of cilta-cel in various clinical settings for patients (pts) with multiple myeloma (MM) and exploring suitability of outpatient administration. Initial results from Cohort A are presented here. **Methods:** Pts from Cohort A had progressive MM after 1–3 prior lines of therapy (LOT), including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), were lenalidomide refractory, and had not received BCMA-targeting agents. A single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg) was given 5–7 days after start of lymphodepletion (daily cyclophosphamide [300 mg/m^2] and fludarabine [30 mg/m^2] for 3 days). Minimal residual disease (MRD) negativity at 10^{-5} was the primary objective, and response rates (per IMWG) and safety (per CTCAE; CRS and ICANS by ASTCT) were secondary outcomes. **Results:** At data cutoff (Feb 2021), the median follow-up was 5.8 months (2.5–9.8). Twenty pts (65% male; median age 60 years [38–75]) had received cilta-cel, with 1 pt treated in an outpatient setting. The median number of prior LOT was 2 (1–3): <3 prior LOT (n=12) and 3 prior LOT (n=8). All pts were exposed to PI, IMiD, and dexamethasone, 95% had received alkylating agents, and 65% had received daratumumab. 95% were refractory to the last LOT, and 40% were triple-class refractory. Overall response rate was 95% (95% CI: 75–100), 75% (95% CI: 51–91) achieved sCR/CR, and 85% (95% CI: 62–97) achieved ≥VGPR. Median time to first response was 1.0 month (0.7–3.3), and median time to best response was 1.9 months (0.9–5.1). Median duration of response was not reached. All 4 pts with MRD-evaluable samples at 10^{-5} at the time of data cutoff were MRD-negative. Hematologic adverse events (≥20%) were neutropenia (95%; grade [gr] 3/4: 90%), thrombocytopenia (80%; gr 3/4: 35%), anemia (65%; gr 3/4: 40%), lymphopenia (60%; gr 3/4: 55%), and leukopenia (55%; all gr 3/4). 85% of pts had CRS (gr 3/4: 10%). Median time to CRS onset was 7 days (5–9), with a median duration of 3.5 days (2–11). CAR-T cell neurotoxicity occurred in 20% of pts (all gr 1/2). ICANS was reported in 3 pts (1 gr 1 and 2 gr 2) with median time to onset of 8 days (7–11) and median duration of 2 days (1–2). One pt had gr 2 facial paralysis with onset at 29 days and duration of 51 days. One death from COVID-19 was assessed as treatment-related by investigator. For the pt treated in an outpatient setting, the safety profile was manageable. **Conclusion:** Early and deep responses with manageable safety were demonstrated after a single cilta-cel infusion at the recommended phase 2 dose. Updated findings will inform suitability of outpatient treatment for this study and for the CARTITUDE-2 and CARTITUDE-4 studies.

OAB-024

Updated results from CARTITUDE-1: Ciltacabtagene autoleucel, a B-cell maturation antigen–directed chimeric antigen receptor T (CAR-T) cell therapy, in relapsed/refractory multiple myeloma (RRMM)

Sundar Jagannath[1], Jesus G. Berdeja[2], Andrzej Jakubowiak[3], Mounzer Agha[4], Adam Cohen[5], Deepu Madduri[6], Parameswaran Hari[7], Tzu-Min Yeh[8], Yunsi Olyslager[9], Arnob Banerjee[10], Carolyn C. Jackson[8], Alicia Allred[10], Enrique Zudaire[10], William Deraedt[9], Xiaoling Wu[11], Lida Pacaud[11], Muhammad Akram[11], Yi Lin[12], Thomas Martin[13], Saad Z. Usmani[14]

[1]The Mount Sinai Hospital; [2]Sarah Cannon Research Institute and Tennessee Oncology; [3]University of Chicago, Chicago, IL, USA; [4]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [5]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [6]Mount Sinai Medical Center, New York, NY, USA; [7]Division of Hematology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [8]Janssen R&D, Raritan, NJ, USA; [9]Janssen R&D, Beerse, Belgium; [10]Janssen R&D, Spring House, PA, USA; [11]Legend Biotech USA, Inc, Piscataway, NJ, USA; [12]Mayo Clinic; [13]Department of Hematology, University of California at San Francisco, San Francisco, CA, USA; [14]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA

Background: Ciltacabtagene autoleucel (cilta-cel) is a CAR-T cell therapy with two B-cell maturation antigen–targeting single-

domain antibodies. The phase 1b/2 CARTITUDE-1 study is evaluating cilta-cel in patients (pts) with RRMM. Here we report updated results from a longer median duration of follow-up of 18 months (mos). **Methods:** Eligible pts had MM, received ≥3 prior regimens (or were double refractory to a proteasome inhibitor and immunomodulatory drug), and received anti-CD38 antibody. A single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg; range, $0.5–1.0\times10^6$) was given 5–7 days (d) after lymphodepletion with 300 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine daily for 3 d. Primary objectives were to assess cilta-cel safety, confirm the recommended phase 2 dose (phase 1b), and evaluate efficacy (phase 2). Cytokine release syndrome (CRS) was graded by Lee et al (Blood 2014) and neurotoxicity by Common Terminology Criteria for Adverse Events (CTCAE), v5.0 in phase 1b. CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by American Society for Transplantation and Cellular Therapy (ASTCT) criteria in phase 2. Here, Lee et al and CTCAE v5.0 were mapped to ASTCT for CRS and ICANS, respectively. **Results:** As of Feb 11, 2021, 97 pts (median of 6 prior lines) received cilta-cel. Overall response rate was 97.9% (95% CI, 92.7–99.7), with 80.4% achieving stringent complete response (sCR) and 94.8% achieving ≥very good partial response. Median time to first response was 1 mo (range, 0.9–10.7), and median time to ≥CR was 2.6 mos (range, 0.9–15.2). Median duration of response was 21.8 mos (95% CI, 21.8–NE). Of 61 pts evaluable for minimal residual disease (MRD), 91.8% were MRD negative at 10^{-5}. 18-month progression-free survival (PFS) and overall survival rates (95% CI) were 66% (54.9–75.0) and 80.9% (71.4–87.6), respectively. Median PFS was 22.8 mos (95% CI, 22.8–NE) for all pts, and not reached for pts with sCR. Grade 3/4 hematologic adverse events (AEs) ≥20% included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). CRS occurred in 95% of pts (4% grade 3/4); median time to onset was 7 d (range, 1–12), and median duration was 4 d (range, 1–14, except 1 pt with 97 d duration). CRS resolved in all but one with grade 5 CRS/haemophagocytic lymphohistiocytosis. CAR-T cell neurotoxicity occurred in 21% of pts (grade ≥3, 10%). 21 deaths occurred during the study after cilta-cel infusion: none within the first 30 d, 2 within 100 d, and 19 after 100 d. Ten deaths were due to disease progression, 6 were treatment-related, and 5 were due to AEs unrelated to treatment. **Conclusions:** At a median follow-up of 18 mos, a single infusion of cilta-cel yielded early, deep, and durable responses in heavily pretreated pts with RRMM, with manageable safety. Cilta-cel is being investigated in other MM populations in earlier lines of therapy and in outpatient settings.

OAB-025

Talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D)×CD3 bispecific antibody, in relapsed/refractory multiple myeloma (RRMM): Updated results of a phase 1, first-in-human study

Niels W.C.J. van de Donk[1], Amrita Krishnan[2], A Oriol[3], Jesus G. Berdeja[4], Paula Rodríguez-Otero[5], Elham Askari[6], María-Victoria Mateos[7], Monique C. Minnema[8], Luciano Costa[9], Raluca Verona[10], Suzette Girgis[10], Thomas Prior[10], Brandi Hilder[10], Jeffery Russell[10], Jenna Goldberg[11], Ajai Chari[12]

[1]Amsterdam University Medical Center, VU University Medical Center, Amsterdam, Netherlands; [2]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [3]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol; [4]Sarah Cannon Research Institute and Tennessee Oncology; [5]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [6]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [7]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca; [8]UMC Utrecht Cancer Center, Utrecht, the Netherlands; [9]University of Alabama at Birmingham, Birmingham, AL, USA; [10]Janssen R&D, Spring House, PA, USA; [11]Janssen R&D, Raritan, NJ, USA; [12]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA

Background: As patients (pts) with MM continue to relapse, new immunotherapy targets are needed. GPRC5D is an orphan receptor that is expressed on malignant plasma cells in MM. Talquetamab (JNJ-64407564) is a bispecific IgG4 antibody that binds to the novel target, GPRC5D, and to CD3 to redirect T cells to kill MM cells. Updated phase 1 results of talquetamab in pts with RRMM treated at the recommended phase 2 dose (RP2D) are presented here. **Methods:** Eligible pts had RRMM or were intolerant to standard therapies. Talquetamab was given either intravenously (IV; range 0.5–180 µg/kg) or subcutaneously (SC; range 5.0–800 µg/kg) weekly or biweekly. Primary objectives of the study were to identify the RP2D (part 1) and characterize talquetamab safety and tolerability at the RP2D (part 2). Adverse events (AEs) were graded by Common Terminology Criteria for Adverse Events v4.03 (cytokine release syndrome [CRS] per Lee 2014). Response was assessed per International Myeloma Working Group criteria. **Results:** As of Feb 8, 2021, 174 pts received talquetamab IV (n=102) or SC (n=72). Across both parts of the study, 28 pts received the RP2D of 405 µg/kg SC weekly, with 10.0 and 60.0 µg/kg step-up doses. Pts treated at the RP2D had a median age of 61.5 years (range 46–80) and received a median of 5.5 prior lines of therapy (range 2–14; 100%/79% triple-class/penta-drug exposed; 71%/18% triple-class/penta-drug refractory; 86% refractory to last line of therapy; 21% had prior B-cell maturation antigen–directed therapy). No dose-limiting toxicities occurred at the RP2D in part 1. Most common AEs at the RP2D were CRS (79%; grade 3 were 4%; median time to onset was day after SC injection), neutropenia (64%; grade 3/4 were 54%), anemia (57%; grade 3/4 were 29%) and dysgeusia (57%; all grade 1/2). Infections were reported in 32% of pts (grade 3/4 were 4%) and neurotoxicity in 7% (no grade 3/4 events). Overall, 75% of pts treated at the RP2D had skin-related AEs (no grade 3/4 events), including 18% with nail disorders. In 24 response-evaluable pts, overall response rate at the RP2D was 63%, with 50% reaching very good partial response or better; 9/17 (53%) evaluable triple-class refractory pts and 3/3 (100%) penta-drug refractory pts responded. The median time to first confirmed response at the RP2D was 1.0 month (range 0.2–3.8). Responses were durable and

deepened over time (median follow-up 6.2 month [range 2.7–9.7+] for responders at the RP2D). Talquetamab exposure at the RP2D was maintained over the maximum EC90 target level from an ex vivo cytotoxicity assay, and consistent T cell activation was seen. **Conclusions:** Talquetamab, at the RP2D of 405 µg/kg SC weekly, demonstrated a high clinical response rate and was well-tolerated in pts with RRMM. Based on pharmacokinetic data, other SC dosing strategies are being explored. The promising efficacy, safety profile and convenience of SC dosing support monotherapy development and combination approaches with this novel agent.

OAB-026

MagnetisMM-1 study of elranatamab (PF-06863135), a B-cell maturation antigen (BCMA) targeted CD3-engaging bispecific molecule, for patients (pts) with relapsed or refractory multiple myeloma (MM)

Bhagirathbhai Dholaria[1], Nizar Bahlis[2], Noopur Raje[3], Caitlin Costello[4], Melhem Solh[5], Moshe Levy[6], Michael Tomasson[7], Harman Dube[8], Michael Damore[8], Hoi Kei Lon[8], Cynthia Basu[9], Athanasia Skoura[10], Edward Chan[11], Suzanne Trudel[12], Andrzej Jakubowiak[13], Michael Chu[14], Cristina Gasparetto[15], Andrew Dalovisio[16], Michael Sebag[17], Alexander Lesokhin[18]

[1]Vanderbilt-Ingram Cancer Center, Nashville, TN; [2]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada; [3]Massachusetts General Hospital Cancer Center; [4]Moores Cancer Center, University of California San Diego, La Jolla, CA; [5]Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA; [6]Department of Medical Oncology, Baylor Scott and White Health, Dallas, TX; [7]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; [8]Oncology Research and Development, Pfizer, San Diego, CA; [9]Early Clinical Development, Pfizer, San Diego, CA; [10]Oncology Research and Development, Pfizer, Pennsylvania, PA; [11]Oncology Research and Development, Pfizer, South San Francisco, CA; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Department of Medicine, University of Chicago Medical Center, Chicago, IL; [14]Cross Cancer Institute, Edmonton, Alberta, Canada; [15]Department of Medicine, Duke University Cancer Institute, Durham, NC; [16]Department of Hematology and Oncology, Ochsner Health, Jefferson, LA; [17]Cedars Cancer Center, McGill University Health Centre; [18]Memorial Sloan Kettering Cancer Center

Background: Elranatamab (PF-06863135), a humanized bispecific molecule, targets both BCMA expressed in MM and CD3 on T cells. MagnetisMM-1 (ClinicalTrials.gov ID: NCT03269136) is a Phase 1 study of elranatamab with the aim of characterizing the efficacy, safety, pharmacokinetics, and pharmacodynamics of elranatamab as single agent and in combination with immunomodulatory agents for pts with relapsed or refractory MM. **Methods:** Pts received single agent elranatamab 80, 130, 215, 360, 600, or 1000µg/kg/week subcutaneously. A modified toxicity probability interval method was used for escalation, with monitoring for dose-limiting toxicity (DLT) to the end of the first cycle. Treatment emergent adverse events (TEAEs) were graded by Common Terminology Criteria for Adverse Events v4.03, and cytokine release syndrome (CRS) by American Society for Transplantation and Cellular Therapy criteria (Biol Blood Marrow Transplant. 2019;25:625). Responses and minimal residual disease (MRD) status (by next-generation sequencing at a sensitivity of 1 × 10-5) were assessed by International Myeloma Working Group criteria. Pharmacokinetics, cytokine profiling, and T cell immunophenotyping were performed. **Results:** 30 pts had received elranatamab as of 4-Feb-2021 at 80 (n=6), 130 (n=4), 215 (n=4), 360 (n=4), 600 (n=6), or 1000 (n=6) µg/kg. Pts had a median of 8 prior treatments; 87% had triple refractory disease, 97% prior anti-CD38 therapy, and 23% prior BCMA-directed antibody drug conjugate or chimeric antigen receptor T cell therapy. Common all causality TEAEs included lymphopenia (n=25, 83%; 20% G3, 63% G4), CRS (n=22, 73%; none >G2), anemia (n=18, 60%; 50% G3, 0% G4), neutropenia (n=16, 53%; 23% G3, 30% G4), thrombocytopenia (n=16, 53%; 17% G3, 20% G4), and injection site reaction (n=15, 50%; none >G2). Both CRS and immune effector cell-associated neurotoxicity syndrome (n=6, 20%) were limited to ≤G2; median durations were 3 and 2.5 days, respectively. No DLT was observed. Exposure increased with dose, and Tmax ranged from 3–7 days. Cytokine increases occurred with the first dose, and increased T cell proliferation was observed in peripheral blood. For doses ≥215µg/kg, confirmed overall response rate (ORR) was 70% (n=14/20) including partial response (PR; n=1), very good PR (VGPR; n=7), complete response (CR; n=1), and stringent CR (sCR; n=5). The majority of patients with sCR achieved MRD negativity. Median time to response was 22 days. In this dosing group, 3 of 4 pts (75%) with prior BCMA-directed therapy achieved response. Confirmed ORR at the recommended phase 2 dose (RP2D) of 1000µg/kg was 83% (n=5/6). **Conclusions:** Elranatamab achieved confirmed ORR of 83% at RP2D with a manageable safety profile for pts with relapsed or refractory MM. These results confirm the feasibility and potential of BCMA-directed immunotherapy for malignant plasma cell disorders, and support further development of elranatamab for pts with MM. This study was sponsored by Pfizer.

OAB-027

Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T-cell therapy, for the treatment of patients with relapsed and refractory multiple myeloma (RRMM): updated results from KarMMa

Larry D. Anderson, Jr[1], Nina Shah[2], Sundar Jagannath[3], Jesus G. Berdeja[4], Sagar Lonial[5], Noopur Raje[6], David S. Siegel[7], Yi Lin[8], Philippe Moreau[9], Ibrahim Yakoub-Agha[10], Michel Delforge[11], Hermann Einsele[12], Hartmut Goldschmidt[13], Katja Weisel[14], Michele Cavo[15], Donna E. Reece[16], Alessandro Rambaldi[17],

Anna Truppel-Hartmann[18], Payal Patel[19], Liping Huang[19], Timothy B. Campbell[19], Kristen Hege[19], Jesús F. San-Miguel[20], Nikhil C. Munshi[21], A Oriol[22]

[1]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center; [2]Department of Medicine, University of California San Francisco; [3]The Mount Sinai Hospital; [4]Sarah Cannon Research Institute and Tennessee Oncology; [5]Winship Cancer Institute, Emory University; [6]Massachusetts General Hospital Cancer Center; [7]John Theurer Cancer Center, Hackensack University Medical Center; [8]Mayo Clinic; [9]University Hospital Hôtel-Dieu; [10]CHU de Lille, Univ Lille; [11]University Hospital Leuven, Leuven, Belgium; [12]University Hospital of Würzburg; [13]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT); [14]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [15]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Università di Bologna; [16]Princess Margaret Cancer Centre; [17]University of Milan and ASST Papa Giovanni XXII; [18]bluebird bio; [19]Bristol Myers Squibb; [20]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA; [21]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System; [22]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol

Background: Patients (pts) with RRMM who were exposed to immunomodulatory agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs) have poor outcomes with subsequent treatments. Ide-cel, a BCMA-directed CAR T-cell therapy, has shown frequent, deep, and durable responses in triple-class exposed pts with RRMM in the pivotal KarMMa study (NCT03361748; Munshi NC et al. N Engl J Med 2021). Here, we report updated results from this trial. **Methods:** Eligible pts had received ≥3 prior regimens (including an immunomodulatory agent, a PI, and an anti-CD38 mAb) and had disease refractory to their last regimen per IMWG criteria. After 3 days of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2), pts received 150–450×10^6 CAR+ T cells (target dose levels). Primary endpoint was overall response rate (ORR); key secondary endpoint was complete response (CR) rate (CR + stringent CR). Other secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** In total, 128/140 enrolled pts received ide-cel. Data are presented for the treated pts. Median age was 61 y. Pts had received a median of 6 (range, 3–16) prior regimens, with 84% being triple-class refractory and 26% penta-refractory (lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab). Most pts (88%) had received bridging therapy. At data cutoff (Dec 21, 2020), the median follow-up among surviving pts was 24.8 mo. In total, 94/128 pts (73%) achieved an overall response, with a CR rate of 33%; median DOR and PFS were 10.9 mo and 8.6 mo, respectively. In pts who achieved ≥CR, median DOR was 21.5 mo and median PFS was 22.4 mo. Outcomes improved at higher doses, with ORR of 81%, CR rate of 39%, median DOR of 11.3 mo, and median PFS of 12.2 mo at 450×10^6 CAR+ T cells; in pts who achieved ≥CR at this dose, median DOR was not reached. Responses were observed in all subgroups, including difficult-to-treat subsets (eg, high tumor burden [ORR, 71%], extramedullary disease [70%], and R-ISS stage III disease [48%]). Median OS was 24.8 mo; the estimated 24-mo OS rate was 51%. The most common any-grade toxicities were neutropenia (91%) and cytokine release syndrome (CRS; 84%). CRS was mostly grade 1/2; 5 pts (4%) had grade 3, 1 pt each had grade 4 and 5 events (both at 300×10^6). Investigator-identified neurotoxicity was reported in 23 pts (18%); 5 (4%) had grade 3 and 0 had grade ≥4 events. Tocilizumab was used in 67 and 3 pts, and steroids were used in 19 and 10 pts with CRS and neurotoxicity, respectively. **Conclusion:** Updated results from the KarMMa trial continue to demonstrate durable and deep responses with ide-cel in heavily pretreated, triple-class–exposed pts with RRMM. Efficacy and safety data are consistent with prior reports and support a favorable clinical benefit–risk profile for ide-cel across the target dose levels.

OAB-028

FAM46C-dependent tuning of endoplasmic reticulum capacity in Multiple Myeloma

Enrico Milan[1], Elena Riva[2], Chiara Fucci[2], Massimo Resnati[2], Tommaso Perini[1], Simone Cenci[1]

[1]IRCCS Ospedale San Raffaele, Milan, Italy; [2]San Raffaele Scientific Institute

Background: Protein secretion is a driving force in evolution and tissue specialization. Plasma cells (PC), responsible for intense antibody (Ab) production, are paradigmatic professional secretors whose differentiation entails rapid endoplasmic reticulum (ER) expansion and concerted expression of the protein translocation, folding and trafficking machinery. A novel player in PC differentiation, recently implicated in Ab immunity is the non-canonical poly(A) polymerase FAM46C/TENT5C. **Methods:** In developing PCs, FAM46C is induced to polyadenylate and enhance the translation of a number of mRNAs encoding Igs and ER-targeted proteins [1,2]. Being deleted or mutated in up to 20% multiple myeloma (MM) patients, but intact in other cancers, the FAM46C gene is among the most frequent genomic hits in MM and a myeloma-specific onco-suppressor [3,4]. **Results:** We have recently shown that the ER-specific action of FAM46C depends on its interaction with the ER transmembrane FNDC3 proteins. As a result, FAM46C concertedly boosts the expression of ER and Golgi proteins, potently upsizing the secretory apparatus and Ig secretion [5]. Our data suggest that in MM the FAM46C gene is under selective pressure to contain the proteosynthetic, oxidative and metabolic stress associated with Ig secretion, favoring myeloma cell survival and growth. In keeping with this, exogenous re-expression of FAM46C in mutated MM cells raised Ig secretory capacity beyond sustainability, causing ATP shortage, ROS accumulation and apoptosis. Interestingly, although able to increase the secretory capacity across different cell types, FAM46C overexpression induced apoptosis exclusively in MM cells, being well tolerated in non-professional secretors, suggesting a key role of the secretory cargo in FAM46C toxicity. Moreover, we discovered

a broader function of FAM46C in ER homeostasis beyond mRNA stabilization. Indeed, we found that FAM46C is part of a novel integrated network coordinating the biogenesis of ribonucleoprotein complexes, ER protein translation and import, and ER expansion, to harmonize massive Ab production with protein homeostasis. Finally, our proteomic analysis unveiled a surprising opposite modulation of signal recognition particle (SRP) proteins mediated by FAM46C. Indeed, while 4 out of 6 SRP proteins were positively regulated by FAM46C, the heterodimeric members SRP9 and SRP14, mediating translational arrest, increased upon FAM46C loss. **Conclusions:** We infer that PCs have the ability to sense FAM46C-induced ER expansion and modulate SRP composition to minimize translational pausing and maximize Ab manufacture. This novel integrated network offers a framework to identify unprecedented highly specific therapeutic targets against PC dyscrasias. **References:** [1] Bilska A., et al, Nat Commun. 2020;11(1):2032. [2] Mroczek S., et al, Nat Commun. 2017;8(1):619. [3] Chapman MA., et al, Nature 2011;471, 467–472. [4] Boyd KD., et al, Clin Cancer res. 2011;17(24):7776-7784. [5] Fucci C., et al, Cell Rep. Cell Rep. 2020;32(12):108162.

OAB-029

Bone marrow adipocytes induce metabolic reprogramming of multiple myeloma cells

Cristina Panaroni[1], Keertik Fulzele[1], Tomoaki Mori[1], Chukwuamaka Onyewadume[1], Allison Maebius[1], Noopur Raje[2]

[1]Massachusetts General Hospital; [2]General Hospital Cancer Center

Background: Obesity-induced increases in bone marrow adipocyte (BMAd) numbers and volume are associated with an increased risk of MM. However, the associated molecular mechanisms have remained largely unknown. We hypothesize that BMAd support MM cells through metabolic reprogramming. **Methods:** BM aspirates of MGUS, SMM, and NDMM patients were used to obtain mature BMAd or stromal cells (BMSCs). Murine BMSC cell-line OP9, MM cell-line 5TGM1, and human-origin MM cell-lines MM.1S, OPM2 were obtained from ATCC. Cell proliferation was assessed by CyQUANT Assay; lipolysis by Lipolysis Assay (Sigma); lipid uptake by flow cytometry (FCM) of fluorescent fatty acids (FA) BODIPY-C12 and -C16, or LipidTox. In-vivo efficacy of FA treatment was assessed in a MM CB17 SCID mouse plasmacytoma model. **Results:** In-vitro co-culture revealed that BMSC-derived adipocytes (Ad) from MGUS/SMM and NDMM donors significantly increased the proliferation of MM.1S MM cells. Similarly, mature murine OP9 Ad cells also increased the proliferation of 5TGM1 murine MM cells. Interestingly, co-cultures showed dramatic decrease in LipidTox-stained lipid-droplet size distribution, suggesting increased lipolysis in Ad, further confirmed by increased glycerol content in conditioned media in the presence of MM cells. Moreover, BMAd from MGUS, SMM, and NDMM patients showed increased expression of genes responsible for lipolysis (NR1H3) and increased FA desaturation (SCD1, FASD2). Although MM cells lacked intracellular lipid storage, OPM2 and 5TGM1 MM cells rapidly took up BODIPY-C12 and -C16 FAs. The FA secreted from Ad were directly taken up by MM cells as shown by transfer of LipidTox-labeled lipids from OP9 Ad to unstained 5TGM1 or OPM2 MM cells as assessed by FCM. The addition of acipomox, a small-molecule inhibitor of lipolysis, decreased LipidTox signal in MM cells compared to untreated OP9 cells. FA are transported into cells through FATP (1-6) or CD36 receptors. Bioinformatics analysis of public Oncomine database showed that FATP1 and FATP4 were highly expressed in 21 human MM cell lines. MM cells from NDMM patients expressed high levels of FATP1 and FATP4. The uptake of BODIPY-C12 and -C16 by 5TGM1 or OPM2 MM cells was significantly reduced in the presence of Lipofermata, a pharmacological small-molecule inhibitor of FATP. Lipidomic analysis of BM aspirates from MM patients showed altered expression of various FA, including arachidonic acid (AA). Low doses of AA (0.125 - 2 µM) increased the proliferation and viability of MM cells whereas high doses (25- 100µM) dramatically decreased it, indicating a bimodal cellular effect of AA. Peritumoral AA treatment in a plasmacytoma model decreased tumor volume significantly. **Conclusion:** We show that MM cells induce lipolysis in BMAd and that the released FFA are then taken up by MM cells through FATPs. Inhibition of either BMAd lipolysis or FFA transporter into MM cells could be a potential novel strategy to prevent MM progression.

OAB-030

Combined targeting of distinct c-Myc and JunB transcriptional programs induces synergistic anti-myeloma activity

Judith Lind[1], Sonia Vallet[2], Karoline Kollmann[3], Osman Aksoy[1], Vincent Sunder-Plassmann[1], Elisabeth Zwickl-Traxler[4], Fengjuan Fan[5], Dagmar Stoiber-Sakaguchi[1], Latifa Bakiri[6], Erwin Wagner[6], Martin Sattler[7], Martin Pecherstorfer[4], Klaus Podar[2]

[1]Karl Landsteiner Priv. University Krems, Austria; [2]Karl Landsteiner Priv. University; University Hospital Krems, Austria; [3]Veterinary University Vienna; [4]University Hospital Krems, Austria; [5]Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and, Wuhan, Hubei, China; [6]Medical University Vienna; [7]Dana-Farber Cancer Institute

Background: Transcription factors (TF) are convergence points of signaling cascades that coordinate cell differentiation, proliferation and survival and are commonly deregulated in cancer, including multiple myeloma (MM). They contribute to the initiation of MM, promote tumor cell growth and drug resistance. Both cMyc, a merging point of the PI3K-, and JunB, a merging point of the MEK/MAPK signaling pathway, play pivotal roles in MM pathogenesis. Exciting novel approaches to inhibit TFs like proteolysis-targeting-chimera (PROTAC) promise to lead to selective tumor cell death with little consequence for normal cells. However, redundancy phenomena of TF-programs are likely to challenge their efficacy.

Here, we report our final results on the combined targeting of distinct cMyc and JunB transcriptional programs. **Methods:** Following CRISPR-loss-of-function screens for cMyc and JunB across MM cell lines and correlation analyses in MM patient datasets, the functional relevance of Brd4/cMyc- and MEK/JunB-induced TF programs was delineated using genomic and pharmacological approaches in 2D and 3D models of the BM microenvironment. Specifically, effects of single or combined targeting of cMyc- and JunB-induced transcriptional programs were analyzed by FACS, WB, qPCR and luciferase assays. In vitro and ex vivo results were finally verified in a MM xenograft mouse model. **Results:** While CRISPR-loss-of-function screens of MM cell lines confirmed the dependency on cMyc and JunB, we did not observe correlative expression levels among these TFs, neither in the publicly available GSE6477 nor in the CoMMpass dataset. In contrast, a significant positive correlation was observed between MEK and JunB, and Brd4 and cMyc expression levels, respectively. The existence of two distinct Brd4/cMyc and MEK/JunB transcriptional programs in MM cells was supported by stable cMyc levels and resultant transcriptional activity upon JunB knockdown, and vice versa. Likewise, MZ-1, a novel PROTAC which targets Brd4, resulted in inhibition of BMSC/IL-6-induced cMyc but not JunB-upregulation. Conversely, neither the MEK inhibitor trametinib nor doxycycline-induced knockdown of BMSC/IL-6-triggered JunB upregulation in TetshJunB/MM.1S cells reduced Brd4/cMyc mRNA/protein levels. Importantly, the activity of MZ-1 and trametinib was predicted by Brd4 and JunB expression levels using mathematical scoring models, respectively. Moreover, combinations of MZ-1 with trametinib or JunB knockdown synergistically inhibited tumor cell proliferation and induced cell death in a 2D and a dynamic 3D model of the MM-BM milieu. Finally, our results were verified in BMSC:TetshJunB/MM.1S vs BMSC:TetshSCR/MM.1S-carrying NSG mice treated with MZ-1 with/without doxycycline or trametinib. **Conclusions:** In summary, our data demonstrate for the first time the existence of non-overlapping cMyc and JunB-regulated transcriptional programs providing the rationale for combined cMyc:JunB targeting strategies for MM therapy.

OAB-031

Circular RNA protein tyrosine kinase 2 promotes cell proliferation, migration and suppresses apoptosis via activating microRNA-638 mediated MEK/ERK, WNT/b[ED]-catenin signaling pathways in myeloma

Fan Zhou[1], Haimin chen[1]

[1]Shanghai Jing'an District Zhabei Central Hospital

Background: Our previous study (Poster in IMW20) observed that circular RNA protein tyrosine kinase 2 (circ-PTK2) was upregulated and correlated with worse clinical features and unfavorable prognosis in multiple myeloma (MM) patients. Thus, this study aimed to further characterize the regulatory function of circ-PTK2 on cell malignant activities and its target microRNA-638 (miR-638) as well as downstream MEK/ERK, WNT/b[ED]-catenin signaling pathways in MM. **Methods:** The effect of circ-PTK2 on MM cell proliferation, apoptosis, migration, invasion and its potential target miRNAs was assessed by transfecting circ-PTK2 overexpression plasmids into U226 cells and circ-PTK2 knock-down plasmids into LP-1 cells. Furthermore, the interaction between circ-PTK2 and miR-638 mediated MEK/ERK and WNT/b[ED]-catenin signaling pathways was validated by rescue experiments. Circ-PTK2 was overexpressed in most MM cell lines compared to normal plasma cells. **Results:** Overexpressing circ-PTK2 promoted proliferation and migration, inhibited apoptosis in U266 cells, but did not affect cell invasion; knocking down circ-PTK2 achieved opposite effect in LP-1 cells. Besides, circ-PTK2 reversely regulated miR-638 expression but not miR-4690, miR-6724, miR-6749 or miR-6775. The following luciferase reporter assay illustrated the direct bind of circ-PTK2 towards miR-638. In rescue experiments, overexpressing miR-638 suppressed proliferation, migration, while promoted apoptosis in both wild U266 cells and circ-PTK2-overexpressed U266 cells; meanwhile, overexpressing miR-638 also suppressed MEK/ERK and WNT/b[ED]-catenin pathways in both wild U266 cells and circ-PTK2-overexpressed U266 cells. Knocking down miR-638 achieved opposite effect in both wild LP-1 cells and circ-PTK2-knocked-down LP-1 cells. **Conclusions:** circ-PTK2 promotes cell proliferation, migration, suppresses cell apoptosis via miR-638 mediated MEK&ERK and WNT&b[ED]-catenin signaling pathways in MM.

OAB-032

Targeting GCK in RAS-mutant multiple myeloma offer a promising therapeutic approach

Shirong Li[1], Jing Fu[1], Jun Yang[1], Huihui Ma[1], Markus Mapara[1], Christophe Marcireau[2], Suzanne Lentzsch[1]

[1]Columbia University; [2]Sanofi

Background: Next generation sequencing revealed frequent mutations of NRAS, KRAS or BRAF in up to 50% of newly diagnosed multiple myeloma (MM) patients. **Methods:** Specific K- or N-RAS knockdowns led to strong decrease in MM cell viability if harbored the respective oncogenic isoform, but minimal effects were observed if only the wild-type isoform was present, presenting RAS signaling as the key driving oncogenes in the mutation bearing patients. Unfortunately, no inhibitor for RAS mutation is available for clinical use in MM. Therefore, key component in the RAS/MAPK pathway may represent an alternative therapeutic target for MM. Germinal center kinase (GCK) is an upstream activator in the MAPK pathway. **Results:** Our data showed that GCK (MAP4K2) knockdown in MM cells induced MM cell growth inhibition, associated with the downregulation of critical transcriptional factors including IKZF1/3, BCL-6, and c-MYC proteins. Moreover, GCK silencing only led to significantly decreased GCK mRNA, however, did not affect IKZF1 expressions at mRNA level. We next tested the effects of GCK inhibitor TL4-12 on MM. Given the fact that RASMut MM cells have higher GCK expression level and are more sensitive to GCK knockdown, we compared mutated RAS MM

cells with wild-type RAS MM cells. TL4-12 significantly inhibited the growth of mutated RAS MM cells, with IC50 5-10 fold lower compared to wild-type RAS MM cell lines. IKZF1/3 are the key targets of the immunomodulatory drugs (IMiDs), which are the backbone of MM therapy. IMiDs bind to cereblon (CRBN) and induce IKZF1/3 protein degradation, which subsequently lead to MM cell growth inhibition. Our data showed that GCK knockdown also downregulates IKZF1 protein level, indicating that IKZF1 is under the regulation of GCK. Concomitant treatment with proteasome inhibitor PS-341 blocked TL4-12 induced IKZF1 downregulation, suggesting that inhibition of GCK induces IKZF1 protein degradation. However, since IMiDs-resistant RPMI-8226 and JJN3 MM cells are sensitive to GCK inhibition, we hypothesized that the IKZF1 degradation mechanism induced by GCK inhibition is different from IMiDs and independent of CRBN. To confirm this hypothesis, we silenced CRBN in N-Rasmut H929 MM cells and examined the response to IMiDs and GCK inhibitor. CRBN silencing in H929 cells resulted in lenalidomide resistance. In contrast, CRBN silencing failed to rescue H929 MM from TL4-12 induced proliferation inhibition and IKZF1 downregulation, confirming that GCK regulated IKZF1 and cell growth is independent of CRBN. **Conclusions:** Taken together, our data demonstrated that GCK inhibition induces cell growth inhibition and triggers apoptosis especially in RASmut MM cells. Importantly, GCK inhibition downregulates IKZF1 via a CRBN-independent mechanism. Our findings thus provide a rationale for the clinical evaluation of targeting GCK in RASmut MM patients and further mechanistic insight into the role of GCK in MM tumorigenesis as well as drug resistance.

OAB-033

Loss-of-function of GABARAP drives tumor resistance to bortezomib-induced immunogenic cell death in multiple myeloma

Annamaria Gulla[1], Eugenio Morelli[1], Mehmet K Samur[2], Cirino Botta[3], Megan Johnstone[4], Giada Bianchi[5], Mariateresa Fulciniti[1], Leona Yamamoto[4], Rao Prabhala[4], Kenneth Wen[4], Paul G. Richardson[2], Yu-Tzu Tai[1], Dharminder Chauhan[6], Teru Hideshima[4], Nikhil C. Munshi[7], Kenneth Anderson[1]

[1]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Dana-Farber Cancer Institute, Boston, USA; [3]Hematology Unit, Department of Oncology, "Annunziata" Hospital of Cosenza, Italy; [4]Dana Farber Cancer Institute; [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [6]Dana-Farber Cancer Institute, Harvard Medical School; [7]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: Resistance to immune approaches poses a major challenge to effective immunotherapy and long-term clinical outcome in multiple myeloma (MM). Here we identified loss-of-function of gamma-aminobutyric acid receptor-associated protein (GABARAP) as a tumor-intrinsic mechanism of resistance to bortezomib (BTZ)-induced immunogenic cell death (ICD), the immunogenic consequence of apoptosis resulting in specific anti-MM immunity via T-cell priming by dendritic cells (DCs). **Methods:** We found that BTZ induces ICD in human and murine MM cell lines that is dependent on the exposure of calreticulin (CALR), which drives DCs-mediated phagocytosis of MM cells. DCs-phagocytosis is followed by a specific T cell activation, with a significant increase of CD4+ effector memory (EM), total CD8+, CD8+ EM, and CD8+ terminally differentiated EM cells. Isolated T cells after co-cultures showed the presence of MM specific CTLs that were able to efficiently induce lysis of MM cells. Our results were validated using primary cells from MM patients. Moreover, induction of a protective immune response was confirmed in vivo. Specifically, treatment of 5TGM1 tumors with BTZ induced a tumor regression in a syngeneic model; and injection of live 5TGM1WT two weeks after regression did not result in tumor development, consistent with induction of immunological memory as confirmed by ELISPOT of mouse splenocytes. We identified a specific ICD signature induced by BTZ in mice; and we found that increased expression of the human orthologs of this signature was positively correlated with OS (p=0.01) in patients enrolled in the IFM/DFCI 2009 study. Notably, these functional immunologic sequelae were abrogated after BTZ treatment of CALRKO MM cells both in vitro and in vivo, confirming the obligate role of CALR exposure in the ICD process. **Results:** By interrogating the IFM/DFCI dataset and focusing on genes involved in ICD processes that were correlated with MM patients clinical outcome, we found that low levels of GABARAP (chr17p13.1), an autophagy regulator and putative CALR binding partner, negatively impact MM patient clinical outcome (EFS, p=0.0032); even excluding HR patients with 17p deletion (EFS, p=0.018). Interestingly, KMS11 cells carrying monoallelic deletion of GABARAP were resistant to induction of ICD by BTZ; and sensitivity was restored after overexpression of the gene. Moreover, GABARAPKO in 3 ICD-sensitive cell lines abrogated the induction of ICD by BTZ; and add-back experiments by pre-treatment with recombinant CALR or GABARAP overexpression in KO clones restored ICD. Finally, CyTOF confirmed that treatment of GABARAPKO cells with BTZ failed to activate an efficient T cell response. **Conclusions:** our study demonstrates that loss-of-function of GABARAP, particularly in HR patients with 17p deletion, contributes to tumor immune evasion and ICD resistance. These studies provide the framework for novel combination treatments to restore anti-MM immunity and improve patient outcome in HR MM.

OAB-034

Evaluating the impact of cytogenetic abnormalities on treatment outcomes in patients with AL amyloidosis: subanalyses from the ANDROMEDA study

Shaji Kumar[1], Angela Dispenzieri[2], Divaya Bhutani[3], Morie Gertz[4], Ashutosh Wechalekar[5], Giovanni Palladini[6], Raymond Comenzo[7], Rafael Fonseca[8], Arnaud Jaccard[9], Efstathios Kastritis[10], Stefan Schönland[11], Charles la Porte[12], Huiling Pei[13], NamPhuong Tran[14], Jessica Vermeulen[15], Giampaolo Merlini[16]

[1]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [2]Mayo Clinic Rochester; [3]Columbia University Medical Center; [4]Mayo Clinic Rochester; [5]University College Hospital; [6]Amyloidosis Research and Treatment Center; [7]Tufts Medical Center; [8]Mayo Clinic; [9]Centre Hospitalier Universitaire and Reference Center for AL Amyloidosis; [10]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece; [11]Universitätsklinikum Heidelberg Medizinische Klinik V; [12]Janssen Global Services; [13]Janssen Research & Development, LLC, Titusville, NJ, USA; [14]Janssen Research & Development, LLC; [15]Janssen Research & Development, LLC, Leiden, The Netherlands; [16]Amyloidosis Research and Treatment Center

Background: Amyloid light chain (AL) amyloidosis is a plasma cell disease characterized by the production of light chains that form amyloid fibril deposits in tissues leading to organ dysfunction and death. Cytogenetic abnormalities are common in patients (pts) with AL amyloidosis, and some are associated with poor outcomes. The ANDROMEDA study (NCT03201965) showed that addition of daratumumab to bortezomib, cyclophosphamide, and dexamethasone (D-VCd) was superior to VCd alone, with higher rates of hematologic complete response (CR) and an acceptable safety profile. Here, we explore outcomes in pts with cytogenetic abnormalities in ANDROMEDA. **Methods:** Pts (N=388) with newly diagnosed AL amyloidosis were randomized 1:1 to D-VCd or VCd for 6 28-day cycles; thereafter, pts in the D-VCd group received daratumumab alone every 4 weeks for ≤24 total cycles. The proportion of pts with t(11;14), amp1q21, del13q14, and del17p13 based on fluorescence in situ hybridization and/or karyotyping was calculated. Overall (at any time during the study) hematologic CR rate and cardiac and renal response rates at 6 months were evaluated for each subgroup and summarized with descriptive statistics. Within each treatment group, hematologic response among pts with and without t(11;14) or amp1q21 was compared. **Results:** 321 pts had testing (D-VCd, n=155; VCd, n=166). In the D-VCd and VCd groups, respectively, 42.9% vs 40.0% had t(11;14), 25.4% vs 20.3% had amp1q21, 16.2% vs 22.0% had del13q14, and 6.7% vs 6.1% had del17p13. At a median follow-up of 20.3 months, the hematologic CR rate was higher with D-VCd vs VCd across all 4 cytogenetic subgroups, ranging from 56–72% vs 0–14% (P<0.05 for all). Organ response rates were numerically higher with D-VCd in all subgroups, except for cardiac response rate in the del17p13 subgroup. In the VCd group, rates of hematologic CR and very good partial response or better (≥VGPR) were 12.5% vs 23.8% and 46.4% vs 56.0% in pts with (n=56) vs without (n=84) t(11;14) and 10.7% vs 19.1% and 53.6% vs 50.0% in pts with (n=28) and without (n=110) amp1q21. In the D-VCd group, rates of hematologic CR and ≥VGPR were 59.3% vs 61.1% and 77.8% vs 80.6% in pts with (n=54) vs without (n=72) t(11;14) and 59.4% vs 59.6% and 81.3% vs 80.9% in pts with (n=32) and without (n=94) amp1q21. **Conclusion:** Consistent with the primary analysis of ANDROMEDA, subgroup analyses showed the benefit of D-VCd vs VCd, irrespective of cytogenetic abnormalities. Rates of deep hematologic response were not impacted by t(11;14) and amp1q21 in patients treated with D-VCd, but were generally lower in VCd-treated patients with t(11;14) and amp1q21. These findings further support the use of D-VCd as standard of care in pts with newly diagnosed AL amyloidosis, regardless of cytogenetic abnormalities.

OAB-035

Minimally invasive profiling of tumor and immune cells to stratify risk in smoldering multiple myeloma (SMM): the iMMunocell study

Rosalinda Termini[1], David Zihala[2], Cirino Botta[3], Catarina Maia[2], Juan José Garcés[4], Evangelos Terpos[5], Albert Pérez Montaña[6], Tomas Jelinek[7], Joan Bargay[8], Enrique Ocio[9], Jose Enrique De La Puerta[10], Joaquín Martínez-López[14], Fernando Solano[12], Maria-Elena Cabezudo[13], Rebeca Iglesias[14], Antonio Garcia-Guiñón[15], Maria Casanova[16], Valentín Cabañas[17], Roman Hájek[7], Heinz Ludwig[18], Hartmut Goldschmidt[19], Hervé Avet-Loiseau[20], Aldo Roccaro Roccaro[21], Jesús F. San-Miguel[22], Bruno Paiva[23]

[1]CIMA; [2]Ostava; [3]Hematology Unit, Department of Oncology, "Annunziata" Hospital of Cosenza, Italy; [4]Clinica Universidad de Navarra, Centro de Investigacion Medica Aplicada (CIMA), Instituto de Investigacion Sanitaria de Navarra (IDISNA), CIBER-ONC number CB16/12/00369; [5]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece; [6]Hospital Universitari Son Espases I HUSE · Department of Hematology; [7]Department of Haematooncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [8]Hospital Son Llàtzer; [9]University of Cantabria; [10]Hospital Universitario de Galdakao; [11]Hospital universitario 12 de Octubre; [12]Hospital Ntra Sra del Prado; [13]H. Moisès Broggi; [14]MD Anderson Madrid; [15]Hospital Universitari Arnau de Vilanova; [16]Hospital Costa del Sol; [17]Hospital Universitario Virgen de la Arrixaca; [18]Wilhelminen Cancer Research Institute; [19]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT); [20]CRCT-Toulouse; [21]ASST Spedali Civili; [22]Clínica Universidad de Navarra,

CIMA, CIBERONC, IDISNA; [23]Clinica Universidad de Navarra, Centro de Investigacion Medica Aplicada (CIMA), Instituto de Investigacion Sanitaria de Navarra (IDISNA), CIBER-ONC number CB16/12/00369

Background: The 2/20/20 model to predict risk of transformation in SMM is established at diagnosis and not periodically re-evaluated, mainly because plasma cell (PC) quantification requires invasive bone marrow (BM) aspirates. It could be hypothesized that dynamic monitoring of tumor biomarkers could improve risk-stratification of SMM patients, but this requires minimally invasive methods to replace those performed in BM samples. Such methods should also monitor immune profiles to identify patients with stable tumor burden/genetics, but at risk of progression due to lost immune surveillance. **Aim:** Compare the prognostic value of PC quantification in BM vs the evaluation of circulating tumor cells (CTCs) in peripheral blood (PB), and to define immune signatures predictive of time-to progression (TTP) in SMM. **Methods:** 300 SMM patients are planned to be enrolled in the iMMunocell study that includes 26 sites across 8 European countries. PB samples are collected every 6 months during three years for next-generation flow (NGF) monitoring of CTCs and immune profiling of the T, NK, B and myeloid cell compartments.Cutoffs for risk stratification according to CTCs were calculated using maxstat.A total of 245 SMM patients were enrolled, and we report here a pre-planned interim analysis on the first 150. **Results:** Thus far, 28/150 (19%) patients progressed to MM. Presence of ≤20% vs >20% PCs in BM by morphology failed to predict different TTP(19% vs 32% progressions at 2 years, respectively; p=0.14). Patients with ≤0.73 CTCs/µL had lower risk of transformation vs those with >0.73 CTCs/µL (15% vs 67% progressions at 2 years, respectively; HR: 5.1, p=4.9e-05). Patients with >0.73 CTCs/µL had median TTP of 17.5 months. Patients with low, intermediate and high-risk SMM according to the 2/20/20 model showed significantly different TTP (p=5.14e-06), but those with high-risk had median TTP not reached. Risk stratification using a new 0.7/2/20 (where 0.7 stands for >0.73 CTCs/µL) achieved identical statistical significance (p=5.14e-06), and patients with high-risk SMM had median TTP of 21 months. By applying the gradient boosting algorithm to the T cell dataset, we identified six subsets with an exhausted phenotype CD4+CD28negTIGIT+CD127lo, CD4+CD28+TIGIT+CD127+, CD4+CD28+TIGIT+CD127+CD25+, CD8+CD28negCD127+, CD8+CD28negTIGIT+ and CD8+CD28negTIGIT+PD1+ whose increased frequency was associated with inferior TTP. Patients showing an expansion of these T cell subsets had higher risk of transformation to active MM (HR: 7.33; p=0.002). **Conclusions:** This is the first study performing CTC and immune monitoring every 6 months in PB samples from patients with SMM. Our results suggest that CTC numbers have greater prognostic value than BM PC counts, and that a new 0.7/2/20 model could be dynamically assessed to identify SMM patients at risk of developing active MM. Beyond CTC numbers,this study is also uncovering key immune cell types associated with disease progression.

OAB-036

Graded renal response criteria and revised renal progression criteria for light chain (AL) amyloidosis

Eli Muchtar[1], Brendan Wisniowski[2], Giovanni Palladini[3], Paolo Milani[4], Giampaolo Merlini[3], Stefan Schönland[5], Kaya Veelkan[6], Ute Hegenbart[7], Angela Dispenzieri[8], Shaji Kumar[9], Nelson Leung[10], Efstathios Kastritis[11], Meletios-Athanasios Dimopoulos[11], Michaela Liedtke[12], Ronald Witteles[12], Vaishali Sanchorawala[13], Raphael Szalat[13], Heather Landau[14], Suzanne Lentzsch[15], J Bladé[16], MT Cibeira[16], Oliver Cohen[17], Darren Foard[18], Ashutosh Wechalekar[18], Morie Gertz[8]

[1]Division of Hematology, Mayo Clinic, Rochester, MN; [2]National Amyloidosis Centre; [3]Amyloidosis Research and Treatment Center; [4]Pavia University; [5]Universitätsklinikum Heidelberg Medizinische Klinik V; [6]Heidelberg university; [7]2University Hospital Heidelberg, Heidelberg, Germany; [8]Mayo Clinic Rochester; [9]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [10]Division of hematology and Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [11]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece; [12]Stanford University; [13]Boston University; [14]Memorial Sloan Kettering Cancer Center; [15]Columbia University; [16]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [17]National Amyloidosis Centre, University College London Medical School, Royal Free Hospital Campus; [18]National Amyloidosis Centre

Background: Renal light chain (AL) amyloidosis manifests as proteinuria with or without renal failure and is associated with a risk of progression to renal replacement therapy (RRT). A significant reduction in circulating amyloidogenic light chain is needed to achieve a renal response. Current renal response criteria are binary defining a renal response as >30% reduction in 24-h proteinuria without worsening estimated glomerular filtration rate (eGFR). Several studies suggest that greater reduction in proteinuria following successful therapy improves renal and overall survival. **Methods:** AL amyloidosis patients diagnosed between 2010 to 2015, achieving at least hematological partial response to therapy and with renal involvement were included. Four renal response categories were formulated based on reduction level in pretreatment 24-h proteinuria in the absence of renal progression: renal complete response (renCR, 24-h proteinuria ≤200 mg/24-h); renal very good partial response (renVGPR, >60% reduction in 24-h proteinuria); renal partial response (renPR, 31-60% reduction in 24-proteinuria); and renal no response (renNR, 30% or less reduction). Renal response was assessed at landmark (6-, 12-, and 24 months from treatment initiation) and as best renal response. Graded renal responses were assessed as predictors for time from diagnosis to RRT and overall survival. **Results:** Seven hundred and thirty-seven patients were included. The median age was 63. Renal stage I, II and III were assigned to 34%, 52% and 14% of patients, respectively. Reduction

in 24-h proteinuria from baseline improved over time with a median reduction of 34%, 50% and 71%, at 6-month, 12-month and 24-months, respectively. At best response, renCR, renVGPR, renPR and renNR were achieved in 27%, 34%, 15% and 24% of patients, respectively. A renal response as early as 6 months after therapy initiation was able to predict time to RRT with an increase in RRT risk with lower level of renal response at that time point (5-year RRT 0%, 3%, 9% and 16% for renCR, renVGPR, renPR and renNR, respectively, P<0.001). Prediction of risk for RRT based on renal response depth improved at 12- and 24-months and at best renal response. Overall survival discrimination based on renal response depth was noted as early as 12 months from therapy initiation and improved with time. eGFR progression (≥25% decrease in eGFR) and proteinuria progression (at least 50% increase to ≥3g/day) were predictive for time to RRT. **Conclusions:** We validated new graded renal response criteria based on reduction in 24-h proteinuria. These 4-level renal response criteria highlight the importance of achieving a deep renal response to improve renal and overall survival. These findings will allow clinicians to make decision on therapy changes or augmentation based on response depth as early as 6-month before irreversible renal failure has developed.

OAB-037

Assessing the prognostic utility of the Mayo 2018 and IMWG 2020 smoldering multiple myeloma risk stratification scores applied post diagnosis

Alissa Visram[1], S. Vincent Rajkumar[2], Prashant Kapoor[2], Angela Dispenzieri[1], Martha Lacy[1], Morie Gertz[1], Francis Buadi[1], Suzanne Hayman[1], David Dingli[1], Taxiarchis kourelis[1], Wilson Gonsalves[1], Rahma Warsame[1], Eli Muchtar[3], Nelson Leung[4], Robert Kyle, Shaji Kumar[5]

[1]Mayo Clinic Rochester; [2]Mayo Clinic; [3]Division of Hematology, Mayo Clinic, Rochester, MN; [4]Division of hematology and Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [5]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA

Background: Smoldering multiple myeloma (SMM) prognostication models routinely used in clinical practice were developed for use at diagnosis. However, retrospective studies in SMM patients have shown that the risk of progression to multiple myeloma (MM) decreases over time. Therefore, this study assessed whether the Mayo 2018 and IMWG 2020 scores could be used dynamically to risk stratify patients post-diagnosis, and whether they could identify SMM patients with evolving disease markers. **Methods:** We retrospective studied 704 SMM patients diagnosed between January 2000 to January 2020. Patients with a baseline FLCr ≥100 and involved FLC ≥10 mg/dL or baseline bone marrow plasma cells ≥60% were excluded. We collected serial laboratory data and re-applied the Mayo 2018 and IMWG 2020 SMM risk stratification models at annual landmark timepoints up to 4 years post SMM diagnosis. Survival analyses were performed using the Kaplan-Meier method. Time to progression was defined as time from diagnosis or landmark timepoint to treatment initiation for MM or systemic AL amyloidosis. **Results:** At SMM diagnosis, 271 (38%) patients were low risk, 228 (32%) were intermediate risk, and 205 (29%) were high risk per the Mayo 2018 score. Applying the IMWG 2020 score at diagnosis, 90 (34%) of patients were low risk, 111 (42%) were low-intermediate risk, 54 (21%) were intermediate risk, and 9 (3%) were high risk. The Mayo 2018 and IMWG 2020 risk scores was re-assessed annually post-diagnosis in patients without progression (respective sample sizes: n=430 and n=197 at year 1 landmark, n=326 and n=143 at year 2 landmark, n=260 and n=106 at year 3 landmark, n=203 and n=73 patients at year 4 landmark). The Mayo 2018 and IMWG 2020 models reliably stratified patients based on progression risk post diagnosis; the respective 2-year progression risk in Mayo 2018 high-risk versus IMWG 2020 intermediate-high risk patients was 51% versus 62% at the 1-year landmark, 60% versus 65% at the 2-year landmark, 47% versus 62% at the 3-year landmark, and 47% versus 45% at the 4-year landmark. Patients evolving to a higher Mayo 2018 or IMWG 2020 risk category during follow up consistently had an increased risk of progression compared to patients with a stable/decreased risk categorization. We showed that patients categorized as Mayo 2018 high-risk at follow-up had a similar risk of progression regardless of whether the baseline risk categorization was low-intermediate versus high-risk (HR 0.87, 95% CI 0.51-1.48, p=0.606 at 2-year landmark; HR 1.01, 95% CI 0.59-1.73, p=0.972 at 3-year landmark; HR 0.75, 95% CI 0.34-1.65, p=0.467 at 4-year landmark). **Conclusion:** Our findings support the use of the Mayo 2018 and IMWG 2020 scores post-diagnosis. We showed that patients migrating to a higher risk category have an increased risk of progression, suggesting that patients evolving to a high-risk score during follow-up should be considered for early intervention treatment approaches.

OAB-038

Graded cardiac response criteria for AL amyloidosis: the impact of depth of cardiac response on survival

Eli Muchtar[1], Angela Dispenzieri[2], Brendan Wisniowski[3], Giovanni Palladini[4], Paolo Milani[5], Giampaolo Merlini[4], Stefan Schönland[6], Kaya Veelkan[8], Ute Hegenbart[8], Shaji Kumar[9], Efstathios Kastritis[10], Meletios-Athanasios Dimopoulos[10], Michaela Liedtke[11], Ronald Witteles[11], Vaishali Sanchorawala[12], Raphael Szalat[12], Heather Landau[13], Suzanne Lentzsch[14], Alexander Coltoff[14], Joan Bladé[15], MT Cibeira[15], Oliver Cohen[16], Darren Foard[3], Ashutosh Wechalekar[3], Morie Gertz[2]

[1]Division of Hematology, Mayo Clinic, Rochester, MN; [2]Mayo Clinic Rochester; [3]National Amyloidosis Centre; [4]Amyloidosis Research and Treatment Center; [5]Pavia University; [6]Universitätsklinikum Heidelberg Medizinische Klinik V; [7]Heidelberg university; [8]2University Hospital Heidelberg, Heidelberg, Germany; [9]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [10]Department of Clinical

Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece; [11]Stanford University; [12]Boston University; [13]Memorial Sloan Kettering Cancer Center; [14]Columbia University; [15]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [16]National Amyloidosis Centre, University College London Medical School, Royal Free Hospital Campus

Background: Binary cardiac response assessment using NT-proBNP is prognostic in light chain (AL) amyloidosis. Previous studies suggested that refining the criteria to multi-level cardiac responses improves prognostic prediction. We aimed to validate a graded cardiac response assessment tool in AL amyloidosis using NT-proBNP or BNP. **Methods:** In this retrospective, multicenter study AL amyloidosis patients who were diagnosed between 2010 and 2015, achieved at least a hematological partial response (PR) within 12 months of diagnosis and were evaluable for cardiac response (defined as baseline NT-proBNP >650 pg/mL or BNP >150 pg/mL) were included. The following response criteria were tested: cardiac complete response (carCR, nadir NT-proBNP≤350 pg/mL or BNP≤80 pg/mL); cardiac very good partial response (carVGPR, >60% reduction in NT-proBNP/BNP); Cardiac PR (carPR 31-60% reduction); and cardiac non response (carNR, ≤30% reduction). Response was assessed at fixed time points (6, 12 and 24 months from therapy initiation) and at best response. The primary outcome was overall survival based on depth of cardiac response. **Results:** Six hundred and fifty-one patients were included. Mayo 2004 cardiac stage II, IIIA and IIIB was present in 47.5%, 38% and 14.5% of patients, respectively (by definition, patients with Mayo stage 1 do not have cardiac amyloidosis evaluable for response). Hematological CR, hematological VGPR and hematological PR was achieved in 38%, 39% and 23% of patients, respectively. Cardiac response improved over time with a median percentage reduction in NT-proBNP/BNP compared to baseline of 15%, 37% and 54%, at 6, 12 and 24 months respectively. At best cardiac response, carCR, carVGPR, carPR and carNR were achieved in 16%, 26%, 23% and 35% of patients, respectively. Patients achieving a carCR were more likely to be in cardiac stage II compared to carVGPR or carPR patients (65% vs 47% each, P30% rise in NT-proBNP/BNP) in multivariate analysis that included age, type of first line therapy, light chain burden, cardiac stage and hematological response. **Conclusions:** We validated the prognostic value of graded cardiac response. These response criteria allow better discrimination of patient populations and assessment of treatment effectiveness in an era of improved therapies for AL amyloidosis. The study emphasizes the importance of early diagnosis which increases the likelihood of deep and durable cardiac responses.

OAB-039

Distinct immunoglobulin heavy-chain variable gene repertoire and its clinical relevance in Waldenström macroglobulinemia/ lymphoplasmacytic lymphoma

Yuting Yan[1], Jun Wang[1], Wenjie Xiong[1], Ge Song[2], Tingyu Wang[2], Shuhua Yi[3], Lugui Qiu[4]

[1]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union; [2]Chinese Academy of Medical Sciences and Peking Union Medical College; [3]CAMS; [4]Institute of Hematology and Blood Diseases Hospital

Background: Waldenström macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL) is a heterogeneous disease whose role of immunoglobulin heavy chain variable gene (IGHV) usage remains unknown. **Methods:** To determine the clinical relevance of IGHV repertoire in WM/LPL treated with standard immunochemotherapy, we performed the immunoglobulin gene rearrangements and complementarity determining region 3 (CDR3) analysis on 136 patients with WM/LPL. **Results:** The IGHV gene repertoire was remarkably biased in WM/LPL. IGHV3-23, IGHV4-34, IGHV3-30, IGHV3-7 and IGHV3-74 accounted for half of the whole cohort. Most of the cases were mutated (97.0%) using a 98% IGHV germline homology cutoff. IGHV3-30 was associated with long heavy chain CDR3, indicating the specific antigen selection in WM/LPL. Patients with IGHV3-7 were significantly more likely to harbor 6q deletion (p<0.001) and complex karyotype (p=0.002). The IGHV hypermutation rate in patients with MYD88 L265P mutation was significantly higher than wildtype patients (p=0.009). IGHV3-23 and IGHV3-74 segments were more frequently detected in MYD88 mutated WM/LPL patients (p=0.025). When we looked into the five predominant IGHV segments mentioned above, we found a trend that IGHV3-23 and IGHV3-74 segments were more frequently detected in MYD88 mutated WM/LPL patients (25.7% vs. 4.3%, p=0.025). Besides, we found IGHV3-7 and IGHV4-59 were represented more in MYD88 wildtype patients compared with MYD88 mutated patients (30.4% vs. 8.9%, p=0,005). IGHV4 segments were higher expressed in MYD88 wildtype patients compared with MYD88 L265P mutated patients (39.1% vs. 21.8%, P=0.083). Moreover, Patients with IGHV4 especially IGHV4-34 had higher level of LDH. IGHV4 was a predictive marker of shorter progression-free-survival. **Conclusion:** WM/LPL appears to be composed of different subgroups based on the IGHV repertoire. The mutational status and the IGHV CDR3 length indicated the role for antigen selection in WM/LPL development. The presence of IGHV4 genes proved to be a potential risk factor associated with outcome which deserved further study.

OAB-040

Clonal hematopoiesis is associated with increased risk of progression of asymptomatic Waldenström Macroglobulinemia

Sabrin Tahri[1], Tarek Mouhieddine[2], Robert Redd[3], Luisa Lampe[4], Katarina Nillson[3], Nang Kham Su[3], Habib El-Khoury[3], Amin H. Nassar[5], Elio Adib[5], Govind Bindra[6], Sarah Abou Alaiwi[5], Lorenzo Trippa[3], David Steensma[7], Jorge J. Castillo[3], Steven P. Treon[3], Irene Ghobrial[8], Adam Sperling[3]

[1]Erasmus MC; [2]Icahn School of Medicine at Mount Sinai; [3]Dana-Farber Cancer Institute; [4]Kiel University; [5]Brigham and Women's Hospital; [6]University of Tennessee Health Science Center; [7]NIBR; [8]Dana-Farber Cancer Institute, Boston, MA, USA

Background: Clonal hematopoiesis (CH) is associated with adverse outcomes in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma undergoing autologous stem cell transplantation. Still, its implications for patients with indolent NHL have not been well studied. Here, we report the prevalence of CH in patients with Waldenström Macroglobulinemia (WM) and its association with clinical outcomes. **Methods:** We retrospectively reviewed clinical data of 602 patients with IgM MGUS, smoldering WM and WM who had clinical next-generation sequencing (NGS) performed on bone marrow aspirates or peripheral blood obtained between October 2014 and February 2020 at the Dana-Farber Cancer Institute (DFCI). An Illumina Truseq amplicon-based NGS assay of 95 genes recurrently mutated in myeloid and lymphoid neoplasms was utilized. Each specimen yielded ~2 million reads and ~1500X average coverage with 90% of amplicons having >200X coverage. Pathogenic driver variants were identified based on mutation type, position, and frequency in published reports and public databases. In order to unambiguously differentiate CH mutations from those in the WM clone, CH was defined by the presence of somatic mutations in DNMT3A, TET2 or ASXL1 (CH-DTA). **Results:** The cohort included 147 patients with MGUS or asymptomatic WM and 453 patients with symptomatic WM with a median age of 66 years (range: 40-89) and 68 years (range: 33-93), respectively, at time of first NGS assay. The prevalence of CH-DTA was 14% in symptomatic WM patients and did not differ significantly in MGUS and SWM (13% and 14%, respectively). Among precursor patients, there was an increased risk of progression to symptomatic WM in those with CH-DTA (7/20 patients with vs. 11/116 without CH-DTA progressed over a median of 54 months [p= 0.002]). In symptomatic WM patients CH-DTA was positively associated with older age (p<0.001) at time of NGS, with a median age of 72 vs. 67 years for patients with versus those without CH-DTA. CH-DTA was not associated with inferior OS with a relatively short median follow-up from diagnosis and NGS assay of 6.7 (95% CI: 6.1-7.6) and 2.5 (95% CI: 2.2-2.8) years, respectively. The most common cause of death was disease progression with no significant difference between those with or without CH-DTA. Patients with CH-DTA had an increased risk of cardiovascular disease (30% vs. 18%, p=0.036). **Conclusion:** We demonstrate that CH is common in WM patients and is associated with increased risk of progression from precursor states but not with inferior survival. Further work is needed to determine how the presence of CH might promote progression to WM and whether it can be incorporated into future risk stratification models. Importantly, our data do not support changes in clinical management or alterations in therapy for patients with WM and coexistent CH and reinforce the need to interpret NGS results within their specific clinical context.

OAB-041

Epithelial-mesenchymal-transition regulated by Junctional Adhesion Molecule-A (JAM-A) associates with aggressive extramedullary multiple myeloma disease

Antonio Solimando[1], Matteo Da Vià[2], Giorgio Croci[3], Paola Borrelli[4], Paula Tabares[5], Andreas Brandl[6], Umair Munawar[7], Torsten Steinbrunn[8], Alessandra Balduini[9], Hilka Rauert-Wunderlich[10], Hannah Manz[11], Paolo Ditonno[12], Roberto Ria[13], Carolina Terragna[14], Nora Trinks[15], Ulrich Terpitz[16], Leo Rasche[17], Andreas Rosenwald[18], Martin Kortuem[19], Michele Cavo[20], Antonino Neri[21], Niccolò Bolli[22], Hermann Einsele[23], Angelo Vacca[24], Andreas Beilhack[25]

[1]Bari University; [2]Department of Oncology and Hemato-Oncology, University of Milan, 20122 Milan, Italy; [3]Division of Pathology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]Laboratory of Biostatistics, Department of Medical, Oral, and Biotechnological Sciences, University "G. d'Annunzio" Chieti-Pescara, 66100 Chieti, Italy; [5]University Hospital Wuerzburg; [6]University Hospital Wuerzburg; [7]Department of Internal Medicine II, University Hospital, 97080 Würzburg, Germany; [8]University Hospital of Würzburg; [9]Department of Molecular Medicine of the University of Pavia, 27100 Pavia, Italy; [10]Institute of Pathology, University of Würzburg and Comprehensive Cancer Center (CCC) Mainfranken, 97080 Würzburg, Germany; [11]University Hospital Wuerzburg; [12]IRCCS Istituto Tumori "Giovanni Paolo II", 70124 Bari, Italy; [13]Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine "G. Baccelli", University of Bari Medical School, 70124 Bari, Italy; [14]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [15]Department of Biotechnology and Biophysics, Julius Maximilian University of Würzburg, Biocenter - Am Hubland, Würzburg, Germany; [16]Department of Biotechnology and Biophysics, Julius Maximilian University of Würzburg, Biocenter - Am Hubland, Würzburg, Germany.; [17]Department of Internal Medicine II, University Hospital, 97080 Würzburg, Germany; [18]Institute of Pathology, University of Würzburg and Comprehensive Cancer Center (CCC) Mainfranken, 97080 Würzburg, Germany; [19]Department of Internal Medicine II, University Hospital, 97080 Würzburg, Germany; [20]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Università di Bologna; [21]University of Milan; [22]Department of Oncology and Hemato-Oncology, University of Milan, 20122 Milan, Italy; [23]University Hospital of

Würzburg; [24]Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine "G. Baccelli", University of Bari Medical School, 70124 Bari, Italy; [25]University Hospital Wuerzburg

Background: Interactions between multiple myeloma plasma cells (MMPC) and the multiple myeloma (MM) niche control cell proliferation, drug resistance, and disease spreading through various adhesion molecules and chemokine receptors. Among these, junctional adhesion molecule-A (JAM-A) mediates MMPC-endothelial interactions and propagates neovascularization. Here we addressed whether JAM-A signaling mediates MMPC invasive behavior orchestrating intra- and extramedullary MM dissemination. **Methods:** We investigated JAM-A expression with flow cytometry and immunohistochemistry in 60 MM patient bone marrow (BM) aspirates and biopsies at different disease stages with and without extramedullary disease (EMD) manifestation. We compared these results with RNA-Seq data from 647 newly diagnosed MM (NDMM) patients collected in the MMRF CoMMpass study. Using bioinformatics, we investigated JAM-A-related pathways with hierarchical cluster analysis. Subsequently, we functionally validated these JAM-A-related pathways regarding epithelial-mesenchymal transition (EMT), invasion, and MM dissemination in vitro. **Results:** The median OS differed significantly in subjects with elevated membrane JAM-A expression levels, dividing the patients in the EMD JAM-Ahigh group with a median OS of 84.1 months, whereas median OS in JAM-Alow patients was not reached, irrespective of the EMD status (log-rank=4.19, P=.04). Immunohistochemistry analysis of BM biopsies confirmed these findings. RNA-Seq analysis corroborated the prognostic impact of JAM-A (log-rank=3.8, P=.051). High-risk patients with EMD and JAM-A expression displayed a unique gene-expression signature. Additionally, we constructed a novel expression cluster subgroup model, revealing complex molecular disease patterns and associations between clinical traits and expression markers. Strikingly, MM patients clustered by JAM-A expression levels and EMD manifestation revealed properties of epithelial-mesenchymal-transition and induced focal adhesion pathways. Notably, functional knockdown of JAM-A in MMPC in vitro not only reduced cell viability but also diminished MMPC adhesion molecules and CD138 surface expression. Furthermore, mTOR/PI3K in vitro inhibition with BEZ235 significantly downregulated surface expression in JAM-Ahigh MM cells. Interestingly, when we inhibited mTOR/PI3K in JAM-Alow MM cells, we observed JAM-A induction. Finally, ensuing functional shRNA knockdown of JAM-A halted MM invasion (P<.002), angiogenesis (P<.0001), migration (P<.002), cell survival (P<.001), and expression of cellular-adhesion system molecules such as integrin-beta-1, fibronectin, RAC1 and RHOA (P<.001). Conversely, overexpressing JAM-A in MM.1S cells changed to an EMT-like phenotype compared to empty vector-infected MM.1S cell controls. **Conclusions:** Collectively, these data reveal JAM-A-mediated signaling critical for EMT transition and invasive behavior. Based on these findings we propose JAM-A as a promising biomarker and novel theragnostic target in MM patients.

OAB-042

Targeting free light chain secretion via Botulinum Neurotoxin is a novel therapeutic strategy in AL amyloidosis by inducing a terminal unfolded protein response

Maria Moscvin[1], Tianzeng Chen[1], Peter Czarnecki[2], Annamaria Gulla[3], Kenneth Anderson[3], Giada Bianchi[2]

[1]Brigham and Women's Hospital; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Background: AL amyloidosis (AL) is an incurable plasma cell (PC) disorder. The solely pathogenic mechanism in AL is deposition of immunoglobulin free light chains (FLC) organized in fibrils in target organs. Surprisingly, therapeutic strategies directly targeting FLC secretion are not available. SNARE proteins, which are the specific target of botulinum neurotoxin (BoNT), are involved in the docking and fusion of secretory vesicles. We hypothesized that certain BoNT serotypes may block FLC exocytosis, causing retention of FLC-loaded vesicles and triggering a terminal unfolded protein response (UPR). **Methods:** Gene expression profiling in a cohort of 170 newly diagnosed multiple myeloma (MM) patients (IFM170) was used to interrogate SNAREs expression in malignant plasma cells. Western blotting (WB) was used to assess SNARE expression across MM and AL cell lines. We developed tetracycline inducible, lentiviral vectors expressing distinct BoNT serotypes (BoNT/A-F), T2A and GFP. Lentivirally transduced cells would express BoNT in a 1:1 stochiometric ratio with GFP, upon doxycycline (dox) administration, allowing for flow cytometry-based analysis. A vector comprising solely T2A and GFP was used as negative control. We transduced AL cell lines with Tet-On lentivirus expressing 7 distinct BoNTs and performed two sets of experiments. First, we performed time-course viability assays on polyclonally transduced cells and compared relative proportion of GFP+ cells over time. Then, we single-cell sorted transduced cells, triggered BoNT expression and assessed GFP kinetic and apoptosis via AnnexinV/DAPI flow cytometry at 24, 48 and 72 hours post dox. SNAREs cleavage following induction of BoNT expression was evaluated via WB in GFP+ clones. To assess if BoNT cytotoxicity correlated with cessation of FLC secretion, we performed a secretion assay in monoclones expressing distinct BoNTs. **Results:** IFM170 GEP analysis showed VAMP2, VAMP3 and SNAP23 as the top expressed SNAREs. This was further confirmed in AL/MM cell lines. By using polyclonally transduced cells, we show that GFP+ cells are rapidly depleted over time after dox, across all serotypes, except BoNT/B, consistent with cytotoxic effect. Similarly, we observed rapid apoptosis in monoclones expressing any BoNT serotypes, except BoNT/B. We noted an association between SNAP23 and VAMP3 cleavage and BoNT toxicity, suggesting that dual targeting of SNAP23/VAMP3 may be necessary to mediate BoNT cytotoxicity. We next show that only BoNTs causing early cytotoxicity significantly inhibited FLC secretion. Cytotoxic BoNTs, activated PERK pathway with eIF2a phosphorylation (p-eIF2a); CHOP and GADD34 upregulation,

presumably through FLC retention. **Conclusions:** We show that cytotoxic BoNTs block FLC secretion, trigger a terminal UPR and induce apoptosis in AL and MM models. We provide proof of concept that targeting FLC secretion has a potential clinical translatability.

OAB-043

Progression and probability of progression are driven by different genomic features in precursor conditions in myeloma

Anil Aktas-Samur[1], Mariateresa Fulciniti[2], Sanika Derebail[3], Raphael Szalat[4], Jill Corre[5], Giovanni Parmigiani[6], Hervé Avet-Loiseau[7], Mehmet K Samur[8], Nikhil C. Munshi[9]

[1]Dana-Farber Cancer Institute; [2]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]Dana Farber Cancer Institute; [4]Dana Farber Cancer Institute; [5]Institut Universitaire du Cancer de Toulouse-Oncopole; [6]Dana Farber Cancer Institute; [7]CRCT-Toulouse; [8]Dana-Farber Cancer Institute, Boston, USA; [9]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: On average 10% of SMM patients progress to symptomatic MM per year with in first 5 years of diagnosis. However, a subset of SMM patients re-classified as high risk patients on the basis of risk markers which identify risk of progression within 2 years. Although recent studies have evaluated the high-risk SMM, genomic background of SMM patients who do not progress to MM after long-term follow-up (>=5 years) has not been described. **Methods:** Here, we evaluated transcriptomic and genomic changes enriched in non-progressor (NP) (no progression after 5 years of follow-up) precursor conditions (N=31) with those progressed within short period time (N=71) and compared them with changes observed in newly diagnosed MM (N=192). Additionally, using transcriptome, epigenome and whole genome profiling we also studied additional unique samples from 18 patients at their precursor stage as well as when progressed to MM. **Results:** Overall, we have observed significantly lower mutational load for NP SMM (median SNV 5460 vs. 7018, p 90% accuracy and >0.80 area under the curve on ROC using ten-fold cross validation. This indicated that not only the load but also the patterns of mutations (type, location, frequency) are different between two conditions. We also found that NP samples have significantly lower heterogeneity (p 80%) with AUC score 0.80. Our transcriptomic analysis measured the distance between progressor and NP SMM as well as MM and found that NP SMM are less similar to MM which is closer to progressor SMM. Epigenomic analysis yield that 75 SEs regions were differentially utilized between precursor and symptomatic MM stage. The targeted genes included BMP6, PRDM1, STAT1 and RAB21 and possibly regulating genes related to oncogenic KRAS activities. **Conclusions:** In conclusion, our results now provide the basis to develop genomic definition of SMM as well as risk driving features.

OAB-044

Anti-CD38 nanobodies as theranostic agents for multiple myeloma

Elodie Duray[1], Margaux Lejeune[1], Mireille Dumoulin[1], Matthias D'Huyvetter[2], Jo Caers[3]

[1]ULiège; [2]Vrije Universiteit Brussel; [3]CHU de Liège

Background: Theranostic agents include molecules with a combined diagnostic and therapeutic capability and nanobodies (Nbs) are increasingly used in this field. Nbs are single-domain antigen-binding fragments that are derived from Camelidae heavy-chain antibodies and have several advantages such as their small size leading to better tissue penetration, their favourable pharmacological properties and their ability to recognise small, buried epitopes. **Methods:** The current project aims to use nanobodies directed against CD38 as diagnostic and therapeutic tools in the management of multiple myeloma (MM) disease. The differentiation marker CD38 is highly expressed on myeloma cells isolated from patients with a newly diagnosed or a relapsing disease. Our Nb, retained for its affinity, stability, its favorable biodistribution and its capacity to recognize myeloma cells in a xenograft model of MM, was coupled to Indium-111 and Lutetium-177 and intravenously injected in tumor bearing mice to assess its diagnostic and therapeutic value. Tumor development was assessed by bioluminescence. **Results:** The binding capacities of 111In-DTPA-Nb2F8 was verified by saturation binding experiments (using serial dilutions of the conjugated Nb) on CD38+ RPMI-8226 cells and internalisation experiments were performed in order to assess their therapeutic potential. A minor internalisation (about 20% of the initial bound activity) was observed in the first hours and remained stable during 24H. Micro-SPECT/CT images of mice bearing CD38+ RPMI-8226 tumors and injected with 111In-DPTA-Nb2F8 showed specific tumor targeting 1 hour and at least until 48 hours after injection with a low background signal already 1 hour post-injection (p.i.), except kidneys. The in and ex vivo biodistribution data revealed uptake values in tumor of 3.1% IA/g at 1h post injection, while the uptake of a labelled control Nb was low 0.54% IA/g confirming the specific targeting of our anti-CD38 Nb. Similar biodistributions were found with 177Lu-DTPA-Nb2F8. In order to assess the therapeutic potential of this nanobody, mice with subcutaneously injected RPMI-8226 cells were randomly categorised into 3 groups (n=10). Mice in each group received 3 consecutive intravenous administrations of a high (17.5MBq) or a low radioactive dose (8.6MBq) 177Lu-DTPA-2F8 or an equal volume of vehicle solution. A dose-dependent regression was observed for both therapeutic regimens, which translated in a prolonged median survival from 43 days for vehicle-treated mice, compared to 62 days (p=0.027) for the low and 65 days for the high (p=0.0007) radioactive dose regimen respectively. **Conclusions:** In conclusion, this is the first report on CD38-binding Nbs used for the identification and treatment of MM cells by conjugating them to diagnostic and therapeutic isotopes.

OAB-045

COVID-19 vaccine responsiveness in patients with Multiple Myeloma and Waldenström Macroglobulinemia

Andrew Branagan[1], Matthew Lei[1], Andrew J. Yee[1], Elizabeth O'Donnell[1], Jorge J. Castillo[2], Noopur Raje[3], Steven P. Treon[2], Catherine Flynn[2], Jill Burke[1], Cynthia Harrington[1], Emerentia Agyemang[1], Clifton Mo[2], Omar Nadeem[2], Paul G. Richardson[4], Allison Maebius[1], Chukwuamaka Onyewadume[1], Cristina Panaroni[1], Kirsten Meid[2], Zachary Bernstein[1], Rebecca Lyons[1], Matthew Waterman[1], Raquel Gallagher[1], Boris Juleg[5], Galit Alter[5], Shayna Sarosiek[2]

[1]Massachusetts General Hospital; [2]Dana-Farber Cancer Institute; [3]Massachusetts General Hospital Cancer Center; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Ragon Institute

Background: Multiple myeloma (MM) and Waldenström macroglobulinemia (WM) are associated with significant immunoparesis. Based on the ongoing COVID-19 pandemic, there is an urgent need to understand whether patients are able to mount a sufficient response to COVID-19 vaccines. **Methods:** Patients were vaccinated with BNT162b2 mRNA (Pfizer/BioNTech), mRNA-1273 (Moderna), or JNJ-78436735 (Johnson & Johnson). SARS-CoV-2 spike protein (S) antibodies were detected with the Elecsys assay (Roche Diagnostics). Primary endpoint is S antibody detection 28 days after final vaccination. Secondary endpoints include functional serologic assessments and T-cell responses at 28 days, 6 months, 9 months, and 12 months. **Results:** 141 patients have been enrolled to date, 136 (91 MM and 45 WM) of whom had initial S antibody assessment. Median antibody titer was 178.0 (IQR, 16.10-1166.0) for MM and 3.96 (IQR, 0-282.8) for WM. S antibody response rate was 91% (83/91) in MM and 60% (27/45) in WM. However, response rates for achieving S antibody >100 U/mL were 56% (51/91) in MM and 33% (15/45) in WM. Vaccine-specific S antibody responses following mRNA-1273, BNT162b2, and JNJ-78436735 were 74% (25/34; p<0.05), 51% (24/47; p=NS), and 20% (2/10; p<0.05) in MM and 67% (10/15; p<0.005), 19% (5/27; p<0.05), and 0% (0/3; p=NS) in WM. Among MM patients with progressive disease, S antibody response >100 u/mL occurred in 45% (9/20) as opposed to 65% (35/54) for VGPR+ (p100 U/mL occurred in 53% (19/36) and 56% (31/55), respectively (p=NS). Among WM patients, S antibody responses >100 U/mL occurred in 73% (8/11) (p<0.05) previously untreated; 0% (0/8) (p<0.05) received rituximab within 12 months; 15% (3/20) (p<0.05) on an active Bruton Tyrosine Kinase (BTK) inhibitor; and 29% (4/14) (p=NS) received other therapies. **Conclusions:** These preliminary data suggest impaired serologic responses following COVID-19 vaccines in patients with both MM and WM. Overall, WM patients showed more severe impairment of COVID-19 S antibody responses. Most previously untreated WM patients achieved S antibody responses, however suboptimal antibody responses were seen in WM patients who received rituximab within 12 months or on active BTK inhibitors. In MM patients, being in disease remission associated with improved S antibody response. Vaccination among MM and WM patients with MRNA-1273 elicited significantly higher S antibody response rates comparison to other vaccines. Complete serologic responses including neutralization and T-cell studies are pending and will be updated. Further understanding of the immunological response to COVID19 vaccination is needed to clarify patients risks, and necessity for booster or alternative protective measures against COVID-19.

OAB-046

COVID-19 infection in multiple myeloma patients – retrospective analysis of 371 Czech patients

Jakub Radocha[1], Ivan Špička[2], Luděk Pour[3], Tomas Jelinek[4], Alexandra Jungova[5], Jiri Minarik[6], Adriana Heindorfer[7], Lukas Stejskal[8], Jana Ullrychova[9], Jarmila Obernauerova[10], Petr Kessler[11], Marek Wrobel[12], Petr Pavlíček[13], Michal Sykora[14], Peter Mikula[15], Vladimir Maisnar[16], Roman Hájek[17]

[1]4th Department of Internal Medicine – Hematology, University Hospital Hradec Kralove, Charles University, Faculty of Medicine in Hradec Králové, Hradec Kralove, Czech Republic; [2]Charles University and General Hospital; [3]Department of Internal Medicine, University Hospital Brno; [4]Department of Haematooncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [5]Hematology and Oncology Department, Charles University Hospital Pilsen; [6]Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic; [7]Department of Hematology, Hospital Liberec, Liberec; [8]Department of Hematology, Silesian Hospital in Opava, Opava; [9]Department of Clinical Hematology, Regional Health Corporation, Masaryk Hospital in Usti nad Labem; [10]Department of Hematology and Transfusion, Klaudians Hospital, Mladá Boleslav; [11]Department of Hematology and Transfusion Medicine, Hospital Pelhrimov; [12]Department of Hematology, Hospital Novy Jicin, Novy Jicin; [13]Department of Internal Medicine and Hematology, University Hospital Kralovske Vinohrady, Prague, Czech Republic; [14]Department of Clinical Hematology, Hospital Ceske Budejovice, Ceske Budejovice; [15]Department of Clinical Hematology, Hospital in Havirov; [16]4th Department of Medicine - Haematology, Charles University Hospital; [17]Department of Hemato-oncology, University Hospital Ostrava and University of Ostrava

Background: COVID-19 disease caused by SARS-CoV-2 coronavirus has affected millions of people worldwide. The mortality of this infection varies with age and comorbidities up to more than 10% in very elderly population. The aim of our study was to determine the disease pattern and mortality rate among multiple myeloma patients. **Methods:** We retrospectively analyzed entries in the Czech Registry of Monoclonal Gammopathies from patients who were infected with SARS-CoV-2 from March 2020 until May 2021. Demographic data, treatment patterns, comorbidities, symptoms of COVID-19, treatment modalities and healthcare utilization was compared in survivors and non-survivors. **Results:** Overall,

371 patients with MM and COVID-19 infection were identified. Median age at covid-19 diagnosis was 69 years (37-91 years), 53.4% (198/371) were males. There were 70.1% (260/371) survivors and 20.8% (77/371) deceased patients, outcome of 9.2% (34/371) of patients is unknown. PCR positivity was seen with median 20 days (1-84 days) in 79 evaluable patients. 6 patients were vaccinated prior to infection (5-68 days). Infection was acquired during actual treatment in 53.1% of patients (197/371). Median number of previous lines administered was 1 (0-7). Treatment preceding infection was most frequently composed of lenalidomide in 50.3%, bortezomib in 42.1% and daratumumab in 19.8%. Symptomatic infection was seen in 74.9% (278/371) of patients with fever being the leading symptom (49.6%) followed by cough (39.1%) and shortness of breath (35.0%). Inpatient treatment was needed in 45.0% (167/371) of patients, intensive care unit was required in 38.9% (65/167) of patients. Median length of in-hospital stay was 11 days (1-53 days). Artificial lung ventilation was necessary in 10.8% (18/167) patients, 24.6% (41/167) needed non-invasive ventilation or high flow oxygen and 35.3% (59/167) of patients needed low flow oxygen. Remdesivir was administered to 10.0% (37/371) and convalescent plasma to 4.9% (18/371) of patients. No difference was seen in mortality according to ISS stage (p=0.609), administered lines of therapy (p=0.119) or achieved treatment response (p=0.418). **Conclusions:** The mortality of MM patients with COVID-19 was very high (20.8%). Healthcare utilization was high with almost half of the infected myeloma patients needing inpatient treatment. No apparent risk factors in terms of disease status or previous treatment were identified. Supported by MH CZ - DRO (UHHK, 00169906) and by the program PROGRES Q40/8.

OAB-047

Plasma cell disorder patients are left vulnerable after one dose of the BNT162b2 mRNA or the ChAdOx-nCOV-19 COVID-19 vaccines

Wei Yee Chan[1], Lara Howells[1], William Wilson[2], Emilie Sanchez[3], Louise Ainley[3], Selina Chavda[3], Emma Dowling[4], Nuno Correia[4], Catherine Lecat[3], Annabel McMillan[5], Brendan Wisniowski[6], Shameem Mahmood[6], Xenofon Papanikolaou[1], Lydia Lee[3], Jonathan Sive[1], Charalampia Kyriakou[1], Ashutosh Wechalekar[3], Rakesh Popat[1], Neil Rabin[1], Eleni Nastouli[3], Kwee Yong[7], Ke Xu[1]

[1]University College London Hospitals NHS Foundation Trust; [2]Cancer Research UK and UCL Cancer Trials Centre, University College London; [3]University College London Hospitals; [4]HCA Healthcare UK; [5]Whittington Hospital; [6]National Amyloidosis Centre; [7]University College London

Background: Concerns have been raised about the ability of patients with plasma cell disorders (PCD) to mount adequate immune responses to vaccination, particularly considering the initial extension to vaccination intervals in the United Kingdom to up to 12 weeks in December 2020, the start of the vaccination roll-out. Protecting this vulnerable patient group with anti-SARS-CoV-2 vaccination is critical. **Methods:** We measured the humoral responses in PCD patients after the first dose of the BNT162b2 and ChAdOx-1 nCOV-19 vaccines. Antibody levels were measured using Elecsys Anti-SARS-CoV-2S assay for quantitative detection of IgG Abs, specific for the SARS-CoV-2 spike-protein receptor binding domain. Positive cut-off of ≥0.80 U/mL defined serologic response. Testing was performed at (or closest to) 4 and 8 weeks post-dose. Baseline nucleocapsid Ab results were available from previous screening in a subset of patients. Clinical information was retrieved from medical records. **Results:** 198 PCD patients (178 multiple myeloma, 15 amyloid, 3 SMM/MGUS, other 2 PCD), median age 63 (range 35-84), had serologic assessment after one vaccine dose against SARS-CoV-2. 69% (138) were on chemo-immunotherapy treatment (CIT) within 4 weeks of first dose. Previous COVID-19 infection and exposure was defined as a positive COVID-19 PCR swab or positive N-antibody at baseline and were excluded from analysis. Patients were tested at median 42 days (range 11-90) after their first dose. After one dose, 68% (135/198) were seropositive, with median Ab titres 21 U/mL (IQR 3.92-133.5). In those with negative baseline Ab test, seroconversion to one dose was 67% (64/96). Forty-one patients were tested more than once after one dose, at median 33 days (12-62) and again at 67 days (38-91). 22 were seronegative at first testing, of these, 6 seroconverted on second testing, prior to second dose. Age ≥70, light chain (LC) disease, disease status less than VGPR, CIT within 4 weeks, low IgM and ASCT more than 12m were statistically significant seronegative predictors on univariate analyses. LC disease, less than VGPR and IgM less than 0.4g/L, retained statistical significance on multivariate analyses. On linear regression analysis in seropositive patients, more lines of treatment and CIT within 4 weeks were significantly associated with lower antibody titres. **Conclusion:** Serologic response to SARS-CoV-2 vaccination is lower in PCD patients than reported healthy controls at 68% after one dose. Further work in PCD is needed to understand how Ab levels correlate to neutralisation capability, cellular responses, protection from infection and how long seroconversion lasts to better define correlates of protection. Nearly a third do not respond to a single vaccine dose causing concerns that PCD patients are left vulnerable with a delayed vaccination strategy and should be prioritised to receiving the second dose at the recommended manufacturers time scale of 3 or 4 weeks.

OAB-048

Suboptimal humoral immune response to SARS-CoV-2 mRNA vaccination in myeloma patients is associated with anti-CD38 mAb and BCMA-targeted treatment

Oliver Van Oekelen[1], Sarita Agte[2], Charles Gleason[3], Komal Srivastava[3], Katherine Beach[3], Adolfo Aleman[1], Bhaskar Upadhyaya[2], Katerina Kappes[2], Tarek Mouhieddine[1], Bo Wang[2], Ajai Chari[4], Carlos Cordon-Cardo[5], Florian Krammer[3], Sundar Jagannath[6], Viviana Simon[7], Ania Wajnberg[8], Samir Parekh[9]

[1]Icahn School of Medicine at Mount Sinai; [2]Icahn School of Medicine at Mount Sinai, Department of Medicine, Hematology and Medical Oncology; [3]Icahn School of Medicine at Mount Sinai, Department of Microbiology; [4]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [5]Icahn School of Medicine at Mount Sinai, Department of Pathology; [6]The Mount Sinai Hospital; [7]Icahn School of Medicine at Mount Sinai, Department of Medicine, Division of Infectious Diseases; [8]Icahn School of Medicine at Mount Sinai, Department of Internal Medicine; [9]Mount Sinai Medical Center, New York, NY, USA

Background: Multiple myeloma (MM) patients are immunocompromised due to defects in humoral/cellular immunity and immunosuppressive therapy. Reports indicate that the antibody (Ab) response in MM after 1 dose of SARS-CoV-2 RNA vaccine is attenuated. Vaccine response kinetics in patients with prior COVID-19 and impact of treatment remain unknown. **Methods:** We analyzed SARS-CoV-2 spike-binding (anti-S) IgG level in 320 MM patients receiving COVID-19 vaccination. Blood and saliva were taken at multiple time points. 69 age-matched healthcare workers were used as controls. **Results:** The 320 MM patients (median age 68 years) received two-dose mRNA vaccines (69.1% BNT162b2, 27.2% mRNA-1273). Median time to diagnosis was 60 months with a median of 2 prior treatment lines (range 0-16). We included 23 patients with smoldering MM. 59 patients (18.4%) were not on active treatment; 148 (43.8%) received anti-CD38 mAb-containing treatment and 36 (11.3%) were on BCMA-targeted therapy. 131 patients (40.9%) exhibited a complete response at last evaluation. 260 patients (81.3%) had anti-S IgG measured >10 days after the second vaccine (median 51 days). Of these, 84.2% mounted measurable anti-S IgG levels (median 149 AU/mL). In the control group, Ab levels were significantly higher (median 300 AU/mL). Ab levels in the 38 vaccinated MM patients with prior COVID-19 were 10-fold higher than those of patients without prior COVID-19 (median 801 vs 69 AU/mL, p<0.001). MM patients on active treatment had lower anti-S IgG levels (p=0.004) compared to patients not on therapy (median 70 vs 183 AU/mL). Notably, 41 patients (15.8%) failed to develop detectable anti-S IgG: 24/41 (58.5%) were on anti-CD38 mAb, 13/41 (31.7%) on anti-BCMA bispecific Ab therapy and 4/41 (9.8%) >3 months after CAR T. Multivariate analysis (corrected for age, vaccine type, lines of treatment, time since diagnosis, response status and lymphopenia) confirmed that anti-CD38-containing (p=0.005) and BCMA-targeted treatment (p<0.001) are associated with not developing detectable anti-S IgG. Clinical relevance is emphasized by 10 cases of COVID-19 after 1 (n=7) or 2 vaccine doses (n=3, all without anti-S IgG) with 1 patient passing due to respiratory failure. **Conclusion:** MM patients mount a suboptimal IgG response after SARS-CoV-2 vaccination with 15.8% developing no detectable anti-S IgG. Ongoing analyses will show kinetics of patients with low-normal Ab levels in comparison to healthy controls. SARS-CoV-2-specific T cell responses and extensive immunophenotyping of >40 patients in the context of vaccination will be reported at the meeting. Immediate implications are the continuation of non-pharmacological interventions, e.g. masking and social distancing, for vulnerable patients. The findings underscore a need for serological monitoring of MM patients following COVID-19 vaccination and for clinical trials assessing use of prophylactic strategies or studies exploring additional immunization strategies.

OAB-049

Poor post-vaccination anti-SARS-CoV-2-antibody response in patients with Multiple Myeloma correlates with low CD19+ B-lymphocyte count and anti-CD38 treatment

Susanne Ghandili[1], Martin Schönlein[1], Marc Lütgehetmann[1], Julian Schulze zur Wiesch[1], Heiko Becher[1], Carsten Bokemeyer[1], Marianne Sinn[1], Katja Weisel[2], Lisa Leypoldt[1]

[1]University Medical Center Hamburg-Eppendorf; [2]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Up to now, only few data are available regarding the efficacy of anti-SARS-CoV-2 vaccines in patients with plasma cell neoplasia. This ongoing observational study aimed to describe the level of post-vaccination anti-SARS-CoV-2-antibodies depending on B lymphocyte count, current therapy, and remission status of patients with multiple myeloma (MM) and related plasma cell dyscrasias, after the first dose of anti-SARS-CoV-2 vaccination. **Methods:** In this single-center study, patients aged 18 years and older with a confirmed diagnosis of MM, monoclonal gammopathies of clinical significance (MGCS) or systemic light-chain amyloidosis (AL) who were eligible for Anti-SARS-CoV-2 vaccination according to the International Myeloma Society recommendations were included. Data were collected between January 1st and May 21th, 2021, at the department of oncology and hematology at the University Medical Center Hamburg-Eppendorf, Germany. The primary aim of this study was to evaluate a possible correlation between antibody titers and CD19+ B lymphocyte count and secondary to identify other possible factors influencing immune response. This study is part of the COVIDOUT trial (NCT04779346). Written informed consent was provided by each patient according to local requirements. **Results:** A total of 82 patients were included in this study. The median age was 67.5 years (range 40-85 years). 78 patients had MM, 2 MGCS, and 2 AL. Overall, 63 patients were vaccinated with mRNA-based and 19 with vector-based vaccines, respectively. At the time of vaccination, 69 (84.1%) patients were under current anti-myeloma treatment. In total, 34 (41%) patients received anti-CD38-targeting therapies and 52 (63%) patients received IMiD-based therapies. 57 (69.5%) patients were in deep remissions (very good partial remission or better) at the time of vaccination. Assessment of anti-SARS-CoV-2 spike protein antibody titer (SP-AbT) took place on a median of 25 days after the first vaccination (SD ± 11.8). A positive SP-AbT was detected in 23% (17/74) of assessable patients. A cut-off value of ≥ 30 CD19+ B cells/µl was significantly positively correlating with higher SARS-CoV-2 SP-AbT. Individuals with current anti-CD38-antibody treatment showed lower SP-AbT and the likelihood for positive titer results was significantly lower

in patients with current anti-CD38 treatment compared to those without. Treatment with immunomodulatory drugs did not harm the development of antibody titers. Furthermore, in multivariable linear regression, higher age and insufficiently controlled disease (≤ partial remission) were significantly negatively correlated with SARS-CoV-2 SP-AbT. **Conclusion:** Based on our results, the majority of myeloma patients respond poorly after receiving the first dose of any anti-SARS-CoV-2 vaccination. Since both low CD19+ B lymphocyte count and CD38-directed therapy negatively impact vaccination response, booster vaccination seems therefore of utter importance.

OAB-050

OCEAN (OP-103): a Phase 3, randomized, global, head-to-head comparison study of Melflufen and Dexamethasone (Dex) versus Pomalidomide (Pom) and Dex in Relapsed Refractory Multiple Myeloma (RRMM)

Fredrik Schjesvold[1], Meletios-Athanasios Dimopoulos[2], Sosana Delimpasi[3], Paweł Robak[4], Daniel Coriu[5], Wojciech Legiec[6], Luděk Pour[7], Ivan Špička[8], Tamás Masszi[9], Vadim Doronin[10], Jiri Minarik[11], Galina Salogub[12], Yulia Alexeeva[13], Antonio Lazzaro[14], Vladimir Maisnar[15], Gábor Mikala[16], Victoria Moody[17], Marcus Thuresson[17], Catriona Byrne[17], Johan Harmenberg[17], Roman Hájek[18], María-Victoria Mateos[19], Paul G. Richardson[20], Pieter Sonneveld[21]

[1]Oslo Myeloma Center, Department of Hematology, Oslo University Hospital and KG Jebsen Center for B Cell Malignancies, University of Oslo; [2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital; [3]General Hospital Evangelismos; [4]Medical University of Lodz, Nicolaus Copernicus Memorial Hospital; [5]Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute; [6]St. John of Dukla Oncology Center of Lublin Land, Department of Hematology and Bone Marrow Transplantation; [7]Department of Internal Medicine, University Hospital Brno; [8]Charles University and General Hospital; [9]Department of Hematology, Semmelweis University, 3rd Department of Internal Medicine; [10]State Budget Healthcare Institution of Moscow, City Clinical Hospital #40; [11]Palacky University and University Hospital Olomouc; [12]V.A. Almazov Chemotherapy of Oncohematology Diseases and Bone Marrow Transplantation Department #2; [13]V.A. Almazov Chemotherapy of Oncohematology Diseases and Bone Marrow Transplantation Department #1; [14]Hospital Guglielmo da Saliceto; [15]4th Department of Medicine - Haematology, Charles University Hospital; [16]National Institute for Hematology and Infectious Diseases; [17]Oncopeptides AB; [18]Department of Hemato-oncology, University Hospital Ostrava and University of Ostrava; [19]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca; [20]Dana-Farber Cancer Institute, Boston, MA, USA; [21]Erasmus MC Cancer Institute

Background: Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate that targets aminopeptidases and thereby rapidly releases alkylating agents inside tumor cells. Accelerated approval in the United States of melflufen + dex for patients (pts) with RRMM was based on promising data from the phase 2 HORIZON study (Richardson, et al. J Clin Oncol. 2021;39:757-767). The phase 3, randomized, head-to-head OCEAN study (NCT03151811) assessed melflufen + dex vs pom + dex in RRMM. **Methods:** Pts with RRMM (2-4 prior lines of therapy [LoTs] including lenalidomide [len] and a proteasome inhibitor) refractory to len within 18 mo of randomization and last LoT were randomized 1:1 (stratified by age, no. of prior LoTs, and International Staging System score) to receive 28-d cycles of melflufen 40 mg intravenously on d1 or pom 4 mg orally (PO) daily on d1 to 21. All pts received dex 40 mg (20 mg for pts ≥75 y) PO on d1, 8, 15, and 22. Pts received therapy until disease progression or unacceptable toxicity (Schjesvold, et al. Future Oncol. 2020;16:631-641). The primary endpoint was progression-free survival (PFS), assessed by independent review committee per International Myeloma Working Group Uniform Response Criteria, with superiority of melflufen vs pom measured using a log-rank P value. Key secondary endpoints were overall response rate (ORR), overall survival (OS), and safety. **Results:** As of 3 Feb 2021, 495 pts were randomized (246 to melflufen; 249 to pom); median age was 68 y (range, 39-91), median prior LoTs was 3, and >99% of pts were len-refractory. In the melflufen and pom groups, median PFS was 6.8 mo vs 4.9 mo (hazard ratio [HR], 0.79 [95% CI, 0.64-0.98]; P=0.0311); median follow-up was 15.5 mo vs 16.3 mo; ORR was 33% (95% CI, 27-39) vs 27% (95% CI, 22-33; complete response, 3% vs 1%; very good partial response, 9% vs 7%; partial response, 20% vs 18%); and OS was 19.8 mo vs 25.0 mo (HR, 1.10 [95% CI, 0.85-1.44]), respectively. With melflufen (n=228) and pom (n=246), grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 90% vs 74%; most commonly thrombocytopenia* (76% vs 13%; occurring with grade 3/4 hemorrhage* in 1% vs 0%), neutropenia* (64% vs 49%; occurring with grade 3/4 infections* in 3% vs 7%), anemia* (43% vs 18%), and infection* (13% vs 22%); and 42% vs 46% of pts had serious TEAEs, respectively. With melflufen and pom, TEAEs led to dose reductions in 47% vs 15% of pts (most commonly thrombocytopenia [31% vs 2%] and neutropenia [12% vs 8%]) and discontinuations in 26% vs 22% of pts, respectively. Deaths occurred in 46% vs 43% of pts with melflufen and pom, with AEs the primary cause of death ≤30 d after last dose in 7% and 9%, respectively. **Conclusion:** Melflufen had superior PFS vs pom, suggesting that melflufen + dex may be an alternative treatment option with a novel mechanism of action for pts with RRMM with len-refractory disease and 2-4 prior LoTs. Analyses of factors impacting OS are ongoing. *Grouped term.

OAB-051

Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), autologous transplantation and MRD response-adapted treatment duration and cessation in newly diagnosed Multiple Myeloma (NDMM)

Luciano Costa[1], Saurabh Chhabra[2], Eva Medvedova[3], Bhagirathbhai Dholaria[4], Timothy Schmidt[5], Rebecca Silbermann[6], Kelly Godby[7], Binod Dhakal[2], Susan Bal[7], Smith Giri[7], Anita D'Souza[2], Robert Cornell[8], Pamela Hardwick[7], James Omel[9], Parameswaran Hari[10], Natalie S. Callander[11]

[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]Medical College of Wisconsin; [3]Oregon Health Sciences University; [4]Vanderbilt-Ingram Cancer Center, Nashville, TN; [5]University of Wisconsin; [6]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [7]University of Alabama Birmingham; [8]Vanderbilt Univeristy; [9]N/A; [10]Division of Hematology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [11]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA

Background: Daratumumab, when combined with PI or an IMiD increases depth of response in MM. Minimal/measurable residual disease (MRD) is an important prognostic factor for long term outcome in patients (pts) with newly diagnosed MM (NDMM), but has not been used to modify therapy. We treated NDMM pts with daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) and employed MRD by next generation sequencing (NGS) to guide the use and duration of Dara-KRd post-autologous transplant (AHCT) and treatment cessation in pts with confirmed MRD negativity. **Methods:** We enrolled pts with NDMM, CrCl ≥40 ml/min, adequate organ function, ECOG performance status 0-2 with no age limit. There was a planned enrichment for pts with high-risk cytogenetic abnormalities (HRCA). Treatment cycles consisted of daratumumab 16 mg/kg IV days 1,8,15,22 (typical reduction in frequency with subsequent cycles), carfilzomib 56 mg/m2 IV days 1,8,15, lenalidomide 25 mg days 1-21 and dexamethasone 40 mg oral/IV days 1,8,15,22 repeated every 28 days. Pts received 4 cycles of Dara-KRd induction, AHCT, and received 0, 4 or 8 cycles of Dara-KRd consolidation, according to MRD status. MRD was evaluated by NGS (ClonoSEQ®) in all pts at end of induction, post-AHCT, and during each 4-cycle block of Dara-KRd consolidation. Primary endpoint was achievement of MRD negativity (<10-5 as defined by IMWG) in the intention-to-treat population. Pts received therapy until achievement of two consecutive MRD <10-5 (confirmed MRD-negativity). Confirmed MRD-negative pts entered treatment-free observation and MRD surveillance ("MRD-SURE" phase) with surveillance for MRD resurgence 6 months after treatment cessation and yearly thereafter. Pts completing consolidation without confirmed MRD-negativity received standard lenalidomide maintenance. **Results:** Among 123 participants, 46 (37%) had 1 and 24 (20%) had 2+ HRCA [gain 1q, t(4;14), t(14;16), t(14;20) or del(17p)]. Median age was 60 y (36-79), 20% had ECOG 2, 21% had high LDH, and 20% R-ISS3. Disease was trackable by NGS-MRD in 96% of pts. Median follow up is 25.1 mo. Most common severe adverse events were pneumonia (N=8), and venous thromboembolism (N=3). Overall, 80% of pts have achieved MRD negativity (78%, 82% and 79% of pts with 0, 1 and 2+ HRCA respectively) and 65% MRD < 10-6 (62%, 73% and 58% of pts with 0, 1 and 2+ HRCA respectively). MRD negativity was reached in 38% of patients post induction, 65% post AHCT and 80% post MRD-directed Dara-KRd consolidation. Response ≥CR was obtained in 86% of pts. Overall 84 pts (71%) have reached confirmed MRD negativity and entered MRD-SURE. **Conclusion:** Monoclonal antibody-based quadruplet therapy, AHCT and MRD response-adapted consolidation therapy leads to high rate of MRD negativity in NDMM. For most patients with NDMM, MRD-directed adaptive treatment offers the prospect of confirmed deep responses and investigation of MRD surveillance as an alternative to indefinite maintenance.

OAB-052

Impact of chromosome 1 abnormalities on newly diagnosed multiple myeloma treated with proteasome inhibitor, immunomodulatory drug, and dexamethasone: analysis from the ENDURANCE ECOG-ACRIN E1A11 trial

Prashant Kapoor[1], Timothy Schmidt[2], Susanna Jacobus[3], Zihan Wei[4], Rafael Fonseca[5], Natalie S. Callander[5], Sagar Lonial[6], S. Vincent Rajkumar[1], Shaji Kumar[7]

[1]Mayo Clinic; [2]University of Wisconsin; [3]Dana Farber Cancer Institute - ECOG-ACRIN Biostatistics Center; [4]ECOG-ACRIN Dana-Farber Cancer Institute; [5]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [6]Winship Cancer Institute, Emory University; [7]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA

Background: Chromosome 1 abnormalities (C1A) are frequently identified in multiple myeloma (MM). We assessed impact of C1A in a post hoc analysis of E1A11 trial. **Methods:** E1A11 randomized newly diagnosed (ND) MM patients (pts) with traditional 'standard risk' features or t(4;14), not intended for upfront transplant, to bortezomib (V) or carfilzomib (K), in combination with lenalidomide (R) and dexamethasone (d), followed by indefinite or 2-year (y) R maintenance. Impact of C1A and ultra-high risk (UHR) MM [≥2 of the following: +1q [gain1q (3 copies) or amplification (amp)1q21 (≥4 copies)], deletion (del)1p and t(4;14)], was assessed. **Results:** Of 1087 pts, 912 were evaluated for +1q (gain1q or amp1q) and 774 for del1p. Gain1q, amp1q and del1p were noted in 23%, 7.5% and 9% pts, respectively. Best responses to VRd or KRd within each response category were similar, irrespective of +1q/del1p status. Within each arm, progression-free survival (PFS) was inferior for pts with +1q versus (v) pts without +1q; median 29 v 42 months (m) for both arms [VRd, HR 1.51 p 0.011; KRd, HR 1.63, p 0.002]. Corresponding 3y overall survival (OS) rates on VRd were 74 v

86% (HR 1.47, p 0.069) and 82 v 88% (HR 1.34, p 0.185) on KRd. Regarding copy number, pts with gain1q v those without +1q had inferior PFS with both VRd (median 29m, HR 1.59, p 0.012) and KRd (median 33m, HR 1.41, p 0.051). OS rates with gain1q were inferior within VRd arm only (3y 71%, HR 1.78, p 0.014; KRd 3y OS 89%, HR 1.02, p 0.93). By contrast, pts with amp1q, v pts without +1q, had inferior outcomes with KRd (median PFS 24m, HR 2.37, p<0.001; 3y OS 62%, HR 2.43, p 0.008) but not with VRd: median PFS 32m, HR 1.43; p 0.186; 3y OS 75%, HR 1.29; p 0.48). Pts with del1p, v those without del1p, had inferior PFS (median 29 v 39m; HR1.49, p=0.042) and OS rates (3y 74 v 85%, HR 2.03; p 0.003) in the entire cohort. Within KRd arm, the respective OS rates were comparable (3y, 87 v 86%, HR 1.10, p 0.818). By contrast, pts with del1p on VRd had inferior OS (3y 60 v 84%, HR 3.30, p<0.001). UHR MM pts had worst outcomes (median PFS, 20 v 38m, HR 2.01, p<0.001; 3y OS, 68 v 85%, HR 1.99, p 0.004). However, OS for UHR MM pts on KRd was similar to that of pts without UHR MM (3-yr, 87 v 86%, HR 0.95, p 0.902; VRd 3-yr, 45 v 84%, HR 4.15, p<0.001). Analyses of treatment effect within subgroups showed superiority of KRd over VRd for OS among pts with gain1q [HR 0.50 (0.28-0.90)], del1p [HR 0.34 (0.13-0.89)] and UHR MM [HR 0.18 (0.07-0.51)], but not amp1q [HR 1.56 (0.64-3.78)]. **Conclusion:** Gain1q or amp1q portends poor outcome among NDMM pts treated with either VRd or KRd. Specifically, pts with amp1q as a sole high-risk abnormality have distinctly poor outcomes with KRd. By contrast, KRd, but not VRd, appears to abrogate the adverse impact of del1p. Given the limitations of the trial design and post hoc subset analyses, longer follow up and confirmatory studies are warranted for definitive conclusions.

OAB-055

Gain and amplification of 1q induce transcriptome deregulation and worsen the outcome of newly diagnosed Multiple Myeloma patients

Mattia D'Agostino[1], Angelo Belotti[2], Elena Zamagni[2], Daniel Auclair[3], Renato Zambello[3], Maddalena Arigoni[4], Antonio Spadano[1], Michele Cea[1], Norbert Pescosta[1], Sonia Ronconi[1], Martina Olivero[5], Caterina Musolino[1], Elisa Genuardi[1], Stefano Molica[1], Vincenzo Pavone[1], Francesca Patriarca[1], Paolo de Fabritiis[1], Barbara Gamberi[6], Raffaele Adolfo Calogero[4], Massimo Offidani[7], Monica Galli[1], Pellegrino Musto[1], Mario Boccadoro[1], Francesca Gay[1]

[1]European Myeloma Network, Italy; [2]Hematology Division, ASST Spedali Civili Brescia, Brescia, Italy; European Myeloma Network, Italy; [3]Multiple Myeloma Research Foundation, Norwalk, US-CT; [4]Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Università degli Studi di Torino, Torino, Italy; [5]Dipartimento di Oncologia, Università degli Studi di Torino, Torino, Italy; [6]Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; [7]AOU Ospedali Riuniti di Ancona, Ancona, Italy; European Myeloma Network, Italy

Background: Gain and/or amplification of chromosome 1q are frequently associated with multiple myeloma (MM). The number of 1q copies correlates with a poor prognosis. Our aim was to evaluate the impact on clinical outcome and the transcriptome changes induced by Gain1q (3 copies of 1q) and 1q amplification (Amp1q, ≥4 copies of 1q) in patients (pts) enrolled in the randomized FORTE trial (NCT02203643). **Methods:** Fluorescence in situ hybridization (FISH) on CD138+ purified bone marrow plasma cells was centralized and performed at baseline. The cut-off level of Gain1q was 10% of nuclei with ≥3 copies of 1q, while Amp1q was defined as ≥20% of nuclei with ≥4 copies of 1q. Transcriptome data from pts enrolled in the MMRF CoMMpass study (NCT01454297) were used to find differentially expressed genes (DEGs) in Gain/Amp1q pts. An independent cohort enrolled in the FORTE trial was subjected to RNAseq and used as validation. **Results:** A total of 474 pts were enrolled in the FORTE trial. 1q copy number was missing in 74 pts; thus, 400 pts were evaluable. The median follow-up was 51 months; 219 (55%) pts belonged to the Normal 1q, 129 (32%) to the Gain1q, and 52 (13%) to the Amp1q group. In a multivariate analysis, progression-free survival (PFS) was shorter in the presence of Gain1q (HR 1.65 vs Normal 1q, p=0.005) and Amp1q (HR 3.13 vs Normal 1q, p<0.001; HR 1.90 vs Gain1q, p=0.002). The median PFS was not reached in the Normal 1q, 53 months in the Gain1q, and 21.2 months in the Amp1q group. Amp1q also predicted a poor overall survival (OS; HR 4.99 vs Normal 1q, p<0.001; HR 2.92 vs Gain1q, p<0.001), with a median survival of 53 months. An ANOVA-like analysis of RNAseq data from the CoMMpass study comparing Gain1q/Amp1q vs Normal 1q pts detected 350 up-modulated and 148 down-regulated genes. These 498 DEGs were able to separate the Normal vs Gain vs Amp1q groups in a principal component analysis. The separation induced by this gene signature was confirmed in an independent set of samples. Many (203/498), but not all, of the DEGs were located on chromosome 1. An ingenuity pathway analysis of the above-mentioned signature showed a deregulation of apoptosis signaling (z-score 2.646) and p38 MAPK signaling (z-score 2.646) pathways. Using IPA, we also checked the presence of inter-gene connectivity, detecting a deregulation of a gene network centered on Myc in Gain/Amp1q pts. Gene deregulation was present in both Amp1q and Gain1q groups and was more prominent in Amp1q patients. Nonetheless, PFKB3, ITGB1, TTN, FBOX32, RELB, TLR7, and AHR genes showed a change in expression direction from down-regulated in Gain1q to up-modulated in Amp1q. **Conclusion:** Amp1q universally predicts poor PFS and OS, despite the use of new drug combinations. A gene network centered on Myc may contribute to the high-risk behavior of these pts. The study of DEGs associated with Gain and Amp1q can identify new 'druggable' targets to be further tested in this high-risk patient population.

OAB-056

A machine learning model based on tumor and immune biomarkers to predict undetectable measurable residual disease (MRD) in transplant-eligible multiple myeloma (MM)

Camila Guerrero[1], Noemi Puig[2], María Teresa Cedena[3], Ibai Goicoechea, Cristina Pérez, Juan José Garcés, Cirino Botta[4], María José Calasanz[1], Norma C. Gutierrez[5], María Luisa Martin Ramos[6], A Oriol[7], Rafael Ríos[8], Miguel Teodoro Hernández[9], Rafael Martinez Martinez[10], Joan Bargay[11], Felipe de Arriba[12], Luis Palomera[13], Ana Pilar González Rodriguez[14], Joaquín Martínez-López[6], Juan José Lahuerta[3], Laura Rosiñol[15], J Bladé[15], María-Victoria Mateos[16], Jesús F. San-Miguel[17], Bruno Paiva[18]

[1]Clínica Universidad de Navarra, Centro de Investigación Médica Aplicada (CIMA), Instituto de Investigación Sanitaria de Navarra (IDISNA), CIBER-ONC number CB16/12/00369; [2]Hospital Universitario de Salamanca, Instituto de investigación biomédica de Salamanca (IBSAL); [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Hematology Unit, Department of Oncology, "Annunziata" Hospital of Cosenza, Italy; [5]Hospital Universitario de Salamanca Hematología. Instituto de investigación biomédica de Salamanca (IBSAL); [6]Hospital Universitario 12 de Octubre; [7]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol; [8]Hospital Universitario Virgen de las Nieves, Instituto de Investigación Biosanitaria, Granada, Spain; [9]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [10]Hospital Universitario San Carlos, Madrid, Spain; [11]Hospital Universitario Son Llatzer, Institut dinvestigacio Illes Balears (IdISBa), Palma de Mallorca, Spain; [12]Hospital Morales Meseguer, IMIB-Arrixaca, Universidad de Murcia, Murcia, Spain; [13]Hospital Clínico Lozano Blesa, Zaragoza, Spain; [14]Hospital Central de Asturias, Oviedo, Spain; [15]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [16]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca; [17]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA; [18]Clinica Universidad de Navarra, Centro de Investigacion Medica Aplicada (CIMA), Instituto de Investigacion Sanitaria de Navarra (IDISNA), CIBER-ONC number CB16/12/00369*

Background: There is expectation of using biomarkers to personalize treatment. Yet, a successful treatment selection cannot be confirmed before 5 or 10 years of progression-free survival (PFS). Treatment individualization based on the probability of an individual patient to achieve undetectable MRD with a singular regimen, could represent a new model towards personalized treatment with fast assessment of its success. This idea has not been investigated previously. **Methods:** We sought to define a machine learning model to predict undetectable MRD in newly-diagnosed transplant-eligible MM patients (n=278). The training (n=152) and internal validation cohort (n=60) consisted of 212 active MM patients enrolled in the GEM2012MENOS65 clinical trial. The external validation cohort was defined by 66 high-risk smoldering MM patients enrolled in the GEM-CESAR clinical trial, which treatment differed only by the substitution of bortezomib by carfilzomib during induction and consolidation. Patients were included in the study based on data availability of 17 parameters ($p \leq .05$) associated with MRD outcomes. **Results:** We started by investigating patients' MRD status after VRD induction, HDT/ASCT and VRD consolidation (GEM2012MENOS65) according to their ISS and Revised-ISS, LDH levels, and cytogenetic alterations. High LDH levels and del(17p13), two features relatively infrequent at diagnosis, were the only parameters associated with lower rates of undetectable MRD. The ISS and R-ISS were not predictive. Therefore, we aimed to evaluate other disease features associated with MRD outcomes and develop more effective models based on machine learning logistic regression. The most effective one resulted from integrating cytogenetic [t(4;14) and/or del(17p13)], tumor burden (plasma cell clonality in bone marrow and circulating tumor cells in peripheral blood) and immune related (myeloid precursors, mature B cells, intermediate neutrophils, eosinophils, CD27negCD38pos T cells and CD56brightCD27neg NK cells) biomarkers. Data obtained for an individual patient can be substituted into our formula, which results in a numerical probability of achieving undetectable (>0.5) vs persistent (0.685 or <0.365 (observed in 102/212 patients), MRD outcomes are respectively predicted with higher confidence. Standard-confidence, high-confidence, and external validation predictions were accurate in 152/212 (71.7%), 85/102 (83.3%), and 48/66 (72.7%) patients respectively. Patients predicted to achieve undetectable MRD using standard and high-confidence values showed longer PFS and OS than those with probability of persistent MRD. **Conclusions:** We demonstrated that selecting a regimen based on probable MRD outcomes, and confirming soon after if that probability was accurate, is a possible new approach towards individualized treatment in MM. The model is available at www.MRDpredictor.com to facilitate its use in clinical practice.

OAB-057

Temporal-weight estimation of the copy number alterations of of 1384 Multiple Myeloma patients defines an ancestrality index impacting patients survival

Andrea Poletti[1], Vincenza Solli[1], Gaia Mazzocchetti[1], Marina Martello[1], Enrica Borsi[2], Silvia Armuzzi[1], Ilaria Vigliotta[2], Barbara Taurisano[1], Elena Zamagni[3], Lucia Pantani[4], Paola Tacchetti[2], Katia Mancuso[4], Serena Rocchi[1], Carolina Terragna[2], Michele Cavo[2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" - Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [3]European Myeloma Network, Italy; [4]University of Bologna DIMES department / IRCCS Azienda

Ospedaliero Universitaria di Bologna Istituto di Ematologia "Seràgnoli"

Background: MM is a hematological malignancy always evolving from pre-malignant stages, with progressive increase of genomic complexity. MM is characterized by a large abundance of copy number alterations (CNA); many of them, regarded as "driver", stack up progressively from early tumor stages, causing biological changes that give rise to tumor hallmarks and malignant phenotypes. The combined application of whole genome analysis and mathematical models allows to deeply describe these alterations and to infer their order of acquisition during oncogenesis from their clonality levels, assuming that clonal ones are more ancestral than subclonal. Aims: (1) To define the temporal order of acquisition of CNA, leading to the onset of symptomatic MM and (2) to define a scoring model able to stratify patients (pts) according to the ancestrality of the alterations observed in their genomic landscape. **Methods:** Genomic data collected from a total of 1384 newly diagnosed MM pts were included in the study: SNPs array data were collected from 514 pts of our Institution (BO dataset); in 870 pts, WES data were downloaded from CoMMpass study. CN calls and clonality levels were harmonized by an analysis pipeline including ASCAT, GISTIC v2 and custom R scripts. Timing estimates were obtained with BradleyTerry2 package. Survival analysis were performed on R. **Results:** A full call-set of CNAs was obtained by harmonizing BO and CoMMpass datasets. The clonality information was first extrapolated from the whole call-set, to define the temporal order of acquisition of non-primary CNAs. CNAs were then accurately ranked, by using the obtained timing estimates, characterized by a quite narrow confidence interval. Of interest, chr 1q gains and chr 13q losses were frequently clonal and ranked as ancestral events, whereas chr 17p losses were late occurring events. By weighting the CNAs carried by any given pts at diagnosis with their relative timing estimate in a combinatorial process, an Ancestrality Index (AI) was defined for each pts (median AI=3.4, IQR=1.7-6.0). The AI was found to be significantly associated with progression free (PFS) and overall survival (OS) (p3.4 (i.e. with a more "ancestral" profile) had a worse outcome as compared to the rest of pts (OS 40% vs 58%, PFS 42% vs 56%, at a median follow up of 92m and 34m, p<0.001).The risk attributed to this "ancestral" category was independent from other high-risk cytogenetic features (i.e. del17p, t(4;14), t(14;20), t(14;20)). **Conclusions:** By means of whole genome analysis and dataset harmonizing, the temporal order of acquisition of MM CNAs has been confidently described. A score reflecting the disease ancestrality of MM pts at diagnosis was generated and associated to survival outcomes. Overall, these findings support the evidence that MM pts at diagnosis carrying an excess of ancestral alterations, expected to likely be drivers, are prone to have a dismal prognosis.

OAB-058

Predictive relevance of sustained MRD negativity and of early loss of MRD negativity during maintenance therapy after transplant in newly diagnosed Multiple Myeloma patients

Angelo Belotti[1], Rossella Ribolla[2], Marco Chiarini[3], viviana Giustini[3], Claudia Crippa[2], Valeria Cancelli[2], Samantha Ferrari[2], Annalisa Peli[2], Chiara Bottelli[2], Chiara Cattaneo[2], Aldo Roccaro[4], Giuseppe Rossi[2], Alessandra Tucci[2]

[1]Hematology Division, ASST Spedali Civili Brescia, Brescia, Italy; European Myeloma Network, Italy; [2]Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; [3]Chemistry Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia; [4]Clinical Research Development and Phase I Unit, ASST Spedali Civili di Brescia, Brescia, Italy

Background: sustained MRD negativity is emerging as a surrogate biomarker of patients (pts)' outcome in clinical trials. We implemented this tool in our clinical practice and we analyzed outcome according to sustained MRD negativity in MM pts treated with autologous stem cell transplantation (ASCT) at our Institution. **Methods:** We retrospectively analyzed the outcome of 77 newly diagnosed MM pts (median age 61 years) diagnosed between January 2015 to December 2019 in ≥ VGPR after ASCT. Bone marrow samples were collected for MRD by 8-color FCM (Sn 10-5) at day +100 after ASCT, before maintenance. Sustained 1 year MRD negativity was also evaluated and the prognostic impact of MRD status on PFS and OS was analyzed. **Results:** out of 77 pts, 28 (36%) were ISS stage 3 and 18 (23%) showed high risk cytogenetics. Patients were treated with the following induction regimens: VTD 51, VRD 5, Dara-VRD 5, KRD 14, KCD 2. Single ASCT with MEL200 conditioning was performed in 49 pts (64%), whereas 28 pts (36%) received double ASCT. Subsequent maintenance was performed with lenalidomide (70), daratumumab-lenalidomide (5), carfilzomib-lenalidomide (2). Response rates were VGPR 26%, CR 61% and sCR 13%. MRD before maintenance was positive in 20 pts (26%) and negative in 57 (74%). Sustained MRD negativity lasting ≥ 1 year was documented in 49 pts (64%), whereas early loss of MRD negative status was observed in 8 (10%) of cases. After a median follow up of 40.2 months, PFS was significantly longer in pts with sustained MRD negativity (≥1 year) compared to MRD positive patients before maintenance: median NR vs 41.4 months, p 0.0002, HR 0.17 (0.044-0.65). The worst PFS (24.7 months) was observed in pts with early loss of MRD negativity (<1 year) and was significantly inferior if compared both to pts with sustained MRD negativity (p<0.0001, HR 0.06 ; 0.01-0.54) and to MRD positive pts before maintenance (p 0.03, HR 0.35; 0.11-0.16), with significantly different outcome of the three subgroups (p<0.0001). Different OS trend was also observed among the three subgroups: NR in sustained MRD negative pts, 58.5 months in MRD positive pts and 35.3 months in pts with early loss of MRD negativity (p<0.0001), although OS difference between sustained MRD negativity (≥ 1 year) and MRD positive pts was not statistically significant on a direct comparison (p 0.054). The worst OS observed

in pts with early loss of MRD negativity (<1 year) was significantly inferior if compared both to pts with sustained MRD negativity (p<0.0001, HR 0.05; 0.003-0.80) and to MRD positive pts before maintenance (p 0.020, HR 0.21; 0.035-1.26). **Conclusion:** we confirm the predictive value of MRD assessment after ASCT and therefore the importance of achieving sustained MRD negativity regardless of different treatment strategies. Moreover, the detection of early loss of MRD negativity can help the physician to identify pts with particularly poor prognosis

OAB-059

Towards a comprehensive multimodal minimal residual disease assessment in multiple myeloma: the role of circulating cell-free DNA to define the extent of disease spreading

Marina Martello[1], Andrea Poletti[1], Enrica Borsi[1], Barbara Taurisano[1], Vincenza Solli[1], Silvia Armuzzi[1], Gaia Mazzocchetti[1], Ilaria Vigliotta[2], Ignazia Pistis[2], Elena Zamagni[3], Lucia Pantani[2], Serena Rocchi[2], Katia Mancuso[2], Paola Tacchetti[2], Ilaria Rizzello[2], Michele Cavo[2], Carolina Terragna[2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" - Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [3]European Myeloma Network, Italy

Background: Multiple Myeloma (MM) is a plasma cell (PC) disorder characterized by the presence of multiple lytic lesions at the time of diagnosis. Recently, cell-free DNA (cfDNA) has proven to resume the heterogeneity of spatially distributed clones. However, the potential of cfDNA to track the evolutionary dynamics and the heterogeneity of MM, possibly anticipating the emergence of therapy resistant residual cells, remains to be confirmed. Aim of this study is to evaluate cfDNA at diagnosis and during follow-up in order to compare this approach with both bone marrow (BM) molecular and whole-body imaging residual disease assessment. **Methods:** A total of 97 patients (pts) were screened at baseline and during follow-up with 18F-FDG PET/CT and NMR, and molecularly assessed by Ultra Low Pass-Whole Genome Sequencing (ULP-WGS). ULP-WGS was used to characterize both the neoplastic PC clone from BM (gDNA) and the cfDNA from peripheral blood. Data were analysed by ichorCNA and Clonality R packages. **Results:** Overall, cfDNA tumour fraction (TF) at diagnosis was significantly lower as compared to gDNA TF [median (M) TF: 3.0%vs.74.4%, respectively]. Nevertheless, high cfDNA TF levels (49/97 pts = 50%, M cfDNA TF: 10%, range : 3.0-40.6%) correlated with high gDNA TF levels (M gDNA TF: 84%, range: 5.9-95.2%). Similarly, a significant correlation was shown between cfDNA TF and the BM plasma cells clone throughout disease progression, highlighting a parallel dynamics of tumour burden from SMM to MM to +3m post-induction (cfDNA TF vs. % CD138+/CD38+ BM cells: 1.5 vs 1.0; 3.0 vs. 2.3; 1.2 vs. 0.01, respectively, p: 0.008). Pts with high cfDNA TF were likely to have more sites of extramedullary disease (EMD) at PET-CT, a higher number of PET lesions and higher tumour metabolic activity, as compared to pts with low TF (EMD 8/49, 17% vs. 2/49, 3.4%; M n. PET lesions: 8 vs. 2; SUVmax: 12.9 vs. 3.9). Similarly, bone involvement as detected by MRI, was more evident in pts with high cfDNA TF (M n. focal lesions: 6 vs. 1). More interestingly, after 3 cycles of induction therapy, imaging and cfDNA TF dynamics were concordant: indeed, in those cases where FDG activity and focal lesions still persisted (4/10=40%: SUVmax 5.8; >2 PET lesions), cfDNA TF as well was still detectable (>1 TF).Finally, the comparison between cfDNA and BM genomic profiles showed an overall concordance of the copy number alterations (CNAs) landscape in most patients (83/97; 86.4%), whereas three patients (10/97; 10,3%) displayed a different genomic profile in cfDNA, as compared to BM. **Conclusions:** although only few cases showed genomic evidence of spatial heterogeneity, in pts with high cfDNA TF, imaging data overall suggested a propensity to a metastatic spread of the disease. Future studies will be addressed to exploit the use of cfDNA in disease monitoring. **Acknowledgements:** AIRC IG2018-22059.

OAB-060

Prospective comparison of contemporary whole body MRI and FDG PET/CT for disease detection and correlation with markers of disease burden in myeloma: results of the iTIMM trial

Martin Kaiser[1], Nuria Porta[1], Bhupinder sharma[2], Daniel Levine[2], Dow-Mu Koh[2], Kevin Boyd[2], Charlotte Pawlyn[1], Angela Ridell[2], Katherine Downey[2], James Croft[1], Alison Bonner[2], Veronica Morgan[2], Simon Stern[3], Lydia Jones[4], Betty Cheung[5], Charalampia Kyriakou[6], Pawel Kaczmarek[7], jessica Winfield[2], Matthew Blackledge[1], Wim Oyen[8], Christina Messiou[9]

[1]The Institute of Cancer Research; [2]The Royal Marsden Hospital, London; [3]Epsom & St Helier University Hospitals NHS Trust, UK; [4]Epsom and St Helier University Hospitals; [5]Croydon University Hospital; [6]University College London Hospital; [7]Surrey and Sussex NHS Trust; [8]Rihnstate Hospital Arnhem and Humanitas University Milan; [9]The Royal Marsden Hospital

Background: Sensitive detection of bone marrow disease and stratified patient management according to clinical risk can confer survival advantages in multiple myeloma (MM). Recent international guidelines include whole body MRI (WB MRI) and Fluorodeoxyglucose (FDG) PET/CT for bone marrow disease imaging in patients with a suspected diagnosis of MM. However, prospective studies comparing detection of MM by contemporary WB MRI as per MY-RADS consensus against FDG PET/CT are few. We report here on protocol-defined endpoints of the iTIMM (NCT02403102) study, which compared WB MRI and PET/CT, their relationship with serum and bone marrow estimates of disease burden, as well as molecular tumor characteristics. **Methods:** The iTIMM study enrolled patients with newly diagnosed MM or at

first relapse, planned to receive autologous stem cell transplantation. Matched baseline diffusion weighted and Dixon WB MRI and FDG PET/CT were performed and baseline clinical data including tumor genetics collected. Scans were double reported for presence of focal and diffuse disease by expert MRI and PET/CT radiologists, blinded to each other's assessment. Paired methods were used to compare burden and patterns of disease on WB MRI compared to FDG PET/CT at baseline. Exploratory endpoints include comparison of baseline WB MRI and PET/CT and their correlation with laboratory parameters, for which data is complete and reported here. **Results:** Sixty patients (35 male; mean age 60 years) were enrolled between May 2015 and March 2018 and underwent paired baseline WB MRI as per MY-RADS and FDG PET/CT. At least one focal lesion was detected in 50/60 patients (83.3%) by WB MRI and in 36/60 patients (60%) by PET/CT. WB MRI was more sensitive (P<0.05, including Holm's correction for multiplicity) for long bones, lumbar spine and pelvis. Four patients in our study showed two or more focal lesions ≥5 mm only on WB MRI but not FDG PET/CT. All lesions detected by WB MRI but not PET/CT were resolving in follow-up scans after treatment, excluding false positives. In 49/60 (81.7%) patients, WB MRI detected diffuse disease, compared to 10/60 (16.7%) by FDG PET-CT; WB MRI was more sensitive across all anatomical areas (P<0.05 (Holm's)). All patients without focal disease presented diffuse disease on WB MRI (n=10). Bone marrow plasma cell infiltration and serum paraprotein levels were significantly higher for patients with diffuse disease on WB MRI, but not PET/CT. All genetically high-risk tumors, defined by t(4;14), t(14;16), del(1p), gain(1q) or del(17p), showed diffuse infiltration on WB MRI. **Conclusions:** Contemporary WB MRI is more sensitive regarding detection of focal and diffuse disease compared with FDG PET/CT; together with its capability to assess response proposing it as a standard for tumor imaging in MM. In addition, measurability of diffuse disease and its association with higher disease burden and high-risk molecular profiles supports WB MRI radiomic biomarker development.

OAB-053

Clinical outcomes of relapsed/ refractory multiple myeloma patients after BCMA-targeted CAR T therapy

Oliver Van Oekelen[1], Tarek Mouhieddine[1], Darren Pan[2], Megan Metzger[3], Sarita Agte[2], Adolfo Aleman[1], David Melnekoff[1], Guido Lancman[2], Alessandro Lagana[1], Shambavi Richard[1], Larysa Sanchez[2], Joshua Richter[4], Hearn Jay Cho[5], Ajai Chari[6], Sundar Jagannath[3], Samir Parekh[7]

[1]Icahn School of Medicine at Mount Sinai; [2]Icahn School of Medicine at Mount Sinai, Department of Medicine, Hematology and Medical Oncology; [3]Mount Sinai Hospital; [4]Icahn School of Medicine at Mount Sinai Hospital; [5]Tisch Cancer Institute, Icahn School of Medicine at Mt. Sinai; The Multiple Myeloma Research Foundation; [6]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [7]Mount Sinai Medical Center, New York, NY, USA

Background: Anti-BCMA chimeric antigen receptor (CAR) T have shown remarkable efficacy in highly pretreated multiple myeloma (MM) patients. With recent FDA approval of BCMA-targeted CAR T in MM and other agents in late stages of development, CAR T is poised to become more widely used. However, the outcomes of MM patients after relapse on CAR T are largely unknown and effective approaches to salvage after CAR T are urgently needed. **Methods:** Demographics, disease characteristics and post-clinical trial outcomes were collected retrospectively on 31 MM patients who relapsed after CAR T therapy at a single academic hospital. **Results:** 31 MM patients had a median age of 61 years at time of disease progression after CAR T; 19 (61%) were male. Median time from diagnosis to CAR T relapse was 74 months (range 22-282). Post-CAR T follow-up was a median of 391 days (range 86-943). Twenty-six patients (84%) had high-risk cytogenetics. Most patients were highly pretreated with a median of 5 prior lines (range 1-18) and 28 patients (90%) had received autologous stem cell transplant (ASCT). Patient exposure/refractoriness included: lenalidomide (100%/74%), pomalidomide (87%/84%), bortezomib (90%/61%), carfilzomib (94%/87%), CD38-mAb (97%/97%) and alkylating agents (100%/54). Fifteen patients (48%) had received DCEP and four patients (13%) had received prior treatment with a non-BCMA-targeted bispecific Ab. The median time to a subsequent treatment following relapse on CAR T was 34 days (range 0-378). At time of analysis, patients had already received a median of 2 subsequent treatment lines (range 1-8). The most common initial treatment after CAR T relapse was chemotherapy with V-DCEP or VD-PACE (10/29, 34%). Stem cell boost was part of the initial approach in five patients (17%) and was performed in 12 patients at any time after CAR T relapse (41%). Five patients (17%) were treated with bispecific Ab immediately after CAR T and 11 patients (38%) received bispecific Ab therapy at any point after CAR T. Best response to initial treatment varied widely (10 PD, 4 SD, 1 MR, 1 PR, 6 VGPR, 7 CR) with overall response rate (ORR, ≥PR) of 48%. Median time to progression was 104 days for the initial treatment and 62 days for the second line after CAR T. Twenty occurrences of durable responses (>120 days, range 126-513) were observed, of which were 4 selinexor-based treatments, 4 with non-BCMA bispecific Ab, 4 involving stem cell boost and 2 venetoclax-based. At the time of analysis, 17 patients (55%) were alive and the median OS after relapse on CAR T was 496 days. **Conclusion:** Studying the prognosis of patients after relapse and the response to subsequent therapy will provide important clinical insights for salvage, especially as CAR T moves to an earlier treatment setting. At the meeting, we will compare and contrast more mature data on the CAR T cohort with >50 patients that relapsed after bispecific Ab therapy.

OAB-054

Single-cell RNA-sequencing identifies immune biomarkers of response to immunotherapy in patients with high-risk Smoldering Myeloma

Romanos Sklavenitis-Pistofidis[1], Ankit Dutta[2], Sylvia Ujwary[3], Robert Redd[4], Alexandra Savell[3], Oksana Zavidij[2], Nang Kham Su[3], Mark Bustoros[2],

Nicholas Haradhvala[5], Francois Aguet[5], Gad Getz[6], Irene Ghobrial[7]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Broad Institute of MIT & Harvard; [2]Dana-Farber Cancer Institute, Harvard Medical School; [3]Dana-Farber Cancer Institute; [4]Harvard School of Public Health; [5]Broad Institute of MIT & Harvard; [6]Massachusetts General Hospital, Harvard Medical School, Broad Institute of MIT & Harvard; [7]Dana-Farber Cancer Institute, Boston, MA, USA

Background: Patients with Smoldering Multiple Myeloma (SMM) are typically observed until progression, but early treatment of high-risk patients may improve outcomes. Clinical and genomic biomarkers can be used to identify SMM patients at high risk of progression, however parallel profiling of the tumor immune microenvironment (TIME) may further improve prediction models. **Methods:** Here, we performed single-cell RNA-sequencing on CD138- immune cells from 40 samples of 14 patients enrolled in a Phase II trial of Elotuzumab, Lenalidomide, and Dexamethasone, in patients with high-risk SMM (E-PRISM) to develop biomarkers for optimal patient selection and monitoring of response to treatment. Specifically, we profiled 33 bone marrow (BM) samples collected at baseline (n=11), cycle 9, Day 1 (C9D1, n=13) and EOT (n=9), and 7 peripheral blood mononuclear cell (PBMC) samples collected at baseline (n=4) and C9D1 (n=3). **Results:** We found that higher abundance of mature B-cells, Th17 cells and GZMK+ T and NK cells and lower abundance of hematopoietic progenitor cells and plasmacytoid dendritic cells are associated with significantly longer progression-free survival (PFS) in SMM patients under treatment. This signal can be summarized by how normal-like the patients' immune composition is at baseline, whereby patients whose immune composition is normal-like have significantly shorter PFS (p=0.031). This model suggests that at least some of the compositional changes observed in disease reflect the immune system's capacity to react successfully to the immune challenge posed by the tumor, which we termed immune reactivity. Baseline immune reactivity may help to identify patients who will benefit the most from early treatment. Furthermore, we found that the expansion of tissue-resident NK cells and exhausted GZMK+ CD8+ T-cells at C9D1 of treatment is associated with significantly shorter PFS (p=0.039), suggesting that these immune biomarkers may help to monitor response to immunotherapy. Lastly, we found that patients would be classified the same way in terms of our immune biomarkers, had we assayed their peripheral blood instead of their bone marrow, suggesting that minimally invasive immune profiling for prognostication and monitoring may be feasible. **Conclusion:** We used single-cell RNA-sequencing to profile the immune microenvironment of patients with high-risk SMM in a Phase II trial of Elotuzumab, Lenalidomide and Dexamethasone and developed immune biomarkers of response to treatment. Our study may usher in a next generation of clinical assays that assess both tumor biology and immune state, as well as common clinical biomarkers, in the marrow or blood, to accurately predict who may benefit from early treatment, monitor response and improve patient outcomes.

POSTER PRESENTATIONS

P-001

Modulation of soluble B-cell maturation antigen levels in patients with relapsed and/or refractory multiple myeloma after treatment with teclistamab and talquetamab

Suzette Girgis[1], Shun Xin Wang Lin, Kodandaram Pillarisetti, Raluca Verona, Diego Vieyra, Tineke Casneuf[2], Damien Fink[1], Xin Miao[1], Yang Chen[1], Tara Stephenson[1], Arnob Banerjee[1], Brandi Hilder[1], Jeffery Russell[1], Jennifer Smit[1], Jenna Goldberg[3]

[1]Janssen R&D, Spring House, PA, USA; [2]Janssen R&D, Beerse, Belgium; [3]Janssen R&D, Raritan, NJ, USA

Background: B-cell maturation antigen (BCMA, CD269), a single transmembrane protein, can be shed as a soluble 6 kilodalton protein fragment (sBCMA) upon cleavage at the transmembrane domain by g[ED]-secretase. Given its selective expression in the B-cell lineage, BCMA is a validated target for multiple myeloma. Teclistamab and talquetamab are CD3 bispecific antibodies developed to recruit CD3+ T cells to BCMA+ or G protein-coupled receptor family C group 5 member D (GPRC5D)+ multiple myeloma (MM) cells, respectively. Levels of sBCMA after teclistamab or talquetamab treatment were evaluated in patients with relapsed and/or refractory MM (RRMM). **Methods:** Serum samples from patients with RRMM in teclistamab and talquetamab phase 1 studies (64007957MMY1001 and 64407564MMY1001, respectively) were collected at various timepoints between baseline and cycle 4 or end of treatment and analyzed for sBCMA by an electrochemiluminescence ligand binding assay. Quantitative analyses of sBCMA data were conducted with reference to a patient's tumor burden and response, and to pharmacokinetic data. **Results:** Teclistamab and talquetamab modulated levels of sBCMA in patients with high (≥50%) and low (<50%) frequency of tumor plasma cells (TPCs) and in high and low risk cytogenetic groups. In cycle 3, a majority of the responders showed sBCMA reductions (teclistamab: 88% [50/57]; talquetamab: 98% [49/50]) compared with baseline. In contrast, non-responders (progressive disease/ stable disease/ minimal response) showed an increase in sBCMA (teclistamab: 80% [33/41]; talquetamab: 49% [24/49]) compared with baseline. A higher magnitude of sBCMA reductions was noted in patients with deep responses. In a few patients who initially responded to teclistamab or talquetamab and then relapsed, sBCMA levels trended toward an initial reduction followed by an increase. Levels of sBCMA correlated with % bone marrow TPCs. A majority of patients with plasmacytoma (based on limited data) appeared to have high sBCMA levels, suggesting that sBCMA could be a comprehensive marker for tumor burden. Teclistamab preliminary population pharmacokinetic analysis showed that sBCMA did not appear to impact teclistamab exposure, suggesting that sBCMA does not act as a sink for teclistamab. **Conclusions:** Changes in the levels of sBCMA upon treatment with teclistamab

and talquetamab correlated with clinical activity, supporting further clinical development. The findings support BCMA as a potential surrogate marker of myeloma tumor burden and as a valuable marker for response in patients with MM.

P-002

Real-world observations and practical considerations of subcutaneous daratumumab administration in multiple myeloma

E. Bridget Kim[1], Elizabeth O'Donnell[1], Andrew Branagan[1], Jill Burke[1], Cynthia Harrington[1], Emerentia Agyemang[1], Noopur Raje[2], Andrew J. Yee[1]

[1]Massachusetts General Hospital; [2]Massachusetts General Hospital Cancer Center

Background: Subcutaneous daratumumab (dara-SC) has several advantages over intravenous daratumumab (dara-IV). It has significantly shorter administration time, lower rates of systemic reactions, and smaller administration volume, while maintaining comparable efficacy and safety. Its fixed dosing allows for easier preparation. At our institution, standard approach is to monitor for 4h following the initial dara-SC dose for those at high risk for systemic reactions, defined as no prior dara use, treatment break ≥90d, or any prior history of reactions. We also administer montelukast and fexofenadine for the first 2 doses of dara-SC in addition to the usual standard pre-medications. Herein, we share our experience with dara-SC use in both dara-naive and dara-exposed patients in order to gain practical insight, such as optimal monitoring duration, considerations for transitioning between dara-IV and dara-SC, and the place of therapy for dara-IV based on adverse events (AEs). **Methods:** Between June 2020 and June 2021, patients who received at least one dose of dara-SC were identified and their record was reviewed for any systemic reactions, hypersensitivity medication use, and patient reported AEs. **Results:** Since June 2020, our dara-SC drug use increased from 38% to 91% of all doses. There were 208 patients who received at least 1 dose of dara-SC. Of 208 patients, 99 (47.6%) were dara-naive and 109 (52.4%) had prior dara exposure – either transitioning from dara-IV on schedule or had dara-IV as a past line of therapy. We identified 124 patients who met the criteria for 4h post dara-SC injection monitoring: dara-naive (79.8%), treatment break ≥90d (18.5%), or prior history of reactions (1.6%). Only 5 experienced systemic reactions, representing 4% among those at high risk. All reactions were mild requiring minimal intervention and occurred following the first dara-SC dose. Onset of reactions and type of intervention during the 4h monitoring window were: hypotension (2h; fluid), nausea/vomiting (2.5h; hypersensitivity medications), and sinus tachycardia (4h), while 2 patients had transient chest pressure/tightness at home (1 within 24h, 1 between 1-6d following the dose). Eleven patients (5%) receiving dara-SC converted back to dara-IV, with AEs being the most common reason. Diarrhea, fatigue, and injection site reactions were among the most frequent patient-reported AEs. When transitioning back to dara-IV, a 90min rapid infusion rate was used if >4 prior dara doses were given. No infusion-related reactions were observed. **Conclusion:** The introduction of dara-SC has significantly improved patient experience. We observed a lower rate of systemic reactions compared to previous reports of 10% with first dose of dara-SC. This may be partly due to our strengthened pre-medication strategy. Opportunities exist to further improve and apply practical considerations when administering dara-SC. Based on our results, shortening on-site monitoring time may be feasible.

P-003

Improving NK cell function in Multiple Myeloma with NKTR-255, a novel polymer-conjugated human IL-15

Rafael Alonso Fernández[1], Laetitia Pierre-Louis[1], Yan Xu[1], Shidai Mu[2], Joaquín Martínez-López[3], Daniel Primo[4], Takahiro Miyazaki[5], Rao Prabhala[6], Kenneth Anderson[1], Willem Overwijk[5], Nikhil C. Munshi[7], Mariateresa Fulciniti[1]

[1]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Dana Farber Cancer Institute and VA Boston Healthcare System, Boston, MA, USA; [3]Hospital universitario 12 de Octubre; [4]Vivia Biotech, Madrid, Spain; [5]Nektar Therapeutics, San Francisco, CA, USA; [6]Dana Farber Cancer Institute; [7]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: Multiple myeloma (MM) is characterized by an immunosuppressive microenvironment that enables tumor development. One of the mechanisms of immune evasion used by MM cells is the inhibition of NK cell effector functions; thus, the restoration of NK cell antitumor activity represents a key goal for new immunotherapeutic approaches, increasing tumor cell recognition, avoiding tumor escape and potentially enhancing the effect of other drugs. **Methods:** Here we investigate the potential of NKTR-255, a novel polymer-conjugated human IL-15 to engage the IL-15 pathway and overcome the inhibitory status observed in NK cells from MM patients. For this purpose, we have analyzed ex vivo and in vivo effects of NKTR-255 on phenotypic features, effector functions and cytotoxicity of NK cells against MM cells. **Results:** We observed that incubation with NKTR-255 was able to tilt the balance towards an activated phenotype in NK cells isolated from peripheral blood mononuclear cells of MM patients, with increased expression of activating receptors (NKG2D, NKp46, NKp30, DNAM-1, CD69, TRAIL) on the surface of treated NK cells. This resulted in an enhanced degranulation, cytokine release and anti-tumor cytotoxicity when the NK cells were exposed to both MM cell lines and primary MM cells. For a more accurate assessment of the effect of NKTR-255 on NK cell activity in an autologous setting in the presence of the bone marrow (BM) milieu, we cultured whole BM samples from non-treated newly-diagnosed MM patients with increasing doses of NKTR-255 for 5 days. NK cells experienced a dose-dependent induction of proliferation and activation (as shown by increased expression of CD69 and NKG2D), which translated in

a reduced viability of CD138+ MM cells in the presence of NKTR-255. We further evaluated the in vivo effect of NKTR-255 in fully humanized immunocompetent mice subcutaneously engrafted with H929 MM cells. Compared to placebo, weekly injection of the mice with NKTR-255 increased the number of circulating NK cells in peripheral blood and delayed tumor growth. Finally, we also tested in vitro and in vivo efficacy of a combination of NKTR-255 with daratumumab. We observed a more efficient antibody-dependent cellular cytotoxicity against MM cells in vitro and decreased tumor growth in vivo, where NKTR-255 rescued CD38+ NK cell levels from depletion by daratumumab. **Conclusions:**Taken together, these results support the restoration and expansion of NK cell activity in MM with NKTR-255, providing rationale for its clinical use as a novel immunotherapeutic approach for MM patients alone or in combination with monoclonal antibodies or other immunomodulatory drugs.

P-004

Pharmacological inhibition and depletion strategies for SLAMF7 CAR-T cells in multiple myeloma

Sophia Danhof[1], Teresa Kilian[1], Anna Schmidt[1], Zeno Riester[1], Sabrina Prommersberger[1], Kersten Heyer[1], Verena Konetzki[1], Hermann Einsele[1], Michael Hudecek[1]

[1]University Hospital Würzburg

Background: Recent and soon-to-expect approvals have significantly increased the number of patients treated with CAR-T cells and clinical responses can be very impressive. However, side effects including cytokine storm, neurotoxicity or on-target/off-tumor toxicity can be challenging to manage. Further, malignant transformation of piggyBac modified CAR-T cells was recently reported in a phase I clinical trial as a potentially life threatening event. Reliable strategies to control or even deplete CAR-T cells are thus urgently needed. **Methods:** We generated SLAMF7 CAR-T cells as previously described and exposed the cells to clinically relevant doses of the following drugs: dexamethasone, fludarabine, mafosfamide, dasatinib, cetuximab, and belantamab-mafodotin. After defined time periods, we evaluated absolute numbers of CAR-T cells and their effector functions against myeloma cell lines (cytotoxicity, cytokine secretion, proliferation). Statistical analysis was performed using one-way ANOVA, followed by Dunnett's multiple comparisons test if appropriate. The study was approved by the local ethics committee. **Results:** Dexamethasone, used in the setting of severe CRS or ICANS, minimally decreased T cell numbers and cytokine release, but did not interfere with lytic capacity of the CAR-T cells. Fludarabine and the pre-activated cyclophosphamide analog mafosfamide, both drugs with potent lymphodepleting properties, significantly depleted numbers of CAR-T cells, reduced antigen-specific proliferation and led to an overall decrease in target cell elimination, even if specific lysis and cytokine release of the few surviving cells was preserved. Of note, fludarabine and mafosfamide similarly depleted unmanipulated T cells. Dasatinib, previously identified as a potent inhibitor of intracellular CAR signaling, had no impact on absolute T cell numbers, however lysis of myeloma cells, cytokine secretion and antigen-specific proliferation were entirely blocked. Evaluation of selective elimination of CAR-T cells with cetuximab, targeting the EGFR transduction marker of our CAR, showed modest CAR-T cell depletion in an ADCC assay. This was potentially related to competing natural killer cell elimination by the SLAMF7 CAR-T cells. To circumvent the problem of impaired ADCC, T cells were genetically engineered to express BCMA to enable simultaneous depletion of T cells and myeloma cells. Exposure to the BCMA-directed antibody-drug conjugate belantamab-mafodotin resulted in potent elimination of BCMA-positive T cells while unmanipulated cells were largely spared. **Conclusions:** In aggregate, our data show that the different drugs can have justification in different clinical settings of CAR-T cell toxicity. While dasatinib and dexamethasone mainly act on T cell function, fludarabine and mafosfamide effectively deplete T cells in an unselective manner. Targeted elimination of CAR-T cells with antibodies can be augmented further by the use of antibody-drug-conjugates.

P-005

Novel strategy of elotuzumab and zoledronic acid with Th1-like g[ED] d[ED]T cells against myeloma

Takeshi Harada[1], Yusuke Inoue[2], Hirofumi Tenshin[3], Asuka Oda[4], Ryohei Sumitani[1], Masahiro Oura[4], Kimiko Sogabe[4], Shiro Fujii[1], Shingen Nakamura[5], Hirokazu Miki[6], Masahiro Hiasa[3], Jumpei Teramachi[7], Masahiro Abe[4]

[1]Department of Hematology, Tokushima University Hospital; [2]Department of Laboratory Medicine, Tokushima University Hospital; [3]Department of Orthodontics and Dentofacial Orthopedics, Tokushima University Graduate School of Biomedical Sciences; [4]Department of Hematology, Endocrinology and Metabolism, Tokushima University Graduate School of Biomedical Sciences; [5]Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences; [6]Division of Transfusion Medicine and Cell Therapy, Tokushima University Hospital; [7]Department of Oral Function and Anatomy, Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University

Background: We are now in the new era of immunotherapies against multiple myeloma (MM) such as anti-CD38 and anti-SLAMF7 therapeutic monoclonal antibodies (mAbs); however, MM progression falls into attenuation and exhaustion of effector cells via immune checkpoint axes such as PD-1/PD-L1 and TIGIT/CD155, leading to hamper the clinical efficacy of these therapeutic mAbs. **Methods:** To overcome this issue, we have been studying the utilization of Vd[ED]2 g[ED]d[ED]T cells in peripheral blood mononuclear cells, which can be expanded and induced as Th1-like phenotype ex vivo using aminobisphosphonates in combination with IL-2, as effectors for MM treatment. The present study was aimed to develop the novel therapeutic strategies of g[ED]d[ED] T cells in combination with anti-MM mAbs. **Results:** The next

generation IMiDs, cereblon E3 ligase modulators (CELMoDs) of iberdomide and CC-92480 have been developed. CELMoDs was able to expand and activate g[ED]d[ED]T cells at much lower dose compared to IMiDs of lenalidomide and pomalidomide, in combination with zoledronic acid (ZA) ex vivo. Since the expanded Th1-like g[ED]d[ED]T cells highly expressed CD16, Fcg[ED]RIIIa without expression of checkpoint molecules such as PD-1, TIGIT, CTLA-4, and LAG-3, we next examined whether anti-MM mAbs, elotuzumab (ELO), daratumumab (DARA), and isatuximab (ISA), induced ADCC in the presence of the g[ED]d[ED]T cells. DARA and ISA did not induce cytotoxicity against CD38-expressing MM cells in the presence of the g[ED]d[ED]T cells; however, addition of ELO further increased cytotoxicity of the g[ED]d[ED]T cells against SLAMF7-expressing MM.1S and OPM-2 cells but not RPMI 8226 cells with marginal SLAMF7 expression, suggesting induction of ELO's ADCC with the g[ED]d[ED]T cells. We next examined the cytotoxic effect of the combinatory treatment on osteoclasts (OCs) because MM cells resides in the bone marrow and the interaction between MM cells and OCs forms vicious cycle of MM cell growth and bone destruction. Of note, OCs, which can be induced from monocytes using M-CSF and RANK ligand, highly expressed SLAMF7 along with elevation of NFATc1 transcription factor. Although the expanded g[ED]d[ED]T cells can target OCs, addition of ELO augmented the cytotoxic effect of g[ED]d[ED]T cells on OCs, suggesting the emergence of ELO's ADCC with Th1-like g[ED]d[ED]T cells towards OCs. As g[ED]d[ED]T cells recognize not only neoantigens but also phosphoantigens (pAgs), we treated MM cells and OCs with ZA to enhance the expression of pAgs, and g[ED]d[ED]T cells then incubated with the ZA-treated cells. ZA-stimulation augmented the cytotoxicity of g[ED]d[ED]T cells towards MM cells and OCs even in the presence of ELO. **Conclusions:** Taken together, our findings demonstrated the effective usage of ELO and Th1-like g[ED]d[ED]T cells with ZA against MM cells and ambient cells in MM bone marrow. Further study is warranted on the effective revitalization and expansion of Th1-like g[ED]d[ED]T cells using CELMoDs.

P-006

Expanded natural killer cells with daratumumab, lenalidomide and dexamethasone combination potentiates antimyeloma activity in a myeloma xenograft model

Je-Jung Lee[1], Jaya Lakshmi Thangaraj[2], Sung-Hoon Jung[3], Manh-Cuong Vo[2], Tan-Huy Chu[4], Minh-Trang Thi Phan[5], Duck Cho[6]

[1]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [2]Chonnam National University Hwasun Hospital, Hwasun; [3]Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [4]BioMedical Sciences Graduate Program, Chonnam National University; [5]Samsung Medical Center, Stem Cell & Regenerative Medicine Institute; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine

Background: Advances in the treatment of multiple myeloma (MM) significantly improved overall survival of patients. Nonetheless, MM still remains an incurable disease. This emphasizes urgent need for novel combination therapies for the treatment of MM. Recently, natural killer (NK) cells are becoming an attractive and safe tool in the field of immunotherapy. **Methods:** Here, we investigated how daratumumab, lenalidomide, and dexamethasone (DRd) treatment potentiate antitumor effects of NK cells in a MM xenograft mouse model. NK cells were expanded and activated using K562-OX40 ligand and membrane-bound IL-18 and IL-21 in the presence of IL-2 and IL-15 from peripheral blood mononuclear cells of MM patients. A human MM xenograft model was established using human RPMI8226-RFP-FLuc cells in NOD/SCID IL-2Rg[ED]null (NSG) mice. Tumor bearing mice were divided into six treatment groups: no treatment, expanded NK cells (eNK), Rd, Rd + eNK, DRd, and DRd + eNK. DRd treatment strongly enhanced the cytotoxicity of eNK by upregulating NK cell's activation ligands and effector function. **Results:** DRd combination with eNK significantly prolonged mouse survival and reduced MM progression and serum M-protein level. Moreover, DRd treatment significantly increased eNK persistence and homing into MM sites. **Conclusions:** Our findings suggest that DRd treatment augments the anti-myeloma effects of ex vivo expanded and activated NK cells by modulating immune responses in MM-bearing mice.

P-007

Exploring a safety switch in NKG2D and BCMA CAR NK-92MI immunotherapy

Elena Maroto Martín[1], Jessica Encinas[1], Almudena García-Ortiz[1], Eva Castellano[1], Laura Ugalde[2], Rafael Alonso[1], Alejandra Leivas[1], Mari Liz Paciello[1], Vanesa Garrido[1], Beatriz Martín-Antonio[3], Guillermo Suñe[3], Teresa Cedena[1], Daniel J. Powell Jr.[4], Paula Río[5], Joaquín Martínez-López[1], Antonio Valeri[1]

[1]Hospital universitario 12 de Octubre; [2]CIEMAT/CIBERER, Hematopoietic Innovative Therapies Division; [3]Hospital Clinic de Barcelona; [4]University of Pennsylvania, Department of Pathology and Laboratory Medicine; [5]2CIEMAT/CIBERER, Hematopoietic Innovative Therapies Division

Introduciton: Despite impressive preliminary efficacy of CAR-T cells in multiple myeloma (MM), NK cell engineering has emerged as a competitive and safer approach, as they entail an 'off-the-shelf' strategy with no graft-versus-host disease. NK-92 is a universal, cheap and fast obtainable cellular therapy previously used in clinical trials. Although modest responses with these cells have been reported in MM, their oncolytic potential can be enhanced by genetic modification. However, there are still reasonable doubts about the efficacy of irradiated NK-92 cells used in clinic. Thus, the aim of our study is to generate a safe and effective CAR NK-92 immunotherapy for MM treatment. **Methods:** NK-92MI cells were transduced with a lentiviral vector expressing NKG2D or BCMA CAR. Single and dual CARs were generated, with same or different

combinations of costimulator domains. CAR NK-92MI cells expressing a safety switch were generated by retroviral transduction with an SFGiCasp9.2A.D[ED]CD19 construct. All populations were purified by FACS sorting to obtain stable modified effectors. In vitro antitumor activity was analyzed against low and high target ligands expressing MM cell lines: U266, similar expression of both BCMA and NKG2DL; XG-1, BCMAhigh and NKG2DLlow; as well as a BCMA knock-out cell line generated by CRISPR-Cas9 system. For in vivo experiments, NSG mice were intravenously injected with 1×10^6 U266 ffLuc-GFP cells. 5×10^6 CAR NK-92MI cells were i.v. administered 48h later, once a week for three weeks. **Results:** CAR NK-92MI cells showed specificity and higher in vitro antitumor activity compared to parental NK-92 cells, as well as lack of hematotoxicity. The combined expression of both NKG2D and BCMA CAR has demonstrated cytotoxic coverage against MM cell lines. In vivo, clinical 10 Gy irradiation dose completely abrogate the efficacy of CAR NK-92 cells in our treatment schedule. Besides, lower irradiation doses are not enough to eliminate NK cells. In order to obtain a safe allogeneic immunotherapy, CAR NK-92MI cells expressing a suicide gene therapy have been generated (99.9% purity) being susceptible to death (near 99% death) upon induction with Rimiducid (AP1903). Currently, iCasp9-CD19 CAR NK-92MI cells are being tested in vivo. **Conclusions:** CAR NK-92MI effectors expressing single and dual CARs have been generated and they all show higher in vitro antitumor efficacy against different MM targets compared to parental NK-92MI cells. In vivo experiments show the inefficacy of irradiated CAR NK-92MI cells as therapeutic strategy in our MM model, leading to the necessity of a combination with a safety switch to ensure an effective and safe off-the-shelf NK immunotherapy for MM treatment.

P-008

First report of a patient with systemic light chain amyloidosis in the course of Multiple Myeloma treated with CAR T cells directed against B-cell maturation antigen

Aina Oliver Caldés[1], Raquel Jiménez[1], Marta Español-Rego[1], MT Cibeira[2], Luis F Quintana[1], Paola Castillo[1], Francesca Guijarro[1], Natalia Tovar[1], Mercedes Montoro-Lorite[1], Daniel Benítez-Ribas[1], Alex Bataller[1], Joan Cid[1], Lorena Perez-Amill[3], Beatriz Martin-Antonio[4], Mari Pau Mena[3], David Moreno[5], Luis Gerardo Rodríguez-Lobato[1], Josep maria Campistol[1], Gonzalo Calvo[1], J Bladé[2], Laura Rosiñol[2], Manel Juan[1], Mariona Pascal[1], Álvaro Urbano-Ispizua[1], C Fernández De Larrea[2]

[1]Hospital Clinic de Barcelona; [2]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [3]IDIBAPS; [4]Fundación Jiménez Díaz; [5]Hospital Clinic de Barcelona, IDIBAPS

Background: Multiple myeloma (MM) remains incurable despite the number of novel therapies that have become available in recent years. Occasionally, a patient with MM will develop a light-chain (AL) amyloidosis due to the deposition of amyloidogenic light chains causing organ dysfunction. Chimeric antigen receptor T-cell (CART) therapy has become the most promising approach in treating cancer patients, especially hematologic malignancies. Our institution has developed a second-generation B-cell maturation antigen (BCMA) CART which is currently being tested in a clinical trial for relapsed/refractory MM. **Methods:** A 61-year-old woman diagnosed with an IgA-lambda symptomatic MM in 2014, with several prior lines of treatment presented with edema and significant non-selective albuminuria (24-hour proteinuria of 2626 mg with urinary M-protein of 307 mg, serum albumin 28 g/L) with preserved renal function (creatinine 0.6 mg/dL) and an increase in serum M protein, with a bone marrow (BM) infiltration by 23% plasma cells. There was no evidence of extramedullary disease by PET-CT and no CRAB signs were found. A subcutaneous fat aspiration and a renal biopsy established the diagnosis of systemic AL amyloidosis without cardiac involvement. At this point AL amyloidosis was the main reason to treat the patient, who received a fractioned dose of 3×10^6/kg BCMA-CAR T cells after lymphodepletion, developing a grade I cytokine release syndrome and treatment-related cytopenias (grade 4 neutropenia and grade 2 thrombocytopenia), with no neurotoxicity. **Results:** On day +28, the patient had already obtained a deep hematologic response with negative measurable residual disease by flow cytometry in the BM. After 3 months, the patient maintained the hematologic complete response and achieved renal response. After 1 year follow-up, the patient remains in hematologic complete remission and renal response with a decrease in proteinuria of 70%. **Conclusions:** Here, we present the first reported case, to our knowledge, of a patient with AL amyloidosis and renal involvement in the course of a MM, successfully treated with CART therapy targeting BCMA. This case suggests that concomitant AL amyloidosis in the setting of MM can benefit from CART therapy, even in patients in which predominant symptoms at the time of treating are caused by AL amyloidosis.

P-009

Assessing the predictive utility of hematologic response for overall survival in patients with newly diagnosed AL amyloidosis: a systematic literature review and meta-analysis

Efstathios Kastritis[1], Arpit Misra[2], Laura Gurskyte[2], Florint Kroi[2], Jessica Vermeulen[3], Eric Ammann[4], Annette Lam[4], Sarah Cote[4], Ashutosh Wechalekar[5]

[1]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece; [2]Ingress Health; [3]Janssen Research & Development, LLC, Leiden, The Netherlands; [4]Janssen Global Services, LLC; [5]National Amyloidosis Centre

Background: Amyloid light-chain (AL) amyloidosis is a rare disease characterized by amyloid fibril deposits made up of toxic light chains causing organ dysfunction and death. Prompt treatment

is crucial to achieve deep hematologic responses, reverse organ damage, and improve overall survival (OS). Recent published studies suggest that hematologic response may be an important predictor of OS in AL amyloidosis. Here, we report the results of a meta-analysis evaluating the association between hematologic complete response (CR) and OS and very good partial response or better (≥VGPR) and OS in patients with newly diagnosed AL amyloidosis. **Methods:** A systematic literature review (SLR) was conducted in November 2020 to identify all randomized controlled trials (RCTs) and comparative observational studies in patients with newly diagnosed AL amyloidosis. Databases were searched for articles published in English in August 2005 or later. Quality assessments were conducted and a feasibility assessment identified studies to include in the meta-analysis. Studies that reported OS hazard ratios (HRs) stratified by hematologic response were included in the analysis. If HRs were not reported, survival curves were digitized, and individual survival and censoring times were reconstructed using an algorithm by Guyot (2012). For curves with missing at-risk patient numbers, individual data were reconstructed manually. Heterogeneity was assessed using the I^2 test and a random effects model was used. Statistical analysis was performed using STATA v16.1. **Results:** The SLR yielded a total of 52 studies (4 RCTs and 48 observational studies). Eight of the 52 studies reported data on hematologic response and OS and were eligible for inclusion in the meta-analysis; of these, 5 reported OS stratified by hematologic CR status and 3 reported OS stratified by ≥VGPR status. The meta-analysis showed that achieving hematologic CR was associated with improved OS (HR, 0.18; 95% confidence interval [CI] 0.13–0.25). The I^2 statistic was 0%, indicating a high degree of consistency across studies and that the heterogeneity observed across studies could be explained by sampling variability alone. Achieving ≥VGPR was also associated with improved OS (HR 0.16; 95% CI 0.09–0.28; I^2 0%). **Conclusion:** The meta-analysis revealed that in patients with newly diagnosed AL amyloidosis, achieving hematologic CR or ≥VGPR was associated with significantly improved OS and substantially decreased the risk of death. Potential limitations include the small number of RCTs (consistent with the rarity of the disease) and inconsistent reporting of results. Overall, these results support the use of deep hematologic response (CR or ≥VGPR) as an endpoint in studies of treatment for patients with newly diagnosed AL amyloidosis. Structured data collection of depth of response in future RCTs will further strengthen these observations.

P-010

An economic model to establish the costs associated with routes of presentation for patients with Myeloma in the UK

Alex Porteous[1], Scott Gibson[2], Lucy Eddowes[1], Mark Drayson[3], Guy Pratt[4], Hannah Parkin[5], Suzanne Renwick[5], Ira Laketic-Ljubojevic[5], Debra Howell[6], Alexandra Smith[6], Simon Stern[7]

[1]Costello Medical, London, UK; [2]Coreva Scientific GmbH & Co KG, Königswinter, Germany; [3]Institute of Immunology and Immunotherapy, University of Birmingham, Edgbaston, Birmingham, UK; [4]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [5]Myeloma UK, Edinburgh, UK; [6]Department of Health Sciences, University of York, York, UK; [7]Epsom & St Helier University Hospitals NHS Trust, UK

Background: Patients with myeloma often face significant diagnostic delay, with over a quarter of patients in the UK diagnosed following emergency presentation (EP) [1]. Compared with other presentation routes, patients presenting as an emergency have more advanced disease, increased complications and poorer prognosis. **Methods:** An economic model was developed using a decision-tree framework and a lifetime time horizon to estimate costs related to presentation routes (EP, general practitioner [GP] suspected cancer referral with a maximum two-week wait [TWW], GP urgent, GP routine and consultant-to-consultant, categorised by Howell et al [2017] [1]) for patients diagnosed with myeloma in the UK. Following diagnosis, patients received one of three first-line management options (observation, active treatment with anti-myeloma drugs, or end-of-life [EOL] care). Those receiving observation were assumed to have a diagnosis of smouldering myeloma but could progress to active myeloma and receive active treatment. Inputs were derived from UK health technology assessments, targeted literature reviews, or based on authors' clinical experience where data were unavailable. Active treatment (drug acquisition, administration, adverse event and monitoring for several treatment lines), complication and EOL care costs were included. The model took a UK National Health Service and personal social service perspective. **Results:** The average, undiscounted, per patient cost of treating myeloma (across all routes) was estimated at £168,000. The average per patient cost associated with EP (£174,987) was higher than for other routes (£151,370–£170,371). Complication and EOL care costs were higher for EP (£56,091) than other routes (£36,987–£49,844). Active treatment at diagnosis comprised 94% of total treatment costs for EP, versus 64–78% for other routes. For EP, 5% of total treatment costs were attributed to patients who received initial observation, but progressed to active disease and received treatment, whilst for other routes this ranged from 20–35%. In the absence of data, active treatment was modelled identically for patients receiving active treatment at diagnosis or after initial observation, thus total treatment costs were similar across routes. Should initial observation impact subsequent active treatment (e.g. duration of treatment-free intervals), total treatment costs may differ between EP and other routes. **Conclusions:** An economic benefit may be associated with earlier diagnosis, gained via reduced complication and EOL care costs, with a difference of £19,104 per patient observed between EP and the GP routine route. The impact of initial observation on subsequent active treatment remains a key data gap. **Reference:** [1] Howell D. Br J Haematol 2017;177:67-71. **Acknowledgements:** This research was conducted free-of-charge on a pro bono basis by Costello Medical.

P-011

18F-FDG PET/MRI for imaging minimal residual disease evaluation in Multiple Myeloma

Gregorio Barilà[1], Filippo Crimi'[2], Susanna Vedovato[1], Massimiliano Arangio Febbo[1], Antonio Maroccia[1], Laura Pavan[1], Giulio Cabrelle[2], Chiara Zanon[2], Cristina Campi[3], Pietro Zucchetta[1], Carmelo Lacognata[2], Gianpietro Semenzato[1], Renato Zambello[5]

[1]Department of Medicine (DIMED), Hematology and Clinical Immunology, Padova University School of Medicine; [2]Department of Medicine (DIMED), Institute of Radiology, Padova University School of Medicine; [3]Department of Mathematics Tullio Levi-Civita, Padova University School of Medicine; [4]Department of Medicine (DIMED), Nuclear Medicine Unit, Padova University School of Medicine; [5]European Myeloma Network, Italy

Background: Functional imaging in Multiple Myeloma (MM) plays a crucial role in defining bone disease response. According to IMWG guidelines,18FDG PET/CT represents the only technique recognized to define imaging minimal residual disease (MRD) negativity. More recently, Whole body Diffusion Weighted Imaging (WB DWI)-MRI represents a non ionizing radiation imaging modality with a potential impact on evaluating myeloma bone disease response. Consequently, patients achieving both PET/CT and WB DWI-MRI negativity after treatment showed improved progression free survival (PFS) as compared to patients with single PET or MRI negativity. In the last years, a novel functional technique combining both 18FDG PET with WB DWI-MRI (PET/MRI) has been developed. In this study, we evaluated PET/MRI for bone disease response assessment in MM. **Methods:** We retrospectively studied 27 patients (12 female and 15 male) affected by newly diagnosed active MM. All patients received a combined 18F-FDG PET/MRI registering T1w signal, T2w STIR (short tau inversion recovery) signal, DWI (diffusion weighted imaging) signal, mean ADC (apparent diffusion coefficient) value and SUV (standardized uptake volume) max value at diagnosis and at the end of the therapeutic program [after autologous stem cell transplantation (ASCT) or consolidation treatment]. PET and MRI negativity was assessed using Deauville score (DS) and MY-RADS Response Assessment Category (RAC). Median age of the entire cohort was 57 years (44-69). Considering high risk disease features, 7/27 cases were ISS III (25.9%), 2/27 were R-ISS III (7.4%) while 7/26 (26.9%) patients harbored high risk FISH abnormalities [including t(4;14), t(14;16) and del17p]. Bone lytic lesions were detected in almost all patients (24/27, 88.9%), followed by anemia (17/27, 63%), hypercalcemia (3/27, 11.1%) and renal injury (2/27, 7.4%). All patients received bortezomib-thalidomide-dexamethasone induction regimen followed by ASCT. **Results:** At the end of the therapeutic program, the overall response rate was 92.6%, with 37% (10/27) achieving a complete response. Regarding baseline PET/MRI evaluation, focal lesions (FLs) were detected in 23 patients, with mean SUVmax of 4.4+/-2.78 and mean ADC of 963+/-264.6 mm2/s. End of treatment PET/MRI showed a PET negativity (DS<3) in 14/27 (51.9%) patients and an MRI negativity (MY-RADS<2) in 18/27 (66.7%) cases. With a median follow up of 33 months, patients with concomitant PET and MRI negativity showed improved PFS with respect to patients with PET or MRI positivity (not reached vs 58 months, p=0.0396). By multivariate analysis, concomitant PET and MRI negativity was associated with better PFS independently from ISS and FISH (p=0.0472). **Conclusions:** To our knowledge, this is the first study evaluating PET/MRI for bone disease response in MM. Our data provide evidence that PET/MRI represents a promising tool for imaging MRD negativity evaluation, with patients being both PET and MRI negative showing improved PFS.

P-012

Automatic bone marrow segmentation in whole-body magnetic resonance imaging: towards comprehensive, objective MRI-phenotypic bone marrow characterization in multiple myeloma

Markus Wennmann[1], Jiri Chmelik[2], Fabian Bauer[1], André Klein[2], Charlotte Uhlenbrock[1], Jakob Lochner[1], Martin Grözinger[1], Lukas Rotkopf[1], Sandra Sauer[3], David Bonekamp[1], Jens Kleesiek[4], Tim Weber[5], Jens Hillengass[6], Hartmut Goldschmidt[3], Heinz-Peter Schlemmer[1], Ralf Floca[2], Niels Weinhold[7], Klaus Maier-Hein[2], Stefan Delorme[1]

[1]Division of Radiology, German Cancer Research Center, Heidelberg, Germany; [2]Division of Medical Image Computing, German Cancer Research Center, Heidelberg, Germany; [3]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; [4]Institue for Artificial Intelligence (IKIM), University Hospital Essen, Germany; [5]Deparment of diagnostic and interventional Radiology, University Hospital Heidelberg; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Background: Whole-body magnetic resonance imaging (wb-MRI) is an important diagnostic tool for staging, risk assessment and response evaluation in myeloma. Wb-MRIs contain approximately 110 million voxels per sequence, and only a limited amount of this information can be processed and reported by radiologists to date. Deep learning has brought striking advances in biomedical image segmentation in recent years. The goal of this work was to establish an automatic whole-body bone marrow (BM) segmentation algorithm for T1-weighted MRI sequence, and to use these segmentations for comprehensive MRI-phenotypic characterization of the BM by subsequent radiomics analysis, bone by bone. **Methods:** For 66 patients with smoldering multiple myeloma (SMM), BM was manually segmented on T1-w images. Thirty different BM compartments were individually labelled: right and left humerus, second to seventh vertebral bodies of the cervical spine (C2-C7), all vertebral bodies of the thoracic (T1-T12) and lumbar (L1-L5) spine, sacrum, right and left hip bone and right and left femur. Data was

split by date by a 3:1 ratio into training-set and independent test-set. A nnU-Net, which is state of the art deep learning framework for medical image segmentation, was trained on the 52 training cases for segmentation of BM compartments, and postprocessing was used to distinguish sides of paired bones (humeri, hip bones, femora). Mean Dice scores report accuracy of automatic segmentations on the test-cases and interrater variability between two radiologists. This study was approved by the institutional review board. **Results:** The mean Dice scores of the nnU-Net segmentation on the 14 test-cases for BM of right and left humerus, C2-C7, T1-T12, L1-L5, sacrum, right and left hip bone, right and left femur were 0.95, 0.94, 0.87, 0.86, 0.84, 0.80, 0.82, 0.84, 0.86, 0.87, 0.88, 0.91, 0.85, 0.85, 0.83, 0.83, 0.87, 0.91, 0.93, 0.93, 0.89, 0.85, 0.85, 0.81, 0.76, 0.88, 0.93, 0.93, 0.97 and 0.97, respectively. The mean Dice scores between segmentations from 2 radiologists on 2 cases for these BM compartments in the same order were 0.94, 0.95, 0.79, 0.86, 0.88, 0.81, 0.78, 0.79, 0.84, 0.81, 0.91, 0.85, 0.89, 0.90, 0.91, 0.91, 0.92, 0.90, 0.90, 0.89, 0.88, 0.92, 0.93, 0.88, 0.88, 0.81, 0.89, 0.89, 0.95, 0.94, respectively. On a descriptive level, we found differences in radiomics signatures between vertebrae with physiological bone marrow, vertebrae with focal lesions and vertebrae with diffuse infiltration in exemplary cases. **Conclusion:** We established automatic, bone by bone BM segmentation in SMM patients with accuracy only slightly worse compared to the interrater variability of radiologists, mostly due to lumbosacral transitional vertebra. In exemplary cases we found different radiomics-signatures between physiological BM and different pathologies, indicating that such BM segmentations can be used for in depth BM characterization from wb-MRI when combined with subsequent radiomics analysis.

P-013

Development of a new risk stratification system for patients with newly diagnosed multiple myeloma using R-ISS and 18F-FDG PET/CT

Juhyung Kim[1], Jung Min Lee[1], Hee Jeong Cho[1], Sung-Hoon Jung[2], Ho-Jin Shin[3], Yeung-Chul Mun[4], Ho Sup Lee[5], Chang-Ki Min[6], Kihyun Kim[7], Je-Jung Lee[8], Joon Ho Moon[9], Sung-Soo Park[10]

[1]Kyungpook National University Hospital; [2]Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [3]Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea; [4]Ewha Womans University School of Medicine; [5]Kosin University Gospel Hospital; [6]Department of Hematology, Seoul St Mary's Hospital, Seoul, Republic of Korea; [7]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [8]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [9]Division of Hematology-Oncology, Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; [10]"Division of Hematology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea"

Background: A high number of focal lesions (FL) detected using PET/CT at diagnosis were found to be associated with adverse prognosis along with Revised International Staging System (R-ISS). In present study, we combined R-ISS with FL using PET/CT to design a reliable and easily applicable risk stratification system in patients with newly diagnosed MM (NDMM). **Methods:** In training cohort, the data of 380 patients with NDMM who underwent 18F-fluorodeoxyglucose (18F-FDG) PET/CT upon diagnosis from 10 hospitals of the Korean Multiple Myeloma Working Party were retrospectively analyzed. All patients were classified by R-ISS and were treated by frontline therapy with proteasome inhibitors (PI) and/or immunomodulatory drugs (IMiD). The K-adaptive partitioning algorithm was adopted to develop the new risk groups with homogeneous survival. Sixty-seven patients in external validation cohort were additionally collected to confirm reproducibility of the new risk groups. **Results:** In the training cohort, 199 patients (52.4%) showed FL > 3 using PET/CT at diagnosis. R-ISS stages I, II, and III were 78 patients (20.5%), 230 (60.5%), and 72 (18.9%), respectively. The combined R-ISS with PET/CT newly allocated NDMM patients into four groups: R-ISS/PET stage I (n=30; R-ISS I with FL≤3), stage II (n=149; R-ISS I with FL>3 and R-ISS II with FL≤3), stage III (n=166; R-ISS II with FL>3 and R-ISS III with FL≤3), and stage IV (n=35; R-ISS III with FL>3). The new R-ISS/PET showed significantly pronounced survival differences according to stages. Two-year overall survival (OS) rates were 96.6%, 89.5%, 75.0%, and 57.9% ($p < 0.001$), and 2-year progression-free survival (PFS) rates were 86.9%, 65.1%, 41.9%, and 15.2% ($p < 0.001$) in stages I, II, III, and IV, respectively. The prognostic role of the R-ISS/PET for survival outcomes was also confirmed in different subgroups classified by transplant eligibility and by types of treatments. In the external validation cohort, the new R-ISS/PET was successfully implemented. Two-year OS rates for were 100%, 89.9%, 82.6%, and 42.0% for R-ISS/PET I, II, III, and IV, respectively ($p = 0.001$). PFS rates at 2 years for each R-ISS/PET were 100%, 74.5%, 57.9%, and 25.6%, respectively ($p = 0.004$). **Conclusion:** The new R-ISS/PET had a remarkable prognostic power for estimating the survival outcomes of patients with NDMM. This system helps discriminate patients with a good prognosis from those with a poor prognosis more precisely.

P-014

Disruption of chromosome territories in Multiple Myeloma

Matheus Fabiao de lima[1], Sabine Mai[1], Aline Rangel Pozzo[1]

[1]University of Manitoba

Background: Multiple Myeloma (MM) is the second most frequent hematologic neoplasm worldwide. MM is currently an incurable disease. MM displays an irregular pattern of gene expression, chromosome alterations and changes in chromosome positioning (relatively to normal plasma cells), which contributes to

genomic instability and the heterogeneous phenotype of individual cells observed in MM. Lamin A/C is a nuclear protein that has been shown to play a critical role in the maintenance of genomic stability and nuclear genome architecture. Recently, our group observed that the expression of lamin A/C was upregulated in MM human cell line (MM.1R) and, importantly, in ten primary treatment-naive MM patient samples. Moreover, the lamin A/C protein was found to exhibit an altered 3D spatial organization. Objective: To investigate the role of lamin A/C on nuclear chromosome organization in MM. **Methods:** The expression of lamin A/C in two MM cell lines (MM1R and RPMI 8226) was confirmed by western blot (WB) and quantitative immunofluorescence (qIF) analysis. qIF confirmed aberrant 3D lamin A/C protein organization. To evaluate changes in CT, we used whole chromosome painting probes and 3D fluorescence in situ hybridization (FISH) followed by our published quantitative analysis (ChromoView) for chromosomes 4, 9, 11, 14, 16, 18, 19 and 22. We observed differences in CT of chromosomes 9, 16, 18 and 22 towards the nuclear center, CT-19 towards the nuclear periphery in MM.1R and CT-4,9,11,14,18,19, and 22 towards the nuclear periphery in RPMI 8226, all compared to control (B-lymphocytes). To evaluate the role of lamin A/C in affecting CT positions, we downregulated lamin A/C protein levels using two different short interfering RNAs (siRNA), for different regions of lamin A/C mRNA, as well as scrambled siRNA. **Results:** Following siRNA but not scrambled siRNA, WB and quantitative image analysis showed for RPMI8226 that lamin A/C protein level was reduced up to ~25% of the endogenous levels at 72-96 hours after transfection, using both siRNAs separately and in combination. After siRNA treatment, we evaluated the effects of lamin A/C downregulation in chromosome positioning. The CT analysis revealed changes in CT4,9,11,14,16,18, and 22 towards the nuclear centre and CT-19 towards the nuclear periphery ($p<0.05$). Interestingly, we found that during lamin A/C downregulation, CT-11,18 and 22 positions in RPMI 8226 returned to the same nuclear distance as observed in lymphocytes. **Conclusions:** Lamin A/C plays a role in genome organization and chromosome positioning. Its disruption alters chromosome positions as described here for the first time. Future investigations will clarify whether these changes affect cell viability, which would suggest that lamin A/C disruption could, in the future, be explored therapeutically for MM.

P-015

Is it time to revisit role of PET-CT imaging and its integration with other parameters in International Myeloma Working Group (IMWG) response assessment criteria?

Jayant Narang[1], Surabhi Bajpai[1], Shweta Narang[1], Katarina Ludajic[1], Kimberely Fernandes-Thomas[1], Zsolt Somodi[1], Arvin Kheterpal[2], Joseph Mikhael[3]

[1]Calyx; [2]Massachusetts General Hospital; [3]International Myeloma Foundation

Background: The landscape of imaging in multiple myeloma has changed drastically since the publication of IMWG 2016 criteria. 18 F-FDG PET-CT (PET-CT) is being used more frequently, for staging, prognosis and clinical decision making. PET-CT is useful for both morphological and the metabolic activity of the plasma cells to predict and monitor clinical response. Studies have shown that subjects who achieved complete response by hematologic criteria but have PET positive lesions have poorer outcome. PET-CT has high sensitivity and specificity for detecting all lesions types. PET negativity has been equated to Minimal residual disease (MRD) negativity, and hence role of both positive and negative PET in IMWG response assessment need to be better defined. Until now extramedullary disease (EMD) and plasmacytoma evaluation have been the focus of response assessment in IMWG, although plasmacytoma is a histological, not an imaging diagnosis. Paramedullary lesions (lytic bone lesions with extraosseous soft tissue component), intramedullary lesions (soft tissue lesions in the medullary cavity) as well as pure lytic bone lesions have not been fully included in the evaluation. There is a need to better define various lesions and disease presentations seen on imaging in myeloma and their role in overall response. Additionally, role of different imaging modalities in clinical trials as well as a standardized imaging schedule, based on the presence of baseline disease burden, should be defined. The purpose of this study is to define and incorporate the imaging manifestations of myeloma of PET-CT into the IMWG criteria. A standardized PET-CT assessment approach is lacking in IMWG 2016, although Italian Myeloma Criteria for PET Use (IMPeTUs), has described PET-CT evaluation in detail, including the cut off for positivity and negativity, aligning it to 5-point Deauville Scoring (5PS). This study will also highlight the importance of PET-CT as a modality of choice in myeloma and provide a standardized methodology to integrate PET in overall assessment. We propose that myeloma lesions should be assessed in two broad categories, target (measurable) and non-target (non-measurable) lesions. Targets should include up to a total of six extramedullary and/or paramedullary lesions. Non-target lesions should include any additional measurable lesions, other soft tissue and bone lesions characteristic of myeloma, which do not meet criteria for target lesions. The status of these lesions along with any new lesions will drive an overall anatomical response. For PET-CT assessments, 5PS should be followed with liver as comparator for positivity. Metabolic responses like Complete metabolic response(CMR) etc. should be derived. An integrated imaging response can then be combined with clinical parameters to provide an overall IMWG response. This proposed guidance will help standardize integration of PET imaging in IMWG response assessment more efficiently and consistently across trials.

P-016

The role [18F]-(2S,4R)-4-Fluoroglutamine as a new positron emission tomography tracer in Myeloma in vivo models.

Denise Toscani[1], Silvia Valtorta[2], Martina Chiu[3], Andrea Sartori[4], Angela Coliva[5], Arianna Brevi[6], Giuseppe Taurino[7], Matteo Grioni[8], Livia Ruffini[9], Federica Vacondio[10], Franca Zanardi[11],

Matteo Bellone[12], Rosa Maria Moresco[13], Ovidio Bussolati[14], Nicola Giuliani[15]

[1]Department of Medicine and Surgery, University of Parma, Parma, Italy; [2]Department of Medicine and Surgery and Tecnomed Foundation, University of Milan Bicocca, Milano, Italy; [3]Department of Medicine and Surgery, University of Parma, Parma, Italy; [4]Department of Food and Drug, University of Parma, Parma, Italy; [5]Department of Nuclear Medicine, San Raffaele Scientific Institute, IRCCS, Milano, Italy; [6]Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, IRCCS, Milano, Italy; [7]Department of Medicine and Surgery, University of Parma, Parma, Italy; [8]Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, IRCCS, Milano, Italy; [9]Nuclear Medicine, "Azienda Ospedaliero-Universitaria di Parma", Parma, Italy; [10]Department of Food and Drug, University of Parma, Parma, Italy; [11]Department of Food and Drug, University of Parma, Parma, Italy; [12]Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, IRCCS, Milano, Italy; [13]Department of Medicine and Surgery and Tecnomed Foundation, University of Milan Bicocca, Milano, Italy; [14]Department of Medicine and Surgery, University of Parma, Parma, Italy; [15]Department of Medicine and Surgery, University of Parma, Parma, Italy

Background: The high glycolytic activity of multiple myeloma (MM) cells is the rationale for use of Positron Emission Tomography (PET) with 18F-fluorodeoxyglucose ([18F]FDG) to detect both bone marrow (BM) and extramedullary disease. However, FDG-PET has some limitations, since there is a portion of MM patients who are negative, and new tracers are actively searched. Glutamine (Gln) addiction has been recently described as a peculiar metabolic feature of MM cells. Yet, the possible exploitation of Gln as a PET tracer in MM has never been assessed thus far and is investigated in this study. **Methods:** We have firstly synthesized enantiopure (2S,4R)-4-fluoroglutamine (4-FGln) and validated it as a Gln transport analogue in human MM cell lines, comparing its uptake with that of 3H-labelled Gln. We then radiosynthesized of [18F]4-FGln and tested its uptake for MM detection by PET in two different murine models and we checked the effect of Bortezomib treatment. **Results:** Both [18F]4-FGln and [18F]FDG clearly identified the spleen as site of MM cell colonization in C57BL/6 mice challenged with syngeneic Vk12598 cells and assessed by PET. NOD.SCID mice subcutaneously injected with human MM JJN3 cells, showed high values of both [18F]4-FGln and [18F]FDG uptake to T/M: 2.3 ± 0.3 and 7.1 ± 2.6, respectively. With both [18F]4-FGln and [18F]FDG radiotracers, BOR treated animals displayed Standard Uptake Values (SUV) mean values significantly lower than controls at post treatment PET. However, [18F]4-FGln better correlated with the tumour volume in NOD.SCID mice, and a reduction of glutaminolytic, but not of glycolytic, tumour volume was evident in mice showing the highest response to Bortezomib. **Conclusion:** Our data indicate that [18F](2S,4R)-4-FGln is a new PET tracer in pre-clinical MM models, yielding a rationale to design studies in MM patients.

P-017

Repeatability and reproducibility of apparent diffusion coefficient measurements of bone marrow in magnetic resonance imaging of multiple myeloma patients

Markus Wennmann[1], Heidi Thierjung[1], Fabian Bauer[1], Martin Grözinger[1], Thomas Hielscher[2], Vivienn Weru[2], Regula Gnirs[1], Sandra Sauer[3], Hartmut Goldschmidt[3], Niels Weinhold[4], David Bonekamp[1], Heinz-Peter Schlemmer[1], Tim Weber[5], Stefan Delorme[1], Lukas Rotkopf[1]

[1]Division of Radiology, German Cancer Research Center, Heidelberg, Germany; [2]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; [4]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [5]Deparment of diagnostic and interventional Radiology, University Hospital Heidelberg

Introduciton: Diffusion weighed imaging (DWI) within whole-body magnetic resonance imaging (wb-MRI) is now recommended for imaging of patients with monoclonal plasma cell disorders, and quantitative ADC measurements are of high relevance for reading and reporting of wb-MRIs. However, the evidence on repeatability and especially on multicentric reproducibility of ADC measurements of the bone marrow (BM) is very limited. The goal of this study was to quantify interrater-variability, repeatability and reproducibility of ADC measurements under variation of MRI scanners and MRI sequences. **Methods:** Fifty-five patients were prospectively included in this IRB-approved prospective study and underwent multiple scans in different settings within a maximum of 3 days between the scans. A standard scan (clinical 1.5T-MRI scanner, standard MRI-protocol) of the pelvic bone marrow was performed. Additionally, several measurements were performed: First, a retest after new positioning of the patient (same 1.5T scanner, same protocol, i.e., repeatability; n=37 paired scans). Second, retest at the same scanner but with different MRI protocol (n=37 paired scans). Third, retest at another 1.5T scanner with a harmonized MRI protocol to the initial setting (n=34 paired scans). Fourth, retest at another scanner with different field strength of 3T (n=40 paired scans). For measurement of ADC, one radiologist manually placed regions of interest (ROI) in a representative area of BM at the posterior iliac crest and a ROI in representative muscle tissue in the same slice. A second rater independently performed a second read of the standard scan. The Bland-Altman-approach was used to assess agreement of the different settings and mean bias, limits of agreement (LoA) and coefficients of variation (CoV) were calculated. **Results:** Absolute bias / relative bias to mean / CoV of ADC measurements for the different retest measurements compared to the standard-scan were as follows: interrater setting -37.9mm^2 s^{-1}/-0.077/15.8%, repeatability -13.0mm^2 s^{-1}/-0.027/14.5%, second protocol -205.1mm^2 s^{-1}/-0.357/33.5%, second 1.5T scanner 5.8mm^2 s^{-1}/0.013/17.0%, 3T

scanner 146.8mm^2 s^{-1}/0.371/41.3%. Normalization to muscle tissue did not improve the high relative bias of the second protocol or the 3T scanner to the standard setting. **Conclusion:** In this study we quantified interrater-variability, repeatability and reproducibility of BM ADC measurements in repeated scans after patient repositioning, different protocols, different MRI scanners and different radiologists. Bias and CoV between two different 1.5T MRI scanners with harmonized protocols were in the range of interrater-variability and repeatability. On the contrary, variation of MRI protocols and field strength of the MRI scanner led to marked bias between ADC-measurements which could not be solved by normalization to muscle tissue. These findings are of high importance for planning of multicentric imaging studies in myeloma.

P-018

Automatic analysis of magnetic resonance imaging in multiple myeloma patients: deep-learning based pelvic bone marrow segmentation and radiomics analysis for prediction of plasma cell infiltration

Markus Wennmann[1], André Klein[2], Fabian Bauer[1], Jiri Chmelik[2], Charlotte Uhlenbrock[1], Martin Grözinger[1], Lukas Rotkopf[1], Sandra Sauer[3], Heidi Thierjung[1], Michael Götz[2], David Bonekamp[1], Jens Kleesiek[4], Tim Weber[5], Jens Hillengass[6], Hartmut Goldschmidt[3], Heinz-Peter Schlemmer[1], Ralf Floca[2], Niels Weinhold[7], Klaus Maier-Hein[2], Stefan Delorme[1]

[1]Division of Radiology, German Cancer Research Center, Heidelberg, Germany; [2]Division of Medical Image Computing, German Cancer Research Center, Heidelberg, Germany; [3]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; [4]Institute for artificial intelligence in medicine (IKIM), University Hospital Essen, Essen, Germany; [5]Deparment of diagnostic and interventional Radiology, University Hospital Heidelberg; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background: Advances in deep learning have made automatic biomedical image segmentation feasible. Additionally, radiomics analysis now allows computer based, in-depth tissue analysis from medical images. The goal of this work was to establish a full-automatic framework combining automatic pelvic bone marrow (BM) segmentation and radiomics analysis of the pelvic BM to predict BM plasma cell infiltration (PCI) directly and automatically from whole-body magnetic resonance imaging (wb-MRI). **Methods:** A total of 541 MRIs acquired at 5 different MRI scanners from 270 patients with all stages of monoclonal plasma cell disorders were included. One-hundred fifty-eight patients who had received MRI at the standard clinical 1.5T MRI scanner and had information on PCI from concomitant BM biopsy at the iliac crest available were split by date into a training set (n=116) for both, nnU-Net and radiomics model, and an independent test set for the framework (n=42). All MRIs without biopsy data were used for training of the nnU-Net only, which is state of the art deep learning framework for medical image segmentation. Manual BM segmentations of the right and left pelvic bone on coronal T1tse images on the training cohort were used for training of the nnU-Net. A random forest classifier was trained on the pelvic radiomics features to predict PCI. The framework was then tested on the independent test set. Dice scores report accuracy of segmentations. Mean absolute error (MAE) in [%PCI] reports the accuracy of the PCI prediction. For comparison, two radiologists rated the diffuse infiltration according to 3 levels of severity (none-to-mild vs. moderate vs. severe). The mean PCI within each severity level from the training set was determined and assigned as a prediction to patients with the same level diffuse infiltration in the test set (the radiologists' PCI prediction). This study was approved by the institutional review board. **Results:** The mean Dice scores of the nnU-Net segmentation for right / left pelvic BM on 8 cases of the test set (last 8 by acquisition date) were 0.94 and 0.94, respectively, the mean Dice scores between manual pelvic BM segmentation of two radiologists on these 8 cases were 0.87 and 0.88. The MAE of the prediction of PCI by the automated framework was 14.3 [%PCI]. The MAE of the radiologists PCI predictions were 16.1 [%PCI] (rater 1) and 16.7 [%PCI] (rater2). **Conclusion:** We established automatic pelvic BM segmentation with radiologist level precision for all stages of monoclonal plasma cell disorders, which is a crucial step towards fully automated analysis of wb-MRI. Radiomics analysis of these segmentations can predict PCI with considerable accuracy. Further improvement of the PCI prediction model is necessary and is currently in progress, by adding additional MRI sequences into the model, enhancing the amount of training data by adding multi-institutional data, and learning about multi-scanner radiomics feature stability.

P-019

Real-world treatment patterns, clinical outcomes, and healthcare resource utilization of individuals with light chain (AL) amyloidosis in Alberta, Canada: a population-based study

Victor H Jimenez-Zepeda[1], Donna E. Reece[2], Rodrigo Rigo[3], Priyanki Gogna[3], Shiying Kong[3], Xun Yang Hu[3], Parv Chapani[3], Winson Cheung[3], Darren Brenner[3], Richard K Plante[4], Kun Shi[4], Asad Husain[4], Dipti Tankala[4], Devon Boyne[3]

[1]Department of Medical Oncology and Hematology, Tom Baker Cancer Centre; [2]Princess Margaret Cancer Centre; [3]Oncology Outcomes Research Initiative, University of Calgary; [4]Janssen Inc Canada*

Background: Amyloid light-chain (AL) amyloidosis is a rare disease with poor survival and significant morbidity. Limited information on the treatment patterns, healthcare resource

utilization (HCRU) and clinical outcomes of Canadian AL amyloidosis patients is currently available. This study analyzed existing administrative claims data to better understand this patient population in the real-world setting. **Methods:** Population-based administrative databases in Alberta, Canada were queried from 2010 to 2019 using a claims-based algorithm to identify potential cases of systemic AL amyloidosis. The medical charts of individuals flagged by the algorithm were subsequently reviewed by a trained clinician to confirm the diagnosis. Baseline characteristics, sequencing of pharmacologic therapies, overall survival (OS), and HCRU were evaluated. Individuals with AL amyloidosis were matched 1:4 with members of the general population based on age and sex. The mean difference in number of healthcare touch points was then estimated. HCRU was assessed starting from the time of diagnosis for individuals with AL amyloidosis and starting from the date of first encounter with the healthcare system within the corresponding calendar year for matched members of the general population. Robust variance estimation was used to address clustering due to matching. **Results:** A total of 215 patients were confirmed to have AL amyloidosis. At baseline, the mean age at diagnosis was 66 years (range: 25 to 93 years). The majority of patients were men (59.5%), had an Eastern Cooperative Oncology Group (ECOG) performance status between 0-1 (60.9%), and had at least one comorbidity (84.7%). Approximately 1 in 3 patients had a concurrent multiple myeloma diagnosis. Renal and cardiac involvement were more common at baseline (67.9% and 55.8%, respectively) than liver involvement (15.3%). CyBorD was given to 66.4% of patients who initiated pharmacologic therapy, while most of the remaining 33.6% of patients received another bortezomib-based combination therapy. The most common 2L therapy was the combination of lenalidomide and dexamethasone which was given to 29.9% of individuals who initiated 2L. Median OS from initiation of 1L was markedly improved in patients diagnosed between 2012-2019 compared to 2010-2011 (63.4 vs. 34.5 months, respectively; log-rank p=0.07). Relative to age-sex matched members of the general population, individuals with AL amyloidosis had 118.7 more encounters with the healthcare system within the follow-up period (robust 95% CI: 79.4 to 157.9). **Conclusions:** Since 2012, CyBorD has been the standard of care for Canadian AL amyloidosis patients. While survival has increased over time, 5-year survival remains low which highlights an unmet need for more effective therapies. Relative to the general population, individuals with AL amyloidosis had significantly higher HCRU, underscoring the high disease burden.

P-020

Altered mRNA splicing identifies novel biomarkers and therapeutic targets in AL (Amyloid light-chain) Amyloidosis

Zuzana Chyra[1], Morgan O'Keefe[2], Tereza Sevcikova[3], Roman Hajek[4], Kenneth C. Anderson[5], Sophia Adamia[6]

[1]Dana Farber Cancer Institute; [2]DFCI/Boston University; [3]Department of Haemato-Oncology/ University Hospital Ostrava; Faculty of Medicine, University of Ostrava; [4]Department of Haemato-Oncology/ University Hospital Ostrava; Faculty of Medicine, University of Ostrava; [5]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [6]Dana-Farber Cancer Institute

Background: Amyloid light-chain Amyloidosis (ALA) is a plasma cell (PC) dyscrasia characterized by the accumulation of amyloid fibrils formed by clonal PCs in the bone marrow (BM). While multiple myeloma (MM) is present at the time of diagnosis in 10% of patients with ALA, nearly 30% of MM patients have subclinical amyloid deposits in the BM and/or in vital organs. Differential diagnoses of ALA, monoclonal gammopathy of undetermined significance (MGUS), and MM are challenging because these malignancies share genetic similarities. Unrecognized ALA in an MM setting can be life-threatening due to the side effects of some MM treatment regimens. Thus, a molecular signature selectively associated with ALA is needed to improve patient outcomes. **Methods:** To identify a selective gene-signature linked to ALA, we evaluated altered mRNA splicing (AltS) events in 8 ALA, 24 MGUS, 33 smoldering MM, 40 MM patient samples and 10 normal donor plasma cells (NPC). We used the custom pipeline to identify AltS events present only in ALA cells and absent in other PC dyscrasias. Gene and transcript level analyses showed that 1609 genes are aberrantly spliced (894 genes are upregulated and 615 downregulated) in ALA patients compared to NPC (P< 001). **Results:** Focusing on upregulated gene-splicing events occurring in the mRNA coding region, we observed significant upregulation of CD200, CDKN2B, and B7H3 splice variants in ALA PCs. Since splicing of these genes was also detected in other PC dyscrasias, custom transcript level analyses were used to identify ALA-specific AltS events. These analyses indicated that ~19% of the mRNAs were aberrantly spliced in each subgroup of patient samples, and ~17% retained introns, a marker of malignant transformation. In ALA patients we identified 1607 unique AltS events on 624 genes, 132 of which retained introns, 429 showed exon skipping alterations, and 250 were subjected to nonsense-mediated decay and degraded. These analyses showed significant upregulation of certain splice variants of CD200 and B7H3 in ALA PCs. These variants are attractive targets for therapy; CD200 and B7H3 are immune checkpoint proteins and targeting them may overcome checkpoint-induced drug resistance. In patient's samples harboring upregulated spliced genes, we evaluated the expression of cis-/trans-splicing molecules. Samples with upregulated AltS variants overexpressed SNRPN70 and RBM8A genes, both of which are part of the U1 spliceosome. Alteration of this complex assembly leads to AltS at the 5'sites of exons, causing intron retention and/or uncontrolled exon skipping. Therefore, targeting these splicing factors has the potential to control AltS in ALA. **Conclusion:** Our study (i) identifies splice variants that are selectively expressed in ALA PCs, (ii) provides potential ALA molecular biomarkers to aid the differential diagnoses of ALA and other PC dyscrasias, and (iii) identifies potential therapeutic strategies targeting altered splicing in ALA.

P-021

Experience with autologous stem-cell transplant (auto-SCT) in patients with systemic light-chain amyloidosis (LA) at our center

Javier Díaz Carbonero[1], Elena Medina Guerrero[2], Albert Pérez Montaña[3], Antonio Gutierrez García[2], Jose María Sánchez Raga[2], María del Carmen Ballester Ruíz[2], María Jiménez Moya[2], Sandra Pérez León[2], Andrea Provencio Rincón[2], Leyre Bento de Miguel[2], Andrés Novo García[2], Lucía García Maño[2], Antonia Sampol Mayol[4]

[1]Hospital Universitario Son Espases; [2]HUSE; [3]Hospital Universitari Son Espases I HUSE · Department of Hematology; [4]Hospital Son Espases, Palma de Mallorca, Spain

Background: Auto-SCT is the standard first-line treatment in patients with LA and good personal status. This procedure achieves haematological responses >70% with an average survival rate of more than 8 years. Depending on patient characteristics and hospital guidelines, prior chemotherapy (CT) is administered, usually with Bortezomib-based regimens. The main determinant of survival in LA is cardiac involvement. The subgroup of patients with cardiac involvement and an indication for Auto-SCT is at the highest risk of complications and mortality and should therefore be strictly selected. **Objective:** Our objective is to review the experience in our center with Auto-SCT in patients with LA. **Methods:** A retrospective descriptive study was conducted at the Son Espases University Hospital between November 2012 and June 2021. Pre- and post-SCT clinical-biological data, complications during transplantation and progression-free survival (PFS) were analyzed. **Results:** Eleven patients with a median age of 59 years at the time of Auto-SCT (range 41-69) were included, of whom 7 were male (64%). Ten patients (90.9%) had renal involvement at diagnosis and 6 (54.5%) had cardiac involvement. According to the Mayo Clinic 2013 prognostic staging score, 6 patients (54.5%) had stage I, 3 patients (27.3%) had stage II and 2 patients (18.2%) had stage IIIb (18.2%). All patients received pre Auto-SCT CT with bortezomib-based regimens. The median pre Auto-SCT left ventricular ejection fraction was 58% (41-79 range). Pre Auto-SCT organ-based chemotherapy response was: 8/10 patients (80%) with renal response; 1/6 patients (16.7%) with cardiac response. Pre Auto-SCT haematological response was: 7 patients (63.6%) complete remission, 1 patient (9%) very good partial response, 1 patient (9%) partial response, 1 patient (9%) stable disease and 1 patient (9%) not assessable. The median number of CD34+ cells infused into Auto-SCT was 3.66×10^6/kg. 10 patients (90.9%) received G-CSF from day +5. 10 patients (90.9%) developed complications during transplantation, 7 of them requiring admission to the Intensive Care Unit (ICU) with a median of 15 days of admission (range 1-24 days), mainly due to acute pulmonary edema - APE (85.7%). 3/7 patients requiring ICU admission passed away, leaving the Auto-SCT-related mortality rate at 27.3%. With a median follow-up of 36 months (range 5-90), a median PFS and an overall survival rate (OS) of 73% (95%CI 46-99) is observed. PFS and OS match because there are no progression events. **Conclusions:** Patients with cardiac involvement prior to Auto-SCT have a high risk of morbidity and mortality, with APE being the main complication in our study. Multidisciplinary management of these patients during Auto-SCT is essential to avoid complications.

P-022

Survival benefit observed with Birtamimab in Mayo Stage IV AL amyloidosis supports initiation of confirmatory AFFIRM-AL phase 3 study

Morie Gertz[1], Radhika Tripuraneni[2], Gene Kinney[2]

[1]Mayo Clinic; [2]Prothena Biosciences Inc

Background: Light chain (AL) amyloidosis is a rare and typically fatal disorder caused by misfolded AL protein, resulting in amyloid deposits in tissues that cause organ dysfunction and failure, most commonly in the heart and kidneys. Birtamimab is an investigational monoclonal antibody designed to indirectly promote phagocytic clearance of amyloid deposits. The phase 3 VITAL study was terminated based on a futility analysis of the composite primary endpoint (time to all-cause mortality [ACM] or time to cardiac hospitalization >90 days after first study drug infusion); the final hazard ratio (HR) numerically favored birtamimab + standard of care (SOC) over placebo + SOC (HR: 0.835, 95% CI: 0.5799, 1.2011; p=0.330). Post hoc analysis of ACM over 9 months revealed a pronounced survival benefit (HR: 0.413, 95% CI: 0.191, 0.895; p=0.025) in patients at high risk for early mortality (Mayo stage IV); proportions of surviving patients were 74% (birtamimab + SOC) and 49% (placebo + SOC). Across all birtamimab trials, no drug-related deaths, dose-limiting toxicities, or major risks were identified. Birtamimab + SOC will provide significant clinical benefit for Mayo stage IV patients with AL amyloidosis versus placebo + SOC (ie, concomitant chemotherapy with a first-line bortezomib-containing regimen). **Methods:** The phase 3, double-blind, placebo-controlled AFFIRM-AL study will enroll up to 150 Mayo stage IV patients with newly diagnosed, untreated AL amyloidosis with cardiac involvement. Patients will be randomized 2:1 to receive either intravenous birtamimab + SOC or placebo + SOC. The primary efficacy endpoint of AFFIRM-AL is time to ACM. Safety endpoints include adverse events, clinical laboratory observations, and immunogenicity analyses. **Results:** The phase 3 AFFIRM-AL study is designed to confirm this effect of birtamimab under a Special Protocol Assessment agreement with the US FDA. If the study is positive, it would confirm the >50% relative risk reduction for ACM in Mayo stage IV disease observed over 9 months with birtamimab in VITAL. **Conclusions:** Birtamimab is the only investigational therapeutic in which a survival benefit has been observed in a post hoc analysis of patients with AL amyloidosis with cardiac involvement. AFFIRM-AL is initiating mid-2021.

P-023

Assessment of liver stiffness with shear wave elastography for hepatic AL amyloidosis

Hirokazu Miki[1], Shingen Nakamura[2], Masafumi Nakamura[3], Ryohei Sumitani[4], Masahiro Oura[5], Kimiko Sogabe[5], Mamiko Takahashi[7], Tomoko Maruhashi[3], Takeshi Harada[4], Shiro Fujii[4], Susumu Nishio[6], Tetsu Tomonari[7], Masahiro Abe[5]

[1]Division of Transfusion Medicine and Cell Therapy, Tokushima University Hospital; [2]Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences; [3]Department of Hematology, Endocrinology and Metabolism, Institute of Biomedical Sciences, Tokushima University Graduate School; [4]Department of Hematology, Tokushima University Hospital; [5]Department of Hematology, Endocrinology and Metabolism, Tokushima University Graduate School of Biomedical Sciences; [6]Ultrasound Examination Center, Tokushima University Hospital; [7]Department of Gastroenterology and Oncology, Institute of Biomedical Sciences, Tokushima University Graduate School

Background: Although liver is often involved in systemic AL amyloidosis, there are few modalities to differentiate amyloidosis from common hepatic disorders with hepatomegaly and serum ALP elevation. Because liver biopsy is an invasive procedure that may cause complications such as bleeding, a non-invasive imaging modality is wanted to diagnose and assess hepatic AL amyloidosis. Ultrasound shear wave elastography (SWE) is a novel imaging modality to evaluate tissue elasticity, which is currently applied to the quantitative assessment of liver stiffness in patients with diffuse liver disease. Herein, we investigated the efficacy of ultrasound SWE for diagnosis of hepatic involvement and assessment of hepatic organ response in patients with AL amyloidosis. **Methods:** Thirteen patients with systemic AL amyloidosis (6 males and 7 females) with a median age of 65 years old (51-84) were studied. Hepatic involvement of AL amyloidosis was observed in 5 out of 13 patients without liver complications to affect liver stiffness. The ultrasound SWE was carried out for the right lobe of the liver, using an M-probe placed on the intercostal space. The long diagonal liver span was 18.24 ± 2.76 vs 13.11 ± 1.15 cm (p=0.003); serum ALP (normal range: 106 - 322 U/L) was 820.0 ± 537.62 vs 233.25 ± 30.52 U/L (p=0.013); and the shear wave velocity in a region of interest in SWE images was 2.02 ± 0.22 vs 1.33 ± 0.10 m/sec (p=0.001) in patients with and without hepatic involvement of AL amyloidosis, respectively. **Results:** The shear wave velocity corresponded well to the severity of hepatic amyloid involvement judged by the liver size and serum ALP levels. The shear wave velocity was decreased after attaining hepatic organ response in 2 patients, while unchanged in those without hepatic response. **Conclusions:** These results suggest that non-invasive ultrasound SWE is instrumental in diagnosis of hepatic involvement and assessment of hepatic organ response in AL amyloidosis, and provides unique information on amyloid deposition in the liver.

P-024

Early relapse is an adverse prognostic marker in systemic immunoglobulin light chain (AL) Amyloidosis

Sriram Ravichandran[1], Steven Law[1], Shameem Mahmood[1], Brendan Wisniowski[1], Darren Foard[1], Marianna Fontana[1], Ana Martinez-Naharro[1], Carol Whelan[1], Jullian Gillmore[1], Helen Lachmann[1], Philip Hawkins[1], Ashutosh Wechalekar[1]

[1]National Amyloidosis Centre

Background: Systemic Immunoglobulin light chain amyloidosis (AL) is a protein-misfolding disorder associated with an underlying monoclonal B-cell or plasma cell dyscrasia. There is little information on how response durability impacts outcomes. It is conceivable that early relapse may confer an adverse prognosis in AL, like in Myeloma. Here, we test the above hypothesis and analyse the factors affecting response durability in a cohort of AL patients treated with frontline Bortezomib. **Methods:** All patients treated with frontline Bortezomib in 2010-2019 are included in the analysis. Patients with primary refractory disease, those with a continuing response but ≤ 24 months follow up, and those who received 2nd line therapy for reasons other than progression are excluded from the analysis. We defined early relapse (ER) as PFS ≤ 24 months. **Results:** 560 patients are included in this analysis. 250 (44.6%) and 310 (55.4%) patients had ER and LR, respectively. The ER group had more advanced cardiac disease (p 20% (p=0.021), ≥ VGPR after 1st line (p 20%, and dFLC < 10 mg/l after treatment, we found serum monoclonal protein [OR 2.636 (95% CI 1.033-6.732), p=0.043] & dFLC < 10 mg/l [OR 0.122 (95% CI 0.063-0.235), p < 0.005)] were significant predictors of early relapse. **Conclusions:** In conclusion, these data identify a high-risk group of patients who relapse early and have a poorer survival (irrespective of their initial response). The depth of response to the initial treatment is a critical determinant of response durability. The early relapses should be considered for clinical trials that can identify treatments with the potential to overcome the high-risk biology of the disease.

P-025

Population-based incidence and survival of AL amyloidosis in Sweden

Sara Rosengren[1], Kristina Carlson[1]

[1]Uppsala University Hospital

Background: There are few reports on the population-based incidence and survival of immunoglobulin light chain (AL) amyloidosis, and in existing studies the number of cases are few. **Aim:** To determine the incidence and survival of systemic AL amyloidosis in the general Swedish population. **Methods:** The diagnosis of light chain amyloidosis requires histopathological evidence and typing of amyloid in tissue biopsy. In the Uppsala and Stockholm County of Sweden, amyloidosis is diagnosed at two different pathology laboratories. Databases from these two departments were searched

for all patients who received the diagnosis code for amyloidosis from the beginning of 1990 until the end of 2015. Area of residency was controlled through the Swedish population register, and patients not living in the Uppsala or Stockholm region were excluded. Patient records were reviewed and all unique cases with a confirmed first diagnosis of systemic AL amyloidosis during the time period were included. Date of death was obtained through the population register, and survival was calculated as time from diagnosis to death or end of follow-up (June 30th, 2021). **Results:** To this date, results from the Uppsala County (in average 307 969 inhabitants during the time period) are available whereas results from the Stockholm County (in average 1.9 million inhabitants) remain to be analyzed. Over the 26-year period, 64 new cases (64% males, median age 74.5 years) of systemic AL amyloidosis were diagnosed in the Uppsala County, which gives a yearly incidence of 8.0 (95% CI 4.7-11.3) cases per million inhabitants. The incidence did not differ significantly between the earlier (1990-2002) versus the later (2003-2015) time period, with a yearly incidence of 7.5 versus 7.8 cases per million inhabitants. Median survival for all patients from the Uppsala County was 7 months (95% CI 2.3-11.7). 6 patients were diagnosed at autopsy, these were not included in the survival analysis. In the later time period, survival was longer (median 9 months) compared to the earlier time point (median 4 months), however the difference was not statistically significant (p=0.3). In 69% of patients heart was the main organ involved, these patients had significantly shorter survival (p=0.049) compared to those with other dominating organ involvement. **Conclusion:** The yearly incidence of 8 cases per million inhabitants is comparable to that previously reported by Kyle et al from the Olmsted County, US. There was no significant change in the incidence over time. With inclusion of results from the Stockholm County, this study will present reliable incidence data with more cases than in the previous population-based studies. In this mostly historic cohort, survival is poor, but with an improving trend over time.

P-026

A prognostic staging system for light-chain amyloidosis using hepatic and renal indicator data of 1064 Chinese patients

Wei Yan[1], Yanze Cao[2], Aijun Liao[1], Wei Yang[1], Jian Li[3], Huihan Wang[1]

[1]Shengjing Hospital of China Medical University; [2]Neusoft Research Institute/Northeastern University; [3]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

Background: Light-chain (AL) amyloidosis frequently involves severe multiple end-organ damage, thus affecting prognosis. As the current disease staging system is based only on cardiac indicators, herein, we propose a new staging system based on multiple organ indicators to supplement the existing system. **Methods:** Patients with AL amyloidosis (n=1064) from 18 Chinese hospitals registered in the nationwide Chinese Registration Network for Light-chain Amyloidosis were enrolled and divided into test and validation cohorts (4:1). Multivariate analyses were performed to identify clinical and laboratory factors for inclusion in the new staging system. A score of 1 was assigned for each of the following—difference between the involved and uninvolved free light chains ≥100 mg/L, estimated glomerular filtration rate <60 mL/min/1.73 m^2, total bilirubin ≥18 µmol/L, cardiac troponin I ≥0.06 µg/L, and N-terminal pro-brain natriuretic peptide ≥3600 pg/mL—to divide the patients into five disease stages (0 to IV). **Results:** Two hundred and twenty (20.7%), 291 (27.3%), 251 (23.6%), 178 (16.7%), and 124 (11.7%) patients had stage 0, I, II, III, and IV disease, respectively. Patients with stages II, III, and IV had median overall survivals of 56.9 months (95% confidence interval [CI], 33.9 to not reached [NR]), 18.6 months (95% CI, 33.9 to NR), and 6.5 months (95% CI, 8.0 to 24.6) (P<0.001), respectively. The 3-year survival estimates for patients with stages 0, I, II, III, and IV were 90.7%, 71.4%, 59.4%, 39.0%, and 22.1%, respectively. **Conclusions:** The new prognostic staging system enhances the risk stratification of patients with AL amyloidosis and is useful when multiple organs are involved.

P-027

Development of an artificial intelligence diagnostic model based on routine laboratory results and echocardiography for the early diagnosis of light chain amyloidosis

Wei Yan[1], tao he[2], jian chen[2], Aijun Liao[1], Wei Yang[1], Jian Li[3], Huihan Wang[1]

[1]Shengjing Hospital of China Medical University; [2]Neusoft Research Institute/Northeastern University; [3]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

Background: In order to enhance the detection rate of light chain amyloidosis(AL) and execute an early and more precise disease management, an artificial intelligence assistant diagnosis system is developed. **Methods:** Through cooperation with 18 hospitals in the Chinese Registration Network for Light-chain Amyloidosis (CRENLA), a nationwide survey was conducted from 2009 to 2020, and 1064 patients with systemic AL amyloidosis were registered and followed. The routine biochemical examination records and echocardiography from 824 patients were collected. Meanwhile 1000 records of non-AL (infectious diseases, rheumatic immune system diseases, hepatic diseases and renal diseases) were also collected. The data set was split into training and test subsets with the ratio of 4:1. An early assistant diagnostic model of MM was established by Gradient Boosting Decision Tree (GBDT), Support Vector Machine (SVM), Deep Neural Networks (DNN), and Random Forest (RF). Out team calculated the precision and recall of the system. The performance of the diagnostic model was evaluated by using the receiver operating characteristic (ROC) curve. **Results:** By designing the features properly, the typical machine learning algorithms SVM, DNN, RF and GBDT all performed well. GBDT had the highest precision (91.7%), recall (95.2%) and F1 score (0.93) for the AL group. The maximized area under the ROC (AUROC)

was calculated. **Conclusion:** The model established by artificial intelligence derived from routine laboratory and echocardiography results can accurately diagnose AL, which can boost the rate of early diagnosis.

P-028

Circulating cytokines present in multiple myeloma patients inhibit the osteoblastic differentiation of adipose and bone marrow stem cells

Ladan Kobari[1], martine Auclair[1], olivier Piau[1], nathalie Ferrand[1], maurice Zaoui[1], francois Delhommeau[1], bruno feve[1], michele sabbah[2], laurent Garderet[4]

[1]Sorbonne Universite; [2]Inserm; [3]Hôpital Pitié Salpêtrière, service d'hématologie, Sorbonne Université

Background: Myeloma is characterized by bone lesions, which are related to both an increased osteoclast activity and a defect in the differentiation of medullary mesenchymal stem cells (MSCs) into osteoblasts. Outside the medullary environment, adipocyte-derived MSCs (ASCs) could represent a source of functional osteoblasts. However, we recently found a defect in the osteoblastic differentiation of ASCs from myeloma patients (MM-ASCs). We aimed to identify the cause of this defect. **Materials and Methods:** We examined the effects of plasma from myeloma patients at diagnosis (MM-plasmas), in complete remission (CR-plasmas) and from healthy donors on the osteoblastic differentiation of MM-ASCs, healthy donor-derived ASCs (HD-ASCs) and healthy donor-bone marrow derived MSCs (HD-BM-MSCs). Alizarin red coloration, alkaline phosphatase activity, RUNX2 and osteocalcin expression determined osteoblastic differentiation while oil-red O staining, PPARg[ED], C/EBPa[ED] and CD36 expression reflected the adipogenic capacity. Cytokine arrays were used along with Elisa assays for identification and quantification of relevant cytokines. RNA sequencing was performed on MM and HD-ASCs. **Results:** Osteoblastogenesis in HD-ASCs was suppressed by MM-plasmas but adipocyte differentiation was unaltered. This defect was reversible once the plasma-derived factors were removed. Using cytokine array and comparing MM-plasmas with HD-plasmas, we identified seven cytokines (ANG1, ENA-78, EGF, PDGF-AA/AB/BB and TARC), besides DKK1, highly increased in MM-plasmas. They separately inhibited the osteoblastic differentiation of HD-ASCs. In contrast, in CR-plasmas, the cytokine plasma levels were almost normal with barely no osteoblastic differentiation inhibition. In addition, the mixture of the 7 cytokines with and without DKK1 inhibited not only the HD-ASCs but also the HD-BM-MSCs. Concomitantly, MM-plasmas enhanced adipogenesis-related gene expression. Comparison of MM-ASCs and HD-ASCs by RNA sequencing showed that two master genes characterizing adipocyte differentiation, CD36 and PPARg[ED], were upregulated in MM-ASCs as compared to HD-ASCs. Moreover, we demonstrated a significant increase in CD36 and PPARg[ED] expression in HD-ASCs in the presence of MM-plasmas or the seven cytokines individually, similarly as in MM-ASCs. Finally, we tried to identify the origin of these cytokines. In CR-plasmas, the cytokine levels were strongly decreased suggesting a malignant plasmocyte secretion. This was reinforced by the detection of the 7 cytokines in three different myeloma cell lines with an especially high secretion of PDGF-AA. **Conclusion:** We conclude that specific cytokines in MM-plasmas, besides the well-known DKK1, inhibit the osteoblastic differentiation of MM- and HD-ASCs with a skewing towards adipocyte differentiation. Of note, this inhibition, by these new circulating cytokines, was also observed on HD-BM-MSCs, suggesting that this could also be the case on myeloma-BM-MSCs.

P-029

1st line combination treatment with proteasome-inhibitor and zoledronic acid is effective in reducing later fractures in multiple myeloma irrespective of MM bone disease

Elise Nivakoski[1], Veera Eskelinen[1], Kirsi Launonen[2], Sakari Kakko[2], Milla Kuusisto[3]

[1]University of Oulu; [2]Oulu University Hospital; [3]Department of Hematology

Introduciton: We examined the medical records of 344 multiple myeloma (MM) patients treated with autologous stem cell transplantation in Oulu University Hospital in 1996-2020. **Methods:** Median age of the patients was 61 years and 54.9% were males. ISS was available for 58.4%, R-ISS for 35.9% and IMWG status for 39.4% of the patients. A total of 72.1% had myeloma-associated bone disease and 47.9% had fracture/s at the time of diagnosis. Altogether 58.3% of the patients received proteasome-inhibitor containing treatment at 1st line. Treatment for MM bone disease was given to 90.8% of the patients, 49.4% received zoledronic acid and 29.6% pamindronate. A total of 28.7% of the patients suffered from later fracture. Median follow-up time in this study was 50 months (1-339). **Results:** MM bone disease at diagnosis was associated with inferior overall survival (p=0.004) as well as with fracture at diagnosis (p=0.005) irrespective of the type of fracture (pathological vs osteoporotic). The site of the fracture showed statistical significance in that fractures in vertebrae or ribs were associated with better outcome (p=0.028). There were fewer later fractures in patients treated with zoledronic acid although this association did not reach statistical significance (p=0.058). This tendency was clearer in patients with no MM bone disease at diagnosis (p=0.049). The best combination treatment to prevent later fractures was the combination of proteasome-inhibitor and zoledronic acid (p=0.019). **Conclusions:** This study suggests that the best treatment option to prevent later fractures might be proteasome-inhibitor combined with zoledronic acid.

P-030

Bone marrow findings of Idiopathic Multicentric Castleman Disease: a histopathologic analysis and systematic literature review

Elizaveta Belyaeva[1], Ayelet Rubenstein[2], Sheila Pierson[3], Delaney Dalldorf[4], Dale Frank[5], Megan Lim[5], David Fajgenbaum[5]

[1]Tulane University School of Medicine; [2]Center for Cytokine Storm & Treatment Laboratory, University of Pennsylvania; [3]University of Pennsylvania; [4]UNC School of Medicine; [5]University of Pennsylvania

Introduciton: Idiopathic multicentric Castleman disease (iMCD) is a polyclonal lymphoproliferative disorder characterized by constitutional symptoms, generalized lymphadenopathy, cytopenias, and multi-organ dysfunction due to excessive cytokines, notably interleukin 6. iMCD is often sub-classified into iMCD-TAFRO, which is associated with thrombocytopenia (T), anasarca (A), fever/elevated C-reactive protein (F), renal dysfunction (R), and organomegaly (O), and iMCD-NOS, which is typically associated with thrombocytosis and hypergammaglobulinemia. The diagnosis of iMCD is challenging as consensus clinico-pathological diagnostic criteria were only recently established and include several non-specific lymph node histopathological features. Identification of further clinico-pathological features commonly found in iMCD could contribute to more accurate and timely diagnoses. **Methods:** We set out to characterize bone marrow (BM) histopathological features in iMCD, assess differences between iMCD-TAFRO and iMCD-NOS, and determine if these findings are specific to iMCD. **Results:** Examination of BM specimens from 24 iMCD patients revealed high proportions of hypercellularity, megakaryocytic atypia, reticulin fibrosis, and plasmacytosis across patients with significantly more megakaryocytic hyperplasia (p=0.001) in the iMCD-TAFRO cases. **Conclusion:** These findings were also consistent with bone marrow findings from 185 published cases of iMCD-NOS and iMCD-TAFRO. However, these findings are relatively nonspecific as they can be seen in various other infectious, malignant, and autoimmune diseases.

P-031

Importance of flow cytometry assessment of circulating plasma cells and its connection with clinical characteristics of primary and secondary plasma cell leukemia

Renata Bezdekova[1], Tomas Jelinek[2], Martin Stork[1], Petra Polackova[1], Lucie Brozova[3], Martina Almasi[1], Ivanna Boichuk[1], Zdenka Knechtova[1], Miroslav Penka[1], Luděk Pour[4], Sabina Sevcikova[5], Lucie Rihova[1]

[1]University Hospital Brno; [2]Department of Haematooncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [3]Masaryk Unversity Brno; [4]Department of Internal Medicine, University Hospital Brno; [5]Masaryk University

Background: Plasma cell leukemia (PCL) is a rare and very aggressive plasma cell (PC) disorder characterized by the presence of circulating plasma cells (cPC) in peripheral blood (PB). Dismal outcome of PCL requires early diagnosis with appropriate analytical tools. Development of flow cytometry (FC) together with some newly analysed antigens may reveal some marker affecting the prognosis of PCL patients. **Aim:** Analysis of phenotypic profile of cPC/PCs to find association with clinical outcomes and to evaluate the prognostic value of analyzed markers. **Methods:** Total of 33 primary and secondary PCL patients were investigated. PCs quantity and phenotype profile was analysed by polychromatic FC in PB and bone marrow (BM). **Results:** Flow cytometry is an excellent method for cPCs identification as a significantly higher number was identified by FC than by morphology. Thus FC should be incorporated as a diagnostic method for preventing late diagnosis of PCL. Although the phenotypic profile of both PCLs did not differ too much, with low level of CD19, CD20, CD27, CD28, CD81 and CD117 expression, some heterogeneously expressed antigens (CD44, CD56, CD200, nestin etc.) may contribute to identification of patients with later extramedullary involvement, high risk of progression and shortened survival. **Conclusions:** FC should be incorporated in PCL diagnostics as not only exact method providing number of cPCs, which is surprisingly overcoming morphology assessment. Moreover, PCL phenotype profile could be connected to patient's diagnosis and possible prognosis as well. **Funding:** Supported by grant AZV NV18-03-00203.

P-032

Clinical characteristics and outcome of 30 patients with poems syndrome in Catalonia: impact of autologous stem cell transplantation in first line and at relapse

Carlos Castillo-Girón[1], MT Cibeira[1], V Clapés[2], L Escoda[3], M Gironella[4], M Fernandez-Aguilera[1], E Abella[5], A Senin[6], J Marti-Tutusaus[9], A Sureda[2], C Talarn[3], Laura Rosiñol[1], A Oriol[8], J Bladé[1], M Rovira[1], C Fernández De Larrea[1]

[1]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [2]Instituto Catalán de Oncología Hospitalet de Llobregat, Barcelona, Spain; [3]Institut Català d'Oncologia-Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain.; [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain.; [5]Hospital del Mar, Barcelona, Spain; [6]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [7]Hospital Universitari Mútua Terrassa, Terrasa, Spain; [8]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol

Background: POEMS syndrome is a rare paraneoplastic disease caused by an underlying plasma cell disorder. The aim of this study is to describe clinical and biological features as well as outcomes

in a series of patients in a real-world clinical setting. **Methods:** We retrospectively analyzed 30 patients with POEMS syndrome consecutively diagnosed and treated at 8 hospitals in Catalonia, Spain, between 1996 and 2021. Medical records were reviewed for clinical and lab features at diagnosis, first-line treatment, autologous stem-cell transplantation (ASCT) and outcomes including progression-free (PFS) and overall survival (OS). Diagnosis was stablished according to published diagnostic criteria (Dispenzieri A, Am J Hematol 2011). Median follow up of alive patients was 13 years. **Results:** Median age of the series was 65 years (range, 42-86). The median serum M-spike was 5 g/L. The heavy chain isotype was IgG in 43% of patients and IgA in 40%, while the light chain isotype was lambda in 87%. Four patients had more than 10% bone marrow plasma cells. VEGF was available in 18 patients and 16 of them (88%) had increased levels (3 times greater than the superior limit). All patients presented peripheral neuropathy, and other clinical features included organomegaly (22 patients), extravascular volume overload (22), endocrinopathy (20), skin lesions (18), thrombocytosis (18) osteosclerotic lesions (17), polycythemia (7), papilledema (7), pulmonary hypertension (4), portal hypertension (4), and Castleman disease (7). The median time between onset of symptoms and diagnosis was 6.3 months. Treatment information was available in 29 patients. Four patients had an isolated bone lesion and received only local radiation therapy, with hematologic and clinical response in 2 of them and a 10-year OS of 87%. Twenty-three patients underwent an ASCT: 15 after chemotherapy (with or without additional radiation therapy) and 8 upfront. Median age at the time of ASCT was 54 years. Conditioning prior to ASCT consisted in melphalan 200 mg/m^2 in 74% of cases and 140 mg/m^2 in 26%. Among 20 evaluable patients for hematologic response, 10 achieved a complete response and 10 obtained a partial response (PR). Eleven (55%) of these hematologic responding patients also obtained a significant organ improvement in a median time of 7 months after ASCT (range, 4–11). Nine patients (41.7%) progressed at a median time of 5 years after transplant, 5 of them received a second ASCT and 3 achieved at least a PR. After the second ASCT, only one patient clinically progressed after 38 months. All the remaining patients remained in response at the last follow-up evaluation. Median PFS and OS of the series were 6 and 12 years, respectively. **Conclusions:** In conclusion, in our experience ASCT proved to be highly effective for patients with POEMS syndrome. When progression is confirmed after the first transplant, a second ASCT may be performed with potential clinical benefit.

P-033

Significant markers in the progression of monoclonal gammopathy of undetermined significance in residents of Gomel region of Belarus

Zhanna Kozich[1], Victor Martinkov[1], Janna Pugacheva[1], Dzmitry Blizin[1], Liudmila Smirnova[2]

[1]State Institution "The Republican Research Center for Radiation Medicine and Human Ecology"; [2]Education Institution "Belarusian Medical Academy Of Postgraduate Education"

Background: The course of monoclonal gammopathy of undetermined significance (MGUS) is often associated with a high risk of its transformation into malignant lymphoplasmacytic diseases. We have reviewed some of the markers most commonly encountered in patients with progression. **Methods:** The study included 159 MG patients with a median age of 61.0 (25% and 75% - 54.0 and 67.0), of which 102 women were observed at the SI "RRCRM&HE" in 2018-2021. The average percentage of tumor plasma cells in the bone marrow was 2.7% (range 0-10%). The presence of clonal cells was detected in 13.2% with IHC. The immunochemical variant with immunoglobulin IgG was in 38.9% of patients, IgA in 7.5% and IgM in 19%; biclonal gammopathy was found in 22% of patients. The LC type kappa or lambda was found in 26.4% of patients. **Results:** During the observation period, disease progression was recorded in 17 MGUS patients. The age of patients over 65 at the time of diagnosis was not significantly associated with the risk of progression (p = 0.114). Hemoglobin level less 120 g/l was determined in 31.4% of patients. In each case, the anemia was induced by causes other than plasma cell proliferation, such as iron deficiency, renal failure. Among MGUS patients who progressed over the observation period, the variant with IgM secretion was 2.46 times more frequent than among patients without progression (p = 0.096, [0.79-11.39]). In patients with the phenotype of tumor cells containing CD20> 20%, disease progression developed in 46.7% of cases, which is 4.73 times more often than in patients without this marker (p = 0.0001, OR 7.98 (95 % CI [2.29-27.86]). Moreover, 80% of the progressed patients with CD20> 20% were with IgM secretion. An excess of CD56> 20% was detected 1.62 times more often in patients with disease progression. When studying CD117 and CD200, it was found that exceeding their level> 20% was more often determined in patients with progression, although the differences were insignificant (p = 0.584, OR 1.64 (95% CI [0.27-9.89]) for CD200 > 20% and p = 0.116, OR 2.83 (95% CI [0.74-10.78]) for CD117> 20%). Progression to MM was more frequently observed in patients with secretion of IgG, IgA and CD56> 20%. An increase in the level of LDH> 280 U/L was observed 4.43 times more often in patients with progression (p = 0.011, OR 5.67 (95% CI [1.32-24.39]). An abnormal ratio of light chains was detected in 85.7% of cases in patients with progression, which is 1.54 times more often than in patients without progression (p = 0.033, OR 4.80 (95% CI [1.01-22.84]). **Conclusion:** The study results have demonstrated that immunophenotypic markers (CD20, CD56 CD117), increased LDH level, immunoglobulin light chain ratio distortion can be useful for predicting the onset of disease progression from MGUS to multiple myeloma or other lymphoplasmacytic tumors in individual patients.

P-034

MAGNAZ trial - A prospective phase II study in patients with monoclonal gammopathy of unknown significance (MGUS) and anti-Myelin Associated Glycoprotein (MAG) Neuropathy and Zanubrutinib Treatment

Monique C. Minnema[1], Josephine Vos[2], Filip Eftimov[2], Alexander Vrancken[3]

[1]UMC Utrecht Cancer Center, Utrecht, the Netherlands; [2]Amsterdam UMC; [3]UMC Utrecht

Introdcution: Polyneuropathy (PNP) associated with IgM monoclonal gammopathy (MGUS), also called IgM-related PNP, is mediated by the anti-neural effect of the M-protein component and is classified as one of the MGUS-related diseases. In around 70% of patients with IgM-related PNP anti-myelin associated glycoprotein (MAG) antibodies are detected. There is no established treatment for IgM-related PNP except anti-CD20 monoclonal antibody treatment with 30% or less clinical responses. There is increasing interest to use Bruton's tyrosine kinase (BTK) inhibitors, approved for the treatment of Waldenstrom Macroglobulinemia, for IgM-related PNP treatment but a formal study is currently lacking. We therefore designed a phase 2 clinical trial to investigate the effect of zanubrutinib, a next generation BTK inhibitor, combined with anti-CD20 monoclonal antibody treatment, in IgM-related PNP with anti MAG antibodies. The primary study endpoint is change from baseline in the Rasch-built Overall Disability Scale (RODS) for inflammatory neuropathies (iRODS) at the end of Cycle 12. The main secondary endpoint is to assess the safety of zanubrutinib treatment in IgM-related PNP as measured by CTCAE, version 5.0. **Methods:** Patients will be treated for a minimum of 6 cycles; patients experiencing hematological response continue until 12 cycles of treatment. All patients will be followed for the duration of 12 cycles for the primary endpoint analysis. Patients who have an anti MAG titer > 10.000 BTU, adequate hematological, renal and hepatic function tests, no hemorrhagic disorder and no New York Heart Association (NYHA) grade 3 or 4 cardiac disease can be included after signing informed consent. Explorative analysis will consist of Next Generation Sequencing of MYD88 and CXCR4 mutations after CD19 selection of the bone marrow aspirate at start. During study participation extensive neurological testing and serum IgM and anti MAG testing will be performed. In total 40 patients will be included and the MAGNAZ study expects to start in Q4 2021.

P-035

AI-based models for the identification of critical genetic biomarkers to distinguish MM from MGUS using the WES data

Vivek Ruhela[1], Akanksha Farswan[1], Anubha Gupta[1], sriram K[1], Gurvinder Kaur[2], Ritu Gupta[2]

[1]IIIT, Delhi; [2]AIIMS, New Delhi

Background: Multiple Myeloma (MM) is preceded by the premalignant stage of Monoclonal Gammopathy of Undetermined Significance (MGUS) and therefore, it is important to identify the genetic factors responsible for progression of MGUS to MM. We have built machine learning (ML) models to identify pivotal genetic biomarkers that distinguish MM and MGUS. **Methods:** Tumor normal matched paired Whole Exome Sequencing (WES) data of 1174 patients of MM and 61 patients of MGUS were analyzed. The data were obtained from dbGaP (phs000748; phs000348), AIIMS, Delhi, India, and EGA (EGAD00001001901). Variants were identified using four variant callers, namely, MuSE, Mutect2, VarScan2, and Somatic-Sniper and; SNVs were annotated using ANNOVAR. Pooled genomic annotations obtained were analyzed to derive significantly mutated genes with 'dndscv' tool. Union of top ranked 250 significantly mutated genes from each variant caller yielded 1316 genes. For each gene, variant count and (maximum, mean, median, and standard deviation of) VAF and AD were used as features which were reduced by principal component analysis (PCA) and only top-3 principal components were selected for each gene. Next, 5 ML classifiers (random forest, decision tree, logistic regression, XGBoost, and SVM) were used to distinguish MM from MGUS. Imbalance of data (95% MM and 5% MGUS cases) was handled by the cost-sensitive loss function in the classifiers. Permutation based feature importance was carried out on top two performing models to infer the most significant features that were mapped back to genes to obtain the top ranking genes for MM and MGUS. **Results:** Cost-sensitive SVM outperformed the rest of the models in balanced accuracy, weighted F1-score, Mathews correlation coefficient (MCC), precision, recall and area under curve (AUC) with values 95.5%, 94.82%, 0.8162, 76.49%, 98.33% and 95.5%, respectively. Top ranking genes identified for MM were: HLA-DQB1 IRF1, MUC6, FGFR3, MUC4, HOXA1, ITPR3, HIST1H1E, MUC12, ITGA2, HLA-DQA2, HUWE1, IGLL5, HLA-DRB5, HLA-DQB2, ILK. Top ranking genes identified for MGUS were: MUC3A, HLA-A, HLA-C, IRF4, JAK1, HDAC2, HLA-DQA1, FRG1, HS6ST1, H2AFV, and HLA-DRB1. HLA-DQB1, IRF1, ITPR3, HOXA1, HIST1H1E, HUWE1, IGLL5, HIPK3, HLA-DQA2, HLA-DRB5, and ILK were found significant for MM; and HLA-A, HLA-C, IRF4, JAK1, HDAC2 HLA-DQA1, HS6ST1, H2AFV, and HLA-DRB1 were found significant for MGUS by the top two ML classifiers. All these genes were found significant in the literature for MM and MGUS. **Conclusion:** MGUS and MM share many common features such as genomic biomarkers, structural variants etc. with the difference of having less impact of mutations in MGUS. Thus, it is challenging to distinguish MM from MGUS. Here, we utilized ML classifiers to distinguish MM from MGUS. Our classifiers are able to identify the significant genes that are helpful in MM vs. MGUS classification that can lead to a better understanding of progression from MGUS to MM.

P-036

Implementation of IgH/k Next Generation Sequencing for Multiple Myeloma Minimal Residual Disease monitoring: advantages in patients' management during daily clinical practice.

Silvia Armuzzi[1], Marina Martello[1], Enrica Borsi[2], Vincenza Solli[1], Andrea Poletti[1], Ilaria Vigliotta[2], Barbara Taurisano[1], Ignazia Pistis[2], Gaia Mazzocchetti[1], Elena Zamagni[3], Lucia Pantani[4], Serena Rocchi[1], Katia Mancuso[1], Paola Tacchetti[2], Ilaria Rizzello[2], Michele Cavo[1], Carolina Terragna[2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" - Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [3]European Myeloma Network, Italy; [4]University of Bologna DIMES department / IRCCS Azienda Ospedaliero Universitaria di Bologna Istituto di Ematologia "Seràgnoli"

Background: The introduction of novel agents into the therapeutic algorithm of Multiple Myeloma (MM) has led to remarkable improvements in the rate of Minimal Residual Disease (MRD) negative status. Sustained MRD negativity is a robust prognosticator and a driver of treatment strategies. Therefore, it is expected that MRD molecular tracking would become critical in the management of MM, and could be included in daily clinical practice. **Aim:** To evaluate the performances of next generation sequencing (NGS), implemented as best practice in MM MRD daily evaluation. **Methods:** A cohort of 166 newly diagnosed transplant-eligible and -ineligible MM pts were screened to define the ID clonotypes. MRD was firstly assessed at achievement of at least a very good partial response during maintenance, and thereafter once a year. In high-risk pts, MRD was also detected between 1° and 2° autologous stem-cell transplantation (ASCT). The ID clonotypes screening has been performed by NGS, using an assay covering IgH and Igk genes (Invivoscribe®). The MRD tracking has been done both by conventional ASO-qPCR and by NGS. Data were analyzed by Lymphotrack Dx and MRD software (Invivoscribe®). **Results:** The ID clonotypes screening was successful in 158/166 pts (95%), even though a small proportion of pts resulted polyclonal (14/158). Overall, 63, 27 and 54 pts had IgH, Igk and IgH/k ID clonotypes, respectively, mainly restricted to the VH3 (47%) family genes. MRD assessment was performed by NGS in 124/144 pts (overall, 96 MRD samples for 64 pts monitored to date), with 10-5 sensitivity in most cases (75/96). 44 pts were assessed during maintenance and 23 achieved MRD-negativity. On the contrary, 20 pts were evaluated between 1° and 2° ASCT, resulting MRD-positive in all cases. Overall, few FU samples (13/96) were reported as "positive-not-quantifiable" (PNQ), since had residual disease levels of 10-7, much lower than the internal control. In a subset of 20 pts with trackable IgH/Igk sequences, pts-specific assays were designed, according to the EuroMRD guidelines. In these pts, MRD was tested both by ASO-qPCR (including a standard curve and healthy donor cells, to define the sensitivity and the specificity, respectively) and by NGS. Overall, ASO-qPCR allowed the tracking of a single MRD clone (with up to 10-4 sensitivity) in 12/20 pts (60%), whereas NGS was feasible in all of them, confirming the ASO-qPCR results, yet with higher sensitivity and >95% confidence. Moreover, in 2 cases, NGS allowed to disclose ASO-qPCR PNQ results due to non-specific amplification, thus unveiling MRD negativity with 10-5 sensitivity. **Conclusion:** NGS has been successfully implemented as best practice in the management of MM pts, showing the superiority of this method over ASO-qPCR conventional approach. The ID clonotype was defined in almost all pts included in the workflow, thus allowing their MRD molecular monitoring, according to the clinical requirements. **Acknowledgment:** AIRC IG2018-22059

P-037

Serum-free light chain and heavy-light chains normalization as markers for negative measurable residual disease in Multiple Myeloma after autologous stem cell transplant

Rui Bergantim[1], Luísa Lacerda[1], Mariana Trigo[1], Pedro Baptista[1], Marta Henriques[1], Andre Pardal[1], Maria João Cardoso[1], Fernanda Trigo[1]

[1]Centro Hospitalar e Universitário São João

Background: Measurable residual disease (MRD) in Multiple Myeloma is widely recognized of significant importance in prognosis. Multi-parameter flow cytometry (MFC) on bone marrow is one of the most chosen techniques to evaluate MRD. Nonetheless, it needs a bone marrow aspiration and time points could be limited due to the invasiveness of the evaluation. Serum-free light chains (sFLC) and heavy-light chains (HLC) assays have high sensitivity to detect blood circulating monoclonal proteins and infer immune reconstitution. They could be used as a peripheral surrogate marker for MRD. **Aim:** Evaluate the correlation between the MFC-MRD negativity and the normalization of sFLC and sHLC in patients with MM after autologous stem cell transplant (ASCT). **Methods:** 27 patients transplanted with IgG or IgA MM were included in this analysis. y. Assays (sFLC, sFLC on serum; MFC on bone marrow) were performed on all patients at a median of 100 days post-ASCT. The kappa/lambda sFLC ratio (FLCr) and involved/uninvolved HLC ratio (HLCr) were used to assess responses using published normal ranges. International Myeloma Working Group (IMWG) response criteria were used to classify treatment responses. MFC was performed according to the Euroflow panel with 10^{-5} sensitivity. Contingency tables were used to compare the serum biomarkers versus the MRD. Positive (PPV) and negative predictive value (NPV) were calculated by Fisher exact. **Results:** HLCr normalized in 18/27 (67%) patients, with FLCr normalization in 13/27 (48%) at 100 days post-ASCT. MFC-MRD negativity at 100 days post-ASCT was noted in 15/27 (56%). Patients. Post-ASCT HLCr and FLCr normalization was found in 9 patients (60%) with MRD negativity. Comparization of MFC MRD negativity and HLCr and FLCr normalization tests showed 86.7% sensitivity, 58.3% specificity, 72% PPV, and 77% NPV (Fisher Test p=0.037). **Conclusions:**

Despite the high percentage of patients with normal HLCr and FLCr in patients in MRD negativity at day 100 post-ASCT, ours results demonstrates that HLCr and FLCr normalization does lack sensitivity when compared to MFC-MRD. HCLr and FLCr could be used in patients with negative MRD to follow patients in more time points to predict relapse and prompt a bone marrow MRD evaluation. This work will be validated in a larger cohort of post-ASCT multiple myeloma patients, taking into account follow-up, namely prediction of relapse and progression-free survival.

P-038

Postinduction minimal residual disease (MRD) within stem cell graft (gMRD) correlates with marrow MRD (mMRD) and progression free survival (PFS) following autologous stem cell transplantation

Guldane Cengiz Seval[1], Klara Dalva[1], Memnune Dilek Öz[1], Şule Mine Bakanay Ozturk[1], Ender Soydan[1], Gunhan Gurman[1], Osman Ilhan[1], Meral Beksac[1]

[1]Ankara University School of Medicine, Department of Hematology

Background: Earlier studies have reported the impact of clonal plasma cell contamination within stem cell grafts as a negative prognostic factor. In this study we aimed to quantify circulating plasma cells (cPCs) by flow in apheresis products (gMRD) and compare with marrow (mMRD) and outcome. **Methods:** All consecutive (September 2006 - July 2020) newly diagnosed transplant eligible multiple myeloma (MM) patients were included prospectively. In the sample drawn for HPSC quantification of the graft and bone marrow (only if response is ≥VGPR), the number of cPCs were quantified by Flow. As described earlier (Montero et al.) undetectable MRD is defined as absence of cPCs at a sensitivity of 10-4 (n=54) between 2006-2016 and 10-5 (n=37) after 2017. MRD assessment is similar in the graft and marrow. Statistical analysis was performed on merged data regardless of sensitivity of MRD assessment. Results were reported in the intention-to-treat (ITT) population for mMRD. **Results:** Patients were given either Bortezomib based triplet without immunomodulatory drug (IMID) ((85.7%)) or with an IMID (17.6%) as induction. The median age was 62 years (range:37-75 years). 86 (94.5%) patients had cytogenetics by FISH at diagnosis, of which 14% had high risk. Extramedullary disease was detectable among 14.3%. Post-induction complete response (CR) was achieved in 28.6% (n=26). Following mobilization, gMRD was detectable in 57.1% of patients. CR rate among gMRD (+) vs. (-) patients were: 14/26 (26.9%) vs 12/39 (30.8%). Kappa coefficient (SE): -0.036, p:0.8) pointing to lack of correlation between gMRD and biochemical response. Undetectable mMRD was reached among 26.4%. Among the patients with CR mMRD detectable vs. undetectable: 15/67 (22.4%) vs 11/24 (45.8%) (SE: -0.151, p:0.03) points to a correlation between mMRD levels and biochemical response. Among 39/91 gMRD(-) patients, undetectable mMRD(-) was also observed in 46.2%. A statistically significant correlation between gMRD and mMRD (SE: 0.364, p<0.001) was calculated. Patients with undetectable gMRD displayed a better PFS compared to patients with detectable gMRD (NR vs 37.5 months). There were insignificant differences in median PFS according to the undetectable mMRD (n=24) at level 10-5 vs 10 -4 (NR vs 37.5 months; p=0.9). In addition, achievement of post-induction undetectable mMRD plus gMRD was also associated with improved PFS (HR: 0.04 p=0.01) with no relapse. Having detectable MRD in either graft or marrow estimates a 2 years-PFS of 61.1 % (p=0.07). **Conclusions:** Our real-world triplet drug induction-based experience shows for the first time postinduction marrow and graft MRD to be correlated with each other and with PFS. A non-invasive cellular residual disease measurement within graft at either 10-4 or 10-5 level may be an additional end point for therapeutic efficacy.

P-039

Adaptation of a myeloma minimal residual disease multi-parametric flow assay for real world practice

Annabel McMillan[1], Thien-an Tran[2], Daria Galas-Filipowicz[3], Yanping Guo[3], Marquita Camilleri[4], Ke Xu[4], Lydia Lee[4], Xenofon Papanikolaou[4], Charalampia Kyriakou[4], Neil Rabin[4], Rakesh Popat[4], Kwee Yong[3], Jonathan Sive[4]

[1]Whittington Hospital; [2]University Hospital of Geneva; [3]University College London; [4]University College London Hospitals NHS Foundation Trust

Background: Achieving minimal residual disease (MRD) negativity during treatment for multiple myeloma (MM) is prognostic for disease free and overall survival. There is limited testing of MRD outside clinical trials, and the need to process fresh samples for multicolour flow cytometry (MCF) assays presents a challenge to laboratories. We set up an 8-colour MCF assay, in collaboration with a reference centre (Leeds HMDS), to identify and quantify malignant plasma cells in bone marrow (to limit of detection 10-5), using a BD LSRFortessaTM Flow Cytometer. We developed a fixation protocol, removing the need for immediate flow cytometer access and carried out a pilot study of MRD status in patients treated with standard non-trial protocols. **Methods:** Initially, 43 fresh samples were processed in parallel with duplicate samples sent to Leeds, with 100% concordance in MRD result. We optimised a novel fixation technique, processing and staining samples within 24 hours, before using 0.4% paraformaldehyde (PFA) to fix, and storing at 4°C, permitting data acquisition up to 6 days later. We tested this on 24 samples and confirmed concordance between fresh and fixed samples, with good correlation in MRD level (Pearson's correlation co-efficient; r=0.95 (95% CI 0.89-09.8); r2= 0.91; p=<0.0001), minimal bias (Bland-Altman; 0.04), and no change in plasma cell phenotype by flow markers. There was no difference comparing fresh samples with those fixed for 1-3 days or 4-6 days. **Results:** Between July 2020 and June 2021, MRD was performed on 76 samples, with 24% (18/76) fixed to facilitate processing. All samples were from transplant eligible MM patients,

with 58 post-induction therapy, on aspirates performed for restaging prior to autologous stem cell transplantation (ASCT). This cohort represents a UK real-world snapshot, with complete response in 28% (16/58) post-induction with NICE-approved bortezomib-based triplet regimens. 17% (10/58) of samples were MRD negative, with no difference in post-induction MRD level between patients with or without R-ISS-defined high-risk cytogenetics (p=0.72). 18 post-ASCT samples were analysed, and 8 (44.4%) were MRD negative; in 8 of these with matched pre-ASCT samples (all MRD positive), 4 were MRD negative post-ASCT. The number of MRD negative samples was significantly higher post-ASCT (p=0.02). **Conclusions:** In summary, we describe an adaptation of the Leeds HMDS 8-colour MRD assay to include a novel fixation step, permitting batching for flow cytometric analysis, without affecting sample validity. This real-world snapshot suggests that less than 20% of patients are MRD negative post standard UK induction therapy, but this increases post-ASCT. Further work on larger cohorts and longer follow up will confirm the prognostic value of MRD assessments outside the trial setting and establish its utility in real world practice.

P-040

CD138-independent strategy to predict relapse in Multiple Myeloma patients

Barbara Muz[1], Feda Azab[1], Mark Fiala[1], Ravi Vij[1], Kareem Azab[1]

[1]Washington University in St. Louis

Background: CD138 has been the gold-standard surface marker to detect multiple myeloma (MM) cells for decades; however, drug resistant minimal-residual disease (MRD) and circulating tumor cells (CTCs) were shown to have lower expression of this marker. We previously published that residual MM cells following treatment in vivo were hypoxic and the combination of hypoxia and chemotherapy such as bortezomib downregulated CD138 expression, thereby making this marker unsuitable for MM detection. Needless to say, accurate number of MM cells is critical in diagnosis, autologous transplantation, MRD and drug efficiency assessment. Moreover, CTCs are considered an unfavorable prognostic factor and indicate an aggressive form of the disease, and therefore detecting CTCs can be used as a powerful prognostic tool for MM. **Methods:** We used an alternative biomarker-set using flow cytometry defining MM cells as any cell that expresses CD38 but excluding T cell (CD3), B cell (CD19), NK cell (CD16), monocyte/macrophage (CD14), neutrophil/eosinophil (CD16), and basophil/dendritic cell (CD123). We demonstrated previously that this approach it widely available due to accessibility of flow cytometry, inexpensive, and works independently of hypoxic-, CD138 expression- and treatment status. We analyzed primary patient samples (n=50) with complete response or very good partial response for MRD and CTCs and correlated the numbers of detected MM with patients' time-to-progression (TTP) obtained from a clinical data base. **Results:** We found that the alternative biomarker-set identifies MM cells more precisely and at higher numbers than CD138 marker by flow or histology. Moreover, we found a correlation between the number of MM cells detected and TTP in these patients: the amount of MM cells detected by the new method ranged between 0.5-7.3%, and patients who progressed sooner than two years had 2.5-fold higher percentage of MM cells compared to patients who relapsed later than 2 years. Similarly, patients who relapsed sooner than 3 years had 4-fold higher number of MM cells than patients who relapsed later than 3 years. We further found that, among all patients who had more than 2% of MM cells detected by the new method had a mean TPP of about 20 months, while patients who had less than 2% had a mean TPP of about 38 months. Testing the prevalence of CTCs in MM patients with progressive disease using CD138 or the new method, demonstrated that CD138 detected minimal amounts of MM cells in all patients (less than 0.1%), while the new method detected a range between 0.1 - 1.8% of MM cells in the peripheral blood. **Conclusion:** These results suggest that the alternative biomarker-set detected MM cells which correlated with relapse in MM patients. Therefore, the amount of residual cells in the bone marrow and circulating myeloma cells can be used as a prognostic marker in MM patients. Further examination to characterize this population and its role in MM relapse is warranted.

P-041

The role of Lenalidomide maintenance and measurable residual disease in a real-life multiple myeloma transplanted population receiving different strategies guided by accessible treatments in Brazil

Anna Beatriz Salgado[1], Roberto J. Magalhães[2], Roberia Pontes[3], Eduarda Barbosa[1], Glicinia Pimenta[1], Helio Dutra[1], Juan Flores-Monteiro[4], Luzalba Flores[5], Alberto Orfao[4], Elaine Costa[1], Angelo Maiolino[2]

[1]Universidade Federal do Rio de Janeiro - UFRJ; [2]Universidade Federal do Rio de Janeiro; [3]Hospital da Criança de Brasília; [4]Translational and Clinical Research Program, Cancer Research Center, Cytometry Service and Department of Medicine, University of Salamanca; Centro de Investigación Biomédica en Red de Cáncer, Instituto Carlos III.; [5]Centro de Investigación Biomédica en Red de Cáncer, Instituto Carlos III; Institute of Biomedicine of Seville, Department of Hematology, University of Seville

Background: Multiple myeloma (MM) treatment and monitoring with MRD-Next Generation Flow (NGF) has evolved fast in the last decade. Nevertheless, its incorporation by low-middle income countries remains challenging. Despite Lenalidomide maintenance (M-Len) after ASCT improves PFS and OS of MM, and MRD-NGF monitoring can discriminate patients (pts) with better outcomes, there is no data about these approaches in real-world pts in Brazil (BR) and Latin America. **Methods:** Here we evaluated in two cohorts of pts guided by drug access, the benefit in outcomes of M-Len and MRD-NGF monitoring after ASCT. The study enrolled pts from public and private healthcare systems (HS). A total of 53 pts with symptomatic MM receiving up-front CTD n=27 or VCD n=26. All pts had a BM sample at D+100 for MRD-NGF following the EuroFlow SOPs with a limit of detection of 10-6

and a complete protein profile to meet the IMWG response and MRD criteria. **Results:** Residual clonal plasma-cells were detected by MRD-NGF in 60% of all pts and in 44% of those in CR/sCR. MRD+ pts and showed a significant inferior outcome in this setting with median PFS of 26 months vs NR (p=0.05). Since Len was restricted to private HS, we evaluated its impact in a subset of 18 pts (30%), with a median treatment time of 20.5 months. In this group only, 2/18 (11%) cases progressed whereas in those with no M-Len, progression occurred in 19/35 (54%), with median PFS NR vs. 21 months (p=0.001). This benefit extended to OS, since in the M-len group had no deaths, in contrast to 11/35 (31%) (p=0.01) deaths without this drug. Combining the M-Len and MRD-NGF monitoring post ASCT allowed the recognition of distinct group outcomes: M-Len /MRD- (n=7) vs no M-Len/MRD+ (n=21) with median PFS NR vs 16 months (p=0.003). The benefit of maintenance improving disease control was clear among MRD+ pts (n=11) vs MRD+ pts with no M-Len (n=21): median PFS NR vs 16 months (p=0.002) and median OS NR in both groups but with a significant difference in the former (p=0.02). In our cohort, most pts admitted to the public HS had access to CTD without Len maintenance (n=24; 45%), while in the private received bortezomib in induction and M-Len post-transplant (n=15; 28%) with some pts having partial access with VCD/ no M-Len (n=11; 22%) or CTD/ M-Len (n=3; 5%). Comparing strategies by drug access CTD/no-M-len in public vs VCD/M-len in private had an impact on both PFS (median of 16 months vs NR; p=0.003) and OS (median NR vs NR; p=0.02). Patients that had access to PI in induction without M-len also had worse outcomes: median PFS NR vs. 21 months for VCD/M-Len vs VCD/no M-Len, respectively (p=0.01), with a trend in OS (p=0.06). **Conclusions:** In real-life, the use of M-Len post-ASCT is associated with better survival outcomes, MRD-NGF was a reproductible and powerful tool to discriminate pts at higher and earlier relapse risk. Inequity of drug access remains a hurdle in countries with constraints, particularly in public HS with a negative impact on survival of MM.

P-042

Sustained minimal residual disease negativity in Multiple Myeloma is impacted positively by stool butyrate and healthier plant forward diets

Urvi Shah[1], Andriy Derkach[1], Peter Adintori[1], Justin Cross[1], Kylee Maclachlan[1], Sham Mailankody[1], Neha Korde[1], Malin Hultcrantz[1], Hani Hassoun[1], Carlyn Tan[1], Sydney Lu[1], Dhwani Patel[1], Gunjan Shah[1], Michael Scordo[1], Oscar Lahoud[1], David Chung[1], Heather Landau[1], Sergio Giralt[1], Ying Taur[19], Ola Landgren[1], Torin Block[2], Jonathan Peled[1], Marcel van den Brink[1], Alexander Lesokhin[1]

[1]Memorial Sloan Kettering Cancer Center; [2]Nutrition Quest

Background: Sustained minimal residual disease (MRD) negativity is associated with improved myeloma (MM) outcomes. The gut microbiome can modulate host immunity through production of short-chain fatty acids, especially butyrate. Stool butyrate-producers are enriched in MRD negative MM (Eubacterium, Faecalibacterium; Pianko et al. 2019) and are associated with post-transplant survival (Eubacterium; Peled et al. 2017). However, microbial features associated with sustained MRD negativity and diet which may impact microbiome and in turn MM outcomes have not been explored. Herein we evaluate the association of diet and microbiome with sustained MRD negativity in MM in the context of lenalidomide maintenance. **Methods:** MM patients eligible for lenalidomide maintenance during first-line therapy were enrolled (NCT02538198). MRD status was evaluated at baseline and annually with BM flow-cytometry (sensitivity >10-5). Sustained MRD negativity was defined as MRD negative for 1 year from enrollment. The relative abundance of butyrate producers and microbiome a[ED]-diversity were calculated from fecal 16S microbiome profiles at baseline, 3 months (m) and annually, along with quantification of fecal butyrate levels at 3m. Dietary patterns were collected using the Block Food Frequency Questionnaire (FFQ), for habitual diet and summarized via the Healthy Eating Index 2015 (HEI2015) scores in which higher scores imply healthier diets. The association between dietary and microbiome data were evaluated by Spearman's rank correlation coefficient. Logistic regression was used to evaluate association between MRD status at 1 year (Y) and microbiome and dietary measurements. Statistical significance was defined using a two-sided significance level at 0.05. **Results:** We had 49 patients with stool samples at 3m, 30 patients at Y1, 32 with stool butyrate levels at 3m, 59 with FFQ data, and the overlap between FFQ and stool samples was 34. The abundance of butyrate producers and/or butyrate levels were significantly associated with total HEI2015 and its components – total vegetables, dark green vegetables, legumes, whole grains, total protein, seafood and plant protein, fatty acids, refined grains, added sugars. Some aspects of healthier HEI score components (especially seafood and plant proteins) were associated with higher stool butyrate producers and butyrate levels at 3m, and sustained MRD negativity at Y1. Additionally, increased diversity, butyrate levels and butyrate producers at 3m was associated with increased MRD negativity at baseline and with sustained MRD negativity. **Conclusion:** In MM patients on lenalidomide maintenance, healthier diets (especially seafood and plant proteins) were associated with increased butyrate at 3m and in turn with higher MRD negativity. This is the first study to demonstrate an association between diet, microbiome, and sustained MRD negativity and provides a rationale for evaluating a targeted dietary intervention prospectively.

P-043

Comparison of MRD detection of autografts in multiple myeloma between novel high-sensitivity EuroFlow-NGF and NGS

Ryota Urushihara[1], Naoki Takezako[2], Takeshi Yoroidaka[2], Takeshi Yamashita[3], Shinji Nakao[1], Hiroyuki Takamatsu[4]

[1]Department of Hematology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa

University; [2]Department of Hematology, Disaster Medical Center of Japan, Tokyo, Japan; [3]Division of Internal medicine , Keiju Kanazawa Hospital; [4]Faculty of Transdisciplinary Sciences, Institute of Transdisciplinary Sciences, Kanazawa University

Background: Autologous stem cell transplantation (ASCT) is still a gold standard treatment in multiple myeloma (MM). So far, we have reported the prognostic value of minimal residual disease (MRD) detection in autografts at ASCT setting using EuroFlow next-generation flow (NGF) and next-generation sequencing (NGS) (Takamatsu et al, ASH 2018). The main problem of EuroFlow-NGF is its lower sensitivity (2×10^{-6}) compared with that of NGS ($<1\times10^{-6}$). **Methods:** The study enrolled 9 newly-diagnosed MM patients whose frozen autografts' cells were preserved. The median age at ASCT was 52 (range 47-61) years and included 4 males and 5 females at ISS I (n=2), II (n=6) and III (n=1). Of there, 4 patients harbored high-risk chromosomal abnormalities including t(4;14) (n=1), t(14;16) (n=1), del17p (n=1), and t(4;14) and del 17p (n=1). All patients received bortezomib-based chemotherapy for induction together with melphalan at 200 mg/m^2 for conditioning before ASCT. Two patients received consolidation therapy with carfilzomib-lenalidomide-dexamethasone (KRD) and all patients received lenalidomide maintenance until progressive disease. Frozen autografts (n=9) and primary myeloma cells (n=1) were thawed for MRD assessment by EuroFlow-NGF and NGS. The EuroFlow-NGF method was based on the previous report (Flores-Montero et al., Leukemia 2017). NGS-based MRD assessment was performed using Adaptive's standardized NGS-MRD Assay (Seattle, WA) (Ching et al., BMC Cancer 2020). The EuroFlow-NGF method was modified to increase the sensitivity of MRD by capturing cells up to 5×10^{7}. **Results:** Because frozen autografts were used in this study, we performed the sensitivity test using the dilution of frozen/thawed primary MM cells in an autograft by EuroFlow-NGF. The sensitivity test revealed a strong correlation between 1×10^{-7} and 1×10^{-4} of MRD level (r=0.9996, p<0.0001). Next, MRD in autografts (n=9) was evaluated using EuroFlow-NGF and NGS. The sensitivity of NGS was 6×10^{-7}–8.7×10^{-5} (median, 8×10^{-7}) using 2–4 mL of autografts; the sensitivity of EuroFlow-NGF was 4×10^{-7}–8×10^{-7} (median, 5×10^{-7}) using up to 20 mL of autografts. MRD levels in autografts using EuroFlow-NGF and NGS correlated with one another (r = 0.9964, P < 0.0001). There was no discrepancy of MRD levels between both methods: negative (n=2), 10^{-6}-10^{-5} (n=4), 10^{-5}-10^{-4} (n=2), 10-4 < (n=1). All high-risk chromosomal abnormality cases (n=4) achieved MRD level $<10^{-5}$. The response on day 100-300 post-ASCT included 6 sCR, 2 CR and 1 VGPR before consolidation/maintenance therapy and all patients achieved sCR at two years post-ASCT and maintained it at three years post-ASCT during lenalidomide maintenance. No progression was observed. **Conclusions:** This modified EuroFlow-NGF method can assess MRD of frozen/thawed autografts and its sensitivity can be increased up to 4×10^{-7} that is comparable to NGS.

P-044

Comparison of 10 Color Flowcytometry and PET/CT for prognosticating MM post-transplant: results from IMPOSE-BORTECON trial

Uday Yanamandra[1], Ankur Ahuja[2], Rajan Kapoor[2], Suman Pramanik[2], Satyaranjan Das[3], Harshit Khurana[3], Kundan Mishra[2], Rajeev Kumar[2], Sanjeevan Sharma[3], Tathagata Chatterjee[2], Velu Nair[2]

[1]Armed Forces Medical College; [2]Army Hospital Research & Referral; [3]Command Hospital Southern Command

Background: The primary hurdle in curing MM is defining a validated minimal residual disease (MRD). Commonly used techniques for assessing MRD in India are multicolor flow cytometry (MFC) and PET/CT. We intended to compare the efficacy of the 10 Color-MFC and PET/CT for prognosticating MM post-transplant. **Methods:** The study is a prospective multicentric randomized controlled study – IMPOSE BORTECON (AFMRC-4905/2016). The primary objective was to compare the PET/CT and MFC for prognosticating the MM patients post-transplant for OS. The secondary objectives were to evaluate universal availability and applicability, patient satisfaction scoring, and financial implications of the MRD techniques. The data from patients enrolled till 31 Dec 2020 were analyzed. All patients underwent MFC and PET/CT (within seven days gap) starting D+100 post-transplant four times at six-monthly intervals. 18F-FDG-PET/CT was scored using IMPeTUs scoring with Deauville 3 considered as Positive (Target Lesion SUVmax > Liver SUVmax). Two readers interpreted the reports with a CoV of 1.2%. MFC was done using Beckmann Coulter, 10 Color 2 tube technique with standard antibodies as EMN guidelines, with the single reader, and all reports were counterchecked by the company scientist for accuracy. PFS and OS were defined as per IMWG guidelines. JMP 15.0 was used for data analysis. **Results:** Of 106 patients constituting 434 simultaneous MRD evaluations, the median age was 52 years (35-66) with male preponderance (61.3%). Of all the patients analyzed, the 2y and 3y were 80% and 60.4%. 29.8% were positive for MRD by MFC, and 37.2% were positive for PET/CT. PET positivity was preceded by a mean of 102d before MFC positivity (SD-338d). On average, PET/CT was positive six months before the MFC and 12 months before clinical relapse by swimmer's analysis. PET/CT positivity was significantly associated with inferior OS compared to positive MFC (p<0.001, p-0.239 respectively) using Kaplan-Meier analysis. The concordance between MFC and PET-CT was not statistically significant (R=-0.101, p-0.7811). Universal availability of MFC was more difficult owing to a lack of standardization and expertise to report the test in real-world settings. On the evaluation of patient feedbacks, 18 patients withdrew consent due to fear of repeated bone marrows for MRD by MFC. Costs were comparable by Markov analysis. **Conclusion:** We have reported higher efficacy of positive PET/CT in predicting the inferior OS than MFC in MM post-transplant. The results of the PET/CT are more easily interpretable, with PET/CT being more acceptable to patients and more widely available with no additional costs. This is the first study from our country to compare the two MRD analysis methods in MM patients.

P-045

Immunoglobulin V(D) J Recombination, Protein Ubiquitination, Cell Adhesion and Sonic Hedgehog Gene Variants are detected among familial Multiple Myeloma subjects following whole exome sequencing

Erman Akkus[1], Timur Tuncali[2], Yildiz Aydin[3], Sevgi Kalayoglu Besisik[4], Emel Gurkan[5], Siret Ratip[6], Ayse Salihoglu[7], Deniz Sargin[8], Ali Unal[9], Aysegul Turcan[10], Meral Beksac[11]

[1]Department of Internal Medicine, Ankara University, Faculty of Medicine, Ankara, Turkey; [2]Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Turkey; [3]Department of Hematology, Florence Nightingale Hospitals, Istanbul, Turkey; [4]Department of Internal Medicine, Division of Hematology, Istanbul University Medical Faculty, Istanbul, Turkey; [5]Department of Hematology, Cukurova University Faculty Of Medicine, Adana, Turkey; [6]Department of Hematology, Acibadem Healthcare Group, Istanbul, Turkey; [7]Department of Hematology, Istanbul University Cerrahpasa Faculty Of Medicine, Istanbul, Turkey; [8]Department of Hematology, Medipol Healthcare Group, Istanbul, Turkey; [9]Department of Hematology, Erciyes University Faculty Of Medicine, Kayseri, Turkey; [10]Society of Cancer Fighters, Turkey; [11]Department of Hematology, Ankara University, Faculty Of Medicine, Ankara, Turkey

Background: Familial multiple myeloma(MM) cases have been associated with some rare, germline variants, mostly among epigenetic modification genes and needs to be validated in other populations. The aim of this study is to investigate formerly reported rare variants in our population and to search for additional ones. **Methods:** Following the ethical committee approval, hematology centers in Turkey were informed for collaboration in this familial MM genetic association study. Inclusion criteria was defined as having one or more first, second or third degree relatives who have plasma cell diseases. After obtaining informed consents, patients' peripheral blood samples or DNAs from pathological samples were collected. NGS analysis have been performed on 33 samples from 23 families, targeting 14 variants in 6 genes, previously reported to be associated with familial presentation (EP300, CDKN2A, USP45, ARID1A, KDM1A, DIS314)(Pertesi et al., Leukemia, 2020). To widen the range of analysis, whole exome sequencing (WES) within 3 families (6 patients) of first degree relatives were carried out. The detected variants were checked against NCBI's dbSNP. Mutation Taster was utilized for probable disease associations. **Results:** 30 MM families(63 patients) were included. Of the patients 69% were first, 4% were second and 27% were third degree relatives. Neither of the previously reported rare variants were detected among the subjects in the targeted sequencing. However, an heterozygote variant (rs3731249) close to the targeted region in CDKN2A was detected in 3 patients. WES detected new variants which were not observed earlier. Family 1:Missense variants in BRIP1 (function: DNA double strand break repair)(rs886053214, rs886053215) and ACD (function: maintain telomere length)(rs1306270247). All of which were predicted as polymorphism, in silico. Family 2:Missense variant in RAG2 (function:V(D)J recombination of Ig and T cell receptor) (rs765298019) predicted as disease causing. Family 3:Missense variant in RET (function: receptor tyrosine kinase)(rs1366681125) predicted as polymorphism. Missense variants in CBL (function: protein ubiquitination)(rs754194646), APC (function: cell adhesion)(rs760591046) and PTCH1 (function: sonic hedgehog) (rs772574714) were predicted as disease causing. All of the variants from the patients were detected as one-copy-alleles. The variant in RAG2 was reported to cause severe combined immunodeficiency and histiocytic medullary reticulosis in homozygous state. The PTCH1 variant is known to give rise to nevoid basal cell carcinoma syndrome. Germline mutations of CBL and APC are related to the juvenile myelomonocytic leukemia, familial AML and familial adenomatous polyposis respectively. **Conclusion:** MM development is a multistep process. As of actual literature, MM susceptibility in familial cases involve various gene variants. Here we suggest the consideration of RAG2, CBL, APC, PTCH1 as additional loci for the progression to familial MM.

P-046

B cell transcriptional coactivator POU2AF1 (BOB-1) modulates the protein synthesis and offers a potential vulnerability in multiple myeloma.

Zuzana Chyra[1], Mehmet K Samur[2], Anil Samur[1], Yao Yao[1], Sanika Derebail[1], Tommaso Perini[3], Yan Xu[4], Eugenio Morelli[5], Sophia Adamia[1], Woojun D Park[6], Charles Lin[6], Ryosuke Shirasaki[1], Constantine Mitsiades[1], Masood Shammas[7], Roman Hájek[8], Mariateresa Fulciniti[5], Nikhil C. Munshi[9]

[1]Dana Farber Cancer Institute; [2]Dana-Farber Cancer Institute, Boston, USA; [3]San Raffaele Scientific Institute; [4]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; [5]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [6]Baylor College of medicine; [7]Dana Farber Cancer Institute and VA Boston Healthcare System, Boston, MA, USA; [8]Department of Hemato-oncology, University Hospital Ostrava and University of Ostrava; [9]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: Multiple Myeloma (MM) is a disease driven by numerous genetic and epigenetic alterations, however true drivers of the disease have yet to be identified. **Methods:** To identify new dependencies and actionable therapeutic targets in MM we integrated gene expression and genetic dependency (CRISPR KO). **Results:** We found that many of the specific and potent dependencies in MM are transcription factors, especially those establishing plasma

cell identity. Among others, the POU2AF1 gene, which encodes the OCA-B/BOB-1, a B cell transcriptional coactivator protein, represented the most striking dependency in MM. Although BOB-1 is expressed throughout B-cell development, we found it to be highly expressed in CD138+ plasma cells from patients with precursor conditions (MGUS and SMM) as well and established MM compared to normal plasma cells (NPC). Loss-of-function studies using shRNA, siRNAs as well as antisense GapMers specific for BOB-1 confirmed significant impact on MM cell viability. Transcriptomic analysis by RNA-sequencing revealed a small set of genes commonly modulated in MM cell lines upon BOB-1 depletion, including the XBP1- BHLHA15 axis involved in lipid synthesis and unfolded protein response (UPR). Interestingly, among the genes most significantly upregulated by BOB-1 depletion was heme oxygenase 1 (HMOX1), that was affected via the NRF2/Keap1 pathway. We observed that HMOX1 expression is significantly lower in MM cells from patients compared to normal plasma cells and correlates with poor clinical outcome, suggesting important role in MM. Moreover, we found that siRNA depletion of HMOX1 reverted the inhibition of MM cell growth caused by BOB-1 KD, confirming significant role for HMOX1 in the BOB-1 addiction observed in MM cells. Next, we performed gene set enrichment analysis (GSEA) and observed ribosome biogenesis pathways and mRNA translation and elongation processes, along with WNT and senescence pathways, to be significantly enriched among genes modulated by BOB-1 depletion in MM cells. Since high protein load is a feature of MM, we evaluated the role of BOB-1 in the translational efficiency of MM cells. In MM cell lines, BOB-1 knockdown decreased de novo protein synthesis, while its overexpression significantly enhances protein synthesis compared to control cells. As MM is characterized by excess production of monoclonal immunoglobulins, we evaluated impact of BOB-1 perturbation on intracellular kappa and lambda light chains production. We observed changes in the intracellular abundance of the light chains with BOB-1 modulation in all MM cell lines tested. As a result, BOB-1 depletion was associated with induction of resistance to proteasome inhibition. **Conclusion:** In conclusion, we report BOB1 as a specific dependency in MM cells with potential role on modulating the protein load/capacity balance in MM cells and therefore the sensitivity to proteasome inhibition.

P-047

Clonal evolution in multiple myeloma evaluated by Whole Exome Sequencing

Ritu Gupta[1], Gurvinder Kaur[1], Akanksha Farswan[2], Lingaraja Jena[1], Anubha Gupta[2], Lata Rani[1], Lalit Kumar[1], Atul Sharma[1]

[1]AIIMS, New Delhi; [2]IIIT, Delhi

Background: Multiple Myeloma (MM) is a plasma cell malignancy characterized by heterogeneous genomic and clinical profiles. Several molecular anomalies may arise clonally prior to diagnosis and continue to evolve temporally with disease progression. These evolving clones may follow either of the evolutionary patterns viz., stable /stable with loss of clone(s)/ linear with a gain of clone(s)/ branching with both loss and gain of clone(s). While founder clones may initiate and drive the pathogenesis, the later (sub)clones may modulate response to therapy and facilitate relapse. This study was designed to investigate temporal changes in the prevalence of clonal mutations with time in MM and if any of these can be defined as actionable. **Methods:** We have sequenced whole exomes of CD38+ enriched plasma cells obtained from 62 MM patients collected at two-time points, i.e., at diagnosis and on progression using Nextera Exome kit and HiSeq2500 sequencer (Illumina). Somatic variants were called using Illumina's Dragen somatic pipeline. **Results:** A marked intraclonal heterogeneity was observed. Branching clonal evolution was observed as most common in more than 70% of patients followed by Linear and Stable with loss of clone in ~15% patients each. Most of the patients with a branching pattern of clonal evolution also had low TMBs (<10) and 2 or 3 founder clones. This study has shown distinct changes in the clonal prevalence of driver genes including oncogenes and tumor suppressor genes during longitudinal follow-up. A few driver genes were found to increase in prevalence (e.g. CCND1, CYLD) while others reduced (e.g. ARID2, HIST1H1D, NCOR1) or remained consistent (e.g. RB1, IRF4) on progression. Similar changes in clonal prevalence were observed for a few actionable genes such as BRAF from diagnosis to progression. **Conclusion:** These findings support the notion that evaluation of mutational landscapes in a time-phased manner may be important in discerning actionable mutations and decision-making for risk-adapted therapies.

P-048

Clinical application of the weighted cytogenetic scoring system in Multiple Myeloma

Yu Yan Hwang[1], Chi Yeung Fung[1], Lisa Siu[2], Ho Wan Alvin Ip[3], Sze Fai Yip[4], Ka Ngai Harry Lau[4], Chi Kuen Lau[5], Harold Lee[6], Kwan Hung Leung[7], Bonnie Kho[8], Howard Wong[8], Cheong Ngai[3], Hoi Ki Karen Tang[3], Joycelyn Sim[3], Yok Lam Kwong[3], Chor Sang Chim[3]

[1]Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong; [2]Department of Pathology, Queen Elizabeth Hospital, Hong Kong; [3]Department of Pathology, Queen Mary Hospital, University of Hong Kong, Hong Kong; [4]Department of Medicine, Tuen Mun Hospital, Hong Kong; [5]Department of Medicine, Tseung Kwan O Hospital, Hong Kong; [6]Department of Medicine, Princess Margaret Hospital, Hong Kong; [7]Department of Medicine, United Christian Hospital, Hong Kong; [8]Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong

Methods: Utility of the weighted cytogenetic scoring system (wCSS) was studied in 250 myeloma patients with complete data on high-risk FISH [t(4;14), t(14;6), del(1p32), amp(1q21) and del(17p)] and lactate dehydrogenase (LDH). **Results:** All patients had bortezomib-based induction, with triplet induction in 88%. Sixty-four (26.2%) had ISS I, 75 (30.7%) stage II and 105 (43%) stage III MM. Fifty-two patients (21.2%) had t(4;14), 25 (10%) del(17p), 26

(10.4%) del(1p32) and 83 (66.8%) amp(1q21). Fifty-nine (23.9%) had wCSS=0, 144 (58.3%) wCSS>0 to ≤1 and 44 (17.8%) wCSS>1. Median survival were 168, 80 and 37 months for wCSS=0, >0 to ≤1, and wCSS>1 respectively (p=9.4 x 10-7). wCSS>1, of which 56.8% had del(17p), was not associated with gender, isotype, ISS III, high LDH or post-induction CR. **Conclusion:** The adverse impact of wCSS>1was partially mitigated by ASCT. Therefore, wCSS is valid in our real-life cohort of myeloma uniform receiving a bortezomib-based triplet induction even without trisomy data.

P-049

The spatial sub-clonal architecture in newly diagnosed myeloma patients revealed by whole genome and single-cell sequencing

Lukas John[1], Alexandra Poos[1], Stephan Tirier[2], Jan-Philipp Mallm[3], Nina Prokoph[4], Alexander Brobeil[5], Sabrina Schumacher[2], Simon Steiger[3], Katharina Bauer[6], Anja Baumann[7], Christoph Rehnitz[8], Carsten Müller-Tidow[9], Hartmut Goldschmidt[10], Stefanie Huhn[11], Karsten Rippe[2], Marc Raab[1], Sandra Sauer[12], Niels Weinhold[1]

[1]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [2]Division of Chromatin Networks, German Cancer Research Center (DKFZ) and BioQuant, Heidelberg; [3]German Cancer Research Center (DKFZ), Heidelberg, Germany; [4]Department of Internal Medicine V, University Hospital Heidelberg; [5]Department of Pathology, University Hospital Heidelberg, Heidelberg, Germany; [6]Open Lab for Single Cell Sequencing (scOpenLab), German Cancer Research Center (DKFZ) and BioQuant, Heidelberg; [7]Clinical Cooperation Unit (CCU) Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg; [8]Department of Radiology, University Hospital Heidelberg, Heidelberg, Germany; [9]Heidelberg University Hospital; [10]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT); [11]Multiple Myeloma Section, Department of Internal Medicine V, University Hospital Heidelberg; [12]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg

Introduciton: Tumor heterogeneity plays a significant role in the development of therapy resistance in multiple myeloma (MM). Focal accumulations of myeloma cells called focal lesions (FLs) have been shown to be the hotspots of spatial tumor heterogeneity, which is characterized by unique tumor sub-clones at different sites in the bone marrow (BM). However, little is known about the sub-clonal architecture in FLs, the mechanisms leading to site-unique mutations, and the link between sub-clones in FLs and treatment-resistance. **Methods:** To fill this gap in knowledge, we used a comprehensive approach to characterize CD138-sorted tumor cells from FLs and random BM aspirates (RBMA) in 12 newly diagnosed MM patients, applying whole genome sequencing (WGS), single-cell(sc)-RNA-sequencing and sc assay for transposase-accessible chromatin (ATAC)-sequencing. Sc data was generated using the 10X Genomics platform. Pre-processing of the sc data was performed with CellRanger and the R-packages Seurat, ArchR and inferCNV were used for downstream analysis. WGS data was analyzed using inhouse pipelines. Mutations, copy-number-variations and mutational signatures were called using mpileup, ACESeq and mmsig. Neoantigen epitopes were predicted using NeoPredPipe. **Results:** In the majority of patients (n=10/12) we found significant differences in the chromosomal and mutational profiles between FLs and paired RBMAs from the iliac crest. To identify the mechanisms underlying heterogenous mutations, we performed mutational signature analysis and found COSMIC signature SBS18 to be enriched in these mutations, suggesting that they were caused by reactive oxygen species. Interestingly several site-unique mutations were predicted as potential neoantigens. Driver gene mutations associated with relapse such as KRAS, CYLD, CDKN2C and TP53, were more often seen in FL sub-clones. Using a combination of WGS, sc-RNA and sc-ATAC-sequencing to characterize these sub-clones in more detail, we found increased regulatory accessibility and expression of genes associated with disease aggressiveness and drug resistance such as CXCR4 and members of the NFKB- and interferon pathways. The latter implies that FLs could play a significant role in the development of treatment resistance. Indeed, comparing sub-clones at baseline and after high-dose melphalan and autologous stem cell transplantation in one patient, we demonstrate expansion of a single tumor cell, which was closely related to the main sub-clone from the baseline FL. **Conclusion:** In conclusion, our data provides novel insights into the mechanisms underlying site-unique mutations and the sub-clonal architecture at different sites in the BM. The combination of bulk and sc-techniques showed that FLs are enriched for sub-clones with genetic, transcriptional and regulatory markers characteristic for aggressive disease and can be the source of relapse in MM-patients. This implies that targeting FLs is essential for achieving a cure of MM.

P-050

Whole Exome Sequencing provides novel insights in synonymous and non-synonymous mutational landscapes of Multiple Myeloma

Gurvinder Kaur[1], Ritu Gupta[2], Lingaraja Jena[1], Akanksha Farswan[3], Anubha Gupta[3], Lalit Kumar[4], Lata Rani[1], Atul Sharma[1]

[1]AIIMS, New Delhi; [2]Lab Oncology, Dr BRAIRCH, AIIMS, New Delhi; [3]IIIT, Delhi; [4]Medical Oncology, Dr BRAIRCH, AIIMS, New Delhi

Background: Recent NGS based genomic studies have established the role of temporal precedence of mutational signatures that initiate and drive pathogenesis of Multiple Myeloma (MM). Almost 100 driver genes have been identified and investigated extensively for driver mutations in MM but their clinical impact remains underestimated. While coding nonsynonymous mutations have been well characterized, the synonymous mutations that can

regulate and impact gene function have not been investigated in depth. In this study, we have co-analyzed both synonymous and nonsynonymous mutations in whole exomes of MM and compared with reported literature for ethnic differences, if any. **Methods:** Whole exome sequencing was performed on malignant plasma cells (PCs) obtained from 71 newly diagnosed MM patients. **Results:** Both synonymous (S) and nonsynonymous (NS) substitutions were analyzed. The C>T substitutions were most common. Other than age linked SBS5, SBS1, ID2, ID8; mutational signatures such as APOBEC related DBS11, defective DNA mismatch repair related SBS15 were also identified. The patients had an average tumor mutation burden of ~10. Nearly half of nonsynonymous mutations were clonal. The most common NS mutations were missense (~18000) followed by those in splice (~3000), 3' or 5'UTR regions (~1500) and nonsense or frameshift (~200). The most frequently mutated oncogenes with NS mutations included KRAS, BRAF, DIS3, TET2 and CREBBP while the commonly NS mutated tumor suppressor genes were KMT2C, ATM, KMT2B and TP53. Frequency of NS mutations in TP53 (~7%) in this study were significantly different from those reported for African American (1.6%) and more closer to Caucasian (6.3%). Mutations (NS) in PARP4 were found at a frequency of 3.9% which is similar to African American (3.9%) and different from Caucasian (1%). In addition, 6 different synonymous mutations were also observed in this gene at a frequency ~ 2% in MM patients in this study. Gene IRF4 also had both NS (3%) and S (~1.5%) mutations. The IRF4 NS mutation frequency (3%) is comparable with Caucasian (3.2%) while it doesnot exist among African Americans (0%). **Conclusion:** In analogy, oncogenes (e.g., LMO2, ARHGEF28, NOTCH1, RET, NOTCH2, DDR2) and tumor suppressor genes (like KMT2C, EP400, RASA2, CYLD) were enriched in synonymous mutations. A consolidated analysis of co-occurrence of both synonymous and NS mutations may help revisit their mechanistic oncogenic and clinical significance in MM.

P-051

Inferior outcomes for Multiple Myeloma (MM) patients (pts) harbouring t(11;14) and the promise of venetoclax, real-world Australian retrospective

Kenneth Lim[1], Dipti Talaulikar[2], Joanne Tan[3], Joanna Loh[4], Pratheepan Puvanakumar[5], James Kuzich[6], Michelle Ho[2], Matthew Murphy[7], Nicole Zeglinas[1], Susan Morgan[3], Michael Low[4], David Routledge[5], Andrew Lim[6], Simon Gibbs[7], Slavisa Ninkovic[1]

[1]St Vincent's Hospital Melbourne, Melbourne, Australia; [2]Canberra Hospital, Canberra, Australia; [3]The Alfred Hospital, Melbourne, Australia; [4]Monash Medical Centre, Melbourne, Australia; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]Austin Health, Melbourne, Australia; [7]Eastern Health, Melbourne, Australia

Background: Traditionally, MM harbouring t(11;14) is considered standard risk disease. In the era of novel therapies however, pts with t(11;14) are reported to have inferior outcomes to other standard risk pts. Evidence of response to the BCL-2 inhibitor, Venetoclax (Ven), has further increased interest in understanding outcomes of t(11;14) pts. Here we aim to describe the historical outcomes of t(11;14) MM and response to Ven in a real-world cohort of Australian pts. **Methods:** This was a retrospective, multicentre study conducted by members of the Australasian Leukaemia and Lymphoma Group, Myeloma Working Party. Cases were identified by interrogation of cytogenetics/FISH database from 2010 to 2019 inclusive. Baseline patient and disease characteristics, treatment exposure and outcomes were extracted from hospital medical records. Descriptive statistics, and survival analyses were performed as appropriate. **Results:** Seventy-four pts [median age 65 years (yrs), range (43-85)] were identified across seven centres. 43% pts had ISS Stage III MM with 88% harbouring additional cytogenetic abnormalities, incl. 13% with gain in 1q and 12% with del(17p). The majority (81%) of pts received proteasome inhibitor (PI)-based 1st line therapy with 60% having an upfront autologous stem cell transplant (ASCT) and 54% having immunomodulatory drug (IMiD)-based maintenance therapy. Two patients received an allogeneic stem cell transplant after ASCT. The overall response rate (ORR) was 86% with 38% achieving very good partial response (VGPR) or better. The median progression free survival-1 (PFS-1) was 1.91 yrs (95% CI 1.73-2.56) [PI-based, n=60, PFS 1.84yrs (95% CI 1.61-2.41) vs IMiD-based, n=5, PFS 4.58yrs (95% CI 1.16-5.51), HR 0.68 p=0.45] The median overall survival (OS) was 5.35 yrs (95% CI 4.12-6.56). Second and third line therapy was predominantly IMiD-based with recent introduction of anti-CD38 monoclonal antibodies (mAbs). Median PFS-2 was 0.77 yrs (95% CI 0.39-0.98) while median PFS-3 was 0.65 yrs (95% CI 0.34-1.16). Eleven pts (median 3 prior lines of therapy) were given Ven [Six pts in combination with PI, three with PI and mAbs and two with dexamethasone]. ORR to Ven was 55% with 45% ≥ VGPR. Median PFS with Ven was 0.54 yrs (85% CI 0.05-2.17). Median PFS for patients with 1-4 lines (n=6) was 1.22 years and median PFS for patients with 5 lines or more (n=5) was 0.54 years, HR 0.56 (95% CI 0.12-2.5). **Conclusion:** For pts harbouring t(11;14), the duration of response to PI-based 1st line therapy is suboptimal even with the use of ASCT consolidation in the majority of patients. Despite multiple prior lines of therapy, Venetoclax shows promising results and every effort should be made for early identification of this cytogenetic lesion. Further studies are required to examine the impact of novel triplet and quadruplet combination therapy and use of venetoclax early in the disease course of this sub-group of patients.

P-052

Identification of novel genetic loci for risk of multiple myeloma by functional annotation

Angelica Macauda[1], Alyssa Clay-Gilmour[2], Klara Briem[2], Matteo Giaccherini[3], Chiara Corradi[3], Yasmeen Niazi[1], Hartmut Goldschmidt[3], Asta Försti[1], Celine Vachon[4], Daniele Campa[5], Federico Canzian[1]

[1]DKFZ; [2]University of South Carolina; [3]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg;

and National Center for Tumor Diseases (NCT); [4]Mayo clinic; [5]University of Pisa

Background: Genetic factors have proven to have an impact on multiple myeloma (MM) susceptibility, with genome-wide association studies (GWAS) discovering 23 loci associated with MM risk. However, much of the heritability of MM remains unexplained. The stringent significance threshold used in GWAS ($p<5\times10^{-8}$) accounts for the numerous statistical tests being performed but is prone to the risk of false negatives. One strategy for reducing the number of tests is to consider only SNPs with heightened prior probabilities of association, according to meaningful biological criteria. The best candidate SNPs identified with this approach can then be tested in additional MM cases and controls from independent populations. We aimed at surveying the effect of single nucleotide polymorphisms (SNPs), predicted to have a functional role, on MM risk. **Methods:** The association study consisted of two GWAS as discovery datasets , namely the InterLymph consortium and the German GWAS and a replication dataset, namely the the International Multiple Myeloma rESEarch (IMMEnSE) consortium, for an overall total of 5442 MM cases and 6174 controls. SNPs were first ranked according to p-value and concordance of the association between the two discovery datasets, then ranked by functional annotation, using bioinformatic tools and databases. We considered the following classes of functional SNPs: missense, synonymous and non-sense SNPs, expression quantitative trait loci (eQTLs), splicing quantitative trait loci (sQTLs),), SNPs in SNPs affecting function of long non-coding RNAs (lncRNA), and SNPs modifying transcription factor binding sites. We prioritized the resulting SNPs for replication in IMMEnSE by p-values for association in InterLymph and German GWAS and by evidence for a functional role. **Results:** In the two discovery datasets, 136 SNPs fit the criteria of association with MM risk with $p<10^{-4}$ and did not map close to known MM risk loci. After pruning for linkage disequilibrium, four SNPs (rs12038685, rs2664188, rs12652920, rs29794) were chosen for replication in IMMEnSE. Among these, rs2664188 showed to be significantly associated also in the replication dataset (OR=1.30, 95% CI = 1.16-1.46, p=0.001). The final meta-analysis including the three datasets, using a random-effect model, confirmed the association (OR=1.18, 95% CI = 1.07-1.30, p=0.0007). **Conclusion:** The G-allele of rs2664188, that showed a consistent association with increased risk of developing MM in all phases of our analysis is an eQTL, according to GTEx., The G-allele is associated with increased expression of the N4BP2 gene in whole blood. N4BP2 encodes a protein which binds to B-cell leukemia/lymphoma 3 (BCL-3), a well-known proto-oncogene, known to play a role in cell proliferation and apoptosis inhibition in myeloma cell lines.

P-053

BoBafit: a Copy Number-clustering tool to refit and recalibrate the diploid region of Multiple Myeloma genomic profiles

Gaia Mazzocchetti[1], Andrea Poletti[1], Vincenza Solli[1], Enrica Borsi[2], Marina Martello[1], Ilaria Vigliotta[2], Silvia Armuzzi[1], Barbara Taurisano[1], Elena Zamagni[3], Michele Cavo[2], Carolina Terragna[2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" - Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [3]European Myeloma Network, Italy

Background: The genetic architecture of Multiple Myeloma(MM) is very complex and heterogeneous and includes a huge variety of copy number alterations(CNAs). CNAs affect almost all chromosomes and, based on their presence, patients can be stratified into several, prognostically meaningful subgroups: in particular, the presence of particular CNAs clearly identify high-risk patients, thus underlining the importance of a precise detection of these chromosomal aberrations. FISH is considered the gold standard to detect CNAs in MM, even though the recent implementation of molecular technologies has highlighted the advantage to simultaneously detect the whole landscape of genomic CNAs. Molecular methods require the use of computational algorithms to estimate CNAs, based on the correct identification of the so-called "diploid region", which need to be defined according to the overall genomic characteristics of the patient analyzed. This topic is crucial in genomically complex diseases, since the employed algorithms might fail the diploid region estimation, leading to a possible incorrect CNAs call and therefore to an incorrect patients' stratification. **Aim:** To design a bio-informatic method able to check and re-calculate the diploid region starting from genomic data obtained by molecular technologies. **Methods:** To this aim, two MM genomic databases have been used, including 595 and 1044 profiles, collected at the "Seràgnoli" Institute of Hematology (SNPs array data) and downloaded from the CoMMpass study (NGS data), respectively; results have been validated on a Breast Cancer(BC) database, including 2133 profiles, downloaded from the TCGA-BRCA project (SNPs array data). R software was used. **Results:** An original R package, named "BoBafit", was designed, aimed at check and recalculate the diploid region with a tumor specific approach. The package included several functions: the main one, DRrefit, refits and recalibrates the wrong diploid regions, using a clustering method and a chromosome list; these tools allow a disease-specific correction, based on the identification of chromosomes commonly not carrying disease-specific CNAs, as defined by the Compute Normal Chromosome function. By applying BoBafit, we showed that 1-3% of CNAs calls needed a diploid region correction and a redefinition of the calls; the package can perform a disease-specific refit, independently from the molecular technique employed (e.g., NGS or SNPs array). **Conclusions:** The use of the BoBafit allowed the correction of inaccurate CNAs calls. The package, based on MM data, has been validated on BC data, thus both confirming the method's robustness and highlighting the importance of diploid region's refit in complex genomic profiles. We propose BoBafit as final step in the CNAs' analysis pipeline, in order to avoid the inaccurate estimate of whole-chromosome either arm-level or focal alterations, finally supporting the correct patient's clinical stratification. **Acknowledgment:** AIRC IG2018-22059.

P-054

TRIM33 loss in Multiple Myeloma is associated with defective DNA repair and sensitivity to PARP inhibition

Roisin McAvera[1], Jonathan Morgan[1], Ken Mills[1], Lisa Crawford[1]

[1]Queen's University Belfast

Background: Chromosomal instability is a hallmark of Multiple Myeloma (MM) with most patients displaying cytogenetic abnormalities which can often act as prognostic indicators. Such abnormalities can arise due to defects in the DNA Damage Response (DDR). TRIM33 is an E3 ligase and transcription co-repressor located on chromosome 1p13.2, a region frequently deleted in MM. Previous studies have shown that TRIM33 is involved in PARP-dependent DDR and regulation of chromosomal stability. Here, we investigated the influence of TRIM33 loss in MM, focusing on its role in the DDR and whether this could be exploited therapeutically. **Methods:** The CoMMpass dataset (IA15 release) was screened to identify patients with copy number (CN) loss of TRIM33 and this was correlated with survival, structural variants and common cytogenetic abnormalities. TRIM33 shRNA knockdown models were established in JJN3 and U266 cells for in vitro studies. Protein expression and interactions were assessed by co-immunoprecipitation, western blotting and/or immunofluorescence. Clonogenic survival assays were used to assess response to Olaparib. **Results:** Previously we identified a subset of MM patients with TRIM33 loss and identified that these patients exhibit significantly more chromosomal structural variants (deletions, inversions, duplications and translocations) ($p<0.0001$) and a significantly poorer overall survival ($p<0.0001$). Additionally, we have determined the frequency of common recurrent primary and secondary cytogenetic abnormalities for these patients. No recurrent primary cytogenetic abnormalities were associated with TRIM33 loss. However, high-risk secondary chromosome 1 aberrations were associated with loss of TRIM33, both del(1p) and gain(1q) ($p<0.0001$ and $p=0.0474$ respectively). In vitro, TRIM33 knockdown resulted in increased formation of 53BP1 foci and increased g[ED]H2AX expression ($p<0.001$) indicating unrepaired DNA damage typical of a DDR defect. Following induced DNA damage using 2Gy irradiation (IR), TRIM33 is recruited to chromatin within 5 minutes, with levels returning to basal by 30 minutes. The chromatin remodelling enzyme ALC1 is known to regulate sensitivity to PARP inhibition and TRIM33 is required for its timely removal from sites of damage. TRIM33 transiently interacts with ALC1 within 15 minutes of 2Gy IR. TRIM33 knockdown did not affect ALC1 expression. However, knockdown did sensitize MM cells to the PARP inhibitor Olaparib reducing the IC50 from 1.7μM to 780nM. **Conclusion:** Here, we show that a subgroup of MM patients have TRIM33 loss and these patients have high-risk disease and poor outcome. We show that TRIM33 is recruited to damaged chromatin where it regulates ALC1 activity. Therefore, TRIM33 loss results in a DDR defect leading to chromosomal abnormalities. However, TRIM33 loss-associated DDR defects can be exploited therapeutically using Olaparib which is currently approved for the treatment of BRCA1/2 mutated breast and ovarian cancers.

P-055

Extracellular RNA: an emerging biomarker for therapeutic monitoring in multiple myeloma

Sridurga Mithraprabhu[1], Rachel Morley[2], Moashan chen[3], Malarmathy Ramachandran[4], Kawa Choi[5], Anna Kalff[6], Krystal Bergin[6], Flora Yuen[6], Jake Shortt[2], Tiffany Khong[4], John Reynolds[4], Andrew Spencer

[1]Australian Centre for Blood Diseases, Alfred Hospital-Monash University; [2]Austin Health; [3]Monash University; [4]Monash University- Alfred Health; [5]Murdoch Children's Research Institute; [6]Alfred Health

Background: Circulating cell-free nucleic acids are currently being explored as biomarkers of non-invasive therapeutic monitoring and response in cancer. Studies measuring cancer-specific circulating cell-free RNA (extracellular RNA – exRNA) have identified correlation with disease status in a number of malignancies. We present emerging evidence that plasma exRNA is analysable and may be informative in understanding multiple myeloma (MM) biology and impact of therapy. **Methods:** Peripheral blood plasma was obtained in Streck RNA BCT tubes and processed for exRNA utilising the QIAamp circulating nucleic acid kit. We performed whole transcriptome sequencing of exRNA from healthy controls (HC; n=10), newly diagnosed MM (ND MM; n=5) and relapsed/refractory (RR MM; n=12) patients to demonstrate the utility of exRNA for biomarker identification. We also performed droplet digital PCR (ddPCR) for exRNA transcripts of candidate biomarkers of lenalidomide (LEN) response in a "test cohort" of samples collected at study entry (baseline) and after five days of LEN treatment (C1D5) in a phase 1b trial of azacitidine in combination with LEN and dexamethasone (DEX) for patients with RR MM (ROAR trial; n= 24 patients). A "validation cohort" was obtained from a phase IIb trial of KappaMab in combination with LEN and DEX in RR MM (KappaMab trial; n=39 patients) at screening and C1D5. Progression-free survival (PFS) and overall survival (OS) were measured from the date of commencing therapy to the date of relapse/progression or death, respectively. The random survival forests methodology was used to identify the exRNA most likely to be associated with PFS and OS. **Results:** Transcriptome comparison between HC, ND and RR MM indicated that ~45% of the exRNA genes were protein-coding genes. We identified 632 differentially expressed genes in MM patients compared to HC, of which 26 were common to NDMM and RRMM. We further identified 54 and 191 genes specific to ND and RR MM, respectively, highlighting the utility of exRNA sequencing for biomarker identification. Evaluation of LEN-related exRNA transcripts utilising ddPCR in the ROAR trial indicated that high Cereblon (CRBN) levels coupled with low levels of SPARC at baseline were associated with shorter OS ($p<0.001$). Patients with high baseline CRBN coupled with low fold change at C1D5 were at the highest risk of progression ($p<0.001$). We investigated this concept in the "validation cohort" (Kappamab trial) and observed results consistent to that of the "test cohort", which showed that lower levels of SPARC and higher levels of IKZF3 were indicators of poor prognosis ($p<0.05$). **Conclusion:**

The data presented here provide the first demonstration of the utility of exRNA for biomarker identification and therapeutic monitoring. It provides the foundation for further exploration and development of exRNA testing as a potentially simple, non-invasive, repeatable strategy in MM.

P-056

HUWE1 orchestrates DNA Repair in response to Replicative Stress in Multiple Myeloma

Jonathan Morgan[1], Roisin McAvera[1], Ken Mills[1], Lisa Crawford[1]

[1]Queens University Belfast

Background: Multiple Myeloma (MM) is an incurable B cell neoplasm characterised by heightened levels of genomic instability that contribute to both development and progression of the disease. HUWE1, an E3 ubiquitin ligase, has been implicated in the DNA damage response (DDR) and genome integrity. Past studies identified more than 5% of patients present with a HUWE1 mutation. Our lab has determined that both MM patients and cell lines with HUWE1 mutations exhibit increased levels of genomic instability manifested by heightened mutation rates (p=0.0023) and increased incidents of micronuclei formation (p<0.0001). This study aimed to elucidate HUWE1's role in DNA replication and to determine how it influences DNA repair in MM. **Methods:** Cells were transfected with SMARTvector Inducible Human HUWE1 shRNA or with a non-targeting control (NTC) shRNA (Dharmacon, Chicago IL, USA). Co-immunoprecipitation was carried out using the Co-IP kit (Thermo Fisher). Replicative stress was induced with 2mM Hydroxyurea (HU) and assessed using immunofluorescence. DNA repair was investigated in (2Gy) irradiated HUWE1 knockdown cells by immunofluorescence staining. **Results:** In line with previous studies, we found that knockdown of HUWE1 in MM cell lines led to an S-phase arrest, suggesting a role for HUWE1 in DNA replication. Using proteomic profiling and co-immunoprecipitation we identified novel putative substrates of HUWE1 that are involved in DNA replication and repair. To address HUWE1's role in the replicative stress response we treated cells with 2mM HU to elicit replication fork stalling and used replication protein A (RPA) foci counts as a measure of the response. We found that HUWE1 depleted cells exhibited significantly less foci and therefore reduced recruitment of replication proteins when treated with HU for 6hrs compared to the NTC control (p=0.0064). This reduced response to replicative stress in HUWE1 knockdown cells was coupled with significantly higher levels of DNA damage at 6hrs (p=0.00421) and this damage persisted at 24hrs after treatment (p=0.0219). To further examine HUWE1's role in the DDR cells were stained for the double strand break (DSB) marker, 53BP1 following irradiation (IR). HUWE1 knockdown cells displayed a reduced capacity to repair DSBs with more 53BP1 foci present at 1hrs (p=0.00254), 4hrs (p=0.0469) and 24hrs (p=0.025) post-IR compared to their NTC counterparts. **Conclusion:** Here we demonstrate that knockdown of HUWE1 results in increased replication stress and a dampened DNA repair capacity in MM cells, most likely underpinned by reduced recruitment of repair machinery. This data coupled with our previous work demonstrating a role for HUWE1 mutations as a driver for genomic instability, outlines a clear position for HUWE1 in maintaining genome integrity in MM. Further exploration of these dysregulated repair pathways in the presence of HUWE1 mutations may offer potential therapeutic targets for a subset of patients in the future.

P-057

A helicase "ASCC3" is coupled to FEN1-mediated genomic instability and cancer cell proliferation

Chengcheng Liao[1], Shidai Mu[1], Jiangning Zhao[1], Subodh Kumar[1], Leutz Buon[2], Srikanth Talluri[3], Mehmet K Samur[2], Masood Shammas[1], Nikhil C. Munshi[4]

[1]Dana Farber Cancer Institute and VA Boston Healthcare System, Boston, MA, USA; [2]Dana Farber Cancer Institute, Boston, MA, USA; [3]Dana-Farber Cancer Institute & Harvard Medical School; [4]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: We have previously reported the identification of FEN1 a driver of genomic instability in myeloma (MM) as well as esophageal adenocarcinoma (EAC) cells. We demonstrated that FEN1 is overexpressed in MM cell lines and in clinical datasets of MM and several other cancers including EAC, and FEN1-knockdown inhibited spontaneous DNA breaks, homologous recombination (HR) activity as well as genomic instability in MM cells. We now show that FEN1-overexpression in non-cancerous (normal fibroblasts and bone marrow/stroma HS5) cells increases DNA breaks and genomic instability, as assessed by micronucleus assay. **Methods:** In order to further evaluate the impact on genomic instability, control and FEN1-overexpressing cells were cultured for three weeks and new genomic changes acquired in cultured relative to "day 0" cells (representing baseline genome), were identified using single nucleotide polymorphism (SNP) arrays. **Results:** Overall, the acquisition of amplification and deletion events were increased by ~ 3-fold in FEN1-overexpressing relative to control cells. Evaluation by RNA sequencing in two different non-cancerous cell types showed that FEN1-overexpression was associated with upregulation of several interconnected pathways including DNA double strand break repair, cell cycle, mitotic G2 M phases, TP53, homologous DNA pairing and strand exchange. Top downregulated pathways included several metabolic pathways and an apoptosis pathway. These data demonstrate a significant role and the impact of FEN1 on DNA repair and genome maintenance, especially HR. We next identified FEN1-interacting proteins from two different MM cell lines (MM1S, RPMI8226) by mass spectrometry. Forty-one proteins interacted with FEN1 in both MM cell lines including two helicases (ASCC3, RUVBL2) and several proteins involved in DNA damage response and recruitment. To investigate the functional relevance of FEN1-ASCC3 interaction, FEN1 was overexpressed in non-cancerous (stromal HS5) cells and ASCC3 was suppressed

in control as well as FEN1-overexpressed cells, and impact on different parameters of genome stability (HR activity, micronuclei) and growth (cell viability and DNA replication) monitored. FEN1-overexpression increased HR activity, whereas ASCC3-knockdown inhibited spontaneous as well as FEN1-induced HR activity. Consistent with these data, FEN1-overexpression also increased genomic instability, whereas ASCC3-knockdown inhibited spontaneous as well as FEN1-induced genomic instability as assessed by micronucleus assay. Importantly, FEN1-overexpression also increased DNA replication (as assessed by BrdU-labelling), whereas ASCC3-knockdown inhibited spontaneous as well as FEN1-induced DNA replication in these cells. **Conclusion:** These data suggest that helicase activity of ASCC3 is coupled to endonuclease activity of FEN1 to cause genomic instability and cancer cell proliferation, and is currently being investigated in MM and other cancer models to develop translational application.

P-058

The dynamics of nucleotide variants in the progression from myeloma precursor conditions to multiple myeloma using targeted sequencing of serial bone marrow samples

Bénedith Oben[1], Charlotte Cosemans[2], Ellen Geerdens[3], Loes Linsen[4], Kimberly Vanhees[5], Brigitte Maes[3], Koen Theunissen[6], Bert Cruys[3], Marta Lionetti[7], Ingrid Arijs[8], Niccolò Bolli[7], Guy Froyen[9], Jean-Luc Rummens[10]

[1]Lab. Experimental Hematology, Dept. Clinical Biology, Jessa Hospital, Hasselt, Belgium. Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium.; [2]Lab. Experimental Hematology, Dept. Clinical Biology, Jessa Hospital, Hasselt, Belgium. Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium.; [3]Lab. Molecular Diagnostics, Dept. Clinical Biology, Jessa Hospital, Hasselt, Belgium.; [4]Lab. Experimental Hematology, Dept. Clinical Biology, Jessa Hospital, Hasselt, Belgium. Activity Center Biobanking, University Hospitals Leuven, Leuven, Belgium University Biobank Limburg (UBiLim), Clinical Biobank Jessa Hospital, Hasselt, Belgium.; [5]Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium. University Biobank Limburg (UBiLim), Clinical Biobank Jessa Hospital, Hasselt, Belgium.; [6]Dept. Hematology, Jessa Hospital, Hasselt, Belgium.; [7]Dept. Oncology and Hemato-Oncology, University of Milan, Milan, Italy.; [8]Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium. Laboratory for Translational Genetics, Dept. Human Genetics, University of Leuven, Leuven, Belgium. VIB Center for Cancer Biology, Leuven, Belgium. Belgian Inflammatory Bowel Dis; [9]Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium. Lab. Molecular Diagnostics, Dept. Clinical Biology, Jessa Hospital, Hasselt, Belgium.; [10]Lab. Experimental Hematology, Dept. Clinical Biology, Jessa Hospital, Hasselt, Belgium. Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium. University Biobank Limburg (UBiLim), Clinical Biobank Jessa Hospital, Hasselt, Belgium.

Background: Multiple myeloma (MM) is known to evolve from the premalignant precursor conditions Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). The exact mechanisms driving this progression are still not completely understood. The continuum between MGUS-SMM-MM provides the opportunity to investigate its evolution. However, collecting paired/serial samples from low and intermediate risk precursors progressing to MM are significantly hindered by the (i) only incidental diagnosis of asymptomatic precursors, (ii) invasive bone marrow (BM) sampling, (iii) very low number of aberrant BM plasma cells (PCs), and (iv) rather irregular disease follow-up. **Methods:** In this study, a unique retrospective collection of paired BM samples was available because of an effective biobanking effort. We had access to 68 archival diagnostic May-Grünwald–Giemsa (MGG)-stained BM smears from 21 progressing low to intermediate risk myeloma precursor patients, 19 MGUS and 2 SMM, with a median time to progression of 6 years. DNA was extracted from these BM smears and Next Generation Sequencing (NGS) was performed using a custom targeted capture-based sequencing panel (Illumina) including coding exons or hotspots of 81 selected myeloma-related genes with the aim to study the evolution of single nucleotide variants (SNVs) and short insertions and deletions (indels). The pooled libraries were paired-end sequenced on a MiSeq instrument (Illumina). **Results:** Data was analyzed with Local Run Manager and annotated with VariantStudio. After filtering, only exonic nonsynonymous and loss-of-function variants with a coverage >30 and a variant allele frequency (AF) >1% were retrieved. A variant detected in the MM phase but not in the prestage of that patient was manually inspected in the data visualization tool of Integrated Genome Viewer (IGV) to assess its presence. With a mean coverage of 636x of the targeted captured region the sequencing depth was sufficiently high to detect low burden variants down to an AF of 1%. A median of 2 variants per patient (range 0 to 5 with a total of 38 variants) was detected. While in 19 patients at least one variant was detected in the MM phase, in 2 patients not a single variant was detected in any of the 81 genes. Interestingly, the majority of variants in MM could already be detected at low AFs in the BM smears sampled in the precursor phase, even many years before progression. The reason why some variants were not detected in a prestage is likely due to sensitivity issues (BM PCs ≤2.5%). The median time of detection of a variant in the precursor stage BM was 49 months (>4 years; range 10 to 105 months) prior to MM progression. **Conclusion:** In conclusion, targeted sequencing of unsorted BM smears from myeloma precursor conditions can already provide relevant insights into the behavior of mutant clones. Paired sample analysis can reveal the genetic architecture of somatic variation in the prestage even with low proliferative PCs in the BM.

P-059

miRNA profiling of CD138+ plasma cells identifies miR-181a-5p overexpression as independent predictor of short-term progression and poor treatment outcome in multiple myeloma

Maria-Alexandra Papadimitriou[1], Aristea-Maria Papanota[2], Panagiotis Adamopoulos[1], Katerina-Marina Pilala[1], Christine-Ivy Liacos[2], Panagiotis Malandrakis[2], Nefeli Mavrianou-Koutsoukou[2], Dimitrios Patseas[2], Evangelos Eleutherakis-Papaiakovou[2], Maria Gavriatopoulou[2], Efstathios Kastritis[2], Margaritis Avgeris[3], Meletios-Athanasios Dimopoulos[4], Evangelos Terpos[2], Andreas Scorilas[1]

[1]Department of Biochemistry and Molecular Biology, Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece; [3]Department of Biochemistry and Molecular Biology, Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece/Laboratory of Clinical Biochemistry - Molecular Diagnostics, Second Department of Pediatrics, School of; [4]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital

Background: The considerable progress made in multiple myeloma (MM) treatment nowadays resulted in significantly prolonged survival. However, the high heterogeneity of patients' response to treatment outlines the need for novel prognostic molecular markers able to support individualized treatment. microRNAs (miRNAs) have emerged as powerful post-transcriptional regulators of gene expression with a crucial role in cancer, while recent advances in high-throughput techniques have unveiled their prognostic utility. Herein, using a miRNA-seq approach we investigated miRNA profiles in association with MM and its precursor states, aiming to reveal potential MM-related miRNAs able to improve patients' risk stratification. **Methods:** Bone marrow aspiration (BMA) samples were collected from 138 MM, 30 smoldering MM (sMM) and 25 monoclonal gammopathy of undetermined significance (MGUS) patients at diagnosis. Mononuclear cells were isolated using Ficoll-Paque, while CD138+ plasma cells were positively selected using magnetic beads with anti-CD138 mAbs. Next, miRNA-seq was performed in CD138+ plasma cells from MGUS (n=4), sMM (n=4) and MM (n=20) patients. Based on miRNA-seq, target prediction and Gene Ontology (GO) enrichment analysis, miR-181a-5p was further evaluated for the first time in CD138+ plasma cells from the total study population. Following RNA extraction and 3'-end polyadenylation, miR-181a-5p levels were quantified using RT-qPCR. Disease progression and patients' death were assessed as clinical endpoint events. Internal validation was performed by bootstrap analysis, while decision curve analysis was utilized to evaluate clinical benefit. Kryukov et al. 2016 served as an external validation cohort (n=151). **Results:** miRNA-seq revealed miR-181a-5p to be concurrently upregulated in MM vs. MGUS/sMM as well as R-ISS III vs. R-ISS I patients. Hematopoietic cell differentiation and apoptosis were significantly enriched following GO analysis. In our screening cohort, miR-181a-5p overexpression was associated with a significantly higher risk of short-term disease progression (HR=2.524; p=0.006) and poor overall survival following treatment (HR=2.629; p=0.027) of MM patients. Consistent with our results, Kryukov et al. validation cohort confirmed the inferior survival outcome of the MM patients with elevated miR-181a-5p levels. Finally, multivariate prognostic models incorporating miR-181a-5p with established disease markers, including R-ISS stage and high-risk cytogenetics offered superior risk-stratification specificity and clinical benefit in MM prognosis. More specifically, Kaplan-Meier analysis showed that the combination of R-ISS stage with miR-181a-5p overexpression could provide a better stratification of MM patients' OS (p=0.001) as well as PFS (p=0.016). **Conclusions:** We identified miR-181a-5p overexpression in CD138+ plasma cells as a powerful independent predictor of adverse disease outcome and higher risk for post-treatment progression.

P-060

Subclone-specific microenvironmental impact and drug response in refractory multiple myeloma revealed by single cell transcriptomics

Karsten Rippe[1], Stephan Tirier[1], Jan-Philipp Mallm[1], Simon Steiger[1], Alexandra Poos[2], Mohamed Awwad[2], Nicola Giesen[3], Nicola Casiraghi[1], Hana Susak[1], Katharina Bauer[1], Anja Baumann[2], Lukas John[4], Anja Seckinger[2], Dirk Hose[2], Carsten Müller-Tidow[5], Hartmut Goldschmidt[6], Oliver Stegle[1], Michael Hundemer[2], Niels Weinhold[4], Marc Raab[4]

[1]German Cancer Research Center (DKFZ), Heidelberg, Germany; [2]University Hospital Heidelberg, Germany; [3]Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany; [4]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [5]Heidelberg University Hospital; [6]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT)

Background: Relapsed/refractory multiple myeloma (RRMM) is characterized by a high inter- and intratumor heterogeneity and a complex interplay of myeloma cells with the bone marrow microenvironment (BME). Accordingly, there is an urgent need to dissect subclone structure, transcriptional heterogeneity and cellular interactions to unravel the molecular mechanisms underlying drug resistance in RRMM. **Methods:** Single cell RNA sequencing (scRNA-seq) of ~210,000 cells from bone marrow aspirates sorted into CD138+ and CD138– fractions was conducted for 20 heavily pretreated RRMM patients. RRMM subclones were called from the scRNA-seq data based on a copy number aberration (CNA)

analysis that was confirmed by interphase fluorescence in situ hybridization and whole genome sequencing. From the scRNA-seq data the composition and abundance of immune cell types in the BME was determined. Interactions of myeloma cells with the BME were characterized by an analysis of the correlated expression of ligand-receptor pairs. Selected findings from the scRNA-seq analysis were validated by flow cytometry. **Results:** Subclones with distinct chromosomal aberrations were reliably identified at the single cell level based on CNAs inferred from scRNA-seq data. The analysis revealed a subclonal 1q-gain (+1q) in 10/20 samples, for which a gene expression signature of recurrently upregulated genes was derived. These +1q subclones frequently expanded during treatment. Furthermore, RRMM cells shaped an immune suppressive BME by upregulation of inflammatory cytokines and close interplay with the myeloid compartment. RRMM cells appear to reprogram the BME by upregulation of inflammatory cytokines and ligands of inhibitory receptors expressed on T and NK-cells. Specifically, the immune cell compartment of RRMM patients displayed an accumulation of PD1+ g[ED]d[ED] T-cells and myeloid populations compared to healthy donors or early disease. In addition, we observed a depletion of hematopoietic progenitors in patients with high expression of genes associated with inflammatory signaling in the BME. Upon treatment with immunomodulatory drugs, reprogrammed plasmacytoid dendritic cells expanded. Focusing on patients with +1q, we found an enrichment of a rare M2-like tumor associated macrophage population while GZMB+ NK effector cells were depleted in these patients, indicating that +1q has a distinct effect on the BME in RRMM. **Conclusions:** Our study resolves transcriptional features of subclones in RRMM and mechanisms of microenvironmental reprogramming. The insight gained in our study on the evolution of RRMM heterogeneity and its bone marrow milieu will support the development of novel treatment approaches and potentially guide clinical decision making.

P-061

Single-cell whole-exome DNA sequencing traces clonal trajectory in paired evolution of MGUS to multiple myeloma

Naser Ansari-Pour[1], Silvia Salatino[2], Nicola Weston-Bell[3], Dean Bryant[3], Luz Yurany Moreno[4], Angelo Vacca[5], Niklas Zojer[6], Andrew Zannettino[7], Rory Bowden[8], David Wedge[9], Surinder Sahota[10]

[1]Weatherall Institute of Molecular Medicine, University of Oxford; [2]Wellcome Centre for Human Genetics, University of Oxford; [3]Cancer Sciences Academic Unit, University of Southampton; [4]University of Texas MD Anderson Cancer Center; [5]University of Bari Medical School; [6]Department of Medicine I, Wilhelminen Cancer Research Institute, Klinik Ottakring; [7]Faculty of Health and Medical Sciences, THE UNIVERSITY OF ADELAIDE; [8]Walter and Eliza Hall Institute in Melbourne; [9]Manchester Cancer Research Centre, University of Manchester; [10]University of Southampton

Background: Accurate measurement of heterogeneity and reconstruction of evolutionary pathways are key to decipher clonal dynamics in tumour origins. Although bulk population genetic sequencing data has been used extensively to understand the life history of tumours, sequencing single cell DNA is likely to provide a much higher resolution of clonal dynamics and yield new insights into competing cellular populations with different genotypes. This is of significant importance when clonal evolution from a benign state to malignant disease is being considered, such as in the clonal evolution of MGUS to multiple myeloma (MM). **Methods:** To this end, we further refined a multiple displacement amplification-based single cell whole-exome sequencing (scWES) protocol and applied it to examine MM cells (2 cases), and in one of these cases, probed evolution from a pre-existing MGUS stage in a paired setting. Single tumour cells were isolated from CD138+CD38+ fluorescence-activated cell sorted populations and CD3+ for T cells as germline controls. We developed a novel computational pipeline to accurately call somatic SNVs/indels and copy number aberration (CNA) events in the form of loss-of-heterozygosity (LOH) and gains in each single cell, identified drivers at the genome-wide level and reconstructed the tumour phylogeny while estimating and accounting for allelic dropout (N=176 single cells, 25× each cell). **Results:** By focusing on the patient that allowed comparison of single cells at pre- and post-malignancy states, we show that pre-malignant subclones can be readily identified, and strikingly that malignant cells arise and expand from one of the MGUS subclones in the combined tumour phylogeny. **Conclusions:** These results suggest that this scWES based method is a pragmatic approach to investigate clonal dynamics by allowing: 1) the analysis of genetic heterogeneity at the genome-wide level (much higher resolution than targeted panels), and 2) at low sequencing costs across large set of cells when compared with whole genome sequencing-based methods.

P-062

The impact of Bortezomib-based induction on chromosome 1q21 gained newly diagnosed Multiple Myeloma of Chinese origin

Hoi Ki Karen Tang[1], Chi Yeung Fung[1], Gareth Morgan[2], Lisa Siu[3], Ho Wan Alvin Ip[1], Sze Fai Yip[4], Ka Ngai Harry Lau[4], Howard Wong[5], Bonnie Kho[5], Harold Lee[6], Kwan Hung Leung[7], Chi Kuen Lau[8], Chor Sang Chim[1], Yu Yan Hwang[1], Joycelyn Sim[1], Cheong Ngai[1], Yok Lam Kwong[1]

[1]Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong; [2]The Myeloma Institute; [3]Department of Pathology, Queen Elizabeth Hospital, Hong Kong; [4]Department of Medicine, Tuen Mun Hospital, Hong Kong; [5]Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong; [6]Department of Medicine, Princess Margaret Hospital, Hong Kong; [7]Department of Medicine, United Christian Hospital, Hong Kong; [8]Department of Medicine, Tseung Kwan O Hospital, Hong Kong

Background: Bortezomib has been reported to favourably impact the outcome of high risk MM predominantly t(4;14) and in some report 17p- its impact on gain 1q21 is unknown. **Methods:** To address this deficit, we have analysed CD138-sorted bone marrow plasma cells in cases treated with bortezomib based induction therapy where age, gender, isotype, ISS, LDH and iFISH were available. **Results:** 1q+ was identified in 167 (66.8%) of the series and was associated with t(4;14) and high LDH but not with other HR FISH abnormalities. Gain 1q+ was not associated with response rate but did associate with shorter event free survival (EFS) (median EFS: 35 months vs 55 months, p=0.05) and overall survival (OS) (median OS 74 months vs 168, p=0.00025). Thus 1q+ was an independent adverse factors for OS together with ISS3, high LDH, del(17p) and t(4;14), multivariate analysis showed that. Of the cases with 1q+, 75 (44.9%) had 3 copies and 92 (55.1%) had >3 copies of 1q21. Fifty-four (32.3%) had ≥50% cells harbouring 3 copies (gain 1q), and 57 (34.1%) had ≥50% cells with >3 copies. Copy number and clone size did not impact on survival. When a risk score of 1 was assigned to each of 1q+, high LDH, high risk FISH and ISS III, OS was shortened incrementally by a risk score of 0 to 4. Post-relapse/progression survival was inferior in those with 1q+ (median 60 months vs median 118 months, p=0.000316). ASCT improved OS for those with 1q+ (median OS 96 months vs 59 months, p=0.000069). In conclusion, 1q+ is an adverse risk factor for OS in MM irrespective of the use of bortezomib but was partially mitigated by ASCT. **Conclusions:** A risk scoring system comprising 1q+, LDH, HR FISH and ISS is a potential tool for risk stratification in MM.

P-063

Pathogenic germline variants in hereditary cancer genes in patients with Multiple Myeloma

Santiago Thibaud[1], Aaron Etra[1], Ryan Subaran[2], Zachry Soens[2], Scott Newman[2], Rong Chen[2], Ajai Chari[3], Hearn Jay Cho[4], Sundar Jagannath[5], Deepu Madduri[1], David Melnekoff[1], Shambavi Richard[1], Joshua Richter[1], Larysa Sanchez[1], Kuan-Lin Huang[1], Alessandro Lagana[1], Samir Parekh[6], Kenan Onel[1]

[1]Icahn School of Medicine at Mount Sinai; [2]Sema4; [3]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [4]Tisch Cancer Institute, Icahn School of Medicine at Mt. Sinai; The Multiple Myeloma Research Foundation; [5]The Mount Sinai Hospital; [6]Mount Sinai Medical Center, New York, NY, USA

Background: GWAS have identified common SNPs & rare high-penetrance variants that explain ~16% of the estimated heritability of multiple myeloma (MM)(PMID 30213928). Pathogenic/likely-pathogenic germline variants (PGV) in hereditary cancer genes (HCG) are common in adult cancer pts (~8%), but prevalence in MM is not known. The aim of our study is to investigate the occurrence of PGV in newly-diagnosed MM (NDMM) and describe clinical characteristics & outcomes of carriers. **Methods:** We analyzed MMRF CoMMpass data & identified 895 NDMM pts with whole-exome sequencing of germline DNA. We used the clinical annotation pipeline from Sema4, a CLIA/CAP certified genetic testing laboratory, to identify pts with PGV according to ACMG variant classification guidelines. We compared clinical characteristics & disease phenotypes of PGV carriers vs non-carriers. We used Chi-Square and Fisher's Exact tests to assess statistical significance. **Results:** We identified 83 PGV in 31 distinct HCG in 79 (8.8%) of 895 NDMM pts (83% European ancestry). Most PGV involved DNA damage repair (DDR) genes (78%), & homologous recombination (HR) genes were the most commonly mutated (34%). PGV in CHEK2 were most common (n=10,1.1% of all MM pts). 2 pts carried PGV in TP53, & 6 pts had mismatch repair (MMR) gene defects (1:149). MM pts with family history (FH) of hematologic malignancy (HM) in a 1st or 2nd-degree relative were more likely to carry PGV (22 vs 7.6%,OR=3.3,p<0.001), an association that remained significant in multivariate analysis (MVA) (OR=4.1,p<0.001). CHEK2 variants were leading drivers of this correlation (OR 18,adjusted p<0.01), & especially protein-truncating founder variant c.1100delC. Likelihood of MM dx before age 40 was significantly higher in PGV carriers (6.3 vs 1.8%,OR=3.7,p=0.025). 25% of those <40y/o carried PGV, but none of these were in DDR-HR genes, a notable difference with other age groups (0 vs 41%,p=0.02). 2/6 MMR PGV were detected in pts <40y/o. In univariate analysis, DDR-PGV carriers had a significant PFS1 advantage (median 52 vs 35 months,p=0.008) & a non-significant OS advantage (p=0.08). PFS1 difference remained significant in MVA adjusting for age, ISS stage, high-risk cytogenetics, treatment type & transplant status (OR 0.65,95% CI 0.44-0.97,p=0.03). **Conclusions:** PGV in HCG were common (8.8%) in this large cohort of NDMM pts of predominantly European ancestry, especially in those with FH of HM (1:4, with high prevalence of CHEK2 variants), and in those <40y/o (1:4). Routine screening in high-prevalence subgroups may be warranted, as carriers can benefit from counseling & enrollment in early cancer detection programs. We observed a clinically & statistically significant PFS1 advantage in PGV carriers, possibly due to increased sensitivity to MM therapies, a well-described phenomenon in other cancers (PMID 33158305). Prospective validation of these findings is needed to better understand prognostic & therapeutic implications of PGV in MM.

P-064

Heterogeneity of bone marrow biopsy and bone marrow aspirate (BMA) in patients with heavily pretreated relapsed/refractory Multiple Myeloma (RRMM)

Anita Boyapati[1], Nathalie Fiaschi[1], Madhav V. Dhodapkar[2], Sundar Jagannath[3], Jeffrey A. Zonder[4], Fang Wang[1], Sandra Coetzee[7], Irene Noguera-Troise[1], Karen Rodriguez Lorenc[1], Glenn Kroog[1], Manish Sharma[1]

[1]Regeneron Pharmaceuticals, Inc; [2]Emory University School of Medicine; [3]The Mount Sinai Hospital; [4]Karmanos Cancer Institute

Background: Despite new regimens approved for RRMM, patients still relapse, and new therapies are needed. T-cell directed therapies that target bone marrow plasma cells (BMPCs), including CD3 bispecific antibodies, have shown promise for the treatment of RRMM. REGN5458, a B-cell maturation antigen (BCMA) xCD3 bispecific antibody, demonstrated an acceptable safety and tolerability profile with early, deep, and durable efficacy in heavily pretreated and triple refractory patients with RRMM [1]. **Aim:** To elucidate disease aspects amenable to T-cell-directed therapies targeting plasma cells, such as REGN5458, we characterized the plasma and immune composition of baseline BMA and core biopsies from patients with RRMM, and evaluated relationships between bone marrow profile, secretory measures of disease, and response. **Methods:** Patients with progressive RRMM (triple refractory or intolerant to prior lines of systemic therapy, including a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody), were treated with REGN5458 (NCT03761108). Matched BMA and biopsy samples obtained at screening were analyzed by multiplex immunohistochemistry (IHC, N=48) and multiparameter flow cytometry (N=81). Cell numbers and phenotypes were correlated to secretory measures of disease, including serum M-protein, immunoglobulin-free light chain (FLC) assays and R-ISS staging. **Results:** Biopsy analysis revealed a variable BMPC burden in RRMM patients. Median percentage of BMPCs by CD138 IHC was 22.5% (range 1–95%). There was no correlation between BMPC burden and serum M-protein levels, but a modest correlation between BMPC burden and serum FLC (rho=0.66; p=0.01). The majority of CD138 biopsy BMPCs in RRMM patients expressed BCMA by IHC; levels varied between patients (median BCMA+ H scores: 45 and 200 for membrane and cytoplasmic staining). BCMA IHC expression was not associated with IMWG response to REGN5458,[1] and did not correlate with soluble BCMA levels at study initiation. BMA analysis by flow cytometry revealed variable levels of abnormal BMPCs in patients with RRMM (median: 2.2% [range 0–68.7%]). BCMA expression was variable in all BMPCs; 53.1% of patients had higher BCMA staining intensity relative to CD38: ratios ranged from 1.2–6.6. Frequency of CD3+ T-cells in CD45+ BMA from RRMM patients ranged from 1.0–63.5%. Preliminary analysis suggests a higher frequency of T cells in R-ISS stage I compared to stage II. T-cell subset distribution in BMA from patients with RRMM reflected low CD8 T_{CM} (5.0%) and predominantly T_{EM} (37.0%) and T_{EMRA} (41.0%). **Conclusions:** Analyses of matched BMA and biopsy samples from heavily pretreated RRMM patients, reveal that most BMPC express BCMA, though soluble vs membrane-bound BCMA levels are heterogenous. Diversity in immune and plasma cell markers and subsets is also observed. Ongoing analyses include correlations of plasma and immune cell profile with response to T-cell-targeting therapies such as REGN5458. **Reference:** [1] Madduri ASH2020 O291.

P-065

CyTOF and single cell RNA sequencing reveal altered T cell phenotypes in Multiple Myeloma patients: implications for immunotherapy

Mattia D'Agostino[1], Maeva Fincker[2], Cristina Panaroni[3], Ashish Yeri[2], Pingping Mao[2], Amanda Moulaison[2], Ryan Tassone[2], Pedro Falcon Estrada[2], Maggie Chen[2], Tiffany Hu[2], Elisa Genuardi[1], Alessandra Larocca[1], Mario Boccadoro[1], Amanda Iniguez[4], Olivia Finney[2], Hans Bitter[2], Noopur Raje[6]

[1]Divisione di Ematologia Universitaria, Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; [2]bluebird bio, Cambridge, MA; [3]Massachusetts General Hospital; [4]ABaloniIniguez@bluebirdbio.com; [6]Massachusetts General Hospital Cancer Center

Background: Immune therapies have had a major impact in multiple myeloma (MM). Responses induced in relapsed and/or refractory MM (RRMM) patients (pts) are unprecedented; however the key challenge is their durability. Most immunotherapeutic approaches rely on the fitness of pts' T cells but exposure to multiple therapies may alter immune cell numbers and function. Here we analyzed and compared the transcriptome and phenotype of T cells from healthy donors (HD), newly diagnosed MM (NDMM) and RRMM pts. **Methods:** Peripheral Blood Mononuclear Cells (PBMCs) from age-matched HD, NDMM and RRMM pts were collected before the start of a new line of treatment. Single cell RNA sequencing (scRNAseq) was performed and proportion of cell types were inferred using a reference PBMC dataset with Seurat. Cell type proportions were also estimated with CyTOF and conventional flow cytometry **Results:** PBMCs from 10 HDs (median age 69, range 53-79), 20 NDMM pts (median age 71, range 54-88), 20 RRMM pts (median age 71, range 54-80) were analyzed. RRMM pts were exposed to 1 (n=8), 2 (n=6) or 3 (n=6) lines of treatment. All RRMM pts were exposed to a proteasome inhibitor, 75% were exposed to an immunomodulatory drug, and 65% received autologous stem cell transplantation. 48 out of 50 samples were processed by scRNAseq, 45 by CyTOF and 33 by flow cytometry. NDMM pts demonstrated a trend towards lower frequency of CD4 T cells compared to HD. This decreased number was accompanied by a decrease in the expression of genes involved in mitochondrial oxidative phosphorylation and an increase in expression of immediate early response genes (e.g. FOS, JUN, JUNB). In the CD8 compartment, CD8 naive cells were lower in NDMM compared to HD. No differences were found on CD8 central memory, effector memory and/or terminal effector populations In RRMM, the proportion of naive CD4 cells was significantly lower compared to NDMM ($p < 0.05$ by scRNAseq and CyTOF). This was confirmed by conventional flow cytometry ($p < 0.05$). No differences in CD4 central memory, effector memory and/or terminal effector proportions were observed. Decreases in the proportion of naive CD4 cells were observed as early as after 1 line of treatment and did not correlate with age, absolute lymphocyte count, previous exposure to lenalidomide or cyclophosphamide cumulative dose. Exposure to higher melphalan doses corelated with lower proportion of CD4 naive T cells. Compared with T cells

from NDMM, T cells harvested from RRMM pts expressed higher levels of activation/exhaustion markers such as PD1 ($p < 0.05$) and HLA-DR ($p < 0.05$). **Conclusion:** T cell phenotypes in MM pts are altered, especially after treatment. These findings may provide the rationale for the investigation of immunotherapy in NDMM and less heavily pretreated MM. Ongoing functional studies will demonstrate whether these phenotypic and transcriptomic changes lead to less fit T cells with consequent impact on effectiveness of T cell directed therapies.

P-066

Effect of Daratumumab (DARA), Cyclophosphamide (C), T Halidomide (T) and Dexamethasone (D) combination of Lymphocyte populations of transplant eligible newly diagnosed Multiple Myeloma patients

Allan Santos[1], Herbert Santos[1], Marco Salvino[2], Juliana santos[3], Sarah Queiroz[4], Larissa Lucas[4], Alessandro Almeida[5], Mariane Santos[1], JOanna Leal[4], Maria da Gloria Arruda[4], Alex torres[1], Edvan Crusoe[5]

[1]Federal University of Bahia- Cytometry and Immunology laboratory; [2]Federal University of Bahia and IDOR- Instituto D'or Oncologia; [3]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil and Federal University of Bahia; [4]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil; [5]Rede D'or Oncologia and Federal University of Bahia

Background: The CTD combination have both an immunomodulatory and immunosuppressive activity on multiple myeloma (MM) patients (pts) treatment. Dara, an antiCD38-antibody, effect on the immune system was already described, but few studies analyzed specifically lymphocytes population. We hypothesized that Dara-CTD combination could impact on lymphocytes subsets during treatment. The primary endpoint was to quantify subpopulations of lymphocytes in TE NDMM pts during Dara-CTD treatment phases. Secondary endpoint was to describe B cells subsets during the same phases. **Methods:** Peripheral blood of 14 pts at four different time points was collected: at diagnose, after four cycles of Dara-CTD, after two consolidation cycles post ASCT and before maintenance therapy. Flow cytometry was used to detect lymphocyte surface molecules including CD3, CD4, CD5, CD8, CD16, CD19, CD20, CD38, CD45 and CD56 in the scatter plot. **Results:** B cells were isolated and subpopulations (naive B cells, non-class switched memory B cells, class switched memory B cells, IgD-CD27- memory B cells and plasmablasts) were detected by CD20, CD24, CD27, CD38, CD45 and IgD. The median of T, B and NK lymphocytes subsets at diagnosis were 1153×10^3/µL, 205×10^3/µL and 284×10^3/µL cells, respectively. After 4 cycles of Dara-CTD the median of T , B and NK cells dropped significantly to 889×10^3/µL , 12×10^3/µL and 11×10^3/µL, respectively ($p<0.05$). The number of the cells after two consolidation cycles post-ASCT, showed T cells full recovery (1087×10^3/µL) while B and NK cells had weakly reconstitution (15×10^3/µL and 34×10^3/µL, respectively). Before maintenance therapy, the median of T, B and NK cells were 1456×10^3/µL, 24×10^3/µL and 33×10^3/µL, respectively. Regarding B cell population, the median of naive B cell decreased after 4 induction cycles from 32×10^3/µL to 1×10^3/µL. Then, after two consolidation cycles post-ASCT the number of B cell increased to 14×10^3/µL and to 18×10^3/µL before maintenance. The present study confirmed that there is a decrease in the number of different lymphocytes populations (T, B and NK) after induction therapy with Dara-CTD. The T cells number recovery after two consolidation cycles post-ASCT, but B and NK cells remain low after the same period. There was a slowly but continuously recovering of B and NK cells, suggesting that Dara-CTD combination allows lymphocytes reconstitution. Analyzing the B cells subpopulations, the naive B cell was the first to show a more significant recovery, although it was below the reference range (33–259). This is the first study that report the lymphocyte profile during Dara-CTD treatment. **Conclusions:** This preliminary data suggest that Dara-CTD induces general lymphopenia on (T, B and NK) populations after induction phase. It was identified that T cells recovery was complete after two consolidations cycles while the recovery of B and NK cells was slowly but continuously.

P-067

High dimensional CyTOF analysis of the immune system of multiple myeloma patients with different responses to lenalidomide maintenance

Raija Silvennoinen[1], Komal Kumar Javarappa[2], Sini Luoma[1], Philipp Sergeev[2], Pekka Anttila[1], Tiina Öhman[3], Markku Varjosalo[3], Marjaana Säily[4], Anu Partanen[5], Marja sankelo[6], Caroline Heckman[7]

[1]Helsinki University Hospital; [2]FIMM; [3]Viikki Campus Helsinki; [4]Oulu University Hospital; [5]Kuopio University Hospital; [6]Tampere University Hospital; [7]Institute for Molecular Medicine Finland

Background: In this phase 2 study patients received 3 cycles of RVD (lenalidomide, bortezomib and dexamethasone) followed by autologous stem cell transplantation (ASCT) and lenalidomide maintenance. We evaluated the bone marrow (BM) immune profile with CyTOF (cytometry by time-of-flight) at treatment start and during lenalidomide maintenance focusing on two different response groups: good and poor responders at pre- and post-treatment phases. Our hypothesis was that there could be distinct differences in immune cell profiles between these groups, especially in T and NK cell subsets and exhausted T-cells. **Methods:** Twenty-six patients were included in this study, 18 from this trial. BM samples were collected from all 18 patients at diagnosis, from 11 the 1st sample when achieved good response during maintenance after a median of 21 (6-46) months and the 2nd sample if good response was maintained after a median of 56 (45-67) months and from 5 patients at relapse after a median of 6 (2-23) months. Patients in good response cohort (n=11) had progression-free survival (PFS) > 5 years. For comparison we included 4 BM samples, taken at good response after ASCT from MM patients not exposed to lenalidomide and 4

BM samples collected from age-matched, healthy donors. **Results:** With a median follow-up of 81 (13-97) months the median PFS was not reached in the good response cohort and was less than 18 months in the poor response cohort. CyTOF analysis revealed distinct good (GR) and poor responder's (PR) immune signatures at baseline level. GR, baseline group has shifted phenotype of T cells toward the CD8 T cells, expressing markers, attributed to the cytotoxicity (CD45RA, CD57), as well as having slightly higher abundance of CD8 TE and lower abundance of CD8 naive T cells. Total T cell amounts were significantly higher in good responders. Increased expression of CD56, CD57, and CD16 were also seen on NK cells in good responders at the baseline, indicating both maturation and cytotoxic potential of NKs. In contrast, a significant decrease of CD56 and CD16 expression suggesting reduced cytotoxic potential and increase of CD57 were seen on NKs in poor responders, baseline indicating senescence status a phenotype associated with exhaustion. Treatment stimulates the expression of cytotoxic/effector-like phenotype on T cells which is confirmed by the significantly increased amounts of CD4 and CD8 effector memory cells, with the respective decrease of naive cells. **Conclusions:** Patients responded to the treatment, have higher effector/cytotoxic cells, expressing higher levels of CD57 and/or CD45RA for T cells, and CD57, CD16, and CD56 for NK cells. Additionally, those patients have less degree of tumor burden as well as decreased expression of chemokine receptors (CCR7, CCR6, CXCR4, CXCR3, and CXCR5). Good responders showed the increase in effector memory CD4 and CD8 subsets of T cells abundance, indicating even the higher cytotoxic effect of immune system.

P-068

Haplotypes rich in activating killer-cell immnuglobulin-like receptor genes are associated with delay on age of myeloma onset

Hasan Yalım Akin[1], Guldane Cengiz Seval[2], Pinar Ataca Atilla[3], Pinar Yurdakul Mesutoglu[4], Taner Otlu[1], Ridvan Anliacik[1], Klara Dalva[2], Gunhan Gurman[2], Meral Beksac[2]

[1]Ankara University Cord Blood Bank; [2]Ankara University School of Medicine, Department of Hematology; [3]Ankara University Stem Cell Institute; [4]3Istinye University School of Medicine Department of Microbiology

Background: Natural killer (NK) cells are known for their anti-tumoral cytotoxic effects. Effector NK-cell functions are controlled by interactions between inhibitory and activating killer-cell immnuglobulin-like receptors (iKIRs and aKIRs) on NK cells in the presence of human leukocyte antigen (HLA) class I ligands on target cells. The aim of this study was to investigate the frequency of KIR genotypes with/without their cognate ligands among myeloma (MM) patients compared to a healthy population. **Methods:** 178 MM patients diagnosed between 2007-2018 enrolled into the study. The median age of patients was 63 (range, 33-95) with ISS:I/II/III:49/36/37; IgG/IgA/Light chain: 58/22/40 and median lines of treatment of three (range, 1-6) (38% history of transplant). As a control group, 449 healthy subjects screened for HLA and KIR genotyping aged median: 42 (7-82) as related/unrelated hematopoietic stem cell donors were included. The Olerup SSP KIR Genotyping Kit (Olerup, Stockholm, Sweden) and Olerup KIR HLA Ligand Detection Kit was used to type KIR and KIR ligands: For KIR genotype comparisons total AA, AB and BB, their telomeric and centromeric motifs were chosen. **Results:** Among aKIR genotypes 2DL5B and 2DS3 were found to be less frequent among MM patients compared to healthy subjects (p=0.001; p=0.04). When KIR receptor genes were evaluated along with their cognate ligands, the frequencies of KIR2DL2 and C1, KIR2DL3 and C1 as well as KIR2DS2 and C1 were found to be less frequent among MM patients (p=0.002; p=0.03; p=0.002). The frequency of patients with aKIR ≥5 was significantly lower among MM patients (P<0.0001). When the total haplotype was compared,AB is more and BB less frequent among patients with similar inheritance of AA (p=0.001). Among MM patients, haplotype AA (with ligands C2+Bw4+) frequency is significantly higher compared to healthy controls (p=0.005). BB haplotype carrying male patients had a four years delay in onset age of diagnosis. This effect was in the opposite direction for females. AA haplotype carrying males had MM diagnosed seven years earlier than negative patients, an effect not visible among females. When the predictors for age at diagnosis was assessed, tAB1 haplotype appears to be a stronger factor (p=0.06) than gender (p=0.76). When impact on early relapse was analyzed cAB1 (n=7) was the only motif to have a minor effect. **Conclusion:** This study is the first to demonstrate activating KIR containing haplotypes to be less frequent among myeloma patients when compared to healthy subjects. Furthermore specifically this effect was confirmed in the presence of their ligands and the haplotypes rich in activating KIRs. Haplotype BB which includes the highest and haplotype AA which has the least number of a KIRs were found to influence the age of onset mainly among males delaying (haplotype BB) or earlier onset (Haplotype AA). Similar analysis among smoldering MM is warranted to provide further evidence.

P-069

Inflammasome-primed neutrophils maintain a pro-tumor microenvironment in Multiple Myeloma

Madelon de Jong[1], Natalie Papazian[1], A. Cathelijne Fokkema[1], Sabrin Tahri[1], Zoltán Kellermayer[1], Michael Vermeulen[1], Mark van Duin[1], Pieter van de Woestijne[1], Annemiek Broijl[1], Pieter Sonneveld[2], Tom Cupedo[2]

[1]Erasmus MC; [2]Erasmus MC Cancer Institute

Background: Multiple myeloma (MM) disease progression is influenced by signals from the bone marrow (BM) microenvironment. Recently, we showed that the MM BM is characterized by inflammatory mesenchymal stromal cells (iMSCs) that transcribe MM survival factors and are predicted to recruit proliferating myeloma cells via CCL2-CCR2 interactions (de Jong et al. Nat Immunol. 2021). iMSCs also transcribed high levels of chemokines

that can bind to CXCR1 and 2. Myeloid cells are known to express CXCR1/2, and have been implicated in both pro- and anti-tumor responses in various malignancies. Therefore, we hypothesized that iMSCs attract and influence myeloid populations in the MM BM. **Methods:** Using flow cytometry, we verified expression of CXCR1/2 on myeloid cell populations in the BM of 5 newly diagnosed MM (NDMM) patients. **Results:** CD15+ neutrophils were the most dominant population expressing these receptors, as 22.4% (± 9.8%) of cells expressed CXCR2 alone, and 72.6% (± 8.0%) expressed both CXCR1 and CXCR2. CD14+ monocytes only expressed CXCR2 (86.9% ± 15.8%). Importantly, less than 1% of myeloma cells expressed these receptors (n = 17 NDMM). As these findings suggested neutrophils as a potential target of iMSC-mediated chemotaxis, we set out to identify MM-associated alterations in this population by performing single cell RNA sequencing of the full neutrophilic lineage (n = 5 NDMM and 2 controls). Interestingly, CXCR1 and CXCR2 transcription was increased in mature neutrophils of MM patients compared to controls. Additionally, mature neutrophils of MM patients had an activated transcriptome as defined by increased transcription of C3AR1, SLPI, and IL6R, the plasma cell supportive factor TNFSF13B (encoding BAFF), and the inflammatory cytokines IL1B and IL18. Transcription of IL1B and IL18 can be regulated by pattern-recognition receptors (PRRs) binding damage-associated molecular patterns (DAMPs) resulting from e.g. matrix breakdown. Transcription of PRRs as TLR1, 2 and 4 was increased in mature neutrophils of MM patients compared to controls. Secretion of IL-1b[ED] and IL-18 relies on the cleavage of pro-forms of these cytokines by the inflammasome, a multiprotein complex that is assembled in response to alarmins. Transcription of inflammasome components PYCARD, NLRP3 and CASP1 was increased in mature neutrophils of patients with MM. Additionally, protein levels of both IL-18 and IL-1b[ED] are increased in BM plasma from MM patients, implicating activated neutrophils as a potential source of these cytokines. **Conclusion:** In MM, mature neutrophils are activated and might interact with iMSCs via CXCR1/2. Moreover, neutrophils are inflammasome-primed and are likely to be a source of increased IL-1b[ED] levels in the MM BM. As IL-1b[ED] can activate normal MSCs to become iMSC, neutrophils and iMSCs may form a feed-forward loop in which activated neutrophils contribute to a pro-MM environment by maintaining iMSC and by directly providing BAFF to tumor cells.

P-070

Peripheral blood monocyte count is a dynamic prognostic biomarker for risk stratification in Multiple Myeloma

Camille Edwards[1], Hamza Hassan[1], Grace Ferri[2], Karina Verma[1], Cenk Yildrim[3], Nathanael Fillmore[3], Nikhil C. Munshi[4]

[1]Section of Hematology/ Oncology, Boston University School of Medicine/ Boston Medical Center; [2]Boston University School of Medicine; [3]Cooperative Studies Program Informatics Center, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC); [4]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: Tumor-associated macrophages, derived from peripheral blood monocytes, support malignant plasma cell proliferation in the bone marrow (BM). Since peripheral blood absolute monocyte count (AMC) could reflect the BM microenvironment, we sought to evaluate the prognostic significance of AMC in multiple myeloma (MM). **Methods:** We used nationwide Veterans Affairs electronic health records to include treatment-naive MM patients diagnosed between 2000 and 2019 without concomitant aplastic anemia, myelodysplastic syndrome, myeloproliferative neoplasm, and acute or chronic leukemia. We obtained AMC ($\times 10^{-3}$) closest to and within 90 days prior to each timepoint: at diagnosis and every 3 months from diagnosis up to 2.5 years. Patients were stratified by AMC: low (1.25). Our selection criteria excluded any treatment-related change in AMC. Overall survival (OS) was evaluated using Kaplan-Meier estimator and logrank tests. Cox models were used for multivariable analysis. **Results:** We identified and analyzed 10,822 patients (median age 70 years; interquartile range [IQR] 63-77) with a median follow up of 2.9 years (IQR 1.3-5.3). At diagnosis, 25.3% of patients presented with abnormal AMC. Patients with low, severely elevated, elevated, and normal AMC at diagnosis had median OS of 2.3, 2.7, 3.1, and 3.6 years ($p<0.001$), respectively. Abnormal AMC 1 year or more after diagnosis was associated with inferior OS (median OS at 2.5 years; 2.0, 2.6, 3.4, and 3.9 years [$p<0.001$] in patients with low, severely elevated, elevated, and normal AMC, respectively). If patients with normal AMC at diagnosis developed an abnormal AMC 1 year or more after diagnosis, median OS was decreased relative to patients who maintained normal AMC. Notably, median OS improved across all AMC groups for patients with MM diagnosed after 2012 when modern therapies became standard of care. After adjusting for known prognostic factors (age, ISS Stage, LDH, creatinine), multivariable analysis showed similar results, with a significant association of OS with AMC at diagnosis and AMC measured up to 2.5 years after diagnosis. Hazard ratios (HRs) at diagnosis were 1.28 (95% confidence interval [CI] 1.06–1.41; $p<0.001$), 1.10 (95%CI 1.04–1.17; $p=0.002$), and 1.19 (95%CI 1.06–1.34; $p=0.004$), and HRs 2.5 years after diagnosis were 1.53 (95%CI 1.22–1.93; $p<0.001$), 1.11 (95%CI 1.00–1.23; $p=0.043$, 1.58 (95%CI 1.22–2.04; $p<0.001$) for low, elevated and severely elevated AMC, respectively. **Conclusion:** Abnormal AMC in MM at diagnosis or follow up is significantly associated with inferior OS, independent of known prognostic factors. Survival was also inferior for patients who had normal AMC at diagnosis and developed abnormal AMC during follow up, possibly suggesting changes in the BM microenvironment. Overall, AMC is a readily available metric that could be included in the risk stratification of MM at diagnosis and beyond.

P-071

Multi-omic analysis of the tumor microenvironment reveals novel associations in a clinical trial of atezolizumab ± daratumumab for relapsed/refractory multiple myeloma

Hearn Jay Cho[1,2], Selma Bekri[1], Sandy Wong[3], Aparna Raval[4], Wout Groeniger[2], Seunghee Kim-Schulze[5], Hui Xie[5], Elisabeth Wassner Fritsch[6], Habib Hamidi[4]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mt. Sinai; [2]The Multiple Myeloma Research Foundation; [3]University of California; [4]Genentech, Inc.; [5]Human Immune Monitoring Center, Icahn School of Medicine at Mt. Sinai; [6]F. Hoffmann-La Roche Ltd

Background: We conducted a Phase 1b trial of atezolizumab (A, anti-PD-L1) ± daratumumab (D, anti-CD38), which targets myeloma cells and has immunomodulatory activity, on the hypothesis that the combination may alter the tumor microenvironment (TME) to favor T-cell activation in relapsed/refractory multiple myeloma (RRMM) (NCT02431208). We undertook multi-omic analysis of samples collected from the TME to understand the immune milieu and potential correlations with clinical outcome. **Methods:** Bone marrow mononuclear cells (BMMNC) and bone marrow plasma were collected from 4 different cohorts, Cohorts A (A-monotherapy), D1 (1–3 prior lines, D-naive, A+D combination therapy), D2 (3+ prior lines, D-naive, A+ D), and D3 (D-refractory, 3+ lines of therapy, A+D), at baseline and on-treatment. Bulk RNA sequencing (RNAseq) was performed using longitudinal CD138+ and CD138- enriched fractions. Mass cytometry immunophenotyping (39 marker CyTOF panel, Fluidigm) and proteomic profiling (multiplex Immuno-Oncology assay [OLink)]) was performed on BMMNC and BM plasma. For the unbiased integrative analysis, Similarity Network Fusion (SNF) algorithm was applied to preprocessed CyTOF, OLink and RNAseq data. **Results:** Data specific and fused patient (pt) similarity networks were derived by unsupervised SNF algorithm from CyTOF, OLink, CD138– RNAseq, and CD138+ RNAseq features. At baseline, networks built using a single data type yielded distinct patterns of pt similarity. However, the fused network, integrating information from all four layers of data types, separated the subjects into three groups which distinguished the D-refractory (D3) and the D2 cohort from the D-naive A and D1 cohorts. Notably, SNF applied to post-treatment CyTOF, CD138+ and CD138– RNAseq data resulted in three clusters that recapitulated the treatment cohorts. The three responders resolved in Cluster 1, which included pts in cohorts D1 and D2. Cluster 2 included the D-naive pts who were treated with A-monotherapy, and Cluster 3 included the D-refractory pts treated with A+D-combo. Pairwise analysis comparing matched treatment samples to baseline identified key biomarkers that are differentially expressed between subgroups. The "one-versus-all" comparisons using the hallmark gene sets in the CD138– gene expression data layer revealed that Cluster 1 is enriched for the T cell gamma delta gene signature and the T effector 6 gene signature, which has been associated with response to cancer immunotherapy treatment such as in Cohort A. In the CD138 positive gene expression layer, the dendritic cells gene signature was significantly increased in Cluster 3, which may indicate a mechanism of resistance in the D–refractory pts. **Conclusions:** Unsupervised machine learning-based integrative clustering analysis of baseline and on-treatment samples from multiple immunologic data types revealed novel associations with pt selection and outcome in both D-naive and D-refractory RRMM pts treated with A ± D.

P-072

Progression and dissemination of experimental multiple myeloma is associated with loss of innate and adaptive immune-mediated tumor control

Zoltán Kellermayer[1], Natalie Papazian[1], Madelon de Jong[1], A. Cathelijne Fokkema[1], Sabrin Tahri[1], Chelsea den Hollander[1], Pieter Sonneveld[2], Tom Cupedo[2]

[1]Erasmus MC; [2]Erasmus MC Cancer Institute

Background: Multiple myeloma (MM) is an incurable plasma cell malignancy and identifying mechanisms driving disease progression and relapse is crucial for development of novel therapies. Although cytotoxic immunity is an important factor in controlling tumor progression, the cells and signals that constitute an effective anti-myeloma immune response within the bone marrow (BM) are incompletely defined. In this study we set out to identify immune-related mechanisms of disease progression in a murine model of MM. **Methods:** C57Bl/6 and KaLwRij mice received 106 5TGM1-GFP murine myeloma cells intravenously. Tumor development was monitored through weekly measurements of M-protein levels. **Results:** Three weeks after tumor injection all KaLwRij mice (18/18) developed myeloma, as defined by >5% tumor cells in BM ("unrestrained tumor") and serum M-protein >2mg/ml, and in all mice tumor cells had infiltrated the spleen. Interestingly, while 39% (7/18) of C57Bl/6 mice had no tumor, 44% (8/18) had low but detectable levels of MM cells (0.1-5% of BM cells, "restrained tumor") while 17% (3/18) presented with an unrestrained myeloma with BM tumor load similar to that seen in KaLwRij mice. In all C57Bl/6 mice MM was confined to the bone marrow with no splenic involvement at day 21. When tumor development in 5TGM1-injected C57BL/6 mice was allowed to proceed for a prolonged period of time, the incidence of mice developing a tumor did not change (59%, 7/12 mice). However, the number of mice with unrestrained tumor increased to 42% (5/12 mice), and 2 out of these 5 mice also developed splenic MM involvement. In addition, 17% (2/12) of mice were characterized by restrained tumor, as they contained low but detectable tumor levels up until 42 days post tumor cell transfer. The time-dependent increase in incidence of mice with high tumor burden suggests an initial immune-mediated restraint of MM that eventually fails, leading first to unrestrained BM disease and then to systemic spread of the tumor. The C57Bl/6 mice with restrained bone marrow myeloma had an expansion of activated mature (CD69+ CD11b+) NK cells as well as activated (Lsel-CD44+CD69+) CD8+ cytotoxic T cells. In contrast, high bone marrow tumor burden and spread of MM cells to the spleen

was associated with a sharp decline in the absolute numbers of both these cytotoxic immune cell subsets. **Conclusion:** Here we provide evidence that loss of innate and adaptive cytotoxic immune populations is associated with progression and dissemination of experimental MM in mice. Transfer of 5TGM1 myeloma cells into C57Bl/6 mice leads to initial tumor control via expansion of innate and adaptive cytotoxic immune cell populations. However, with time, immune-mediated restraint of MM fails, exemplified by loss of NK cell and CD8+ T cell expansion, culminating in tumor outgrowth in the BM and eventual systemic dissemination. This in vivo model will allow for generation of novel insights into the mechanisms of immune escape by MM cells.

P-073

PDZ proteins, SCRIB and DLG1, regulate CD86 surface expression, myeloma growth, and survival

Tyler Moser-Katz[1], Catherine Gavile[2], Benjamin Barwick[3], Kelvin Lee[4], Lawrence Boise[3]

[1]Emory University; [2]University of Utah, Salt Lake City, Utah; [3]Winship Cancer Institute, School of Medicine, Emory University, Atlanta, GA, USA; [4]Indiana University School of Medicine

Background: We have previously demonstrated that the cytoplasmic region of CD86 confers a survival phenotype in myeloma cells and regulates IRF4 and Integrin b[ED]7 expression. Here, we show that the cytoplasmic tail is important for surface expression of CD86. **Methods:** We transfected HEK293T with either full length CD86 (CD86FL) or a mutant lacking the cytoplasmic tail (CD86TL). CD86FL can properly traffic to the cell surface while CD86TL cannot effectively export from the Golgi apparatus. We developed additional truncation mutants of the CD86 cytoplasmic tail and identified that several regions of the tail are required for proper trafficking out of the Golgi. While the truncation mutants traffic CD86 more effectively than CD86TL, they never fully phenocopy CD86FL surface expression. One specific region for proper transport is a three amino acid-long PDZ binding motif at the C-terminus of the tail. Using BioID analysis, we identified two PDZ-domain containing proteins, SCRIB and DLG1 as proximal to the CD86 cytoplasmic tail. **Results:** Using the CoMMpass dataset, we identified that high SCRIB expression is a poor prognostic indicator for progression free (p=0.00022) and overall (p=0.000132) survival. We observed co-localization of SCRIB and DLG1 with CD86 in myeloma using confocal microscopy. Using a doxycycline-inducible CRISPR-Cas9 system, we deleted SCRIB and DLG1 in two myeloma cell lines, KMS18 and RPMI8226. Ablation of SCRIB or DLG1 decreased CD86 surface expression 3 days following activation of the Cas9 enzyme via doxycycline addition. Additionally, we found that knockout of SCRIB or DLG1 results in significantly decreased cell proliferation and viability in these cell lines. SCRIB and DLG1 have been classically studied in the context of apical-basal polarity indicating a possible role for regulating CD86 expression in time and space. We found decreased localization of SCRIB/DLG1 with CD86 at areas of cell-cell contact, presumably where CD86 binds to CD28 to signal for myeloma cell survival. These regions of contact have increased surface expression of CD86 relative to areas where there is no cell contact. This is only prevalent in myeloma cells, and we observed uniform distribution of expression of CD86 throughout the membrane of CD86FL-transfected HEK293T. This suggests that SCRIB and DLG1 transport CD86 to the cell surface, and binding with CD28 may help to stabilize CD86 surface expression. Ablation of SCRIB and DLG1 also decreases IRF4 and Integrin b[ED]7 expression, suggesting that SCRIB and DLG1 may contribute to CD86-mediated growth and survival signaling. **Conclusion:** Our data supports a role for PDZ proteins as regulators of myeloma cell signaling and viability. Study of PDZ-proteins and their binding motifs may be warranted as numerous surface proteins in myeloma cells such as ICAM-1 and CD138 contain PDZ-binding motifs. The PDZ-binding motif may represent a specific region that can effectively be targeted and may be an attractive strategy for novel therapeutics.

P-074

Assessing the immune microenvironment with multiplex immunofluorescence histochemistry demonstrates proximity of cytotoxic T-cells to plasma cells in patients with newly diagnosed multiple myeloma

Slavisa Ninkovic[1], Simon Harrison[2], Louise Purton[3], Hang Quach[4]

[1]St Vincent's Hospital Melbourne, Melbourne, Australia; [2]Peter MacCallum Cancer Centre; [3]St. Vincent's Institute of Research; [4]University of Melbourne, St Vincent's Hospital, Melbourne, Australia

Background: A dysfunctional immune tumour microenvironment (iTME) facilitates disease progression in MM. Using multiplex immunohistochemistry (mIHC) we aim to describe quantitative and qualitative changes in CD3+CD8+ T-cells (Tcytotoxic) in patients with MGUS, ND and relapsed/refractory MM (RRMM) and assess spatial proximity to PCs. **Method:** Formalin-fixed, paraffin-embedded trephine sections from pts with MGUS (n=32), NDMM (n=65) and RRMM (n=59) were sequentially stained for CD138, CD3, CD8 and checkpoint receptors (CPs) Tim3, Lag-3 and PD-1 (Figure 1). Halo® image analysis platform was used for cell segmentation and phenotyping, facilitating enumeration of Tcytotoxic populations and analysis of proximity to PCs. Descriptive statistics and ordinary one-way ANOVA were applied as appropriate. **Results:** Patient demographics, disease characteristics, treatment (including prior therapies, where applicable), best response, duration of response, median progression free (PFS) and overall survival (OS) will be presented for all cohorts. There was no difference in BM cellularity or total number of nucleated cells assessed across the cohorts (p=0.16 and p=0.25). PC % was higher in the ND and RRMM compared to MUGS cohort (p<0.001). The average distance between Tcytotoxic and PCs was similar between the cohorts (p=0.38), but a higher proportion of Tcytotoxic were within 50µm of a PC in the ND cohort (p=0.0036, 90.8±15.8% (ND) vs. 77.6±19.5% (MGUS) and 80.1±25.9%

(RR)). The % of unique PCs with a single Tcytotoxic within 100µm is higher in patients with MGUS and RRMM than NDMM (p=0.0007). There was no difference in the %CD3+, %CD3+CD8+ or %CD3+ cells expressing CD8 (p=0.22, p=0.62, p=0.48). CP expression on Tcytotoxic was similar (Tim3 p=0.46, Lag-3 p=0.35; PD-1 p=0.54) with no difference in dual or triple CP expression. Sub-analyses assessing CP expression patterns and Tcytotoxic/PC proximity within individual cohorts based on response to treatment/disease progression are to follow. **Conclusion:** Multiplex IHC is a novel technique to assess the iTME. While there is no discernible quantitative difference in cytotoxic T-cells or checkpoint receptor expression, we demonstrate increased proximity of cytotoxic T-cells to plasma cells in newly diagnosed patients suggestive of a more robust immune system compared to multiply treated patients.

P-075

Myeloid derived suppressor cells are not elevated in monoclonal gammopathies

Lucie Rihova[1], Klara Bilikova[1], Renata Bezdekova[1], Petra Polackova[1], Miroslav Penka[1], Luděk Pour[2], Sabina Sevcikova[3]

[1]University Hospital Brno; [2]Department of Internal Medicine, University Hospital Brno; [3]Masaryk University

Background: The immunologically tolerant microenvironment may support a development of malignant multiple myeloma (MM) from precancerous monoclonal gammopathy of undetermined significance (MGUS) and blocks the efficacy of immunotherapy in existing MM as well. Myeloid derived suppressor cells (MDSC) represent heterogeneous group of cells with immunosuppressive activity and capability of promotion of tumor growth in MM. Their increased number and negative effect was described in MM but usually not in other monoclonal gammopathies (MGs). **Aim:** Identification and enumeration of MDSC subsets in different MG subjects and comparison of their number with healthy controls. **Methods:** Whole peripheral blood of 30 newly diagnosed and untreated MGs (2 MGUS, 7 MM with AL amyloidosis and 21 MM) and 13 healthy controls was used. Incubation with combination of MoAbs CD16/CD15/HLA-DR/CD14/CD45/CD11b/CD33/CD66b was done. Samples were analysed on BD FACSCanto II (BD Biosciences) after NH4Cl lysis and reanalysed with Infinicyt SW (Cytognos). **Results:** Whole leukocytes were distributed into subpopulations using progressive gating strategy allowing detection of MDSC derived from granulocytes (G-MDSC) and monocytes (M-MDSC) with elimination of dendritic cells (DCs) and other contaminating cells (basophils etc.). There were found no differences in M- and G-MDSC relative and absolute count when compared whole MG group and controls. Even selection of MG with ≥95 % clonal plasma cells (PCs) or MGs with presence of circulating PCs or MGs with >30 g/l monoclonal Id protein did not show statistically different values of both MDSC subsets in comparison with control samples. The only statistically different value was decreased number of DCs in MGs. **Conclusion:** Although elevated levels of MDSC in MM were previously published, this study did not prove it probably due to the different gating procedure. However, it was able to clearly define all leukocyte subsets in peripheral blood, thus only higher numbers of dublets may affect the final count of MDSC. Interestingly, low density neutrophils and tumor associated neutrophils should not be easily distinguish from MDSC, so their better characterization is needed in the future. The isolation and verification of MDSC immunosuppressive potential should be the next step in their analyses. Supported by MH CZ - DRO (FNBr, 65269705).

P-076

Evaluating the changes treatment elicit on the immune repertoire of the myeloma niche using patient-derived multiple myeloma organoid models.

Cesar Rodriguez[1], Hanadi Mohammed Rashad[2], Giovanni Insuasti[3], Jonathan Scolnick[4], Graca Almeida-Porada[2]

[1]Mount Sinai Tisch Cancer Institute; [2]Wake Forest Institute for Regenerative Medicine; [3]Wake Forest School of Medicine; [4]Proteona

Background: Multiple myeloma (MM) cells have an intricate interaction with immune components of the bone marrow (BM) niche that are key for survival and drug resistance. Evaluating the immune system in ex-vivo models has been a challenge that is being partially overcome by xenografts or 3D cultures that replicate the tumor niche. The purpose of this study is to use an established 3D myeloma organoid platform to evaluate changes in cellular immunity within a tumor niche caused by different therapeutic agents using patient-derived BM aspirate samples. **Methods:** MM patients scheduled for BM biopsy were consented and 3-5 ml of aspirate was collected. Mononuclear cells from BM aspirates were co-cultured and suspended in Matrigel. Individual 40-50µm 3D organoids were placed in each well of a 48-well plate. Partial exchange of media containing RPMI, GM-CSF, IL6, IL7, and EGF (cocktail #3) was performed every 2-3 days. Organoids from the same patient were exposed to different drugs on day 5 for 48 hours and the following tests performed at different time points: viability with ATP, immunohistochemistry, flow-cytometry, chemosensitivity assays, AlamarBlue, RayBio, and cell sequencing (Proteona). The primary objective was to maintain viability of the 3D organoid components long enough to study the immune components in the MM tumor niche over an extended period of time. Secondary objective was to evaluate the impact therapies may have on the immune cell function within the tumor niche to identify targetable mechanisms of resistance/sensitization. **Results:** Patient-derived BM aspirate samples were collected and used for this study. Number of organoids made and conditions tested varied based on sample quality and quantity. Organoid lifespan using Matrigel and partial exchange of cocktail #3 allowed for heterogeneous and adequate viability for up to 21 days as seen by flow and histology. Expansion of immune cells was seen during the course of the experiments with variability based on the conditions exposed to (see graph attached). When analyzing for chemosensitivity, there was not a significant

difference seen between some agents likely due to the low drug concentrations used. Despite of that, cytokines on supernatant and gene expression profiling at different time points showed distinct changes in immune cell activity from the same patient when exposed to different conditions (see image). These findings suggest off-tumor targets drugs may have on the tumor niche. **Conclusion:** This platform maintained viability of MM cells and its stroma for up to 21 days with good representation of its immune compartment. Immune cells such as dendritic cells, NK cells, and T-cell showed changes in activity and gene expression after exposure to different therapeutic agents using this organoid model. Further studies to evaluate how to optimize the activity of the immune cells within the MM tumor niche and better understand the impact current therapies have are needed.

P-077

Bone marrow microenvironment analysis of exosomal microRNAs in multiple myeloma, extramedullary disease and plasma cell leukemia

Jana Gregorova[1], Monika Vlachova[1], Lenka Radova[1], Lucie Brozova[1], Renata Bezdekova[2], Lucie Rihova[2], Martina Almasi[2], Martin Stork[2], Luděk Pour[3], Jiri Minarik[4], Roman Hájek[5], Sabina Sevcikova[1]

[1]Masaryk University; [2]University Hospital Brno; [3]Department of Internal Medicine, University Hospital Brno; [4]University Hospital Olomouc; [5]Department of Hemato-oncology, University Hospital Ostrava and University of Ostrava

Background: Multiple myeloma (MM) is a heterogeneous plasma cell (PC) malignancy. These malignant PC are dependent on the bone marrow (BM) microenvironment. However, a subclone of PCs can escape the BM microenvironment and infiltrate soft tissues and organs in the so-called extramedullary disease (EMD). This subclone may also escape to peripheral blood; if there are more than 20% of circulating PC (cPC), the disease is reclassified as plasma cell leukemia (PCL). All cells in the BM microenvironment release exosomes. Exosomes are small membranous vesicles that originate from internal multivesicular bodies; they are found in all body fluids, including peripheral blood, breast milk, etc. Exosomes are important in intercellular communication, and they have been implicated in disease relapse, resistance to chemotherapy and many other processes important for tumorigenesis. They contain proteins and nucleic acids, such as microRNAs (miRNAs) - short non-coding RNA molecules that are involved in many physiological and pathological processes. **Aims:** The aim of this work was to analyze expression of exosomal miRNAs in BM plasma samples of MM, EMD and PCL patients. **Methods:** Exosomes were isolated using qEV columns. MiRNAs were isolated from exosomes using qEV original Size Exclusion Columns, following miRNA isolation using miRNeasy Micro Kit. For next generation sequencing (NGS), 8 MM, 7 EMD and 8 PCL samples were used. Results from NGS were validated on 40 MM, 25 EMD and 21 PCL samples by RT-qPCR using Taqman Advanced MiRNA Assays. **Results:** NGS analysis showed 1128 different miRNAs that were present in analyzed samples. Out of these, 239 miRNAs were found in at least 8 samples and had more than 1 read per million; thus, they were included in subsequent analysis. Out of these miRNAs, there are 6 miRNAs ($p<0.05$) that are significantly dysregulated between MM, EMD and PCL patients. Furthermore, 11 miRNAs ($p<0.05$) were significantly dysregulated between MM and EMD patients, 4 miRNAs ($p<0.10$) between MM and PCL patients and 7 miRNAs ($p<0.05$) between PCL and MM patients. We validated 6 miRNAs which were differentially expressed between MM, EMD and PCL. **Conclusions:** Using NGS, we showed that they are differentially expressed exosomal miRNAs between MM, EMD and PCL patients suggesting their role in pathogenesis of these diseases. This work was supported by AZV 17-29343A and AZV 18-003-00203.

P-078

Prognostic value of immune cells in the multiple myeloma bone marrow microenvironment: a meta-analysis within silico and in vitro validation

Antonio Solimando[1], Nicola Susca[1], Paola Borrelli[2], Matteo Da Vià[3], Maria Antonia Frassanito[1], Vanessa Desantis[1], Ilaria Santarella[1], Assunta Melaccio[1], Roberto Ria[4], Hermann Einsele[5], Angelo Vacca[1]

[1]Bari University; [2]Laboratory of Biostatistics, Department of Medical, Oral, and Biotechnological Sciences, University "G. d'Annunzio" Chieti-Pescara, 66100 Chieti, Italy; [3]Department of Oncology and Hemato-Oncology, University of Milan, 20122 Milan, Italy; [4]Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine "G. Baccelli", University of Bari Medical School, 70124 Bari, Italy; [5]University Hospital of Würzburg

Background: During multiple myeloma (MM) immunoediting, the immune cells can be effective in eliminating the initiating tumor MM cells (MMPCs) in the elimination phase or at least, in the equilibrium phase, which can prompt functional dormancy at early stages. However, malignant MMPCs can take advantage of immune dysfunction and permissive immune microenvironment to escape immune elimination, proliferate and generate active MM. **Methods:**We performed a systematic literature search of public databases through July 2021, investigating predefined biomarkers and immune-microenvironment MM component and their association with survival following PRISMA guidelines. The following search terms (MeSH) were used on each database: (multiple myeloma) AND (mast cell* OR macrophage* OR dendritic cell* OR NK cell* OR regulatory T cell* OR CD3 T-lymphocyte* OR CD4 T-lymphocyte* OR CD8 T-lymphocyte* OR B cell* OR CTLA-4 antigen* OR Antigen* CD274 OR PD-L1 OR PD1 OR BCMA OR SLAMF7) AND (observational OR case-control OR cohort OR overall-survival OR OS). To corroborate our data and investigate at a gene-expression level the prognostic value of deregulated genes (FDR<0.1 & P<0.05) we used a Cox-regression model in the CoMMpass dataset (n=326, IA15 release). We defined gene sets for 7 categories of T cell evasion, including the presence of immune

suppressor cells, immune checkpoints, metabolic checkpoints, stromal cells, imbalanced antigen presentation, tumor cell death, and occurrence of oncogenic pathways. Gene expression analysis from pre-treatment bone marrow samples, purified for plasma cells followed 2 stages: first, we obtained ridge regression Cox models for overall survival (OS) for sets of genes that represent T cell evasion in a discovery set which were applied to the validation set; next, we tested each individual gene per gene set versus OS in Cox regression analysis. **Results:** Studies that adjusted for important clinical covariates (such as international staging system ISS and revised-ISS) showed that higher levels of CD8+ cytotoxic T cells were associated with improved OS (HR = 0.69; 95% CI, 0.55–0.95) and PFS (HR = 0.70; 95% CI, 0.42–0.89), while increased CD 56/57+ NK cells (HR = 0.54; 95% CI, 0.27–0.91) were associated with improved OS; MM with increased FoxP3+ T regulatory cells (HR = 2.23; 95% CI, 1.45–3.36) had worse OS. Analyzing individual genes resulted in 33 genes that showed a significant association with OS in the discovery cohort and the remaining 4 genes in the validation cohort. These genes predominantly belonged to the family of immune checkpoint ligands being represented by ITGB1 (HR 0.69; CI 0.61-0.83), CD40 (HR 0.74; CI 0.62-0.89), TIM3 (HR 0.81; CI 0.72-0.91), and FABP5 (HR 0.78; CI 0.69-0.92). Subsequently, we functionally validated the downstream pathways related to cytoskeleton rearrangement, proliferation, epithelial-mesenchymal transition, and dissemination in vitro. **Conclusions:** Conclusively, we propose this immune basket as a promising theragnostic tool in MM.

P-079

IL10R inhibition reprograms tumor-associated macrophages and reverses drug resistance in Multiple Myeloma

Jennifer Sun[1], Barbara Muz[1], Kinan Alhallak[1], Chaelee Park[1], Berit Lubben[1], Mark Fiala[1], Ravi Vij[1], Abdel Kareem Azab[1]

[1]Washington University in St Louis

Background: Multiple myeloma (MM) is a cancer of plasma cells within the bone marrow (BM) and remains to be incurable. Tumor-associated macrophages (TAMs) are a major immunosuppressive component in the tumor microenvironment and display the pro-tumor M2 phenotype, supporting tumor proliferation, survival, and drug resistance. Targeting TAMs to block their pro-tumor functions represent a promising class of cancer immunotherapy. IL10 is a key immunosuppressive cytokine that leads to recruitment and development of TAMs. In this study, we investigate the role of IL10 in MM TAM development, and hypothesize that inhibition of IL10/IL10R signaling in TAMs will reprogram them for MM killing and overcome drug resistance. **Methods:** Macrophage (MF[ED]) polarization to M1 (CD80+) or M2 (CD163+) is determined by antibody staining and flow cytometry. In vitro and ex vivo studies were carried out in our lab's proprietary 3D tissue-engineered BM model (3DTEBM). First, we compared TAM M2/M1 ratio as well as IL10 cytokine levels in the BM of healthy and MM subjects. To study the role of IL10 in TAM development, we co-cultured MF[ED] with increasing MM cells or rhIL10 in the 3DTEBM for 3 days and analyzed the resulting M2/M1 ratio. To determine the effect of IL10R inhibition, MM and MF[ED] co-cultures, or unsorted patient BM were treated with or without 5ug/ml a[ED]-IL10R monoclonal antibody (mAb), and TAM phenotype was analyzed after 3 days. Additionally, humanized huCD34-NCG mice were inoculated with MM cells and treated with a[ED]-IL10R mAb 3 times/week for 2 weeks; mice femurs were flushed and BM cells were analyzed for TAM phenotype. Finally, we investigated a[ED]-IL10R mAb as combination treatment with chemotherapy in MM-GFP and MF[ED] co-cultures; MM survival was determined by count of GFP+ cells and apoptosis was determined by Annexin/PI staining with flow cytometry. **Results:** Compared to healthy subjects, M2/M1 ratio in MM patient TAMs were 3-fold higher, and BM IL10 level was 3.8-fold higher. Additionally, increasing MM cell ratio in co-cultures induced TAM polarization to M2, and was contributed by IL10. Importantly, a[ED]-IL10R mAb was able to reverse MM induced M2 TAM phenotype in vitro, ex vivo, and in vivo. Moreover, the presence of TAMs resulted in significant MM proliferation and chemotherapy resistance toward lenalidomide and dexamethasone. However, combination treatment with a[ED]-IL10R mAb completely reversed the drug resistance and abrogated cancer cells in vitro, partially due to induction of apoptosis in MM cells. **Conclusions:** In summary, we have shown that MM induced M2 polarization of TAMs in an IL-10 dependent fashion, and disruption of IL10/IL10R signaling reversed M2 phenotype in TAMs, and overcame TAM-supported drug resistance. Future studies are warranted to examine mechanism behind overcoming drug resistance as well as the effect of a[ED]-IL10R immunotherapy in vivo and in patients.

P-080

Single-cell transcriptomic analysis of bone marrow NK cells reveals loss of activated cytotoxic NK cells in Multiple Myeloma

Sabrin Tahri[1], Madelon de Jong[2], Natalie Papazian[1], A. Cathelijne Fokkema[1], Zoltán Kellermayer[1], Pieter van de Woestijne[1], Mark van Duin[1], Annemiek Broijl[1], Pieter Sonneveld[2], Tom Cupedo[2]

[1]Erasmus MC; [2]Erasmus MC Cancer Institute

Background: Multiple Myeloma (MM) disease progression and therapy response are influenced by cues of the microenvironment including tumor control by a cytotoxic immune response. Natural killer (NK) cells are notable mediators of the cytotoxic immune response to MM, and important effector cells in recent immune-mediated therapies. NK cells are drivers of antibody-dependent-cellular cytotoxicity in therapies based on anti-CD38 monoclonal antibodies such as Daratumumab. Classically, NK cells are divided based upon CD56 expression into a cytokine-producing CD56bright subset, releasing cytokines such as IFN-g[ED], TNF-a[ED] and GM-CSF, and a cytotoxic CD56dim subset. However, accumulating evidence suggests much larger heterogeneity in the

NK cell compartment and modulation of these NK cell subsets could impact response to NK cell-driven immunotherapies. Here, we used single-cell RNA sequencing to investigate the heterogeneity and MM-driven alterations of the NK cell compartment in the bone marrow of newly diagnosed MM patients undergoing first-line Daratumumab-containing therapy. **Methods:** We performed single-cell RNA sequencing of the CD38+ and CD38- fractions of viably frozen bone marrow aspirates from 19 newly diagnosed MM patients and 5 non-cancer control patients. NK cells were identified in silico by transcription of KLRF1, KLRD1, GNLY and NKG7 resulting in a single-cell transcriptomic dataset of 30,373 NK cells from MM patients and 8,865 NK cells from control patients. **Results:** After integration of the datasets, bone marrow NK cells formed eight distinct transcriptomic clusters. Conventional CD56bright and CD56dim NK-cells were identified by increased transcription of GZMK or GZMB, respectively. The GZMK+CD56bright NK cells contained both a cluster of naive and a cluster of activated NK cells. The GZMB+CD56dim NK cells consisted of 5 subclusters. To identify MM-induced alterations in NK cell subsets we compared GZMK+CD56bright vs GZMB+CD56dim cluster composition and distribution between control and MM patients. Control bone marrow was dominated by GZMB-transcribing cytotoxic CD56dim NK cells, represented by a low cytokine-producing GZMK+CD56bright vs cytotoxic GZMB+CD56dim ratio. In contrast, MM bone marrow was characterized by heterogeneity in the ratio of cytokine-producing GZMK+CD56bright vs cytotoxic GZMB+CD56dim NK cells. A subset of patients presented with a complete reversal of this ratio. This altered composition was due to a loss of cytotoxic GZMB+CD56dim NK cells, and more specifically a loss of NK cells with a transcriptome suggesting recent activation. **Conclusion:** Here we present a transcriptomic overview of NK cells in MM bone marrow at the single-cell level. A subset of MM patients has a loss of activated cytotoxic GZMB+CD56dim NK cells, suggestive of reduced cytotoxic anti-tumor responses. Current analyses are focused on clinical implications of NK cell alterations in response to Daratumumab-based therapies.

P-081

A novel circulating miRNA involved in T cell senescence of multiple myeloma patients

Xiaojing Wei[1], Hao Sun[1], Lixin Gong[1], Teng Fang[1], Zhen Yu[1], Lanting Liu[1], Yi He[1], Lugui Qiu[1], Xiaoke Ma[2], Mu Hao[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin; [2]School of Computer Science and Technology, Xidian University, Xi'an, China.

Background: Many circulating miRNAs were reported as biomarkers of multiple myeloma (MM),but the functions of these circulating miRNAs are not clarified recently .The aim of this work is to identify novel biomarkers of circulating miRNAs in diagnosis and prognosis for MM and reveal their function in the pathogenesis of MM. **Methods:** MiRNAs profiling in serum(n=15) and MM cells(CD138+, n=10) were analyzed by RNA-sequencing of MM patients. The common dysregulated miRNAs(P<0.05) were identified via Veen Diagram analysis in serum and MM cells between MM patients and healthy donors, then validated by RT-PCR. ROC analysis and Kaplan-Meier(K-M) analysis were performed to evaluate the differently expressed circulating miRNAs in diagnosis and prognosis in MM patients, respectively. Exosomes of serum were isolated and characterized by dynamic light scattering, transmission microscopy, and western blot analysis. **Results:** There were stable and specific miRNA expression profiles in serum and tumor cells of MM patients. The miRNA profiling of MM serum showed that there were 74 differential circulating miRNAs(P<0.05), among which 56 miRNAs(75.7%) were down-regulated and 18 miRNAs were up-regulated(24.3%). MiRNA profiling of MM cells showed that there were 376 miRNAs differentially expressed(P<0.05), of which 87(23.1%) were down-regulated and 289(76.9%) were up-regulated. Veen analysis found 36 common dysregulated miRNAs both in serum and tumor cells of MM. There were 22.3% of differential miRNAs located on chromosome 1 and 17. Five circulating miRNAs(miR-27b-3p, miR-145-3p, miR-628-3p, miR-342-5p and miR-30e-3p) were further confirmed differentially expressed in MM patients(n=201) by RT-PCR. K-M analysis showed that MM patients with low level of miR-27b, miR-145, and miR-628 had shortened PFS and OS. Strikingly, comparing to the decreased level of miR-27b in MM patients serum, miR-27b was enriched in the exosome of serum. MM patients with low level of serum miR-27b displayed lower CD3+T cells and CD3+CD4+T cells in peripheral blood. Our further study found increased proportation of senescent T cells in MM patients with low level of serum miR-27b, especially in CD8+T cells. In order to confirm T cell senescent phenotype, PBMCs were co-cultured with MM patients serum exosomes which mimic the in vivo situation. Flow cytometry analysis showed the CD28 expression was notably decreased on the CD3+ T cells in the co-culture group. In addition, RT-PCR and flow cytometry analysis showed that overexpression of miR-27b significantly down-regulated the level of CD28 in jurkat cells, a T cell line. These findings suggested an immune suppressive microenvironment in MM patients with lower level of serum miR-27b. **Conclusion:** Circulating miRNA works as a usful biomarker in diagnosis and prognosis of MM. Strigently, serum miR-27b is a novel circulating miRNA involved in T cell senescence of multiple myeloma patients which indicated the poor outcome of patients with MM.

P-082

Delineating CDK9- regulated molecular events for the development of rationally derived multiple myeloma treatment strategies

Osman Aksoy[1], Judith Lind[2], Vincent Sunder-Plassmann[2], Martin Pecherstorfer[3], Sonia Vallet[4], Klaus Podar[4]

[1]Karl Landsteiner University of Health Sciences; [2]Karl Landsteiner Priv. University Krems, Austria; [3]University Hospital Krems,

Austria; [4]Karl Landsteiner Priv. University; University Hospital Krems, Austria

Background: Despite major advances in multiple myeloma (MM) therapy over the last 2 decades, most patients relapse. The identification of novel targets and development of derived treatment approaches are therefore urgently needed. Aberrant expression of various cyclin-dependent kinases (CDKs) in solid and hematologic malignancies including MM, results in the loss of proliferative control and enhanced survival. The serine-threonine kinase CDK9, a subunit of pTEFb, in particular, is a major transcriptional regulator of numerous oncogenes. Past studies have suggested CDK9 as a potential therapeutic target in MM. However, CDK9-regulated molecular events in MM are only partly understood. By delineating CDK9-dependent pathophysiologic effects, the present study proposes rationally derived anti-CDK9-containing novel MM treatment strategies to improve patient outcome. **Methods:** Following expression profiling, CRISPR loss-of-function screen and correlation analyses in MM cell line and patient cells, the regulatory impact of CDK9 on downstream target genes was outlined using genomic as well as pharmacological approaches in 2D/3D MM models of the tumor microenvironment. Functionally, CDK9-regulated molecular effects as well as anti-MM activity of anti-CDK9-containing rationally derived treatment combinations were determined by gene arrays, qPCR, flow cytometry, and western blot, proliferation and survival analyses. **Results:** Strongly suggested by a significant induction of CDK9 mRNA expression levels progressing from normal plasma cells to cells from patients with MGUS, smoldering MM and MM; siRNA and CRISP loss-of-function screens across various MM cell lines confirmed their growth dependency on CDK9. Correlative expression levels indicated a functional role of CDK9 (but not for CDK2 and CDK7) on Mcl-1, cMyc, Mdm2, RNA Pol II, and IRF4, but not other genes (e.g. Bcl-2) in the CCLE as well as CoMMpass and GSE5900/GSE2658 MM patient datasets. Indeed, siRNA-mediated CDK9 silencing decreased protein levels of Mcl-1, cMyc, Mdm2, RNA Pol II, and IRF4, and consequently tumor cell survival. Similarly, the novel, selective CDK9-directed proteolysis-targeting chimera Thal-sns-032 induced a reduction of mRNA/ protein levels of Mcl-1, cMyc, RNA Pol II, and IRF4 but not of other potential targets (e.g. Bcl-2) in a dose- and time-dependent manner. Moreover, Thal-sns-032 reduced Mdm2 and thereby increased p53 protein levels. Consequently, Thal-sns-032 inhibited tumor cell proliferation and survival both in tumor cell- and tumor cell:BMSC co-cultures. Rationally derived combination strategies of Thal-sns-032 for example with venetoclax, but also other investigational and established MM therapies induced synergistic anti-MM effects within the tumor microenvironment. **Conclusion:** In summary, by delineating CDK9-regulated molecular events in MM, our studies strongly support the therapeutic role of targeted CDK9-therapy and rationally derived MM combination treatment strategies.

P-083

Rejuvenated BCMA-specific CD8+ Cytotoxic T lymphocytes derived from induced pluripotent stem cells for treatment of Multiple Myeloma

Jooeun Bae[1], Shuichi Kitayama[1], Laurence Daheron[2], Zach Herbert[4 1], Nikhil C. Munshi[3], Jerome Ritz[2], Shin Kaneko[4], Kenneth Anderson[3]

[1]Dana Farber Cancer Institute; [2]Harvard University; [3]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System Medical School; [4]Kyoto University

Background: This study reports on the reprogramming of B-Cell Maturation Antigen (BCMA)-specific CD8+ cytotoxic T lymphocytes (CTL) to induced pluripotent stem cells (iPSC) and their differentiation into rejuvenated antigen-specific CD8+ CTL as a potential therapeutic option to effectively treat cancer patients. Along with characterization of BCMA-specific iPSC by key stem cell markers, pluripotency potential and normal karyotypes, we further detected their polarization into mesoderm development associated with activation of transcriptional regulators SNAI2, TBX3, PLVAP, HAND1 and CDX2 during embryoid body formation. BCMA-specific iPSC clones utilized distinctive commitment pathways during T cells re-differentiation. RNAseq analyses of the "iPSC committed to rejuvenated memory CD8+ T cells" showed unique transcriptional profiles as evidenced by upregulation of transcriptional regulators determining CD4/CD8 T cell differentiation ratio, memory CTL formation, NF-kappa-B / JNK pathway activation, and cytokine transporter/cytotoxic mediator development. In parallel, regulators controlling B and T cell interactions or CD4+ Th cells and inhibitory receptor development were downregulated. The rejuvenated CD8+ BCMA-specific CTL re-differentiated from the iPSC demonstrated (1) mature T cell phenotype and highly enriched central and effector memory T cells without induction of checkpoint molecules; (2) high proliferation and poly-functional anti-myeloma activities in an antigen-specific and HLA-A2-restricted manner; (3) specific immune recognition of cognate HLA-A2 heteroclitic BCMA72-80 (YLMFLLRKI) peptide; and (4) distinct sole clonotype for T cell receptor. Furthermore, the specific iPSC clones maintained their differentiation potential into CD8+ T cells upon sub-cloning or long-term culture under feeder-free culture conditions. **Conclusion:** In conclusion, these results establish a framework for iPSC-based regenerative medicine to provide rejuvenated and highly functional memory CD8+ BCMA-specific CTL as an adoptive immunotherapy to improve patient outcome in multiple myeloma.

P-084

Venetoclax monotherapy is feasible and efficient in patients with bcl-2 overexpressing relapsed/refractory multiple myeloma at high-risk sites: a case series

David Cordas dos Santos[1], Elena Stauffer[1], Tanja Paul[2], Martina Rudelius[2], Sebastian Theurich[1]

[1]Department of Medicine III, LMU University Hospital Munich; [2]Institute of Pathology, LMU Munich

Background: Patients with relapsed/refractory multiple myeloma (RRMM) after numerous treatment lines represent a difficult to treat population and prognosis is poor especially in case of extramedullary manifestations that involve high-risk sites such as the central nervous system (CNS). Venetoclax is an oral, selective bcl-2 inhibitor with a beneficial pharmacological profile and penetrance into the CNS. Recent studies demonstrated high responses to venetoclax in RRMM patients with t(11;14) or high bcl-2 expression on a transcriptional level. However, the prognostic and predictive value of bcl-2 expression is still under debate. Especially, detection of bcl-2 protein expression by immunohistochemistry (IHC) is not well established as a biomarker in RRMM. Here, we present three cases of bcl-2 IHC positive RRMM patients with high-risk manifestations that showed deep end enduring treatment responses to venetoclax monotherapy. **Methods:** We report on three consecutive RRMM patients treated between 2019 and 2021. At initial diagnosis none of the patients had a t(11;14). At relapse FISH was not evaluated but two of three patients showed a strong cyclin D1 expression. In all patients, IHC staining of MM cells in bone marrow biopsies and cerebrospinal fluids demonstrated a strong and homogeneous bcl-2 protein expression at relapse, respectively. Venetoclax was dosed up to 800 mg daily and all patients remained on this dose level. **Case 1:** Penta-refractory RRMM patient. Basic data: 72 y/o, male, IgG lambda, high-risk (HR) cytogenetics: no, extramedullary manifestations: no, prior lines: 8. **Case 2:** RRMM patient with CNS involvement. Basic data: 61 y/o, male, IgM lambda, HR cytogenetics: no, extramedullary manifestations: soft tissue, intraspinal, meningeal, intracerebral, prior lines: 7. **Case 3:** RRMM patient with extramedullary relapse after auto-allo-SCT. Basic data: 71 y/o, male, asecretory, HR cytogenetics: del(17p), extramedullary manifestations: soft tissue, prior lines: 6. **Results:** Regarding the first case, two months after venetoclax beginning, IgG levels dropped to normal range reaching a VGPR (Duration of response (DOR) is 7 months). In the second case a CR was achieved in PET-CT and MRI scans 5 months after beginning of venetoclax treatment (DOR 15 months). A follow-up PET-CT staging of the third case showed a CR of the previously described extramedullary manifestations three months after venetoclax dosing. There were no hematological adverse events in any of the cases. **Conclusion:** Venetoclax monotherapy was well-tolerated in these three RRMM patients without any severe hematologic or infectious adverse events. Moreover, even in the two patients with extramedullary high-risk manifestations, treatment responses were deep and long lasting. Future studies should systematically investigate the value of bcl-2 protein expression as a prognostic and predicitive biomarker in RRMM patients.

P-085

Updated outcomes on Lenalidomide (Len) refractory MM patients'

Annita Ioanna Gkioka[1], Mavra Papadatou[2], Alexandros Gkiokas[2], Aspasia Koudouna[2], Vasiliki Bartzi[2], Aikaterini Bitsani[2], Theodoros Iliakis[2], Maria Dimou[2], Vasileios Pardalis[2], Panayiotis Panayiotidis[2], Marie-Christine Kyrtsonis[2]

[1]National and Kapodistrian University of Athens; [2]1st Department Of Propaedeutic Internal Medicine Athens

Background: Lenalidomide refractoriness constitutes an adverse factor of survival in MM as Lenalidomide relapsing/resistant patients were reported to respond difficultly to next treatment line. Lenalidomide is widely administered in doublet, triplet, or quadruplet schemas as first line treatment or relapse and is the only approved drug for maintenance treatment in MM. Almost all MM patients will become at some time point Len refractory. Len resistance definitions and cautious evaluation is still lacking. **Aims:** To update a previous study from our group (ref) assessing Len-dex treated MM patients' outcomes according to elapsed time until relapse under treatment. **Methods:** 186 patients were studied. 158 Len-Dex treated at any line and 18 receiving maintenance after ASCT, after informed consent was obtained initially. They were separated into 5 groups, including patients (1) with no response within two months (defined as primary resistant MM - PRMM) in the first, (2) progressing under treatment within 6 months from Len initiation in the 2nd (referred as very resistant MM - VRMM) , (3) presenting progression under treatment within 7-12 months (Resistant MM - ResMM), (4) initially sensitive (ISMMP), progressing under treatment after more than 12 months and less than 4 years and (5) long-lasting response presenting eventually relapse (RALR) after more than 4 years from Len initiation. Statistical analysis was performed by conventional methods with the SPSS 21 software. **Results:** Of the 158 len-dex-treated, 16 were PRMM, 23 VRMM, 25 ResMM, 70 ISMMP, 24 RALR. Median overall survival after Len (LenOS) was 3 months (as it was in the former analysis) for PRMM patients with 2,4,4, 3,1,2 being in 1st , 2nd ,3rd and > 4th line treatment. Only 5 PRMM patients received next treatment line after len and managed a further time to next treatment of 9 months. VRMM shared a slight increase of one month in survival after Len, 7 months LenOS vs 6 months in the former analysis, while median LenOS in ISMMM was the same (39 months). RALR patients improved their median LenOS to 87 months compared to 64 observed in previous data. The difference observed may be interpreted by the new agents available for MM treatment. LenOS was significantly different between all groups ($p<0.0001$). Median time from lenalidomide maintenance treatment to relapse was 28months. Three patients while on maintenance became resistant at 4 months (2pts) and 6 months (1pt) respectively. **Conclusions:** We confirmed our results that outcomes are very poor for PRMM and VRMM that constitute a minority of patients that probably cannot be rescued at present. Therapeutical efforts

and innovation are mandatory for ResMM and ISMMP. Improved outcomes observed in RALR patients are encouraging in the era of novel agents and monoclonal antibodies availability.

P-086

Quantitative seroproteomics analysis of Multiple Myeloma patients treated with Tagraxofusp, a novel CD123-directed targeted therapy, identifies novel cytokine-mediated mechanism of action

Arghya Ray[1], Ting Du[1], Clifton Mo[2], Arturo Olguin[3], Janice Chen[3], Christopher Brooks[3], Tariq Mughal[4], Paul G. Richardson[5], Dharminder Chauhan[1], Kenneth Anderson[6]

[1]Dana-Farber Cancer Institute, Harvard Medical School; [2]Dana-Farber Cancer Institute; [3]Stemline Therapeutics, Inc.; [4]Stemline Therapeutics, New York, NY; Tufts University School of Medicine, Boston, MA.; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Background: We previously described a tumor-promoting and immunosuppressive role of plasmacytoid dendritic cells (pDCs; CD123/IL-3R+) in multiple myeloma (MM) pathogenesis (Chauhan et al. Cancer Cell, 2009; Ray et al, Leukemia, 2018). Tagraxofusp, an FDA-approved (for patients with blastic plasmacytoid dendritic cell neoplasm [BPDCN]) novel targeted therapy directed against CD123, can trigger anti-MM activity by decreasing the viability of MM-promoting pDCs. These observations led to a recently completed phase 1/2 clinical trial of tagraxofusp and pomalidomide/dexamethasone in relapsed/refractory MM patients (NCT02661022). The treatment regimen demonstrated preliminary safety and efficacy, with 5 of 9 heavily pretreated patients achieving durable partial response (PR) (ASH 2019). Here, we report the early results of our translational correlative studies using bone marrow (BM), peripheral blood (PB), and serum from the study cohort. **Methods:** Tagraxofusp is a bioengineered targeted therapy directed to CD123 developed by fusing human IL-3 to a truncated diphtheria toxin (DT) payload (Stemline Therapeutics, NY). pDCs and patient MM cells were purified from BM/PB samples after informed consent, and quantified using FACS, as described (Ray et al, Leukemia, 2018). A novel high throughput seroproteomics platform SOMAscan was used to analyze 1,310 protein analytes in serum samples from MM patients (n = 9). SOMAscan data were subjected to meta-analysis to generate heatmaps, followed by hierarchical cluster analysis. SOMAscan results were validated with ELISA using supernatants from MM patient pDCs cultured with or without tagraxofusp. **Results:** Analysis of BM/PB samples from MM patients receiving tagraxofusp therapy showed a distinct reduction in the frequency of viable pDCs [average 2% at screening vs 0.75% post-tagraxofusp; n = 6; p = 0.036]. Of note, pDCs isolated from tagraxofusp-treated patients showed decreased ability to trigger MM cell growth. SOMAscan analysis of patient serum before and after tagraxofusp therapy showed alterations in the levels of 100 proteins [Median Fold Change in expression: 0.39 to 4.5; n = 6; 3 each; p < 0.05]. Importantly, tagraxofusp treatment reduced pDC-related soluble proteins including IFN-g[ED] fold change: 0.8, treated vs untreated; p < 0.05). Our earlier study showed that pDC-MM interactions triggered secretion of IL-3, which in turn promotes both pDC survival and MM cell growth. Importantly, tagraxofusp decreased serum IL-3 fold change 0.75, treated vs untreated; p < 0.05), consistent with tagraxofusp attenuating the survival of tumor-promoting pDCs. **Conclusions:** Our correlative science studies validate the target specificity of tagraxofusp against MM pDCs in relapsed and refractory MM patients enrolled in a phase 1/2 clinical trial. Our study favors further evaluation for this novel therapeutic to improve the clinical outcome of patients with MM. Further combination studies are planned.

P-087

Real world efficacy and safety of venetoclax in t(11;14) multiple myeloma in Hungary

Virág Szita[1], Gábor Mikala[2], András Kozma[2], János Fábián[2], Apor Hardi[2], Hussain Alizadeh[3], Péter Rajnics[4], László Váróczy[5], László Rejtő[5], Tamás Szendrei[6], Árpád Illés[5], István Vályi-Nagy[2], Tamás Masszi[7], Gergely Varga[8]

[1]Department of Internal Medicine and Hematology, Semmelweis University, Budapest; [2]National Institute for Hematology and Infectious Diseases, Department of Hematology and Stem Cell Transplantation, South Pest Central Hospital, Budapest; [3]1st Department of Internal Medicine, University of Pécs, Pécs; [4]Department of Hematology, Teaching Hospital Mór Kaposi, Kaposvár, and Faculty of Health Sciences, Institute of Diagnostics, University of Pécs, Pécs; [5]Department of Hematology, Institute for Medicine Clinical Center, University of Debrecen, Debrecen; [6]Teaching Hospital Markusovszky, Szombathely; [7]Department of Hematology, Semmelweis University, 3rd Department of Internal Medicine; [8]Department of Internal Medicine and Hematology, Semmelweis University, Budapest

Background: Despite therapeutic advances, multiple myeloma remains incurable. Venetoclax, a selective bcl-2 inhibitor may be a step toward personalised therapy for t(11;14) patients, but questions remain about its optimal use. **Methods:** We retrospectively evaluated hematologic response, survival and safety after venetoclax treatment in t(11;14) myeloma patients in Hungary. **Results:** Overall, 49 patients from seven clinical centers were reported. We divided patients into two groups based on the clinical setting: 32 relapsed/refractory patients, who received venetoclax after multiple lines of therapy, often in an ultimate effort; and 17 frontline patients, who achieved unsatisfactory response to standard first line therapy and were treated with venetoclax as reinduction before intended ASCT. We observed remarkably good hematological response rates (ORR): 94% in the relapsed/refractory group and 100% in the frontline setting. This translated into a median PFS of 9.6 months and

a median OS of 14.6 months in the relapsed group; median PFS and OS were not reached in the reinduction group. Known adverse prognostic factors, such as 17p deletion, kidney failure or 1q21 amplification did not convey significantly worse prognosis in our study. Almost one third of patients had impaired kidney function during venetoclax therapy, including three patients requiring dialysis. Clinically relevant improvement was observed in 42% of these patients; dialysis could be stopped in all three cases. Notably, our study also included six plasma cell leukemia patients, with a remarkable median PFS of 10 months and over one year median OS in relapsed disease. Vulnerable patients with PCL, renal failure or refractory disease reported more adverse events, requiring supportive measures or dose adjustment, but cessation of venetoclax therapy did not become necessary. **Conclusion:** Venetoclax therapy is a promising option with few side effects and very good response rates for t(11;14) patients, both in the frontline and in the relapsed setting

P-088

Indirubin-3'-monoxime acts as an alternative proteasome inhibitor and confers new regimens for the treatment of Multiple Myeloma

Zhen Yu[1], Lanting Liu[1], Kefei wang[2], Hao Sun[1], Xiaojing Liu[1], Weiwei Wei[1], Lu Wang[2], Ying Li[2], Yaozhong Zhao[2], Yi He[1], Gang An[3], Fancui Meng[4], Shuhua Yi[2], Dehui Zou[1], Changjiang Huang[4], Tao Cheng[2], Lugui Qiu[5], Mu Hao[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin; [2]CAMS; [3]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [4]Tianjin Key Laboratory of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research; [5]Institute of Hematology and Blood Diseases Hospital

Background: Multiple myeloma (MM) is still an incurable malignancy of plasma cells. Despite the therapeutic benefit of the proteasome inhibitor (PI) bortezomib, drug resistance still accounts for majority of tumor relapses and cancer-related death in MM patients. Thus, exploring the mechanism underlying BTZ resistance and investigating a novel treatment strategy are urgent requisites for clinical practise. Indirubin-3'-monoxime (Id-3) is an active ingredient of a traditional Chinese medicine. **Method:** In the present study, we firstly investigated Id-3 effects on myeloma treatment in patient primary samples and myeloma cell lines. We also investigated the molecular mechanism of Id-3 treatment on MM cells via in vivo and in vitro study. **Results:** We first reported that Id-3 is an effective cytotoxicity agentia against MM cells growth by inducing the MM cells apoptosis. Id-3 treatment also effectively induces the cell death in bortezomib-resistant MM cell lines and primary myeloma patient samples. Stringently, we found there is a synergistic anti-MM effect between Id-3 and bortezomib. The treatment with lower dosage combination of Id-3 and bortezomib exhibited a notably inhibition of the growth of myeloma cells both in xenograft mouse model and MM-PDX model. Mechanism study revealed that Id-3 treatment efficiently inhibited the chymotrypsin-like and caspase-like activity of proteasome in MM cells. The level of the proteasome 11s activator, PA200 (PSME4) and PA28g[ED] (PSME3) was significantly down-regulated both in mRNA and protein level. GEO datasets analysis showed that the high levels of PSME4 and PSME3 were over-expressed in relapsed patients and MM cell lines which correlated with the drug-resistance of MM cells. Kaplan-Meier analysis showed that patients with high-levels of PSME3 or PSME4 had the shortened survival. Knocking-down the level of PSME4 or PSME3 by shRNA noteworthy inhibited the cell growth and enhanced the sensitivity to bortezomib of MM cells. In vivo study also found that down-regulated the level of PSME3 or PSME4 can suppress the proliferation of MM cells and prolong the survival of MM-bearing mouse. **Conclusions:** Taken together, our study supported that Id-3 is an effective agentia against the survival of MM cells both in bortezomib-sensitive and -resistance ones. We further identified that the 11s proteasome activators, PSME3 and PSME4, were down-regulated effectively by Id-3 treatment. High-levels of PSME3 or PSME4 were correlated with the inferior outcome of MM patients. Down-regulating PSME3 and PSME4 by Id-3 or shRNA could efficiently suppressed the growth of MM cells and improve the survival of MM-bearing mice. Our study provides the rational evidence for the clinical application of Id-3 in the treatment of MM.

P-089

Identification of novel targets in multiple myeloma for "undruggable" RAS/CDK signaling cascade

Sophia Adamia[1], Zuzana Chyra[2], Morgan O'Keefe[2, 3], Shruti Bhatt[2], Kenneth Wen[1], Geoffrey G. Fell[2], Yu-Tzu Tai[7], Ivane Abiatari[8], Anthony Letai[2], David M. Dorfman[10], Teru Hideshima[1], Kenneth Anderson[12]

[1]Dana-Farber Cancer Institute; [2]DFCI; [3]Boston University; [7]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [8]Ilia State University; [10]Pathology, Brigham And Women's Hospital, Professor, Pathology, Harvard Medical School; [12]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Background: RAS/CDK-dependent pathways play essential roles in multiple myeloma (MM) pathogenesis; both pathways are undruggable. We evaluated molecular changes associated with pathway-level responses after RAS/CDK inhibition to identify novel molecular targets. **Method:** in our previous studies MM cells were treated with selected Erk1/2 and CDK4/6 inhibitors (Ei, Ci) to target RAS/CDK pathways. Our studies indicate strong synergistic (IC<0.5) MM cytotoxicity triggered by Ei+Ci treatment, which in a dose-dependent manner arrested MM cells in G0/G1 phase

and activated mitochondrial apoptotic signaling. Ei+Ci treatment decreased Erk1/2, CDK4/6, and p-Erk1/2 levels in MM cells, and also induced inhibition of key targets (c-myc, p-RSK,-RB, E2F1) of RAS/CDK cascade. Our studies in patient samples indicate that MM cells co-cultured with or without autologous BM stromal cells remain equally sensitive to Ei+Ci, suggesting that Ei+Ci combination can overcome the protective effects of the MM BM milieu. An in vivo study demonstrated a significant (P=0.0004) MM burden decrease in Ei+Ci-treated mice. Our studies therefore suggesting on-target activity of these inhibitors in vitro/vivo. **Results:** We evaluated mRNA splicing changes in MM cells, with and without Erk1/2 knockdown or with Ei+Ci treatment. Unsupervised clustering of deregulated genes showed dose-dependent treatment effects. Upregulation in response to Erk1/2 knockdown and downregulation due to treatment with Ei+Ci were considered spliced gene signatures linked to RAS/CDK modulation. Gene/pathway enrichment analyses of these genes showed their involvement in cell proliferation and regulation of epigenetic networks in MM. Importantly, these analyses suggest that overexpression of RAVER1/SNRPB core splicing regulator genes are associated with RAS/CDK pathway regulation. These genes encode subunits of U1/2/4/5 spliceosome complexes and are involved in intron retention processes, a marker of malignant transformation. We evaluated expressions of RAVER1 and SNRPB in 558 MM patent samples and 10 normal donor BM PCs and observed significant (p<2e-11) upregulation of both genes in clonal PCs with progression from MGUS to sMM, and to overt MM. SNRPB overexpression is associated with shorter overall patient survival (p<0.01), while RAVER1 has a trend toward poor outcomes. SNRPB proteins are also overexpressed in MM cells. Evaluating SNRPB effects on RNA splicing showed upregulation of transcripts with full intron retention or transcripts with cryptic stop codons utilizing intronic sequences causing their partial retention. Thus, SNRPB overexpression contributes to aberrant transcriptome splicing associated with RAS/CDK cascade in MM. **Conclusions:** Our studies show an association between RNA processing and RAS-CDK pathways in MM, identify a core splicing protein, SNRPB, as a novel target for modulating this undruggable cascade, and suggest that targeting spliceosome complexes is a promising therapy.

P-090

BRAF V600E multiple myeloma patient salvaged with triple MAPK inhibition after CAR T relapse

Sarita Agte[1], Muhammad Elnaggar[2], Christos Adamopolous[2], David Melnekoff[2], Adolfo Adleman[2], Katerina Kappes[3], Paula Restrepo[2], Oliver Van Oekelen[4], Violetta Leshchenko[2], Poulikos I Poulikakos[2], Alessandro Lagana[2], Daniel Verina[4], Sundar Jagannath[4], Samir Parekh[5]

[1]Icahn School of Medicine at Mount Sinai, Department of Medicine, Hematology and Medical Oncology; [2]Icahn School of Medicine at Mount Sinai; [3]Icahn School of Medicine at Mount Sinai, Department of Medicine, Hematology and Medical Oncology; [4]Mount Sinai Hospital; [5]Mount Sinai Medical Center, New York, NY, USA

Background: Despite a growing arsenal of treatment choices, patient relapse post-BCMA-targeted CART therapy remains a challenge and the therapeutic path is still undefined. Among the most frequently observed actionable mutations, BRAF V600E, is present in ~7% of multiple myeloma (MM) patients. The availability of selective inhibitors of BRAF V600E makes this a valuable therapeutic target. However, the clinical efficacy of these inhibitors has been limited and short-lived, frequently due to feedback-induction of BRAF dimers. Novel studies revealed that the multi-kinase inhibitor regorafenib is a potent and selective inhibitor of dimeric BRAF. They have further demonstrated relief of these negative outcomes by inhibiting BRAF in both its monomeric and dimeric form in combination with MEK inhibition leading to more efficacious and tolerable treatment. (Adamopoulos C. et al. Cancer Discov. 21). We present a case of a MM patient with BRAF V600E mutation salvaged with a triple therapy inhibition strategy after relapsing following anti-BCMA CART therapy. **Method:** A 61-year-old male with penta-refractory MM (IgA lambda), ISS stage 3 with hyperdiploidy, gain of 1q21 and del13 was treated with anti-BCMA CART therapy, achieving a best response of VGPR, and disease progression after 6 months. He was temporarily salvaged with BCNU/Mel ASCT and achieved a best response of PR until progression with extramedullary disease (subcutaneous skin lesions in lower extremities) and elevated lambda free light chains (FLC, 126.4mg/l) at 6 months. **Results:** Targeted sequencing showed a BRAF V600E mutation was present prior to CART therapy in his bone marrow and persisted in his bone marrow and a plasmacytoma with a VAF of 41% at this current relapse. A western blot analysis of bone marrow aspirate confirmed BRAF V600E with a specific antibody, and showed phosphorylation of ERK, which was diminished with trametinib. Longer exposure to trametinib confirmed a feedback loop activating MAPK which was abrogated with the BRAF dimer inhibitor regorafenib. With these findings the patient was started on targeted therapy based on combination of a BRAF monomer-inhibitor, dabrafenib (100mg, orally twice daily), a MEK-inhibitor, trametinib (1.5mg, orally for 21/28 days daily), and a BRAF dimer inhibitor, regorafenib (40mg, orally once daily). Within 3 months of treatment initiation, prompt reduction in subcutaneous skin lesions and 80% reduction in free lambda FLC (27.5 mg/l) was observed. Furthermore, the patient had good tolerance to all three medications with minimal side effects (grade 1 fatigue) and continues treatment. The treatment regimen allowed the patient to carry out activities of daily living and return to work. **Conclusion:** Post-CART failure treatment is a challenging and unmet need. NGS may identify targeted therapy that would be able to salvage patients with a tolerable side effect profile.

P-091

Genome-wide CRISPR/Cas9 screening identifies proteasome-related specific vulnerabilities as potential treatment options of proteasome inhibitor-resistant multiple myeloma

Besse Andrej[1], Besse Lenka[1], Lorina Büchler[1], Sara Stolze[2], Amin Sobh[3], Marianne Kraus[1], Hirofumi Nakagami[2], Christoph Driessen[4]

[1]Laboratory of Experimental Oncology, Clinics for Medical Oncology and Hematology, Cantonal Hospital St Gallen, Switzerland; [2]Protein Mass Spectrometry Group, Max Planck Institute for Plant Breeding Research, Cologne, Germany; [3]Division of Hematology/Oncology, University of Florida Health Cancer Center, Gainesville, Florida, United States; [4]Clinics for Medical Oncology and Hematology, Cantonal Hospital St Gallen, Switzerland

Background: Proteasome inhibitors (PI) have evolved as central backbone for multiple myeloma (MM) treatment and significantly contributed to improved patient outcomes. While the most MM patients initially respond to PI-based therapy, the majority develops resistance over the course of disease, and ultimately dies from PI-refractory MM. Therefore, identification of highly active treatment for patients with PI-refractory MM is an unmet clinical need. The biology of PI-refractory MM is still not fully understood and we lack treatment approaches that target specifically its biology. We have previously established multiple models of PI-resistant MM that reflect also features present in PI-refractory MM patients. Here, we applied genome-wide functional screening using the CRISPR/Cas9 system to identify essential drug targets and pathways in PI-resistant MM. **Methods:** Genome-wide CRISPR/Cas9-based screening with Brunello library was used in bortezomib (BTZ)-resistant L363 and RPMI-8226 cells, adapted to grow in the presence of 90 nM BTZ. The overlapping BTZ genetic sensitivity candidates were further validated in BTZ-adapted L363, RPMI-8226, MM1S and AMO-1 cells using shRNA silencing or single-gene specific knockout or genetic overexpression using CCK8 viability assay. Subsequent functional analysis of the highest ranking BTZ sensitivity candidates in BTZ-adapted cells included apoptosis and cell cycle analysis, qPCR and western blotting, SILAC, proteasome activity determination using activity-based probes and FRAP analysis. **Results:** CRISPR/Cas9-screening identified two candidate genes for BTZ sensitivity, KIAA0368 (ECPAS) and PSME1, as consistent screening hits in two independent MM cell lines. Both genes are related to proteasome function, but do not build the proteasome core particle. Specific knock-down or knock-out of KIAA0368 sensitized PI-naive cells to BTZ in a range of 1.2-2 fold, while sensitizing BTZ-adapted cells to BTZ in a range of 4.4-9.5 fold. Likewise, overexpression of PSMF1, an inhibitor of PSME1/2 complex, sensitized BTZ-resistant as well as sensitive cells to BTZ. KIAA0368-depleted BTZ-adapted cells showed accumulation of poly-ubiquitinated proteasome substrate proteins, induction of the unfolded protein response, cell cycle arrest and induction of apoptosis, together with changes in protein synthesis after the treatment with 50 nM BTZ. FRAP analysis of cells with GFP-tagged PSMD6 revealed that the intracellular mobility of proteasomes in KIAA0368-depleted cells was reduced. Importantly, proteasome activity was not impaired in KIAA0368-depleted cells. **Conclusion:** PI-resistant MM cells selectively show a high dependency on the proteasome-related gene KIAA0368, which is involved in controlling the intracellular mobility of proteasomes. KIAA0368 therefore represents a novel candidate to specifically re-sensitize PI-resistant MM cells to proteasome inhibitor treatment, via targeting proteasome trafficking instead of proteasome activity.

P-092

Multiple Myeloma cells depend on the DDI2/NRF1-mediated proteasome stress response for survival

Tianzeng Chen[1], Matthew Ho[2], Jenna Briere[3], Maria Moscvin[1], Peter Czarnecki[4], Kenneth Anderson[5], Keith Blackwell[6], Giada Bianchi[4]

[1]Brigham and Women's Hospital; [2]Mayo Clinic, Rochester, MN; [3]Clark University; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [5]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [6]Joslin Diabetes Center

Background: Multiple myeloma (MM) cells depend on the ubiquitin-proteasome system for survival. Proteasome inhibitors (PIs) are FDA-approved in MM and have radically improved patient survival. However, acquisition of resistance is inevitable. The proteasome stress response (PSR) contributes to proteostasis via de novo proteasome biogenesis. The PSR master regulator NRF1 is constitutively degraded by the proteasome in homeostatic conditions, but in face of proteasomal insufficiency, it is deglycosylated by NGLY1, cleaved by the aspartic protease DDI2, and translocates to the nucleus, to induce proteasome subunit gene transcription. Pharmacological targeting of NGLY1 was recently shown to sensitize cells to PIs. **Hypothesis:** We hypothesize that blocking DDI2 or NRF1 could target an intrinsic vulnerability of MM and represent an innovative therapeutic strategy to overcome PI resistance. **Methods:** We used MM cell lines with distinct baseline sensitivity to PIs, including AMO1-VR, an isogenic AMO1 cell line adapted to grow in continuous bortezomib. NRF1 cleavage and nuclear localization were assessed via western blotting. We used CRISPR-Cas9 to knock out (KO) DDI2/NRF1. Cell viability or tumor growth of DDI2/NRF1 KO versus non-targeting gRNA-edited cells were compared in in vitro and in vivo growth competition studies, respectively. Addback studies were performed by stably expressing WT or aspartic protease dead DDI2 in DDI2 KO AMO1-VR monoclones. Chymotryptic-like proteasome activity was measured via cleavage of a fluorescent substrate. Proteasome subunit PSMA7, PSMB5, PSMB6 and PSMD11 transcription was evaluated via real time PCR. **Results:** Full length and cleaved NRF1 is detectable in MM cell lines and positively correlates with polyubiquitinated proteins, suggesting constitutively active PSR in MM. DDI2/NRF1 KO is cytotoxic alone or in combination with PI carfilzomib in MM cells with distinct PI sensitivity, including de-novo PI-resistant KMS20. In vivo, DDI2 KO leads to reduced plasmacytoma formation in NSG mice and results in prolongation of animal survival. DDI2 KO in AMO1-VR sensitizes to carfilzomib. Further, DDI2 KO blocks NRF1 cleavage and nuclear import, thereby impairing proteasome subunit transcription and CT-L proteasome activity in baseline conditions and following carfilzomib treatment, resulting in increased sensitivity to PI. Wild-type, but not catalytically-dead DDI2 addback rescues these phenotypes, confirming a causative link. **Conclusions:** MM cells exhibit baseline activation of NRF1 and are dependent upon DDI2 for survival. DDI2 KO blocks NRF1 cleavage and nuclear translocation, causing impaired proteasome

subunit biogenesis and recovery of CT-L proteasome activity, thereby increasing sensitivity to PI. Add-back of wild-type, but not of catalytically-dead DDI2 fully rescues these phenotypes. Our study provides the preclinical rationale for development of novel therapeutics targeting DDI2/NRF1 in MM.

P-093

Ubiquitin receptor PSMD4/Rpn10 as therapeutic target in Multiple Myeloma

Ting Du[1], Yan Song[1], Arghya Ray[1], Dharminder Chauhan[1], Kenneth C. Anderson[2]

[1]Dana-Farber Cancer Institute, Harvard Medical School; [2]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Background: Our prior studies showed that targeting Ubiquitin Receptor (UbR) Rpn13 upstream of the 20S proteasome signaling cascade overcomes proteasome-inhibitor (PI)-resistance (Yan et al. Leukemia 2016; Yan et al, 2021 BCJ--please complete reference details). Besides Rpn13, 19S-associated UbR PSMD4/Rpn10 also plays a key role in chaperoning ubiquitinated substrate proteins for downstream 20S proteasomal degradation.In the present study, we show that inhibition of PSMD4 triggers potent anti-MM activity using both in in vitro and in vivo models of MM, including against PI-resistant MM cells. **Methods:** Cell viability, and apoptosis assays were performed using WST/ CellTiter-Glo assay, and Annexin V staining, respectively. PSMD4 knockout 293 cell line was generated using CRISPR/Cas9. Doxcycycline (Dox)-inducible PSMD4-knockdown (KD) MM cell line was generated using short hairpin RNA (shRNA). A xenograft human MM model was used to characterize the role of PSMD4 on tumor progression. Statistical significance was assessed with Student's t test. **Results:** 1) MM patient gene expression profiling database showed that PSMD4 expression inversely correlates with overall survival (n=175; p = 0.00064). 2) RT-PCR, immunoblotting, and immunohistochemistry of MM patient BM showed higher PSMD4 levels in patient MM cells and MM cell lines versus normal cells. 3) Transient transfection of MM cells including, bortezomib-resistant MM cells with PSMD4-siRNA decreased their viability; conversely, transfection with PSMD4-WT rescued cells from growth-inhibitory activity of PSMD4-siRNA. Western blotting confirmed knockdown of PSMD4 by PSMD4-siRNA versus scrambled (scr)-siRNA, and restoration of PSMD4 levels in cells transfected with PSMD4-WT versus PSMD4-siRNA. 4) CRISPR/Cas9-PSMD4-KO showed reduced cell growth. 5) Both PSMD4-KO and PSMD4-KD cells showed elevated levels of polyubiquitylated proteins, indicating blockade of proteasome-mediated protein degradation; 6) PSMD4 blockade triggered apoptosis, cell-cycle arrest, activation of caspases, and endoplasmic reticulum stress response signaling in MM cells; and finally, 7) Transplantation of Dox-inducible PSMD4-KD MM.1S cells in mice correlated with significantly reduced tumor growth. **Conclusion:** Our preclinical data validates targeting UbR PSMD4/Rpn10 to enhance cytotoxicity and overcome PI resistance in MM, as well as provides the basis for the development and clinical evaluation of PSMD4 inhibitors to improve patient outcome.

P-094

ABT-199 and epigenetic modifiers: promising novel combinations for the treatment of Multiple Myeloma

Lyndsey Flanagan[1], Triona Ní Chonghaile[1], Siobhan Glavey[1], Michael O'Dwyer[2]

[1]Royal College of Surgeons in Ireland; [2]Department of Medicine/ Haematology, NUI, Galway, Republic of Ireland

Multiple Myeloma (MM) is a malignancy of the antibody-producing plasma cells. Despite improvements to treatment throughout the years, it remains an incurable and fatal disease [1]. Therefore, novel innovative therapies are needed for relapsed/ refractory MM. The anti-apoptotic BCL-2 family of proteins (BCL-2, BCL-XL and MCL-1) are critical regulators of the intrinsic apoptotic pathway and determine the survival of human MM cells [2,3]. The anti-apoptotic BCL-2 proteins represent attractive therapeutic targets in MM. Recently, ABT-199, a selective BCL-2 inhibitor, was FDA approved for the treatment of CLL and AML. The aim of the study is to develop a biomarker to identify MM patients that are reliant on BCL-2 and could be treated with ABT-199. To assess anti-apoptotic dependence, we used BH3 profiling, a functional assay that interrogates BCL-2 protein interactions using synthetic BH3 peptides to measure the loss of mitochondrial membrane potential. We screened a panel of BH3 mimetics in MM cells and patient bone marrow samples; ABT-199 (selective BCL-2 inhibitor), ABT-263 (BCL-2, BCL-xL and BCL-W inhibitor), WEHI-539 (BCL-XL inhibitor) and AMG-176 (selective MCL-1 inhibitor). The BH3 profile data and BH3 mimetics sensitivity data revealed that there is a diverse anti-apoptotic dependence in MM cell lines and primary patient samples. In addition, we aim to identify novel combination treatments that will induce BCL-2 dependence in MM cells, enhancing sensitivity to ABT-199 treatment. We performed a small molecule screen to identify epigenetic modifiers that could induce BCL-2 dependence in two MM cell lines. The screen included the following classes of epigenetic drugs: histone deacetylase inhibitors, histone methyltransferase inhibitors, DNA methyltransferase inhibitors and BET inhibitors. Interestingly, two classes of the epigenetic drugs, were synergistic with ABT-199 in three MM cell lines, (CI <0.8). Furthermore, we confirmed enhanced cell death by Annexin V/PI staining following both ABT-199 and the two classes of epigenetic drugs in two patient MM samples ex-vivo. Future work will focus on determining the mechanism of enhanced cell death induced by the epigenetic drugs to improve the response to ABT-199 treatment. **References:** [1] O. Landgren, B. M. Weiss, in Leukemia. (England, 2009), vol. 23, pp. 1691-1697. [2] A. Letai, M. D. Sorcinelli, C. Beard, S. J. Korsmeyer, Antiapoptotic BCL-2 is required for maintenance of a model leukemia. Cancer Cell 6, 241-249 (2004). [3] V. Del Gaizo Moore, K. D. Schlis, S. E. Sallan, S. A. Armstrong, A. Letai, BCL-2 dependence and ABT-737 sensitivity in acute lymphoblastic leukemia. Blood 111, 2300-2309 (2008).

P-095

Normal human tissue expression of G-protein coupled receptor 5D (GPRC5D), a promising novel target for Multiple Myeloma, is restricted to plasma cells and hard keratinized tissues

Rachel Goldsmith[1], Ingrid Cornax[1], Jing Ying Ma[1], Xiang Yao[1], Ping Peng[1], Vinicius Carreira[1]

[1]Janssen Research & Development

Background: GPRC5D is an attractive target for treatment of multiple myeloma (MM) due to its high expression on MM cells, and favorable normal tissue expression profile that suggests a low risk for on-target/off-tumor toxicity. However, current literature and public databases report conflicting data for normal GPRC5D RNA and protein expression. For example, cerebellum is reported to have very low levels of GPRC5D mRNA by some sources whereas others report its absence. Likewise, the GTEx database has high maximum expression in the skin, but very low median expression; this is also reflected in the high variability of GPRC5D mRNA levels in skin assessed by RT-PCR reported in the literature. The protein expression data in Human Protein Atlas cannot be used to verify RNA expression because it was obtained using an unvalidated, polyclonal antibody with low specificity by protein array. Other sources of protein expression are incomplete and did not assess critical tissues. Clarification of GPRC5D expression in normal tissues is critical to understanding potential on-target/off-tumor risks to patients treated with GPRC5D-targeted therapies. **Methods:** Key human tissues of interest for protein expression studies were identified through literature search and analysis of an internal RNAseq database. Further elucidation of normal GPRC5D expression in those tissues of interest was done using IHC and ISH on FFPE human tissue samples, including: skin, lung, tongue, tonsil, parotid gland, salivary gland, sublingual gland, submandibular gland, choroid plexus, cerebellum, and brainstem-medulla (inferior olivary nucleus, ION). The primary antibody used was a mouse anti-GPRC5D monoclonal antibody (Abcam, Ab55044, clone 6D9) qualified for its sensitivity and specificity in positive and negative control FFPE human cell pellets. The RNA-ISH GPRC5D probe for human was from ACD (Hs-GPCR5D, cat#489699). All test samples underwent QC screens for IHC and ISH, and only samples that passed were included in the definitive experiments. Stained slides were examined by a pathologist for presence and localization of IHC and ISH signals. **Results:** By IHC and ISH, GPRC5D is expressed in epithelial cells of the hair follicles in the skin (the number of hair follicles in skin samples explains the variability in RNA expression), and at the base of the epithelial columns supporting the filiform papillae (keratinized structures in the tongue). In all other tissues assessed, GPRC5D protein was observed only in interstitial plasma cells. Mild GPRC5D RNA expression was detected by ISH in the motor neurons of the ION (without IHC correlate); its close connection with the cerebellum may explain the very low levels of GPRC5D mRNA expression that have been reported in the literature. **Conclusion:** These data support that GPRC5D is not broadly expressed in normal tissues beyond resident plasma cell populations and hard keratinized tissues.

P-096

Tackling pyrimidine biosynthesis - CTP Synthase 1 is a novel target in the treatment of multiple myeloma

Christina Pfeiffer[1], Arnold Bolomsky[1], Niklas Zojer[1], Martin Schreder[1], Hélène Asnagli[2], Andrew Parker[2], Heinz Ludwig[1]

[1]Department of Medicine I, Wilhelminen Cancer Research Institute, Klinik Ottakring; [2]Step Pharma

Background: Clinical progress in patients with high-risk multiple myeloma (MM) is limited and median survival remains at less than two years. Overexpression of cell cycle and proliferation-related genes is frequently observed in high-risk MM and novel treatment strategies for these patients are urgently needed. While the demand for pyrimidines is saturated via salvage pathways in resting cells, proliferating cells depend on the de novo synthesis of pyrimidines to meet the high demand for nucleotides. We therefore speculated that this pathway represents an attractive target in proliferation-associated high-risk myeloma. **Methods:** In silico analysis of publicly available gene expression data sets was used to analyze CTP Synthase 1 (CTPS1) expression in different MM subgroups. In vitro, CTPS1 was evaluated as a target via generation of CRISPR/Cas9 CTPS1 knock-out cell lines. Apoptosis induction, cell cycle analysis and membrane potential of the cells were analyzed by flow cytometry. Additionally, the CTPS1 inhibitor STP938 (Step Pharma) was tested in 12 MM cell lines for its anti-myeloma properties. Uridine and cytidine rescue experiments were used to confirm the specificity of the compound. Previously established resistance models to pomalidomide and carfilzomib were used to demonstrate the efficacy of STP938 in advanced disease stages. **Results:** In silico gene expression analysis revealed an upregulation of CTPS1 in MM and plasma cell leukemia patients compared to healthy-donor bone marrow plasma cells. Additionally, CTPS1 was found to be upregulated in patients with a proliferative gene expression pattern and high expression levels were linked to poor patient outcome. In vitro, stable CTPS1 knock-out clones failed to proliferate in the absence of exogenous cytidine which can be recycled via the nucleotide salvage pathway. Proliferation inhibition was accompanied by induction of an S-phase cell cycle arrest and apoptosis. The highly specific CTPS1 inhibitor STP938 showed potent inhibition of cell viability in 6 out of 12 cell lines. In accordance with the results obtained in genetic perturbation experiments we observed apoptosis induction, S phase arrest, and loss of mitochondrial membrane potential upon treatment with STP938. Addition of mM concentrations of exogenous cytidine, but not uridine, protected MM cell lines from apoptosis underlining the specificity of STP938. Importantly, the compound remained effective in models resistant to carfilzomib and pomalidomide. **Conclusions:** Our in silico data establish CTPS1 as a potential novel target for proliferation associated high-risk disease. In vitro, the essential role of CTPS1 was confirmed by CRISPR/Cas9 deletion and the CTPS1 inhibitor STP938 was found to be highly efficacious in inducing

apoptosis in several myeloma cell lines. Pre-clinical experiments have thus confirmed the drugability of CTPS1 and therefore strongly support the further evaluation of STP938.

P-097

Preclinical validation of Ecto-5' Nucleotidase (NT5E/CD73) as a novel immunotherapeutic target in Multiple Myeloma

Arghya Ray[1], Ting Du[1], Dharminder Chauhan[1], Kenneth Anderson[2]

[1]Dana-Farber Cancer Institute, Harvard Medical School; [2]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Background: The interaction of plasmacytoid dendritic cells (pDCs) with multiple myeloma (MM) cells, and T- or NK-cells in the bone marrow (BM) microenvironment triggers enhanced tumor growth, as well as inhibits innate and adaptive immune responses. In the present study, we analyzed the genetic changes in MM cells triggered by co-culture with pDCs using next generation sequencing (NGS), and identified that pDC-MM interactions induce metabolic enzyme Ecto-5' Nucleotidase (NT5E/CD73) in both pDCs and MM cells. CD73 has been implicated in cancer metabolism and immunosuppression via nucleotide metabolism pathway. **Methods:** Purified MM patient pDCs (n=3) were co-cultured with MM cells (1pDC/5MM; n=3) for 48h, followed by separation of MM cells from pDCs by flow. Total RNA from MM cells was subjected to RNAseq analysis using Illumina NGS. Data were analyzed by VIPER workflow to generate differential expression. The log2FC (fold change) values in co-cultures vs MM alone, with a False Discovery Rate adjusted p value of <0.05, was considered significant. Cytotoxic T lymphocyte (CTL) assay: MM patient BM CD8+ T-cells were co-cultured with autologous pDCs (pDC:T/1:10) in the presence or absence of anti-CD73 Ab (0.5 µg/ml) for 3 days; pre-stained MM cells were added for 24h (10T:1MM), followed by FACS quantification of viable MM cells. **Results:** A total of 9200 and 9250 genes were differentially expressed based on negative binomial distribution (DEseq2) and linear (Limma) RNA-seq models, respectively (p<0.05). MM cells cultured with (n=3) or without pDCs (n=3) clustered into two distinct groups, indicating contact-dependent transcriptional changes in MM cells after co-culture. pDC-MM interaction regulates several pathways including DNA replication/repair, cell cycle, and nucleotide metabolism. We showed that: 1) pDC-MM interactions induce transcription of adenosine-signaling pathway enzyme NT5E/CD73 in MM cells (1.34-fold increase after co-culture; p=0.0002); 2) Both pDCs and MM cells express CD73, and pDC-MM interactions further increase CD73 levels in MM cells (p=0.008); 3) pDC-MM interactions increase adenosine generation (5.5-fold), and importantly, CD73 blockade by anti-CD73 Ab decreases adenosine production (p=0.0167); 4) CD73 blockade activates MM pDCs, evidenced by the increased expression of CD40/CD83/CD86/HLA-DR on pDCs, and also restores pDCs ability to activate autologous T cells; 5) Targeting CD73 induces MM-specific CD8+ CTL activity against autologous MM cells; and 6) a combination of anti-CD73 Ab and TLR7 agonist triggers more potent MM-specific CD8+ CTL activity against autologous MM cells than either agent alone (%viable MM: anti-CD73 Ab:70%; TLR7 agonist:60%; combo:30%; p=0.009;n=7). **Conclusions:** Our preclinical data therefore suggest that the therapeutic targeting of CD73, alone or in combination with TLR7 agonist, represents a promising novel strategy to restore host anti-MM immunity.

P-098

Super-enhancer-driven PPP1R15B as an oncogenic and potential therapeutic target in Multiple Myeloma

Sinan Xiong[1], Jianbiao Zhou[2], Tze King Tan[3], Sabrina Hui-Min Toh[3], Kalpnaa Balan[3], Yunlu Jia[4], Tae-Hoon Chung[5], Takaomi Sanda[2], Wee-Joo Chng[6]

[1]Yong Loo Lin School of Medicine, National University of Singapore; [2]Yong Loo Lin School of Medicine/Cancer Science Institute of Singapore, National University of Singapore; [3]Cancer Science Institute of Singapore, National University of Singapore; [4]Department of Surgical Oncology, Sir Run Run Shaw Hospital, Zhejiang University; [5]Cancer Science Institute of Singapore, National University of Singapore; [6]Yong Loo Lin School of Medicine/Cancer Science Institute of Singapore, National University of Singapore, Department of Hematology-Oncology, National University Cancer Institute of Singapore (NCIS), National University Health System (NUHS)

Background: Growing evidence suggests that alterations in epigenetic landscape contribute to pathogenesis of multiple myeloma (MM). MM cells are highly dependent on unfolded protein response signaling pathways due to high level of endoplasmic reticulum stress. Phosphorylation of eIF2a[ED] can attenuate protein translation. The PPP1R15B(denoted as R15B hereafter) gene encodes a regulatory subunit of eIF2a[ED]-specific phosphatase complex. In this study,we identified super enhancer (SE)-driven oncogenes specific in MM with a particular focus on a candidate gene R15B, whose functional roles in MM remain largely elusive. **Methods:** We performed H3K27Ac ChIP-seq on MM cell lines, primary MM patient samples, normal CD138+ plasma cells and memory B cells. ROSE analysis was used to annotate SEs and their associated genes. A combination of public data mining, RNAi, overexpression and CRISPR/Cas9 technologies were conducted to determine the oncogenic effects of R15B in MM. Transcriptome analysis of MM cell line H929 with R15B KD and scrambled control was performed. To further study the interactions between SE and its promoters, we are currently working on HiChIP. **Results:** We have identified R15B as one of the SE-associated genes specific to MM patient samples and cell lines. SE activity was correlated with the expression level of R15B. Higher expression of R15B predicted poor overall survival of MM patients, suggesting its clinical relevance in MM pathogenesis. R15B KD or KO significantly reduced cell viability, clonogenicity and induced G2/M arrest. ChIP-qPCR assays showed that C/EBP-b[ED] is strongly enriched at R15B SE region. We also found that

salubrinal, a selective inhibitor of eIF2a[ED] phosphorylation, inhibited MM cell proliferation in a dose-dependent manner. **Conclusions:** Our integrative approaches identified R15B as a novel SE-driven oncogene. We propose that targeting R15B may serve as a new approach for effective anti-myeloma therapy, which warrants further clinical investigation.

P-099

Perturbation of CDK7 and super-enhancer driven transcriptional programs synergistically halts multiple myeloma cell proliferation

Yao Yao[1], Woojun D Park[2], Eugenio Morelli[3], Mehmet K Samur[1], Nicholas Kwiatkowski[1], Yan Xu[3], Behnam Nabet[1], Chandraditya Chakraborty[1], Marta Chesi[4], Nathaniel Gray[5], Rick Young[6], Kenneth Anderson[3], Charles Lin[2], Nikhil C. Munshi[3], Mariateresa Fulciniti[3]

[1]Dana-Farber Cancer Institute, Boston, USA; [2]Baylor college of medicine; [3]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Department of Medicine, Mayo Clinic Arizona,; [5]Stanford University; [6]MIT Department of Biology

Background: With the deluge of available genomic data in recent years, it is becoming evident that MM cells are characterized by cell cycle dysregulation, epigenetic heterogeneity, and perturbation of the transcriptional landscape. We here elucidated the biological role of CDK7 and explored the functional consequence of its inhibition in MM using chemical and genetic approaches, including a recently reported selective CDK7 covalent inhibitor YKL-5-124, and engineered systems for rapid CDK7 protein degradation (dTAG). As previously shown with non-selective inhibitors, CDK7 inhibition via YKL-5-124 was active against a large panel of 25 MM cell lines and observed a significant inhibition of MM cell proliferation, with a significantly lower IC50 compared to PHA-activated normal donor peripheral blood mononuclear cells (PBMCs), suggesting a specific sensitivity of MM cells to CDK7 inhibition. The efficacy of YKL-5-124 was confirmed in vivo in several murine MM models. Selective pharmacological degradation of endogenously tagged CDK7 and inducible KO/KD cell systems confirmed impact of CDK7 inhibition on MM cell proliferation supporting the view that CDK7 is a pharmacologically relevant target for MM. Gene expression analysis after CDK7 inhibition in MM1S and H929 cells revealed that transcripts for only a subset of genes were substantially affected by treatment with low dose of YKL-5-124, showing a strong leading-edge enrichment for downregulation of E2F expression program, cell cycle, DNA damage, and MYC targets. We have indeed confirmed a potent reduction in phosphorylation of RB protein, with consequent decrease of E2F activity in MM cells confirmed using E2F-driven luciferase reporter. These data support the notion of CDK7 as a central hub in the oncogenic CDK-pRb-E2F pathway in MM cells, with its expression and activity positively correlated with E2F transcriptional output in patient cells. **Conclusion:** Importantly, dual inhibition with low doses of YKL-5-124 and BRD4 inhibitor JQ1 respectively, displayed superior activity against a panel of MM cell lines and primary MM cells compared to single perturbation alone by both converging on a subset of key SE-associated dependencies as well as impacting distinct oncogenic expression programs. Isobologram analysis revealed strong synergism with a combination index (CI) <1.0 at all tested doses, including in the cell lines with intrinsic resistance to YKL-5-124 or JQ1, while PBMC from healthy donors were less sensitive to the combination therapy In conclusion, our study demonstrates that CDK7 represents an attractive molecular vulnerability in MM to be exploited therapeutically alone or in combination.

P-100

Serum protein electrophoresis screening as a part of health-check program in Korea

Sun Min Lee[1], Hyunji Choi[1], Young-Hye Cho[1]

[1]Pusan National University Yangsan Hospital

Background: Plasma cell myeloma and monoclonal gammopathy of undetermined significance (MGUS) have markedly increased in Korean population, especially in older age group. Serum protein electrophoresis (sPEP) with total protein level, can provide information about the overall distribution of serum protein and enables screening of plasma cell neoplasms. In this study, we analysed the results of sPEP screening in the hospital health-check program. **Methods:** The sPEP was performed for 1405+2490 individuals, aged 23-83 years, who had visited in the health-check program of Pusan National University Yangsan Hospital for 10 years since 2010. The sPEP tests were performed using kit reagent (Protein 6 assay, Sebia, France) with automated multi-capillary electrophoresis system (Capillary 2, Sebia). According to the patterns of sPEP, we classified the whole data for 7 different groups. **Results:** Among total of 3895 cases, 76.5% showed normal pattern including 164 cases which have only mildly decreased early alpha-2 fraction consisted with haptoglobin. Thirty cases (0.8%) showed acute inflammatory disease pattern with increase of alpha fractions. 11.0% of cases had mildly increased gamma fractions and 2.0% have more than 1.5 g/dL of the calculated quantity of gamma fraction. Three male patients were newly diagnosed as plasma cell myeloma and 36 cases were diagnosed as MGUS. The prevalence of plasma cell proliferative disorders in this study, 1.0% was lower than the previous report of Korea and similar that of large previous reports of large China population. **Conclusion:** sPEP provides information about overall protein abnormalities in serum and is considered as the single most useful test for the detection of plasma cell neoplasm. As the prevalence of plasma cell proliferative disorders has been increasing, we suggest that sPEP may useful and cost-effective for screening in the health-check program.

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Detection of m-protein in acetonitrile precipitates of serum by MALDI-TOF mass spectrometry: a novel methodology

Nikita Mehra[1], Gopal Gopisetty[1], Subramani Jayavelu[1], Arivazhagan Rajamanickam[1], Jayachandran Perumal Kalaiyarasi[1], Parathan Karunakaran[1], Venkatraman Radhakrishnan[1], Sagar Tenali Gnana[1], Thangarajan Rajkumar[1]

[1]Cancer Institute (WIA)

Background: MALDI-TOF-mass spectrometry (MS) has demonstrated superior analytical sensitivity for the detection of M-protein. We present the results of an alternative methodology by MALDI-TOF mass spectrometry (MS) for M-protein analysis. **Methods:** Serum samples from patients with newly diagnosed plasma cell dyscrasias (MGUS, multiple myeloma, plasmacytoma and AL amyloidosis) with evidence of monoclonal gammopathy underwent a direct reagent-based extraction process using acetonitrile (ACN) precipitation. Serum k[ED] and l[ED] were validated using immuno-enrichment by anti-k[ED] and anti-l[ED] biotin-labelled antibodies immobilised on streptavidin magnetic beads. MALDI-TOF MS measurements were obtained using alpha-cyano-4-hydroxycinnamic acid as a matrix. The images obtained were overlaid on apparently healthy donor serum samples to confirm the presence of an M-protein peak. **Results:** Characteristic M-protein peaks were observed in the ACN precipitates of serum within the predicted k[ED] and l[ED] mass/charge (m/z) range. The k[ED] and l[ED] peaks were confirmed by immuno-enrichment analysis. Sixty-seven patient samples with monoclonal gammopathy were chosen for ACN precipitation and analysed by MALDI-TOF MS. There was a demonstrable peak suggestive of M-protein in all the samples. The characteristic "polytypic-like" M-protein was additionally observed in patient samples with AL amyloidosis. The Daratumumab peak was additionally identified in one patient on D-VRd induction therapy. The concordance rate with serum immunofixation electrophoresis and serum free light chain analysis was 95%. **Conclusions:** We report the results of a low-cost process using ACN precipitation to enrich k[ED] and l[ED] light chains for MALDI-TOF MS analysis. **Disclosure of Conflicts of Interest:** Gopal Gopisetty, Nikita Mehra, Subramani Jayavelu, Indian provisional patent application no: 202041009443 filed in March 2020

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Genomic and systemic metabolism differences associated with racial disparities in Multiple Myeloma

Emily Gallagher[1], Alessandro Lagana[1], Yuanhui(Jasmine) Huang[1], David Melnekoff[1], Sundar Jagannath[2], Samir Parekh[3]

[1]Icahn School of Medicine at Mount Sinai; [2]The Mount Sinai Hospital; [3]Mount Sinai Medical Center, New York, NY, USA

Background: Racial disparities exist in the prevalence of multiple myeloma (MM) and monoclonal gammopathy of unknown significance (MGUS), with significantly higher prevalence in African American/ black (AA) compared to non-AA individuals. AA patients are also younger than non-AA at the time of diagnosis. We aimed to determine if differences in systemic metabolism and genetics might contribute to these racial disparities in MM. **Methods:** Studies were approved by the IRB and IACUC. We used a large health system electronic medical record database to characterize the metabolic phenotype of AA and white individuals with MM. Body mass index (BMI) was calculated from height and weight measures. BMI≥30kg/m2 defined obesity. HbA1c ≥6.5% defined diabetes. Genomic analysis was performed by extracting mutational signatures from tumor samples of MM patients as previously described, and comparing their prevalence between AA and white patients. We used an immunodeficient non-obese mouse model of type 2 diabetes (Rag1-/-/MKR) and controls (Rag1-/-) for in vivo MM1.S xenograft studies. **Results:** Of our population of 3170 people, 2128 individuals were AA (21.7%) or white (78.3%). Females comprised 53.2% (n=246) of the AA population and 40.2% (n=669) of the white population. The highest prevalence of obesity was in AA women (46%) > white men (41%) > AA men (36%) > white women (35%). The prevalence of diabetes was greater in AA men (37%) and women (34%) than white men (24%) and women (19%). BMI was a poor predictor of diabetes in the AA population with MM, where diabetes affected 1 in 5 AA individuals with normal BMI, but only 1 in 12 white individuals. Genomic characterization of AA patients, revealed a significant enrichment for the COSMIC SBS1 clock-like mutational signature in AA patients compared to white ($p < 0.05$), which was confirmed after adjusting for age. The SBS1 signature correlates with the age of individuals and may represent a cell division clock. Our finding suggests accelerated aging in AA MM patients, which is concordant with younger age at diagnosis. The male Rag1-/-/MKR mice had hyperglycemia and insulin resistance, and were not obese relative to control mice when fed a regular chow diet. The MM1.S tumor xenografts grew much more rapidly in the Rag1-/-/MKR mice compared with controls; 60 days post injection, tumors were approximately 5 times larger than controls and ex vivo analysis of protein lysates revealed increased activation of the insulin receptor (IR) / insulin-like growth factor 1 receptor (IGF-1R) and mTOR signaling pathway. **Conclusions:** In our large diverse cohort of individuals with MM, we found significant racial disparities in the prevalence of obesity and type 2 diabetes, in addition to enrichment of a clock-like mutational signature in MM from AA individuals. In our mouse model, MM xenografts grew more rapidly in the diabetic mice and had more activation of mTOR signaling, a pathway known to regulate clock and aging gene signatures.

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Profiling the myeloma cell surface proteome reveals CCR10 as a potential immunotherapeutic target

Bonell Patino-Escobar[1], Corynn Kasap[1], Ian Ferguson[1], Martina Hale[1], Arun Wiita[1]

[1]University of California San Francisco, San Francisco, CA, USA

Background: Targeting surface antigens upregulated on malignant plasma cells is one of the most promising approaches to improve outcomes for multiple myeloma (MM) patients. Surface markers with approved therapeutics include CD38, BCMA, and SLAMF7, with many more under development. However, none of these therapies are known to be curative. Furthermore, the "surfaceome" of cancer cells regulates tumor proliferation, migration, and endogenous immune cell interactions. There remains a need to identify new surface antigens that can serve as new immunotherapeutic targets and/or reveal surface protein biology in MM. **Methods:** We used glycoprotein "Cell Surface Capture" proteomics to define the MM "surfaceome". Across four cell line models, we quantified 1245 proteins annotated as membrane-spanning in Uniprot; 530 are high-confidence plasma membrane proteins. We integrated our proteomic data with publicly-available mRNA datasets and bioinformatic prediction algorithms to create a ranking system for possible single-antigen immunotherapy targets. Primary patient samples were obtained under an IRB-approved tissue banking protocol. **Results:** Four of the top six targets by our ranking are already being clinically investigated in MM: BCMA, TACI, ITGB7, and SLAMF7. We thus probed other high-scoring proteins found in our proteomic data that, to our knowledge, have not yet been explored as therapeutic targets. To this end, we found the chemokine receptor CCR10 to be robustly expressed on MM cells per the CCLE but with minimal expression on other tumor cell lines. Data from GTEx and the Human Blood Atlas also suggest low mRNA expression on non-hematopoietic tissues and markedly higher mRNA expression on plasmablasts than other hematopoietic cells. By flow cytometry we verified markedly increased CCR10 expression on MM models compared to B-cell cancers. In patient bone marrow aspirates we also confirmed CCR10 expression on patient tumor cells as well as T-regulatory cells. We developed proof-of-concept Chimeric Antigen Receptor (CAR) constructs using CCL27, the native chemokine ligand of CCR10. We found these CAR's could robustly activate Jurkat T-cells when co-cultured with CCR10+ MM cell lines, suggesting CAR functionality. However, we found that while peripheral blood CD8+ T-cells do not express detectable CCR10 at baseline, T-cell activation during CAR-T production leads to CCR10 upregulation and thus fratricide with functional cyotoxic CAR-T's. Current efforts involve T-cell engineering to avoid this fratricide and thus develop preclinical therapeutic candidates targeting CCR10. **Conclusion:** Our surface proteomic profiling provides a powerful resource to discover new biology and immunotherapeutic strategies in MM. CCR10 serves as potential immunotherapeutic target in this disease. CCR10 upregulation on plasma cells warrants further investigation into the role of the CCL27-CCR10 axis in MM pathology.

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Targeting the mitochondrial protease CLPP in Multiple Myeloma

Tommaso Perini[1], Laura Oliva[1], Maria Materozzi[1], Laura Cassina[1], Mehmet K Samur[2], Ugo Orfanelli[1], Enrico Milan[1], Alessandra Boletta[1], Nikhil C. Munshi[3], Simone Cenci[1]

[1]IRCCS Ospedale San Raffaele, Milan, Italy; [2]Dana-Farber Cancer Institute, Boston, USA; [3]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: Mitochondria are enticing potential targets against cancer, owing to their role as signaling hubs orchestrating key homeostatic functions. Of special interest is ClpP, a resident mitochondrial protease suggested to maintain OXPHOS by degrading damaged protein components and regulating the assembly of mito-ribosomes. While the exact role of ClpP in mammals remains unclear, its manipulation has been shown to induce leukemic cell death. Prompted by its distinctive expression in malignant plasma cells (PCs), we investigated the role of ClpP in maintaining mitochondrial and cellular homeostasis in multiple myeloma (MM) cells and tested it as a possible anti-myeloma target. **Methods:** We analyzed the expression of ClpP mRNA in public and proprietary datasets of normal and malignant PCs and MM cell lines. We performed stable shRNA-mediated knockdown of ClpP (ClpPkd) in MM cell lines and analyzed its sequelae combining electron microscopy, Seahorse and ATP assays, transcriptomics, proteomics, and metabolomics. A proteolytically inactive ClpP mutant (ClpPmut) was expressed to entrap ClpP substrates for subsequent mass spectrometry identification and wet validation. **Results:** ClpP mRNA was significantly higher in bone marrow-purified malignant vs. normal PCs, and MM cells were the highest ClpP-expressing human cancer cell lines. Attesting to a crucial role in myeloma, ClpPkd MM cell lines disappeared from culture due to rapid onset of cell cycle arrest and apoptosis. Intriguingly, toxicity in MM proved independent of the currently acknowledged ClpP-controlled mitochondrial functions, i.e., mito-ribosome assembly and OXPHOS maintenance. Indeed, Seahorse demonstrated different bioenergetics across MM lines, ranging from mixed oxidative/glycolytic to almost exclusively glycolytic. Yet, ClpPkd failed to abate ATP in glycolytic MM lines, but proved equally toxic across all lines, thus unveiling an energy-independent vulnerability. To unbiasedly define the role of ClpP in MM, we undertook a threefold orthogonal approach employing RNA-seq, proteomics, and metabolomics. Their integrated analysis upon ClpPkd revealed an unexpected impact of ClpPkd on protein translation in the cytosol via the processing of nuclear-encoded RNA, coupled with metabolic changes indicative of impaired fatty acid oxidation and pentose phosphate pathway. Finally, mass spectrometry of ClpPmut-entrapped partners identified myeloma-specific mitochondrial substrates, including chaperones and enzymes involved in RNA metabolism and oxidative stress. RNA-seq analyses are further characterizing the pathways impacted by ClpPkd and guiding wet validation experiments. **Conclusions:** Overall, our data strongly suggest that ClpP is vital to MM cells due to a novel non-bioenergetic function, and that its manipulation is lethal via a broad perturbation of mitochondrial and cellular homeostasis.

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Mass spectrometry and artificial neural networks for discrimination of extramedullary Multiple Myeloma

Jana Gregorova[1], Sabina Adamová[1], Lukas Pecinka[1], Lukas Moran[1], Volodymyr Porokh[1], Martin Stork[2], Luděk Pour[3], Josef Havel[1], Petr Vanhara[1], Sabina Sevcikova[1]

[1]Masaryk University; [2]University Hospital Brno; [3]Department of Internal Medicine, University Hospital Brno

Background: Multiple myeloma (MM) is the second most common hematological malignancy of the elderly. The bone marrow is infiltrated by malignant plasma cells. MM may progress into so-called extramedullary disease (EMD). EMD occurs when a subclone of clonal plasma cells migrates out of the bone marrow and infiltrates soft tissues. **Aims:** We focused on the analysis of low molecular weight molecules in peripheral blood of 20 MM and 20 EMD patients using MALDI-TOF mass spectrometry to create a diagnostic tool based on prediction by artificial neural network, which should distinguish different groups of diseases. **Methods:** Matrix-Assisted Laser Desorption/Ionization Time-of Flight Mass Spectrometry (MALDI-TOF MS) has become an indispensable research tool, which is used for analysis of biomolecules and various organic molecules. Artificial Neural Networks (ANN) are components of artificial intelligence inspired by biological neural networks. Using ANN, we can model complex non-linear systems, as previously published. In our previous study, we recorded mass spectra of MM and healthy donor samples. ANN specifically predicted MM samples with high sensitivity, specificity and accuracy. **Results:** The RStudio was used for statistical analysis, where the data were evaluated using Principal Component Analysis (PCA) and Partial least squares discriminant analysis (PSL-DA). Using MALDI-TOF MS, it was possible to distinguish between samples of MM patients and healthy donors, as well as MM and EMD patients. Informative patterns in mass spectra served as inputs for ANN that specifically distinguished between healthy donors and patients. **Conclusion:** We demonstrated that using MALDI-TOF MS coupled with ANN is a useful tool that can distinguish between healthy donors and patients. Thus, it can be used as a fast alternative to conventional analyses.
This study was supported by grants of the Ministry of Health of the Czech Republic, grant nr. NV18-08-00299, AZV 18-03-00203.

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Targeting DNA2 overcomes myeloma cells' metabolic reprogramming in response to DNA damage

Natthakan Thongon[1], Andrea Santoni[1], Jintan Lui[2], Natalia Baran[1], Feiyang Ma[3], Christopher Jackson[1], Pamela Lockyer[1], Irene Ganan-Gomez[1], Yun Qing[4], Min Jin Ha[4], Matteo Marchesini[1], Caleb Class[4], Matteo Pellegrini[3], Lin Tan[5], Philip Lorenzi[5], Marina Konopleva[1], Simona Colla[1]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Molecular, Cell and Developmental Biology, University of California, Los Angeles, CA, USA; [4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: DNA damage resistance is a major barrier to effective DNA-damaging anticancer therapy in multiple myeloma (MM). To discover novel mechanisms through which MM cells overcome DNA damage, we investigated how MM cells become resistant to antisense therapy targeting ILF2, an important DNA damage regulator in 1q21 MM. **Method:** We continuously treated MM cells with an ILF2-targeting antisense (ILF2-ASO) or control non-targeting antisense (NT-ASO) for 3 weeks to see if ILF2-ASO exposure leads to the selection of MM clones intrinsically resistant to DNA damage or activates compensatory mechanisms to overcome ILF2 depletion-induced DNA damage. **Results:** Single-cell RNA sequencing (scRNA-seq) analysis revealed that DNA damage-resistant ILF2-ASO-treated cells had significantly upregulated oxidative phosphorylation (OXPHOS), DNA repair signaling, and reactive oxidative species (ROS). Metabolomic analysis of MM cells after long-term exposure to ILF2-ASO showed a significant enrichment of tricarboxylic acid cycle (TCA) intermediates. Consistent with these results, ILF2-ASO-resistant MM cells were significantly more sensitive to the OXPHOS inhibitor IACS-010759 than ILF2-ASO-sensitive cells were. These data suggest that MM cells can undergo an adaptive metabolic rewiring to restore energy balance and promote survival in response to DNA damage. We then hypothesized that ILF2-ASO-resistant cells' metabolic reprogramming relies on the repair of DNA damage induced by ILF2 depletion or by the generation of ROS from activated mitochondrial metabolism and that targeting DNA repair proteins involved in these processes overcomes DNA damage resistance. We used a CRISPR/Cas9 screening strategy to identify DNA repair genes whose loss of function suppresses MM cells' ability to overcome ILF2-ASO-induced DNA damage. Compared with those in NT-ASO-treated cells, DNA2-targeting sgRNAs in ILF2-ASO-treated JJN3 cells were significantly depleted after 3 weeks of treatment, suggesting that DNA2 is needed to promote resistance to ILF2 depletion. Accordingly, the DNA2 inhibitor NSC105808 (NSC) significantly enhanced ILF2-ASO-induced apoptosis. To dissect the mechanisms of DNA2 inhibition-induced synthetic lethality, we evaluated whether DNA2 activity is essential to maintain activated OXPHOS, which ILF2-ASO-resistant cells require to survive. The quantification of mitochondrial respiratory activity in NT-ASO- and ILF2-ASO-treated MM cells exposed to NSC for 3 days showed that DNA2 activity inhibition significantly decreased the oxygen consumption rate while increasing ROS production in only ILF2-depleted cells. Transmission electron microscopy analysis showed that NSC-treated ILF2-depleted cells had fragmented mitochondrial cristae structures, whose perturbations affect the OXPHOS system structure and impair cell metabolism. **Conclusion:** In conclusion, our study has revealed a novel mechanism through which MM cells

counteract oxidative DNA damage and maintain mitochondrial respiration after metabolic reprogramming.

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NCOR2 mediated MYC upregulation drives drug resistance in multiple myeloma independent of Cereblon

Tomoaki Mori[1], Rakesh Verma[1], Cristina Panaroni[2], Keertik Fulzele[1], Rie Matsubara[1], Noopur Raje[3]

[1]Massachusetts General Hospital, Harvard Medical School; [2]Massachusetts General Hospital; [3]Massachusetts General Hospital Cancer Center

Background: MYC upregulation is associated with multi-drug refractory patients in multiple myeloma (MM). We isolated patient derived MM cells with high MYC expression and discovered that NCOR2 was down-regulated in these cells. NCOR2 is a transcriptional coregulatory protein and its role in MM remains unknown. **Method:** To define the role of NCOR2 in MM, we created NCOR2 knockout human myeloma cell lines and demonstrated that NCOR2 knockout led to high MYC expression. **Results:** Furthermore, NCOR2 knockout conferred resistance to pomalidomide, BET and HDAC inhibitors, independent of Cereblon (CRBN), indicating high MYC expression as a cause of multidrug resistance. Moreover, NCOR2 interacted with the nucleosome remodeling and deacetylase (NuRD) complex and repressed the expression of CD180 by directly binding to its promoter and inducing MYC expression. Next, we generated lenalidomide-resistant and pomalidomide-resistant human myeloma cell lines. Whole exome sequencing revealed that these cell lines acquired the same exonic mutations of NCOR2. These cell lines showed NCOR2 down-regulation and MYC up-regulation independent of CRBN and demonstrated resistance to BET and HDAC inhibitors. **Conclusion:** Our findings reveal a novel CRBN independent molecular mechanism associated with drug resistance. Low NCOR2 expression can serve as a potential biomarker for drug resistance and needs further validation in larger prospective studies.

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Renal response to rescue treatments in Relapsed Refractory Multiple Myeloma (RRMM) patients with renal impairment: final data of a large, observational, prospective study (MIR50)

Antonio Garcia-Guiñón[1], Enrique Morales[2], A Sureda[3], Esther González-Garcia[4], María Soledad Durán[5], Fernando Escalante[6], M Gironella[7], Tomás José González-López[8], Rafael Duro[9], Manuel Pérez Encinas[10], Paz Ribas[11], Elena Cabezudo[12], Rafael Lluch García[13], Ignacio Español[14], Valentín Cabañas[15], Ricardo García-Muñoz[16], José Antonio Márquez[17], Mireya Navarro[18], Javier de la Rubia[19]

[1]Hospital Universitari Arnau de Vilanova; [2]Hospital Universitario 12 de Octubre. Madrid. Spain; [3]Instituto Catalán de Oncología Hospitalet de Llobregat, Barcelona, Spain; [4]hospital Universitario de Cabueñes; [5]Complejo Hospitalario de Jaén; [6]Complejo Asistencial Universitario de León; [7]Hospital Universitari Vall d'Hebron, Barcelona, Spain.; [8]Hospital Universitario de Burgos; [9]Hospital Universitario Virgen de la Macarena; [10]Hospital Clínico Universitario de Santiago de Compostela; [11]Hospital Universitario Dr Peset Aleixandre; [12]Hospital Sant Joan de Déu; [13]Hematology Department, University Hospital La Ribera, Valencia, Spain; [14]Hospital General Universitario Santa Lucía; [15]Hospital Universitario Virgen de la Arrixaca; [16]Hospital San Pedro Logroño; [17]HOSPITAL UNIVERSITARIO BASURTO; [18]BMS; [19]Hematology Department, University Hospital La Fe, Valencia, Spain

Background: Renal impairment (RI) is a common complication of multiple myeloma (MM) and has been associated with poor survival. MIR50 is an observational, prospective, multicenter study aimed to evaluate the renal response (RR) to treatment in patients (pts) with RRMM. **Methods:** Renal and MM responses are evaluated according to IMWG criteria in pts with moderate RI (mRI;CrCl 30–50mL/min) or severe RI (sRI;CrCl<30mL/min). Besides, estimated glomerular filtration rate (eGFR) by the Cockroft-Gault (CG), Modification of Diet in Renal Disease(MDRD) and Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI) formulas were compared to analyze renal function. **Results:** We included 282 pts with a median (range) of 76 (70-81) yo (52% male, 44% ISS3, 40% in 2nd or later relapse). Overall, 181(64%) pts had mRI and 100(36%) pts had sRI. Arterial hypertension (HT) was the most frequent comorbidity. Patients with sRI, compared with mRI, had a more advanced phase of MM, BJ type MM, ISS3 disease, HR cytogenetic, diabetes mellitus, and primary malignancies other than MM. Pts were treated with lenalidomide (LEN) (109,43,8%) or bortezomib (BORT)-based treatment (61,24,5%),respectively. Median follow-up was 15.2(range,7.2-33.8) months(mo). Overall response rate was 49.0% w/o differences in renal subgroups (mRI:48.5%;sRI:50.0%). Basal renal function (mean[SD]) at rescue treatment initiation was very similar for the three equations (CG:33.1[11.5], MDRD:35.1[14.3], CKD-EPI:34.7[14.4] mL/min/1.73m2). RR was 20.8%(CG), 27.3%(MDRD), and 27.3%(CKD-EPI) with a moderate correlation between CG and either MDRD(r[ED]=0,90) or CKD-EPI(r[ED]=0,92), while agreement between MDRD and CKD-EPI equations was almost perfect(r[ED]=0,99). The only factor to negatively influence the improvement in renal function in multivariate analysis was HT(p=0.02). During follow-up 88(35.3%) pts developed acute kidney injury (AKI), more frequently observed among patients with sRI (51.2% vs 27% in mRI). Only 16(18.2%) pts recovered from AKI. PFS and OS in the overall series was 8.3 (6.8-11.1) and 20.9(16.1-27.1) mo, respectively w/o differences according to renal subgroups. The main cause of death was disease progression (49.1%). Median (95%CI) PFS and OS were significantly different among rescue treatments (p<0.0001 both), being 13.3(9.6-15.7) and 28.8(21.4-36.5) mo for LEN, 8.5(5.5-12.0) and 24.8(16.1-33.8) mo for BORT, and 5.7(4.4-7.7) and 9.9(7.7-16.8) mo for

other therapies. Finally, OS was significantly shorter in patients who developed AKI compared to those who did not (55.1[45.6-70.2] vs 71.7[62.6-83.8] mo,p=0.01). **Conclusion:** This study shows that HT was the most frequent comorbidity in pts with RRMM and RI. Patients with CrCl <30mL/min had a more advanced phase of MM, BJ type MM, ISS3 disease, and high-risk cytogenetic. In addition, these patients develop AKI more frequently, associating an unfavourable impact on OS. LEN- and BORT-based treatments can improve RI in approximately 20-27% of pts.

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The impact of SLiM criteria in myeloma in a real-life population: clinical characteristics, treatment and outcome from the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR)

P.Joy Ho[1], Elizabeth Moore[2], Cameron Wellard[2], Hang Quach[3], Hilary Blacklock[4], Simon Harrison[5], Emma-Jane McDonald[6], Zoe McQuilten[7], Erica Wood[7], Peter Mollee[8], Andrew Spencer[9]

[1]Institute of Haematology, Royal Prince Alfred Hospital; [2]Transfusion Research Unit, Monash University; [3]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [4]Dept of Haematology; [5]Peter MacCallum Cancer Centre; [6]Canterbury District Health Board; [7]Monash University; [8]Princess Alexandra Hospital; [9]The Alfred Hospital

Background: In addition to 4 CRAB criteria, 3 biomarkers were adopted as myeloma-defining events: clonal marrow plasma cell (PC) percentage ≥60%, serum free light chain ratio (SFLCR) ≥100 and >1 MRI focal lesion, known as SLiM (SixtyLightchainMRI), but there has been no analysis of their clinical impact. **Methods:** We compared the characteristics, treatment & outcomes of 1686 pts diagnosed by CRAB and 132 pts by SLiM enrolled in the MRDR from 2013 - 2018, to assess the impact of these criteria on clinical practice and treatment outcomes. **Results:** Patient & Disease characteristics. In 132 SLiM pts, 48 had SFLCR≥100, 58 BMPC>60% and 26 were known to have both, nil had MRI lesions (limited by MRI availability). CRAB pts included a higher proportion with advanced stage ISS-3 (35.6% v 10.7%, p <0.001), R-ISS-3 (16.0% v 2.5%, p=0.001) and poor performance status (ECOG 2 to 4: 24.7% v 8.3%, p<0.001). Renal impairment was more prevalent in CRAB vs SLiM (eGFR 67 v 79 ml/min, p<0.001) and median Hb was lower (108 v 117 g/L, p<0.001). Median BM PC (60% v 50%, p = 0.004) and SFLCR (100 v 39; p<0.001) were higher in SLiM than CRAB. There was also a trend for a higher incidence of FISH anomalies in CRAB v SLiM - 65.8% v 55.3% (p=0.07). **Outcomes:** OS was longer in SLiM than CRAB (median 76.3 v 65.2 m, p=0.02, HR 1.75), with no difference in PFS (30.8 v 30.2 m, p=0.30, HR 1.17). However PFS2 was superior for SLiM of 48.7 m v 38.2 m for CRAB (HR 1.38, p=0.06). No difference in best response rates (≥PR & ≥VGPR) was seen in SLiM v CRAB. Within SLiM, comparing 3 groups: those who satisfied the criteria of SFLCR>100 only (SFLC group, n=28), PC≥60% only (PC group, n=34) or both (n=20), pts with <PR was 3.6% in SFLC group, 17.6% in PC group, and 20% for pts with both (p=0.04), indicating that pts who satisfy PC criteria (alone or together with SFLCR) have a higher risk for suboptimal response. **Discussion:** We found differences in characteristics between SLiM and CRAB pts – higher BM PC infiltration and SFLCR in SLiM, and a trend for higher incidence of FISH anomalies in CRAB. SLiM pts had a median OS 11.1 m longer than CRAB, but no difference in PFS1 or response rates. The OS difference of ~1 yr could reflect the earlier initiation of therapy in SLiM. However the trend for a longer PFS2 for SLiM indicates improved treatment outcome to therapy at first relapse, suggesting the shorter PFS2 of CRAB pts may result from residual or re-emerging drug-resistant clones. **Conclusions:** In a real-life population our findings support the benefit of earlier initiation of therapy by SLiM criteria, with an improved OS and a trend towards improved outcome at first relapse (PFS2). Patients with PC criteria in the SLiM cohort have an increased risk for suboptimal response compared to those who satisfy SFLC criteria alone.

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Multiple Myeloma treatment patterns and outcomes in the public and private healthcare systems in Brazil: one country, two worlds

Vania Hungria[1], Rosane Bittencourt[2], Gracia Martinez[3], Juliana santos[4], Denise Almeida[5], Vera Figueiredo[6], Danielle Farias[7], Karla Zanella[8], Larissa Muniz[9], Diego Mendonça[10], Rodrigo Abreu[10], Juliana Senra[10], Ederson Mattos[11]

[1]Department of Hematology and Oncology, Clínica São Germano, São Paulo, Brazil; [2]Hospital de Clínicas de Porto Alegre - HCPA da Universidade Federal do Rio Grande do Sul; [3]Hospital das Clínicas de São Paulo, São Paolo, Brazil; [4]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil and Federal University of Bahia; [5]Hospital São Vicente de Paulo; [6]Hospital do Servidor Público de São Paulo; [7]Hospital das Clinicas da Universidade Federal de Goiás; [8]CEPON - Centro de Pesquisas Oncológicas; [9]Casa de Saúde Santa Marcelina; [10]Medical Affairs, Takeda Distribuidora Ltda.; [11]Centro de Ensino e Pesquisas - Fundação Dr. Amaral Carvalho

Background: Over the past two decades, the approval of several novel drugs has broadened therapeutic options for multiple myeloma (MM) patients, but has also raised concerns about increasing drug expenses and healthcare costs in general. Access to these treatments in public and private settings in Brazil differs significantly and it is unknown if shortcomings in treatment availability affect patient outcomes. The aim was to understand the patient characteristics, treatment patterns and MM patient outcomes in private and public settings in Brazil. **Methods:** MMyBrave is an observational, retrospective study with no control group. Eligible patients were diagnosed with active MM between January 1, 2008 and December 31, 2016 (cut-off date), at 17 public and private medical centers in Brazil. The MM diagnosis was performed according to investigator assessment. Data collection started on June 2018, after

ethical approval, and progressed until August 2019. Demographic and clinical characteristics were collected. Patients were stratified according to eligibility to transplant (intention-to-treat analysis) and treatment setting (public or private health systems). The overall survival (OS) was analyzed using the Kaplan-Meier (KM) curve and Cox's proportional-hazards model. **Results:** A total of 943 patients were included. Private and public centers accounted for 44.9 and 55.1% of patients, respectively. The age (≥65 years) and female percentage at private and public centers were 64.2 and 63.4%; and 43.6 and 48.6, respectively. The International Staging System stages I, II, III and stage unknown were: 26.7, 22.6, 25.7 and 25.0 at private centers and 13.3, 20.2, 27.4, 39.1 at public centers. A total of 47.9% (50.2% private and 46.1% public) were eligible for autologous stem cell transplantation (ASCT). Proteasome inhibitor (PI) regimens (mainly bortezomib-based) were used by 52.8% at private centers (57.3% in ASCT eligible; 48.3% in ASCT ineligible). MM patients in the private health system had a higher overall survival (OS) than those in the public setting (75.9 x 63.3 months, p = 0,007). **Conclusion:** Real-world MM patient outcomes at private and public institutions in Brazil were quite different, with significantly higher OS in those followed in the Brazilian private healthcare system. Disease staging and treatment response were found as independent OS predictors, regardless reimbursement setting and ASCT eligibility. These preliminary results raise the hypothesis that the superior OS among patients in the private healthcare system may be due to a wider availability of therapies.

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Relapse with plasmacytoma after upfront autologous stem cell transplantation in multiple myeloma

Sung-Hoon Jung[1], Tan-Huy Chu[2], Kihyun Kim[3], Jae Hoon Lee[4], Yeung-Chul Mun[5], Soo-Mee Bang[6], Dok Hyun Yoon[7], Chang-Ki Min[8], Ho Sup Lee[9], Je-Jung Lee[10]

[1]Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [2]BioMedical Sciences Graduate Program, Chonnam National University; [3]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan UniversitySchool of Medicine, Seoul, Korea; [4]Gachon University Gil Medical Center; [5]Ewha Womans University School of Medicine; [6]Seoul National University Bundang Hospital; [7]Asan Medical Center, University of Ulsan College of Medicine; [8]Department of Hematology, Seoul St Mary's Hospital, Seoul, Republic of Korea; [9]Kosin University Gospel Hospital; [10]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea

Background: Plasmacytoma has been reported to be associated with poor prognosis in patients with multiple myeloma (MM). In this study, we evaluated the incidence of plasmacytoma and survival outcomes in newly diagnosed MM who underwent upfront autologous stem cell transplantation (ASCT). **Method:** This study retrospectively analyzed the data of 303 patients with MM who underwent upfront ASCT between April 2000 and April 2018 from 8 institutes in Korea. A total of 52 patients (17.1%) had plasmacytoma at relapse after upfront ASCT. Of them, 27 patients showed paramedullary plasmacytoma (PMD) and 25 patients showed extramedullary plasmacytoma (EMD). **Results:** Patients with plasmacytoma at initial diagnosis had more plasmacytoma at relapse than those without plasmacytoma (37.1% vs. 11.2%). Over a median follow-up of 66.0 months, patients with plasmacytoma at relapse had significantly inferior overall survival (OS) than those without plasmacytoma (43.9months vs. 100.7 months, P <0.001), but the OS did not significantly differ between patients with EMD and those with PMD (56.6 months vs. 42.2 months, P = 0.464). After relapse, all patients received salvage therapy with borteozmib or lenalidomide-based regimen, but progression free survival (PFS) after relapse was significantly shorter in patients with plasmacytoma than those with no plasmacytoma (6.4 months vs. 12.4 months, P <0.007). **Conclusion:** This study showed that plasmacytoma was frequently developed at relapse after upfront ASCT in patients with plasmacytoma at initial diagnosis and plasmacytoma at relapse was significantly associated with poor prognosis.

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Evaluation of real-world frontline treatment for multiple myeloma by race

Ankit Kansagra[1], Benjamin Derman[2], Andrew Belli[3], Eric Hansen[3], Stefanie Goran[3], Ching-Kun Wang[3]

[1]University of Texas Southwestern Medical Center; [2]The University of Chicago Medical Center, Section of Hematology/Oncology; [3]COTA, Inc.

Background: African Americans (AA) are disproportionately affected by multiple myeloma (MM) with over double the incidence and mortality rates as compared to white patients. Although there have been significant therapeutic advances for the treatment of MM over the last 20 years, research has suggested that these benefits may not be uniform across racial groups. We sought to explore racial disparities in multiple myeloma using contemporary real-world data (RWD). **Methods:** A total of 1790 patients meeting the study criteria were identified in the COTA real-world database, a de-identified database of RWD derived from the electronic health records of healthcare providers in the United States. Study eligibility criteria included active MM diagnosis after Jan. 1, 2015, and white (n=1494) or AA (n=296) race. Patient characteristics and treatment patterns were summarized by line of therapy (LOT). LOT was assigned programmatically on the retrospective RWD using an algorithm based on IMWG criteria and clinical guidance. Time to next treatment (TTNT) was calculated using the Kaplan-Meier method. **Results:** In comparison to white patients, the AA cohort consisted of younger (median age 61.0 vs 66.0 yrs, p<0.001) and majority female patients (52.4% vs 40.9%, p<0.001). Both racial cohorts were predominately treated in the academic setting (AA: 68.9% vs white: 67.7%). AA patients had significantly longer median [IQR] time to first-line (1L) treatment (24.0 [10.0, 48.3] vs 19.0 [7.0, 36.0] days, p=0.002), as well as longer time to first stem-cell transplant (SCT) (218.0 [176.0, 322.5] vs 185.0 [145.0, 261.0]

days, p<0.001). Overall, 1L treatment types were similar across racial cohorts; the most common 1L treatment was proteasome-inhibitor (PI) in combination with immunomodulator (imid) and steroids (AA: 41.6% and white: 42.4%). Similar proportions of patients received 1L SCT by racial group (13.9% and 15.9% among AA and white patients, respectively). Among patients that received 1L PI, differences were observed between types of 1L PI regimen, with a greater proportion of AA patients receiving bortezomib-based treatment (80.0% vs 71.3%) and lower proportion receiving carfilzomib-based treatment (16.9% vs 23.8%, p=0.03). No significant differences were observed between TTNT across racial and PI subgroups from 1L to 2L treatment. **Conclusions:** These findings suggest that frontline treatment patterns were similar by race in a contemporary real-world cohort treated predominately in the academic setting. Despite delays in 1L therapy initiation among African American patients, TTNT from 1L to 2L were similar. Additional disparities were observed in testing rates for 1p deletion and tp53. Future analyses will investigate treatment patterns by practice setting and expand into later LOTs to further elucidate if academic practices and uniform treatment patterns drive similar outcomes by race.

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Improving the risk stratification of multiple myeloma with a nucleotide editor/inflammation-based scoring system

Afsaneh M. Shariatpanahi[1], Sarah Grasedieck[2], Matthew C Jarvis[3], Faezeh Borzooee[4], Reuben Harris[3], Mani Larijani[4], Kevin Song[5], Arefeh Rouhi[1], Florian Kuchenbauer[6]

[1]BCCRC/UBC; [2]Michael Smith Laboratories; [3]University of Minnesota; [4]Simon Fraser University; [5]Vancouver General Hospital; [6]BCCRC/LEUKEMIA-BMT PROGRAM OF BC/UBC

Background: Current clinical prognostication of newly diagnosed MM (NDMM) patients relies on clinical parameters and/or recurrent genetic changes, which mainly reflect early events in the development of MM. However, recent insights into the pathogenesis of MM highlighted genome/transcriptome editing through APOBEC genes as well as inflammation as drivers for the onset and progression of MM. **Aims:** To build a superior nucleotide editor/inflammation-based risk scoring system reflecting biological processes that drive the progression of MM. **Method:** We hypothesized that a prognostic score reflecting biological processes as well as clinical features is superior to the currently used classification systems for MM patients, such as ISS, R-ISS and the Mayo clinic classification. The Multiple Myeloma Research Foundation CoMMpass study genomics dataset, combining mRNA Seq and clinical data from more than 700 patients, allowed us to evaluate the prognostic value of demographic and clinical parameters, cytogenetics, and gene expression levels of APOBEC family as well as inflammation-modulating cytokines of MM patients. We calculated hazard ratios and Kaplan-Meier survival estimates for all extracted features. Combining clinical variables that were significantly associated with PFS and OS, we then applied machine learning approaches to identify the most accurate classification model to define a new risk score that is easy to compute and able to stratify NDMM patients more accurately than cytogenetics-based classifiers. **Result:** Based on our machine learning models, we defined a weighted OS/PFS risk score (Editor-Inflammation score) based on expression of APOBEC2, APOBEC3B, IL11, TGFB1, TGFB3, as well as b[ED]-2-microglobulin and LDH serum levels, that achieved the best classification outcome and showed superior performance compared to ISS and R-ISS. Of note, cytogenetic abnormalities did not proof relevant have therefore not been included in the EI score. Besides superior overall risk stratification, the EI score further allowed to identify subgroups of MM patients with very good prognosis who do not significantly benefit from bone marrow transplantation maintenance therapy. **Conclusion:** Our findings support the adoption of molecular biomarkers, reflecting dynamic biological processes rather than cytogenetics for a more accurate risk classification of MM. Considering that mRNA-seq is as cost effective as FISH and is being increasingly adopted by diagnostic centers, the EI score is a unique approach to shed light on underlying molecular mechanisms that drive disease progression and the development of true risk-adapted treatment strategies.

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Healthcare resource utilization and morbidities in patients with idiopathic Multicentric Castleman Disease

Sudipto Mukherjee[1], Rabecka Martin[2], Brenda Sande[2], David Kauffman[3], Jeremy Paige[3], David Fajgenbaum[4]

[1]Cleveland Clinic; [2]EUSA Pharma; [3]Eversana; [4]University of Pennsylvania

Background: Human herpesvirus-8-negative/idiopathic multicentric Castleman disease (iMCD) is a heterogeneous group of diseases characterized by a proinflammatory hypercytokinemic state with a wide range of systemic manifestations ranging from generalized lymphadenopathy to death in severe cases. Limited data have shown increased prevalence of organ dysfunction and cancers in iMCD patients. The objective of this study was to assess healthcare resource utilization and patterns of iMCD-related morbidities in a real-world setting. **Methods:** Retrospective analysis of administrative claims for ~31 million US patients enrolled from 1/1/2017-12/31/2019. Patients were identified as iMCD if they had an ICD-10 code for Castleman disease (CD) and ≥2 codes corresponding to minor criteria from the iMCD consensus diagnostic criteria. Exclusion criteria were history of HIV or HHV-8. Index diagnosis date (IDD) was defined as the first time a patient received a diagnosis for CD using the new ICD-10 code (D47.Z2) or the general ICD-9 code for lymphadenopathy (785.6) that included CD, whichever was diagnosed first between 2006 and 2019. Included patients were followed for up to 5 years from IDD. **Results:** We identified 271 iMCD patients, 161 women (59%) and 110 men (41%), mean age 51 years (range: 6-90). Average post-diagnosis follow up was 2.8 years after IDD (range: 0.3-14.1). Within first year of iMCD diagnosis, 49.1% of patients required inpatient hospitalization

and 54.6% had at least one emergency room visit. Over a five-year period following initial iMCD diagnosis, patients had an average annual hospitalization rate and emergency room visit rate of 23.9% and 30.5%, respectively. The annual rate of hospitalizations and emergency room visits for the entire database of ~31 million patients were 9.0% and 20.6%, respectively. The average annual prevalence of morbidities in the iMCD cohort (vs. prevalence in entire database) was 5.7% (vs. 0.3%) for hematologic malignancies, 4.6% (vs. 2.5%) for non-hematologic malignancies, 3.9% (vs. 0.6%) for thromboses, 2.6% (vs. 0.6%) for renal failure, and 1.9% (vs. 0.5%) for respiratory failure. Based on an average annual iMCD incidence of 3.1 (95% CI, 1.2-9.0) cases per million and average prevalence of 9.7 (95% CI, 5.3-18.6) cases per million, we estimated the average duration of documented disease as 3.1 years after diagnosis. **Conclusion:** We found a high rate of hospitalizations, emergency room visits, organ dysfunction, and malignancy in the five years following iMCD diagnosis, compared to the general population. The average duration of documented disease was 3.1 years, which may reflect a combination of poor survival, changes in health insurance, miscoding, or resolution of symptomatic disease. Further studies are needed to compare outcomes to age-matched controls and determine whether these adverse outcomes are broadly seen across iMCD patients or instead attributable to a smaller subset of more severe cases.

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Increased mTORC2 pathway activation in lymph nodes of iMCD-TAFRO

Alexis Phillips[1], Joseph Kakkis[1], Sheila Pierson[1], David Fajgenbaum[1]

[1]University of Pennsylvania

Background: Idiopathic multicentric Castleman disease (iMCD) is a rare and life-threatening hematologic disorder involving polyclonal lymphoproliferation and organ dysfunction due to excessive cytokine production, including interleukin-6 (IL-6). Data demonstrate that IL-6 inhibition is effective in 34-50% of patients. mTOR, which functions through mTORC1 and mTORC2, is a recently-discovered therapeutic target. The mTOR inhibitor sirolimus, which preferentially inhibits mTORC1, has led to sustained remission in a small cohort of anti-IL-6 refractory iMCD patients with thrombocytopenia, anasarca, fever, renal dysfunction, and organomegaly (TAFRO). However, sirolimus has not shown uniform effect, potentially due to its limited mTORC2 inhibition. **Method:** To investigate mTORC2 activation in iMCD, we quantified the mTORC2 effector protein pNDRG1 by immunohistochemistry of lymph node tissue from six iMCD-TAFRO and eight iMCD patients who do not meet TAFRO criteria (iMCD-not-otherwise-specified; iMCD-NOS). Eight metastasis-free sentinel lymph nodes were selected as normal controls (sentinels). Tissue from six ALPS lymph node samples was selected as a comparator group. **Results:** First, we evaluated mTORC2 activation in iMCD-TAFRO and iMCD-NOS. In iMCD-TAFRO, pNDRG1 expression was significantly elevated in the interfollicular space (P = 0.005), germinal centers (P = 0.002), and mantle zones (P = 0.007) relative to sentinels. Positive pNDRG1 staining was significantly increased in the interfollicular space (P = 0.005) of iMCD-NOS lymph nodes relative to sentinels and there was a no difference in the germinal centers (P = 0.59) and the mantle zones (P = 0.30). Next, we compared pNDRG1 expression in iMCD-TAFRO and iMCD-NOS to ALPS, a disease characterized by aberrant mTOR activation that is effectively treated with sirolimus. While ALPS patients consistently respond to sirolimus, data from the ACCELERATE registry show that 6/11 (54.5%) iMCD cases treated with sirolimus did not achieve a response. We therefore hypothesized that mTORC2 may be more highly elevated in iMCD, suggesting a potential mechanism of resistance to sirolimus. Our results revealed significantly increased pNDRG1 staining in iMCD-TAFRO germinal centers relative to ALPS (P = 0.02) and non-significantly increased staining in the interfollicular space (P = 0.18) and mantle zones (P = 0.11). There were no differences in pNDRG1 expression between iMCD-NOS and ALPS in any region. Notably, the strongly positive pNDRG1 cells had spindle-shaped morphology resembling stromal cells. This result contrasts with the pS6-positive cells in iMCD that have been shown to represent monocytes, plasma cells, and as-yet-undefined cells with myeloid-appearing morphology. **Conclusion:** These results suggest increased mTORC2 activity in iMCD and that duel mTORC1/mTORC2 inhibitors may be a rational therapeutic approach. We also observed potential differences in mTORC2 activation between iMCD-TAFRO and iMCD-NOS, although this should be validated.

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Extramedullary expansion of Myeloma plasma cells into CNS

Lucie Rihova[1], Renata Bezdekova[1], Petra Polackova[1], Martin Stork[1], Viera Sandecka[1], Luděk Pour[2], Sabina Sevcikova[3]

[1]University Hospital Brno; [2]Department of Internal Medicine, University Hospital Brno; [3]Masaryk University

Background: Multiple myeloma (MM) is characterised by a presence of clonal plasma cell (a-PC) which are usually localised in bone marrow (BM) as a heterogeneous suspension, not often as solitary lesion. A BM microenvironment dependency is lost in a subset of patients and a-PCs spread out of BM, probably because of changes in adhesive molecules expression. Circulating myeloma PCs (cPCs) were detected in peripheral blood of almost all MM. Moreover, primary and/or secondary extramedullary disease (soft tissue and/or bone-related) was revealed in many patients. On the other hand, presence of a-PCs in cerebrospinal fluid (CSF) is relatively rare. **Aim:** Detection of a-PCs in CSF and comparison of their phenotype with other compartments. **Methods:** CSF of 15 relapsed MM patients was analysed by polychromatic flow cytometry (FC). Centrifuged samples were immediately incubated with MoAb (mostly CD38/CD138/CD45/CD19/CD56/CD14/CD5/CD27), lysed by NH4Cl and analysed. **Results:** Whole group of analysed CSF has median of leukocytes 231 with range 19-6013. Myeloma a-PC infiltration was detected in 26.7 % (4/15). Only a-PCs were detected, these were always CD19- and in 50% CD56+. Phenotype

profile in CSF, bone marrow, peripheral blood and tumour was similar according to CD19 and CD56. Flow cytometry is a highly efficient method for a-PCs detection. **Conclusion:** Unfortunately, for these small samples more markers have to be analysed simultaneously to perform diagnostics and to analyse a-PCs as well, so only 8-colour FC is relatively insufficient in term of detail a-PC phenotype assess. All CSF+ patients were almost refractory to the treatment and they have cPCs in peripheral blood, extramedullary relapse was detected in 2 patients as well. It is evident, that prognosis of patients with CNS infiltration is generally poor. Supported by Ministry of Health of the Czech Republic, grant nr. 17-29343A.

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The history of survival improvement in patients with Multiple Myeloma through real-world data in a 45-year period at a single institution

Luis Gerardo Rodríguez-Lobato[1], Arturo Pereira[1], C Fernández De Larrea[2], MT Cibeira[2], Natalia Tovar[1], Raquel Jiménez[1], David Moreno[3], Aina Oliver Caldés[1], Laura Rosiñol[2], J Bladé[2]

[1]Hospital Clínic de Barcelona; [2]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [3]Hospital Clinic de Barcelona, IDIBAPS

Background: The prognostic landscape of multiple myeloma (MM) has evolved significantly over the last few decades. After the introduction of high-dose melphalan followed by autologous stem cell transplantation (HDM-ASCT) and, more recently, the first generation of proteasome inhibitors and immunomodulatory drugs have been implemented. There are, however, few data measuring such improvement in real-world patients. This study aimed to investigate trends in survival improvement over 45-years, and the associated clinical factors, in an unselected population of patients with MM in a single tertiary center. **Methods:** Between 1970 and 2015, 1161 consecutive MM patients were included in the study. Patients were classified into three calendar periods (1970-84, 1985-99, and 2000-15), according to the treatment which they received; polychemotherapy, HDM-ASCT, and novel drugs, respectively. We analyzed relative (RS) to accurately evaluate MM-related death rates after excluding the mortality expected in the general population. In addition, we chose the Brenner's period method to estimate RS in patients diagnosed after 2000 in order to detect any recent advance towards statistical cure. **Results:** After a median follow-up of 3.6 years (IQR: 1.4-6.5), 953 (82.1%) patients had died and 208 (19.9%) were censored alive. Median follow-up for survivors was 7.7 (IQR: 5.3-12.0) years. Median survival steadily improved from 1.7 years in 1970-1984 to 3.0 years in 1985-1999, and to 5.1 years in 2000-2015 ($p<0.001$). The estimated proportion of patients diagnosed before 2000 who survived more than 20 years was 6% (95% CI: 4.0-8.0). The 5-year RS improved from 27% in 1970-1984 to 38% in 1985-1999, and 56% in 2000-2015, and the 10-year RS improved from 10%, to 21%, to 33%, respectively. Patients younger than 65 years old, and those with ECOG performance status (PS) < 2, and Durie-Salmon stage I/II benefited the most from the improved survival, mainly in the 2000-2015 period. Nevertheless, even patients with ECOG PS ≥ 2 and Durie Salmon stage III improved their RS after 2000 in comparison with the two precedent calendar periods. At the multivariate Poisson regression analysis, increased age, poor ECOG PS, and advanced Durie-Salmon stage were independently associated with smaller improvements in RS. The estimated RS by Brenner's method in the patients diagnosed between 2000 and 2015 did not showed evidence of bending to the horizontal, which discarded statistical cure. **Conclusions:** The survival rates of real-world patients with MM have improved over the last 50 years. The largest improvement was seen in younger patients and in those diagnosed after the year 2000, although older patients and those with more advanced disease or poor PS have also benefitted from increased survival. Unfortunately, there is no evidence for statistical cure and 5.1 years as median survival in the last time period still leaves significant room for improvement.

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An interim analysis of the Turkish Myeloma Registry among patients who have received up to two lines of therapy

Omur Gokmen Sevindik[1], Zübeyde Nur Özkurt[2], Can Boğa[3], Sevgi Kalayoglu Besisik[4], Yıldız Ipek[5], Ayfer Gedük[6], Aybüke Harmandalı[7], Ayşe Salihoğlu[8], Handan Haydaroğlu Şahin[9], Mehmet Sönmez[10], Filiz Vural[11], Olga Meltem Akay[12], Meltem Kurt Yüksel[13], Senem Maral[14], Ömer Ekinci[15], Hakkı Onur Kırkızlar[16], Atakan Tekinalp[17], Nazlı Demir[18], Mustafa Merter[15], Güray Saydam[11], İnci Alacacıoğlu[19], Zeynep Arzu Yeğin[20], Mutlu Kasar[21], Metban Mastanzade[22], Güner Hayri Özsan[19]

[1]Medipol Univesity; [2]Gazi University Faculty of Medicine; [3]Başkent University Hospital; [4]Department of Internal Medicine, Division of Hematology, Istanbul University Medical Faculty, Istanbul, Turkey; [5]Dr. Lütfi Kartal City Hospital; [6]Kocaeli University Faculty of Medicine; [7]Tepecik Education and Research Hospital; [8]Istanbul University Cerrahpaşa Faculty of Medicine; [9]Gaziantep University Şahinbey Research and Practice Hospital; [10]Karadeniz Teknik University Faculty of Medicine; [11]Ege University Faculty of Medicine; [12]Koç University Hospital; [13]Ankara University Faculty of Medicine; [14]Dışkapı Yıldırım Beyazıt Training and Research Hospital; [15]Fırat University Faculty of Medicine; [16]Trakya University Faculty of Medicine; [17]Meram University Faculty of Medicine; [18]Istanbul Şişli Hamidiye Etfal Education And Research Hospital; [19]Dokuz Eylul University, Faculty of Medicine; [20]Gazi University Faculty of Medicine; [21]Başkent University Hospital; [22]Istanbul University Istanbul Faculty of Medicine

Background: To investigate the demographics and treatment details of the myeloma patients who were diagnosed and followed up in Turkey and received up to two lines of therapy. **Methods:** Patients who were recorded on the database of Turkish Myeloma Registry project were included in this study if they had only received one or two lines of therapy. Demographics, patient, and disease

related parameters both at the time of diagnosis and at the follow up and treatment outcomes were presented. **Results:** A total of 532 patients were included in the study 44% of the patients were female. Median age at the time of diagnosis was 63 (30-106). 47.7% of the patients were diagnosed with IgG myeloma. According to the ISS risk stratification, 20.4% of patients had ISS 1, 34.7% of patients had ISS 2 and remaining 44.9% had ISS 3 disease. Defining high risk disease as harboring one or more of these following cytogenetic abnormalities; del 17p, t(4;14), t(14;16) or t(14;20); 7.1% of the patients were classified as having a high risk disease. Most commonly used frontline therapy approach was bortezomib cyclophosphamide dexamethasone (VCD) (76.5%) and followed by bortezomib dexamethasone (VD) (8.8%), VRd (7.1%). Overall response rates (a better response than stable disease) were 87.6% in VCD induced patients; 63.3% in VD induced patients and 92% in VRd induced patients. The PFS obtained by these frontline approaches was 17.8 months in patients who were able to proceed with high dose chemotherapy with ASCT support and 8.4 in patients who were not able to ($p<0.01$), with an overall PFS of 15.3 months. With regard to the induction approach, PFS was 21.1 months for VRD, 15.3 months for VCD and 7.6 months for VD ($p=0.08$). Regarding maintenance, 23.6% of patients were maintained by lenalidomide alone, 62.7% of patients were maintained by a combination of lenalidomide and dexamethasone or bortezomib alone (2.7%). PFS after the first line of the treatment was 22.2 months in maintained patients and 12.2 in un-maintained patients (HR: 0.532, $p=0.001$, CI95% 0.359-0.790). Regarding the second line therapy Rd was the leading option (34.8%) and VRd (17.8%), Carfilzomib based (16.3%), VCD (8.1%) were the followings. **Conclusion:** As the main concern of this study was to document the demographic features and clinical parameters of a Turkish Myeloma population and to give an idea about the treatment patterns and outcomes in frontline setting and first relapse an overall survival was not calculated. Progression free survival obtained after frontline therapy was relatively shorter than the ones which were presented by other real-world registries. Outcomes of second line therapy will be presented as follow up after 2nd line therapy exceeds a certain threshold. We hope, the results obtained from this study can have a role in the approval and re-imbursement of the current standard of care options.

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The prognostic impact of the UK Myeloma Research Alliance Risk Profile in untreated patients with multiple myeloma who received melphalan, prednisolone, and bortezomib: an ad hoc analysis of JCOG1105

Tomotaka Suzuki[1], Dai Maruyama[2], Ryunosuke Machida[3], Tomoko Kataoka[3], Noriyasu Fukushima[4], Nobuyuki Takayama[5], Rie Ohba[6], Ken Omachi[7], Yoshitaka Imaizumi[8], Masahito Tokunaga[9], Hiroo Katsuya[10], Isao Yoshida[11], Kazutaka Sunami[12], Mitsutoshi Kurosawa[13], Nobuko Kubota[14], Hiroaki Morimoto[15], Miki Kobayashi[16], Kazuhito Yamamoto[17], Yoshihiro Kameoka[18], Yoshitoyo Kagami[19], Takayuki Tabayashi[20], Masaki Maruta[21], Tsutomu Kobayashi[22], Shinsuke Iida[23], Hirokazu Nagai[24]

[1]Department of Hematology and Oncology, Nagoya City University Hospital, Nagoya, Japan; [2]Department of Hematology Oncology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research; [3]JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan; [4]Department of Hematology and Oncology, Hiroshima University Research Institute for Radiation Biology and Medicine, Hiroshima, Japan; [5]Department of Hematology, Kyorin University School of Medicine, Tokyo, Japan; [6]Department of Clinical Oncology and Hematology, The Jikei University Daisan Hospital, Tokyo, Japan; [7]Department of Hematology Oncology, Tokai University School of Medicine, Kanagawa, Japan; [8]Department of Hematology, Nagasaki University Hospital, Nagasaki, Japan; [9]Department of Hematology, Imamura General Hospital, Kagoshima, Japan; [10]Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan; [11]Department of Hematologic Oncology, National Hospital Organization Shikoku Cancer Center, Ehime, Japan.; [12]Department of Hematology, National Hospital Organization Okayama Medical Center, Okayama, Japan.; [13]Department of Hematology, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan.; [14]Department of Hematology, Saitama Cancer Center, Saitama, Japan; [15]Department of Hematology, University of Occupational and Environmental Health, Kitakyusyu, Japan; [16]Department of Hematology and Oncology, Japanese Red Cross Nagoya Daini Hospital, Nagoya, Japan; [17]Department of Hematology and Cell Therapy, Aichi Cancer Center, Nagoya, Japan; [18]Department of Hematology Nephrology, and Rheumatology, Akita University Graduate School of Medicine, Akita, Japan.; [19]Department of Hematology, Toyota Kosei Hospital, Toyota, Japan; [20]Department of hematology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; [21]Department of Hematology, Clinical Immunology and Infectious Diseases, Ehime University Hospital, Ehime, Japan.; [22]Department of Hematology and Oncology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; [23]Department of Hematology and Oncology, Nagoya City University Hospital, Nagoya, Japan; [24]Department of Hematology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

Background: The UK Myeloma Research Alliance Risk Profile (MRP) (Lancet Haematol 2019) was developed as a prognostic score for transplant-ineligible, newly diagnosed multiple myeloma (NDMM) patients. MRP consists of widely available clinical parameters, such as WHO performance status (PS), International Staging System (ISS), age, and C-reactive protein (CRP) level. However, as MRP was developed in clinical trials in which immunomodulatory drugs were used as induction regimens, its applicability to patients who were treated with bortezomib (BOR)-based regimens remains elusive. We conducted an exploratory analysis to assess the utility of MRP using data from JCOG1105, a randomized phase II trial in which two modified MPBs (melphalan,

prednisolone, and BOR) were compared (Br J Haematol 2021). Furthermore, the clinical factors associated with poor outcomes among patients included in JCOG1105 were evaluated. **Methods:** The data of 88 transplant-ineligible patients with NDMM enrolled in JCOG1105 between July 2013 and April 2016 were analyzed. Progression-free survival (PFS) and overall survival (OS) in each MRP risk were estimated using the Kaplan-Meier method and compared using the log-rank test. Clinical parameters associated with poor prognosis were evaluated in univariable and multivariable Cox regression analyses. **Results:** The baseline characteristics of the 88 patients were as follows: a median age of 72 (range, 65–79) years, 20 (23%) had PS ≥2, 13 (15%) with LDH > upper normal limit (UNL), and median CRP level of 1 mg/L (range, 0–140). Forty-six (52%) and 16 (18%) patients had ISS II and III disease, respectively. MRP was evaluated in 87 patients (excluding one patient with missing data on CRP levels) and was classified as low (n=51), medium (n=16), and high risk (n=20). With a median follow-up of 47.3 (range, 10.4-71.1) months, the 3-year PFS and OS of all 88 patients were 20.5% (95% confidence interval [CI]: 13–29%) and 81.8% (95% CI: 72–88%), respectively. In patients with MRP low, medium, and high risk, the outcomes were as follows: a 3-year PFS of 26%, 19%, and 10% and a 3-year OS of 84%, 69%, and 85%, respectively. A higher MRP risk was not significantly associated with a poorer PFS and OS. In multivariable analysis, LDH > UNL (Hazard Ratio [HR]: 4.73, 95% CI: 1.71–13.13) and b[ED]2MG ≥ 3.5 mg/dL (HR: 2.86, 95% CI: 1.20–6.81) were significantly associated with poor OS. PS ≥2 was not associated with poor OS (HR: 0.85, 95% CI: 0.33–2.23). **Conclusion:** Higher MRP risk scores were not significantly associated with poor outcomes in patients who received MPB in this exploratory analysis. Large-scale studies aimed at evaluating the applicability of MRP in NDMM patients treated with BOR-based regimens are needed.

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Patients with Multiple Myeloma on treatment with Anti-CD38 or Anti-BCMA agents have a suboptimal humoral response following COVID-19 vaccination

Evangelos Terpos[1], Maria Gavriatopoulou[1], Ioannis Ntanasis-Stathopoulos[2], Alexandros Briasoulis[2], Sentiljana Gumeni[2], Panagiotis Malandrakis[1], Despina Fotiou[2], Eleni-Dimitra Papanagnou[2], Magdalini Migkou[2], Foteini Theodorakakou[2], Maria Roussou[2], Evangelos Eleutherakis-Papaiakovou[2], Nikolaos Kanellias[2], Ioannis Trougakos[2], Efstathios Kastritis[1], Meletios-Athanasios Dimopoulos[3]

[1]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece; [2]National and Kapodistrian University of Athens; [3]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital

Background: Recent data suggest a suboptimal antibody response to COVID-19 vaccination in patients with hematological malignancies, especially under immunosuppressive therapy. Herein, we evaluated the development of neutralizing antibodies (NAbs) against SARS-CoV-2 in patients with plasma cell neoplasms after vaccination with either the mRNA BNT162b2 or viral vector AZD1222 vaccine. **Methods:** Serum of both patients and controls was collected on day 1 (D1; before the first BNT162b2 or AZD1222 dose), on day 22 (D22; before the second dose of the BNT162b2 or 3 weeks post the first AZD1222 dose) and on day 50 (D50; 4 weeks post second dose of the BNT162b2 or 7 weeks post the first AZD1222 dose). NAbs against SARS-CoV-2 were measured using FDA approved-ELISA methodology. **Results:** Patients with MM (n=213), SMM (n=38) and MGUS (n=25) and 226 healthy controls, of similar age and gender, were enrolled in the study (NCT04743388). Two hundred and fifteen patients (77.9%) were vaccinated with the BNT162b2 and 61 (22.1%) with the AZD1222 vaccine. Vaccination with either two doses of the BNT162b2 or one dose of the AZD1222 vaccine leads to lower production of NAbs against SARS-CoV-2 in patients compared with controls both on day 22 and on day 50 (P<0.001 for all comparisons). After the first dose of the vaccine, on D22, the median NAb inhibition titer was 27% (IQR: 15.3-42%) for patients versus 38.7% (IQR: 22-54.3%) for controls (P<0.001). On D50, the median NAb inhibition titer was 62.8% (IQR: 26-88.9%) for patients versus 90% (IQR: 58-96.4%) for controls (P<0.001). The respective number of patients and controls who developed NAb titers ≥50% (clinically relevant titers) was 158 (57.3%) and 183 (81%), respectively (P<0.001). Furthermore, MM patients showed an inferior NAb response compared with MGUS on day 22 (p=0.009) and on day 50 (p=0.003); MGUS patients' NAb development was similar to controls. Importantly, active treatment with either anti-CD38 monoclonal antibodies or belantamab mafodotin and lymphopenia at the time of vaccination were independent prognostic factors for suboptimal antibody response following vaccination (OR: 9.4, 95% CI: 1.7-51.1, p=0.009, OR 2.9, 95% CI: 1.2-7.1, p=0.002 and OR: 3.5, 95% CI: 1.8-6.7, p=0.019, respectively). Seventy-one (33%) and 68 patients (31.6%) reported mild reactions after the first and second dose of the BNT162b2 vaccine, respectively. Twenty (32.8%) patients vaccinated with the first dose of AZD1222 also presented with local reactions. **Conclusion:** In conclusion, MM patients have lower humoral response following SARS-CoV-2 vaccination compared to gender- and age-matched controls. Treatment with anti-CD38 and belamaf-based regimens as well as lymphopenia at the time of vaccination independently predicted for poor NAb development. These data underline the need for timely vaccination, ideally during a treatment-free period, and for continuous vigilance on infection control measures.

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Accompanying with additional complex karyotype is a poor prognostic factor in patients with multiple myeloma with high-risk cytogenetics in the era of novel agents

Hideki Uryu[1], Noriko Nishimura[1], Yuko Mishima[1], Yuko Ishihara[1], Yuko Shirouchi[1], Mikako Tanba[1], Dai Maruyama[1]

[1]Department of Hematology Oncology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research

Background: High-risk cytogenetic abnormality (CA) influences the prognosis of multiple myeloma (MM) even in the era of novel agents. However, prognostic heterogeneity could exist in MM patients with high-risk CA and additional cytogenetic aberrations are possibly correlated with worse outcomes. We conducted a retrospective study in patients with MM with high-risk CA to evaluate whether the outcomes are different in each high-risk group and whether the existence of additional chromosomal abnormalities would lead to poor outcomes. **Method:** Patients with newly diagnosed MM (NDMM) in our institute between February 2006 and December 2020 were enrolled in this retrospective cohort. We analyzed only patients who were treated with novel agents including proteasome inhibitor and/or immunomodulatory drugs. All of cytogenetic abnormalities were analyzed from bone marrow samples. In this cohort, we defined high-risk CA as del(17p), t(4;14), t(14;16), and/or 1q21 gain, all of which were identified using FISH analysis. We surveyed additional chromosomal aberrations using G-banding testing. Complex chromosomal abnormality was defined as three or more chromosomal aberrations accompanying with at least one structural aberration. The survival was calculated by the Kaplan Meier method, and statistical analysis was performed by the Log-rank test. Factors affecting OS and PFS were evaluated using Cox proportional hazard model. **Results:** We analyzed 36 MM patients who had high-risk CA at initial diagnosis. Twelve patients had del(17p), 16 had t(4;14), four had 1q21 gain, and four had more than one high-risk CA; two patients with t(4;14) and 1q21 gain, one with del(17p) and 1q21 gain and one with del(17p), t(4;14), and 1q21 gain. G-banding testing showed that patterns of complex chromosomal abnormality were found in nine patients. No significant differences in progression-free survival (PFS) and overall survival (OS) were seen between each high-risk CA group. The tendency of shorter PFS and OS was observed in patients with concurrent complex chromosomal karyotype than patients with no additional chromosomal aberrations. Furthermore, we found that the existence of complex cytogenetic abnormality by G-banding was correlated with poor PFS by multivariate analysis (hazard ratio 4.01, 95% confidence interval 1.35–11.9, p = 0.012). In addition, seven of nine MM patients with complex chromosomal karyotype had concurrent plasmacytoma. **Conclusion:** Although the limitation of retrospective study design and the small sample size exists, our findings indicate that the coexistence of complex chromosomal abnormality, probably which reflects aggressive disease status like extraosseous or extramedullary disease, could be associated with poor prognoses of MM patients with high-risk CA.

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Quality of life reported outcomes in published research on AL Amyloidosis: a systematic literature review

Sotirios Bristogiannis[1], Ashutosh Wechalekar[2], Brendan Wisniowski[2], Shameem Mahmood[2], Sajitha Sachchithanantham[3], Charalampia Kyriakou[4]

[1]NHS Hillingdon Hospital; [2]National Amyloidosis Centre; [3]NHS Guy's and St Thomas' Hospital; [4]University College London Hospitals NHS Foundation Trust

Background: Recent advances in the treatment of AL Amyloidosis have considerably prolonged survival outcomes. Hence, disease and therapy-related quality of life are becoming important treatment endpoints. Patient reported outcome measures (PROMs) are increasingly considered the gold standard for evidence-based adjustments of treatment to enhance patients' wellbeing. The objective of this study was to identify the QOL questionnaires (QOLQs) used in literature for AL Amyloidosis and assess their validity. **Methods:** A systematic literature search of PubMed, Medline and EMBASE databases was undertaken to identify QOLQs used in research when assessing QOL in patients with AL Amyloidosis up to May 2021.The validity of these tools in this context were assessed in accordance with the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) quality criteria. **Results:** 246 publications were originally identified and screened for relevance to the study by two independent investigators. Review of these reports excluded from further analysis 92 that were duplicates, 13 case-reports, 11 reports that were not relevant to AL Amyloidosis, 56 with no detail reference to QOL, 13 reporting QOL without using QOLQs or PROMs and 4 review articles. 57 reported studies met criteria, 47 observational studies and 10 prospective clinical trials reported QOL and PROM(s) results in AL Amyloidosis and could be analysed further. Thirteen different questionnaires were occasionally used to report QOL outcomes (SF-36; EQ-5D-3L; FACT-G; PROMIS-GH); HPRSS; DT; EORTC QLQ-C30; KCCQ-12; GAF; SWLS; STAI; CESD; MDASI). The most commonly (35/ 58 publications) used was the SF-36. None is AL Amyloidosis specific, but they have been traditionally applied in similar diseases (Multiple Myeloma) or its complications (Congestive Heart Failure). Literature data when open QOL questionnaires were used in AL Amyloidosis patients, identified QOL issues that severely impact their vitality, mobility, physical function, working capacity, family and social role, leisure activities, sleep quality and mental health. None of the QOLQs used succeeds to mirror effectively these Al Amyloidosis patient-raised issues (poor content validity). Also, none met COSMIN validation criteria, and only the PROMIS-GH and SF-36 showed acceptable internal consistency (Cronbach's a>70). **Conclusions:** This literature review showed that currently applied QOLQs /PROMs in observational and clinical trial studies on AL Amyloidosis are general questionnaires and lack validity evidence. Thus, there is need for the development of a new disease specific AL Amyloidosis QOLQ that can be used to represent quality of life issues and guide treatment adjustments and novel therapies' approval.

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The impact of COVID-19 on the treatment regimens of myeloma and AL amyloidosis patients

Katie Joyner[1], Jayne Galinsky[1], Solène Clavreul[1]
[1]Myeloma Patients Europe

Background: As the COVID-19 pandemic unfolded in 2020, Myeloma Patients Europe (MPE) recognized that the pandemic was impacting the healthcare and lives of people with myeloma and AL amyloidosis, and their caregivers. Findings from a small UK study suggested that myeloma patients were more likely to die from COVID-19 than members of the general population who contracted the virus [Cook et al, 2020]. Focus groups were conducted to learn more about the impact of COVID-19 on the lives of patients and their families, with a focus on its impact on diagnosis and treatment. **Method:** MPE researchers conducted four online focus groups in Europe examining the views and experiences of myeloma and AL amyloidosis patients and caregivers during the COVID-19 pandemic. Fifteen patients and two caregivers took part. Thirteen patients had myeloma and two had AL amyloidosis. Participants were from Spain (n = 6), the UK (n = 2), Belgium (n = 2), Germany (n = 2), the Netherlands (n = 1), Iceland (n = 1), Israel (n = 1), Poland (n = 1), and Romania (n = 1). Eleven patients had been diagnosed within the last few years, while four were living with myeloma for a decade or longer. Ten patients were receiving active treatment for myeloma or AL amyloidosis during the pandemic, while others were in remission. **Results:** Sixty percent of study participants reported that the COVID-19 pandemic negatively affected their treatment. Three patients said that medicines given in hospital (by infusion or injection) were delayed due to COVID-19 restrictions. Sometimes, the frequency of these treatments was reduced. In contrast, most patients taking oral medicines (tablets) reported that their treatment continued as normal. Seven participants said their or another patient's invasive procedure (such as a bone marrow biopsy or stem cell transplant) had been delayed. These procedures took place after approximately 1–6 months later than originally scheduled, once HCPs and patients felt it was safe to do so. One patient reported an improvement in her treatment due to the pandemic restrictions. Her 4- to 5-hour long infusions of daratumumab in hospital had been switched to subcutaneous injections with fewer side-effects. **Conclusions:** Findings suggest that COVID-19 had an impact on patients with myeloma and AL Amyloidosis and their treatments. Some aspects of this may be positive, with preference data showing that patients have a preference for oral administrations (Fifer et al, 2020) and as such, switching patients to at home treatment regimens may have both avoided treatment delays and also been in line with patient preferences for treatment administration. MPE suggest that the administration of treatments should be examined regularly. COVID-19 upended existing treatments and other healthcare services, but patients and their healthcare providers should be reviewing options on an ongoing basis to ensure both high quality of care and changes in patient preferences over time.

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Use of the European Organisation for research and treatment of cancer quality of life Multiple Myeloma questionnaire (EORTC QLQ-MY20): a review of the literature 25 years after development

Katie Tinsley[1], Kim Cocks[1], Mike Greenwood[1], Jane Wells[1], Sotirios Bristogiannis[2], Charalampia Kyriakou[3]
[1]Adelphi Values; [2]NHS Hillingdon Hospital; [3]University College London Hospitals NHS Foundation Trust

Background: The EORTC QLQ-MY20 is a widely used myeloma-specific patient-reported outcome measure originally developed in 1999. It consists of 20 items covering Disease Symptoms (DS), Side Effects (SE), Future Perspectives (FP) and Body Image (BI). Novel treatments and multiple lines of therapy mean the treatment for myeloma patients and life expectancy has changed dramatically and there is a need to ensure the measurement of health-related quality of life remains current for these patients. The original validation study was almost exclusively in newly diagnosed patients reflecting the nature of clinical trials at the time. This review was conducted as part of an EORTC funded grant to update the QLQ-MY20, with the aim of summarising the published literature from the QLQ-MY20 to date including any further validation results for the QLQ-MY20. **Methods:** Literature search was conducted using the Ovid SP platform (Medline, EMBASE and PsycINFO) from 1996 (first release of the questionnaire). Abstracts were included if they were reporting: a clinical study using the QLQ-MY20 or validation studies. Information about the study design was extracted alongside whether the population were newly diagnosed or relapsed, and the supplementary instruments used alongside the QLQ-MY20. For randomised control trials, information on the type of analysis and results were also extracted. For validation studies data on the instrument structure and data distribution, reliability, validity and ability to detect change/interpretation of change scores was extracted. **Results:** 656 abstracts were screened to 74 included papers (65 clinical studies, of which 21 were interventional clinical trials, and 9 validation studies). Supplementary instruments used alongside QLQ-C30 and MY20 included BPI-SF (Brief pain inventory short form), EQ-5D-5L (generic preference-based measure), FACT-GOG-Ntx (neurotoxicity) and the EORTC QLQ-CIPN20 (chemotherapy induced peripheral neuropathy). In contrast with the original validation study, 34 out of 43 clinical studies included either exclusively relapsed patients (n=24) or a mix of newly diagnosed and relapsed (n=9). DS and SE were the most commonly reported results from the QLQ-MY20. Further validation studies supported the factor structure, reliability and validity, with the only potential issue being observed ceiling effects for the BI subscale. **Conclusions:** The shift in HRQOL measurement to patients experiencing multiple lines of treatment and novel treatments, highlights the need for updating the conceptual model for the QLQ-MY20. Interviews are currently underway internationally with 90 patients and 20 healthcare professionals to identify the issues relevant to myeloma patients today. The current questionnaire has been shown to be

psychometrically valid and can be supplemented in the interim using item banks or existing questionnaires to cover new side effects specific to novel treatments.

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Trial in progress: a mixed methods approach to understanding treatment experience of individuals receiving standard of care Isatuximab using patient reported, wearable, and digital health outcomes

Elisabet Manasanch[1], Rahul Banerjee[2], Kelly Brassil[3], Nina Shah[4]

[1]The Unversity of Texas MD Anderson Cancer Center Department of Lymphoma Myeloma; [2]The University of California San Francisco; [3]Pack Health; [4]Department of Medicine, University of California San Francisco

Background: Relapsed/refractory multiple myeloma (R/R MM) is associated with potential for decreased quality of life and increased symptom burden. As new therapeutic approaches emerge for the R/R MM population, further insight is needed regarding the treatment experience of individuals in the real-world setting. Patient reported outcomes (PROs) have demonstrated utility not only in tracking symptom burden during treatment, but also improving outcomes, including overall survival for individuals from whom PROs are collected and responded to in the clinical setting. The use of multimodal data sources, informed by PROs, may provide a richer understanding of the real-world experience of R/R MM, its management, and its impact on quality of life. Through the triangulation of qualitative and quantitative data, this trial-in-progress aims to evaluate the experience of adults with R/R MM receiving standard of care isatuximab in the real-world setting. **Methods:** Fifty adults with R/R MM receiving standard of care isatuximab will be enrolled across 2 sites, The University of California San Francisco and The University of Texas MD Anderson Cancer Center. Consented participants will be enrolled in a 3-month digital health coaching program through which ePROs, and activity data from wearable devices, will be collected. PRO measures include the Patient's Qualitative Assessment of Treatment- Real World (PQAT-RW), Patient Global Impression of Change/Severity (PGIC/S), FACT-G (Item GP5-side effect bother), EORTC-QLQ-C30, QLQ-MY20, EQ5D. Demographic, as well as clinical data, including treatment history, healthcare utilization, and co-morbidities, will be collected via each participant's electronic health record. These data will be complemented by qualitative data from a purposefully selected cohort of study participants for which a focus on treatment experience will be assessed, ranging from infusion burden to toxicity management, to overall quality of life. Triangulation of data will be used to evaluate the treatment experience of individuals on standard of care isatuximab specifically, and R/R MM generally. Outcomes will be analyzed with attention to the relationship between demographics, including race and ethnicity, and treatment experience as reflected in both the qualitative and quantitative data. **Conclusions:** As the treatment landscape continues to evolve, insights into the experience of individuals in the real-world setting are important to recognize challenges and to optimize the management of R/R MM. By capturing insights via diverse PRO tools including both validated measures of quality of life and symptom burden, as well as physical activity and qualitative data, this study seeks to enhance the literature and implications for clinical practice for individuals receiving treatment for R/R MM in the real-world setting.

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Family reported outcome measures and patient reported outcome measures in Multiple Myeloma patients

Kareem Midlig[1], Regina Draliuk[1], Barbara Silverman[2], Meir Preis[1], Mouna Ballan-Haj[1]

[1]Carmel Medical Center; [2]Gertner Institute and Tel Aviv University

Background: Multiple myeloma (MM) is one of the most common hematological malignancies. The disease is characterized by multiple symptoms resulting from the disease itself, from complications related to therapy, and as a result of the involvement of other organ systems. MM influences various aspects of patient's and family's lives. Therefore, there is a need to better understand the balance between disease control and symptoms management. **Objectives:** The main goal of this study is to emphasis the power and importance of Patient Reported Outcome Measures (PROMs) and Family Reported Outcome Measures (FROMs) as additional tools for patient assessment. This study evaluated the correlation between Patient Reported Outcome Measures (PROMs) and Family Reported Outcome Measures (FROMs) and disease evaluation according to the International Myeloma Working Group (IMW) response criteria in active myeloma patients. A comparison between patient and family reporting (PROMs & FROMs) and the staging of the disease according to the revised international staging system (R-ISS) was done. In addition, this study examined the confounders that may explain the relationship between PROMs and FROMs and disease evaluation. **Methods:** This is a quantitative, prospective, observational study of active patients with MM. During the study, the participants completed questionnaires of PROMs and FROMs at intervals of 3 months for one year. In addition, we monitored multiple clinical measures of patient response to treatment. Required sample size was calculated using Win-Pepi software, using 5% significance and 80% power. For a correlation of 0.4 between Patient and Family Reported Outcomes and MM clinical evaluations, the minimum sample size required is 47 patients, and for a correlation of 0.50, the minimum sample size required is 37 patients. **Results:** Fifty-seven patients participated in this study. After 3 months of treatment, a better disease evaluation was associated with improvement in disease symptoms or side effect reported by patient. Furthermore, a better disease response was associated with a better body image scale and better future perspective. We observed a similar association after 6 and 9 months. In addition, the more the patient reported side effects or disease symptoms, the more it affects the family member (PROMs were positively correlated with FROMs).

A better body image and future perspective reported by patient was associated with a lower effect on family member (PROMs were negatively correlated with FROMs). These finding was supported by the fixed model analysis, which showed a significant effect of disease symptoms, appetite loss, physical function, future perspective and global satisfaction in prediction of clinical status. **Conclusion:** There is a significant relation between PROM/FROM and the typical assessment tools. This study highlights the power of PROM/FROM tools to evaluate patient from his point of view and to adjust the treatment accordingly.

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Quality of life, psychological distress, and prognostic awareness in caregivers of patients with Multiple Myeloma

Elizabeth O'Donnell[1], Yael Shapiro[1], Omar Nadeem[2], Andrew J. Yee[1], Jacob Laubach[2], Andrew Branagan[1], Kenneth Anderson[3], Clifton Mo[2], Nikhil C. Munshi[4], Irene Ghobrial[2], Adam Sperling[2], Emerentia Agyemang[1], Jill Burke[1], Cynthia Harrington[1], Paul G. Richardson[2], Noopur Raje[1], Areej El-Jawahri[1]

[1]Massachusetts General Hospital Cancer Center; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School and VA Boston Healthcare System

Background: Multiple myeloma (MM) is an incurable hematologic malignancy requiring long-term, continuous therapy. Although caregivers of MM patients play a critical role in supporting their loved ones throughout the illness course, studies examining caregiver quality of life (QOL), psychological distress, and prognostic awareness are lacking. **Methods:** We conducted a cross-sectional, multisite study of patients undergoing treatment with MM (excluding maintenance therapy) and their caregivers between 6/2020-3/2021. Eligible caregivers were identified by the patient as the primary caregiver and enrolled to 1 of 3 cohorts based on lines of therapy: 1) newly diagnosed receiving first-line therapy; 2) 2-3 lines; 3) ≥4 lines of therapy. Caregivers completed validated questionnaires to assess their QOL, psychological distress, and perceptions of prognosis. Patients also completed validated questions to assess their perception of prognosis. We used descriptive statistics to describe caregiver QOL, psychological distress, and perception of prognosis. We then descriptively compared psychological distress and perception of prognosis between patient and caregiver dyads. **Results:** We enrolled 127 caregivers of MM patients (newly diagnosed (n=43), 2-3 (n=40), and ≥ 4 lines of therapy (n=44)). Median caregiver age was 61.8 years (range 24.0-81.9); 71.7% (91/127) were female. Caregiver QOL and psychological distress did not differ by lines of therapy. The rate of clinically significant depression, anxiety, and PTSD symptoms were 15.8% (20/127), 44.1% (56/127), and 24.4% (31/127), respectively. When examining dyads, caregivers reported higher rates of clinically significant anxiety symptoms (44.4% vs. 22.5%) compared to MM patients. Caregivers reported less clinically significant depression symptoms (15.3% vs. 24.2%) and similar rates of clinically significant PTSD symptoms (24.2% vs 25.0%). Overall, 89.6% (112/125) of caregivers reported that it is 'extremely' or 'very' important to know about the patient's prognosis and 55.6% (70/126) stated that they had received adequate information regarding the patient's prognosis. Most caregivers (84.2%, 101/120), reported that the oncologist told them the patient's cancer was incurable. In contrast, only 53.6% (59/110) of caregivers reported that they thought the patient's cancer was incurable and 37.9% (58/114) acknowledged that the patient is terminally ill. When examining dyads, caregivers were more likely to report that the patient is terminally ill (50.1% vs. 30.1%). There was no difference in caregivers' and patients' report that the oncologist said MM is incurable (83.3% vs. 84.2%). **Conclusions:** Caregivers of patients undergoing treatment for MM experience substantial psychological distress across the disease continuum. Interventions are needed to improve caregivers' QOL, to reduce their psychological distress and to enhance caregiver perceptions of the patient's prognosis to facilitate informed decision-making.

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Evaluation of the support and knowledge provided by the chatbot (virtual conversation agent) Vik Multiple Myeloma in the management of the disease

Lucie Puron[1], Marie Pierres[1], Matthieu Javelot[1], Nicolo Prosa[1], Laurent Gillot[2], Philippe FERNANDES[3], Valentin MORISSEAU[3], Laurent Frenzel[4]

[1]JANSSEN Cilag France; [2]AF3M; [3]Wefight; [4]Hôpital Necker-Enfant Malade

Background: Multiple myeloma is a bone marrow cancer that affects more than 5,000 new patients each year in France [1] and requires individualized care for each patient. Faced with questions that patients and their relatives may have about the management of the disease, the Vik multiple myeloma (MM) chatbot has been created to accompany them throughout their care. This virtual companion is a mobile application that mimics a natural conversation thanks to Artificial Intelligence (AI). **Method:** A survey was conducted among adult users of Vik MM between March and May 2021. First, the socio-demographic and medical characteristics of the users were collected, then their knowledge was assessed through 10 different questions about the disease (diagnosis, symptoms, treatments, etc.). The last section allowed the evaluation of the users' satisfaction with Vik MM in terms of help, support, and reassurance. Comparative analyses were performed with parametric tests (chi-squared). **Results:** The 154 respondents to the survey had a median age of 65 years, with an equal distribution of men and women. Concerning the knowledge of the users on multiple myeloma, 87% of them indicated that Vik MM helped them to better understand the disease. This increase in knowledge was observed in various user

profiles, with more or less history with the disease. 76% of the users who had been diagnosed more than 3 years ago declared that they had a better understanding of multiple myeloma thanks to Vik MM. This gain in knowledge linked to content sharing on the disease could be observed as early as 14 days on Vik MM (77% of correct answers vs. 58% for new users, p-value <1%). The users were therefore clearly more confident about their answers (94% vs. 62% among new users, p-value <0.1%). Moreover, sharing content on multiple myeloma allowed 65% of Vik MM users to make less demands to their hematologist. Despite a relatively low use of digital tools in the management of their disease (73% did not use them or used them only occasionally), users expressed a real appreciation for Vik MM. Indeed, 92% of them indicated that they were satisfied with it and 81% found it comforting. Moreover, 74% of the users considered that Vik MM helped them to make better decisions. **Conclusion:** In a population that is not oriented towards digital health tools, Vik Multiple Myeloma has allowed users to educate themselves and gain significant confidence about their disease after only 14 days spent on the application. Vik multiple myeloma also provided them with a significant moral support in the context of a disease that has a heavy burden on their daily life. **Reference:** [1] https://www.santepubliquefrance.fr/docs/estimations-nationales-de-l-incidence-et-de-la-mortalite-par-cancer-en-france-metropolitaine-entre-1990-et-2018-volume-2-hemopathies-malignes

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Health-related quality of life (HRQL) among real-world Ide-Cel–eligible patients (pts) with relapsed/refractory Multiple Myeloma (RRMM): results from the Connect® MM registry

Lynne Wagner[1], Rafat Abonour[2], Sikander Ailawadhi[3], Brian G.M. Durie[4], Cristina J. Gasparetto[5], James W. Hardin[6], Hans Lee[7], Mohit Narang[8], Robert Rifkin[9], Howard Terebelo[10], Kathleen Toomey[11], Prashant Joshi[12], Amit Agarwal[12], Julia Braverman[12], Devender S. Dhanda[13], Mia He[12], Sundar Jagannath[14]

[1]Wake Forest School of Medicine; [2]Indiana University; [3]Mayo Clinic; [4]Cedars-Sinai Medical Center; [5]Duke University Medical Center; [6]University of South Carolina; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]Maryland Oncology Hematology, US Oncology Research; [9]Rocky Mountain Cancer Centers, US Oncology Research, Denver, CO, USA; [10]Providence Cancer Institute; [11]Steeplechase Cancer Center; [12]Bristol Myers Squibb; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]The Mount Sinai Hospital

Background: For pts with MM, HRQL is a key determinant of treatment choice in late-line therapies such as ide-cel, a BCMA-directed CAR T cell therapy. In KarMMa (NCT03361748), 54.2% of pts showed clinically meaningful improved HRQL from baseline to quarter (Q) 3, as measured by EQ-5D-5L; 8.5% experienced deterioration (Blood. 2020;136 [Suppl]:28–29). Analysis of HRQL in pts who received alternate, non-CAR T cell therapies could contextualize the impact of ide-cel on HRQL. The Connect® MM Registry (NCT01081028) is a large, US, multicenter, prospective observational cohort study of largely community-based pts with newly diagnosed MM (NDMM) at study entry. It was used for a descriptive analysis assessing HRQL outcomes in triple-class exposed real-world pts who met KarMMa trial eligibility criteria but received alternate therapies. **Method:** From 2009-2016, the Registry enrolled 3011 pts with symptomatic NDMM diagnosed ≤2 months prior to study entry at 250 community, academic, and government sites across the US. Pts agreed to complete HRQL forms at study enrollment and every Q of follow-up. Pts with RRMM included in this analysis met KarMMa eligibility criteria. HRQL was measured from the time of KarMMa eligibility (D1) using EQ-5D-3L and FACT-MM total score instruments. **Results:** As of data cutoff (7 Feb 2020), 32 pts with RRMM from the Registry met KarMMa eligibility criteria. Median age was 64.1 y (range, 45.5–88.8). Median time to D1 since initial diagnosis was 3.4 y (range, 1.6–5.5); 24 pts (75%) had prior stem cell transplant; median prior lines of therapy was 7.5. At D1, pts initiated regimens that included IMiDs (n=20), proteasome inhibitors (n=15) and anti-CD38 monoclonal antibodies (n=7). HRQL form completion rate at Q3 was 64.7%. The baseline index score was 0.73 for Registry pts. Median EQ-5D-3L score (range) at D1 (n=21) was 0.761 (0.263–1) and 0.708 (0.263–1) at Q3 (n=11). At D1, 30% of pts experienced clinically meaningful improvement in EQ-5D-3L from baseline; 35% each experienced no change or deterioration in HRQL. By Q3, 20%, 30%, and 50% of pts experienced improvement from baseline, no change, and deterioration in HRQL, respectively. By Q3 post treatment initiation, a substantial proportion of ide-cel–eligible real-world pts with RRMM from the Connect MM Registry who received various alternate (non-CAR T cell) MM regimens experienced meaningful deterioration of HRQL (measured by EQ-5D-3L) from D1 over time. **Conclusion:** In the context of the KarMMa trial, it was observed that a higher proportion of pts on ide-cel experienced meaningful improvement in HRQL (measured by EQ-5D-5L) and fewer pts experienced deterioration by Q3 after treatment. Limitations of this analysis may include small sample size and use of different versions of EQ-5D assessments. HRQL remains an important goal of MM treatment, and therapies that improve HRQL should be developed explicitly. These results support the need for replication in a larger pt sample and complement clinical trial findings.

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ITHACA, a randomized multicenter phase 3 study of Isatuximab in combination with Lenalidomide and Dexamethasone in high-risk smoldering Multiple Myeloma: safety run-in preliminary results

Irene Ghobrial[1], Paula Rodríguez-Otero[2], Youngil Koh[3], Joaquín Martínez-López[4], Gurdeep Parmar[5], Miles Prince[6], Hang Quach[7], Javier de la Rubia[8], Emil Hermansen[9], Vania Hungria[10], Sevgi Kalayoglu Besisik[11], Jin Seok Kim[12], Xavier Leleu[13], Valdas Peceliunas[14],

Fredrik Schjesvold[15], Franck Dubin[16], Christine Devisme[16], Lucie Lepine[18], Sandrine Macé[16], Corina Oprea[16], María-Victoria Mateos[19]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [3]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [4]Departamento de Hematología, Hospital 12 de Octubre, Complutense University, CNIO, Madrid, Spain; [5]Illawarra Cancer Care Centre, Wollongong, NSW, Australia; [6]Immunology and Molecular Oncology, Epworth Healthcare and University of Melbourne, Melbourne, Vic, Australia; [7]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [8]Hematology Department, University Hospital La Fe, Valencia, Spain; [9]Department of Haematology, Zealand University Hospital, Roskilde, Denmark; [10]Department of Hematology and Oncology, Clínica São Germano, São Paulo, Brazil; [11]Department of Internal Medicine, Division of Hematology, Istanbul University Medical Faculty, Istanbul, Turkey; [12]Department of Hematology, Severance Hospital, Seoul, Republic of Korea; [13]Service d'Hématologie et Thérapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France; [14]Hematology, Oncology and Transfusion Medicine Department, Vilnius University Hospital, Vilnius, Lithuania; [15]Oslo Myeloma Center, Department of Hematology, Oslo University Hospital and KG Jebsen Center for B Cell Malignancies, University of Oslo; [16]Sanofi, Vitry-sur-Seine, France; [18]Excelya, Boulogne-Billancourt, France; [19]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca

Background: High-risk smoldering multiple myeloma (HR-SMM) is associated with a greater risk of progression to symptomatic disease, suggesting the need for early, efficacious therapeutic interventions to improve outcomes. The ongoing, randomized Phase 3 ITHACA study (NCT04270409) is evaluating efficacy and safety of the anti-CD38 monoclonal antibody isatuximab (Isa) in combination with lenalidomide (R) and dexamethasone (d) (Isa-Rd) vs Rd in patients (pts) with HR-SMM. We report here preliminary results from the safety run-in part of this trial. **Methods:** The primary objective was to confirm the recommended dose of Isa in combination with Rd. Pts were eligible if diagnosed with SMM within 5 years and HR-SMM defined by the Mayo '20-2-20' and/or updated PETHEMA model criteria. Minimal residual disease and imaging by MRI and low-dose whole-body CT/PET-CT will be assessed at fixed time points. **Results:** As of April 12, 2021, 23 pts (median age, 63 [28–85] years; median time from initial diagnosis, 1.14 [0.1–5.2] years) had received Isa 10 mg/kg once weekly then biweekly (QW-Q2W) in combination with Rd. The median number of cycles was 7 (range, 4–10) and median duration of treatment exposure was 29.7 (range, 16.0–38.0) weeks. Two pts met the Mayo clinical model criteria, 13 pts the PETHEMA model criteria, and 8 pts both models' criteria for HR-SMM. No pt presented with focal lesions at baseline. Seven (30.4%) pts developed 8 grade ≥3 non-hematologic treatment-emergent adverse events (TEAEs): COVID-19 pneumonia, insomnia (2 each), papular rash, muscle spasm, retinal detachment and hyperglycemia (1 each); no pt experienced a grade 5 TEAE and no pt discontinued treatment due to a TEAE. Serious TEAEs were COVID-19 pneumonia (n=2, grade ≥3) and pneumonia, musculoskeletal chest pain and pyrexia (n=1 each, grade <3). The most common, mostly grade 1–2 TEAEs were insomnia (39%) and constipation, headache, and peripheral edema (22% each). Infusion reactions were reported in 2 pts (8.7%) (grade 2, infusion day 1/cycle 1). By laboratory results, no grade 3–4 anemia or thrombocytopenia was observed; grade 3 neutropenia was reported in 5 pts (21.7%), with no grade 4. Isa exposure and CD38 receptor occupancy were in accordance with other MM studies, reaching target saturation in bone marrow plasma cells. The overall response rate was 86.9%; 21.7%, 17.4%, and 4.3% of pts have so far achieved very good partial response (VGPR), complete response (CR) and stringent CR (sCR), respectively. **Conclusions:** Addition of Isa 10 mg/kg QW-Q2W to Rd was associated with a favorable safety profile in pts with HR-SMM, which compares well with Rd literature data in the same patient population. Isa-Rd has shown encouraging preliminary efficacy (21.7% sCR/CR and 43.4% ≥VGPR rates) in pts with HR-SMM. These results confirm the recommended dose of Isa for the randomized part of the Phase 3 ITHACA study, which will further evaluate efficacy and safety of Isa-Rd in HR-SMM. **Funding:** Sanofi.

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Frequent magnetic resonance imaging partially reduces the development of end organ damage in patients with smoldering myeloma

Jens Hillengass[1], Markus Wennmann[2], Thomas Hielscher[2], Tobias Baeuerle[3], Barbara Wagner[4], Jennifer Mosebach[5], Marc Raab[6], Sandra Sauer[7], Stefan Delorme[2], Hartmut Goldschmidt[8]

[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [2]German Cancer Research Center; [3]University of Ehrlangen; [4]University of Heidelberg; [5]Diagnostikum Berlin; [6]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [7]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; [8]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT)

Background: Osteolytic lesions are a hallmark of multiple myeloma (MM) and are present in 80% of patients at first diagnosis. Since they can lead to instabilities, fractures, and pain they go along with a significant impact on the quality of life of patients. By definition, patients with smoldering multiple myeloma (SMM) don't have osteolytic lesions yet. Modern diagnostic technologies like magnetic resonance imaging (MRI) or positron emission tomography with computed tomography (PET/CT) allow for detection of focal accumulations of myeloma cells before the actual bone has been destroyed. In SMM the presence of these lesions has been identified as risk factor for progression into symptomatic disease and has together with a free light chain ratio of ≥100 and a plasma cell infiltration of the bone marrow of >/=60% been identified

as "biomarkers of malignancy" indicating necessity of systemic treatment. **Methods:** To investigate if frequent, longitudinal whole body (WB) MRI helps to predict the development of MM in general and osteolytic lesions in particular the current prospective study has enrolled 96 evaluable patients with SMM and has followed them with WBMRI every 6 months and clinical and serological markers every 3 months. Bone marrow biopsies were only performed when clinically indicated. **Results:** The 1-, 2-, and 3-year progression rates with application of the current diagnostic criteria were 10%, 19% and 25%, respectively. Of 22 patients progressing into MM, 7 showed biomarkers of malignancy only without associated end organ damage. Four of those progressed with >1 focal lesion (FL) in MRI or a growing FL without osteolytic lesion (OL), and 3 due to a serum free light-chain ratio ≥100. The remaining 15 patients (68%) who progressed into MM still suffered from end-organ damage at progression. In all but 1 patient, OL showed a corresponding FL in WBMRI at time of diagnosis of the respective OL. The time between first appearance of a FL and the diagnosis of the OL was highly variable. **Conclusion:** Applying biomarkers of malignancy and frequent WBMRIs reduced the proportion of patients suffering from end-organ damage at progression to 68%. This supports the current development to initiate therapeutic or preventive treatment in patients with high risk SMM identified by markers beyond the biomarkers of malignancy in the current disease definition.

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The impact of CD56 expression in smoldering Multiple Myeloma

Laura Notarfranchi[1], Rosanna Vescovini[2], Roberta Segreto[3], Sabrina Bonomini[3], Paola Storti[2], Valentina Marchica[2], Gabriella Sammarelli[3], Giannalisa Todaro[2], Naomi Soressi[2], Dario De Giovanni[2], Jessica Burroughs-Garcia[2], Denise Toscani[2], Anna Benedetta Dalla Palma[3], Nicola Giuliani[4]

[1]Facoltà di medicina dell'Università di Parma; [2]Facoltà di Medicina e Chirurgia Università di Parma; [3]Ospedale Maggiore di Parma; [4]Department of Medicine and Surgery, University of Parma, Parma, Italy

Background: The identification of risk factors for progression is critical in the clinical management and appropriate follow up of patients with SMM. Several prognostic score identify in SMM patients the main risk factors for progression to MM, but new parameters to identify possible progression in SMM need to be defined. The aim of this study was to investigate the possible role of the immunophenotype and the role of CD56 expression as risk factor for progression. **Method:** We retrospectively evaluated a cohort of SMM patients admitted to a single haematological center between 2014 and 2019. We analyzed a total cohort of 80 patients diagnosed with SMM according to the IMWG diagnostic criteria. All patients analysed underwent to Bone Marrow (BM) examination and imaging evaluation was performed. Both immunophenotypic and FISH analysis were performed of BMPCs. **Results:** Overall 25 patients of the entire cohort progressed to MM with a median the time to progression (TTP) of 24 months. Firstly, we validated the currently score of progression in our cohort. We found that percentage of BMPCs and presence of immunoparesis were significantly correlated with progression to MM ($p<0.05$ for each variable). Afterwards, we confirmed the SMM risk stratification models. "Pethema" (p=0.0006), Mayo score (p=0,0092), "20-2-20" score (p=0.0001) and also the "Danish score" (p= 0.003) turned out statistically significant. Then, we investigate the possible role of CD56 expression in the risk of progression, by flow cytometry analysis and its association with a variety of clinicopathological parameters. We found that the median TTP in CD56- SMM patients was shorter than TTP in CD56+ ones (11 months vs 31 months, p = 0.08). Moreover CD56- patients progressed without a significant increase of the Monoclonal Component as compared to CD56+ ones (p=0.0062). This was also confirmed by the increase in the bone marrow infiltrate value which was statistically significant only in the CD56+ group (p:0.0006 vs p:0,17). The same result was also assessed with the Beta2microglobulin value (p: 0,001 vs p: 0,13). Finally, we compared CD56 expression to cytogenetic abnormabilities and we found a relationship between CD56 expression and the hyperdiploidy, a good prognosis factor. CD56- SMM patients had a significant lower presence of hyperdiploidy as compared to those with CD56+ BMPCs (p=0.04). Also this result reinforces the thesis that lack of CD56 is associated with a poorer prognosis and could be a possible factor for a more aggressive disease associated with unfavorable prognostic parameters. **Conclusion:** In conclusion, our data confirmed that in SMM patients the factors, which mostly impact on the short-term risk of progression to active MM, are the entity of the PCs infiltrate and the immunoparesis. Therefore, our study identified CD56 as a possible marker of poor prognosis in patients with SMM. Indeed the lack of CD56 expression could be a factor for a more aggressive disease regardless to the tumoral burden.

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Monoclonal proteinuria ≥200 mg/24h predicts progression risk in asymptomatic multiple myeloma with a free light chain ratio ≥100

Alissa Visram[1], S. Vincent Rajkumar[1], Prashant Kapoor[2], Angela Dispenzieri[1], Martha Lacy[1], Morie Gertz[1], Francis Buadi[1], Suzanne Hayman[1], David Dingli[1], Taxiarchis kourelis[1], Wilson Gonsalves[1], Rahma Warsame[1], Eli Muchtar[3], Nelson Leung[4], Robert Kyle[1], Shaji Kumar[3]

[1]Mayo Clinic Rochester; [2]Mayo Clinic; [3]Division of Hematology, Mayo Clinic, Rochester, MN; [4]Division of hematology and Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN

Background: A baseline involved to uninvolved free light chain ratio (FLCr) ≥100 with involved free light chain (iFLC) ≥10 mg/dL is considered a multiple myeloma (MM)-defining event (MDE). However, prior reports have demonstrated the presence of multimeric light chain aggregates which contribute to increased FLC levels due to impair renal light chain clearance. Therefore, we aimed

to compare the disease progression risk in patients with high versus low urine monoclonal protein (uMCP) excretion in the setting of an elevated serum FLCr. **Methods:** We retrospectively evaluated untreated smoldering MM (SMM) and asymptomatic MM patients diagnosed between January 1, 2000 and January 10, 2020. Included patients had a baseline bone marrow plasma cell (BMPC) burden of 10-59% without concomitant end organ damage (hypercalcemia, anemia, renal failure, or lytic lesions on x-ray or cross-sectional imaging; "CRAB" MDE). Patients with a baseline FLCr ≥100 and iFLC >10 mg/dL were included if they had a 24-hour urine collection and electrophoresis. Survival analyses were performed using the Kaplan-Meier method. Progression was defined as treatment for systemic AL amyloidosis or symptomatic MM (typical "CRAB" MDE). SMM patients treated due to evolving biomarkers or "SLiM" MDE were censored. Cox proportional hazards models were used for uni- and multivariable analyses. A two-sided p-value <0.05 was considered statistically significant. **Results:** We included 822 patients without MDE besides elevated FLCr (n=120 with FLCr ≥100, n=702 with FLC <100). Patients with a FLC ≥100 were grouped based on 24-hour uMCP excretion (≥200 mg/24h [n=35], <200 mg/24h [n=85]). Among included patients with a baseline FLCr ≥100, the median iFLC was 79.9 (IQR 42.9-131.5) mg/dL and median FLCr was 207.1 (IQR 137.7-400.3). Patients with a FLCr ≥100 and high (≥200 mg/24h) versus low (<200 mg/24h) uMCP excretion had a median iFLC of 101 versus 66.5 mg/dL (p=0.001), median estimated glomerular filtration rate (eGFR) 74.4 versus 74.6 mL/min/1.73m2 (p=0.505), and median BMPC burden of 30% versus 21% (p=0.088). The 2-year risk of progression to symptomatic MM or AL amyloidosis was significantly higher in patients with uMCP excretion ≥200 versus <200 mg/24h (36.2% versus 13.5%, respectively; HR 2.79, 95% CI 1.57-4.96, p<0.001). After adjusting for baseline eGFR, BMPC burden, and iFLC, and light chain isotype, the progression risk was still 2.7 times higher in patients with high versus low uMCP excretion (HR 2.66, 95% CI 1.39-5.10, p=0.003). However, the progression risk was similar in patients with a baseline FLCr <100 versus those with a FLC≥100 and uMCP <200 mg/24h (log rank p=0.127). **Conclusion:** Increased uMCP excretion (≥200 mg/24h) in the setting of a FLCr ≥100 is an unfavorable prognostic marker. Our findings underscore the importance of conducting a 24-hour urine assessment at diagnosis and may help refine the subset of patients with FLCr ≥100 in whom pre-emptive therapy is warranted.

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Lenalidomide versus Thalidomide or Bortezomib as maintenance regimen for non-transplant patients with multiple myeloma: multi-center real world experiences in China

Zhe Zhuang[1], Lei Shi[2], Ying Tian[3], Dongmei Zou[4], Ru Feng[5], Fei Dong[6], Yanping Ma[7], Hong Yu[8], Wei-wei Tian[9], Shuangjiao Liu[1], Liang-Ming Ma[10], Rong Fu[8], Hongmei Jing[6], Hui Liu[5], Wanling Sun[4], Wenming Chen[3], Yin Wu[3], Li Bao[2], Junling Zhuang[1]

[1]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; [2]Department of Hematology, Beijing Jishuitan Hospital, China; [3]Department of Hematology, Beijing Chao-Yang Hospital of Capital Medical University, Beijing, China; [4]Department of Hematology, Xuanwu Hospital of Capital Medical University, China; [5]Department of Hematology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Science, China; [6]Department of Hematology, Peking University Third Hospital, Beijing, China; [7]Department of Hematology,The second Hospital of Shanxi Medical University, Taiyuan, China; [8]Department of Hematology, Tianjin Medical University General Hospital, Tianjin,China; [9]Department of Hematology, Shanxi Bethune Hospital of Shanxi Medical University, Taiyuan, China; [10]Department of Hematology,The second Hospital of Shanxi Medical University, Taiyuan, China

Background: The current situation of maintenance (MT) after front-line therapy in non-transplant patients with multiple myeloma (MM) is not adequate in China. Hence, we conducted this multi-centered retrospective real-world study on efficacy and safety of the mainstream maintenance regimens, thalidomide (T-MT), lenalidomide (L-MT) and bortezomib (B-MT). Clinical data of newly diagnosed MM patients were collected from 9 centers of North China MM Registry from January 2010 to December 2020. The progression-free (PFS) and overall survival (OS) from maintenance, and adverse events were recorded. **Method:** A total of 316 patients were enrolled including 156 in T-MT, 113 in L-MT and 47 in B-MT. At baseline, the gender ratio, paraprotein isotype, ISS, R-ISS, and response evaluation before MT were comparable. Patients on L-MT were older. Greater proportions of patients in L-MT and B-MT had high-risk cytogenetic abnormalities (HRCA), defined as amplification 1q21 (1q21+), deletion 17p (17p-), t(4,14), t(14,16). **Results:** The median follow-up duration was 41.0, 21.9 and 20.7 months (m) in T-MT, L-MT and B-MT, respectively. Disease progression rate was 63.5%, 46% and 31.9%. Mortality rate was 29.5%, 19.5% and 8.5%. The median PFS was 23.7m in T-MT, compared with 23.5m in L-MT and 30.8m in B-MT (p=0.48). Median OS was 79.5m in T-MT, whereas not reached (NR) in the others (p=0.21). Patients reaching complete response (CR) or stringent CR (sCR) before MT had prolonged PFS compared to those with very good partial response (VGPR) or less in T-MT (28.7m vs 17.2m, p=0.048) and L-MT (29.9m vs 14.8m, p=0.01), while comparable in B-MT (NR vs 30.8, p=0.15). OS was similar despite of different response before MT. Patients with 1q21+ on T-MT had shorter PFS compared to those without (16.3m vs 22.8m, p=0.18), so did impaired median OS (53.1m vs 80.6m, p= 0.003). 1q21+ did not affect PFS in L-MT group (23.5m vs 27.4m, p=0.69), or B-MT (NR vs 30.8m, p=0.73). OS was not reached. Only a few patients with 17p-, yet also presented remarkably inferior PFS (6.8m vs 22.8m, p=0.007) and OS (32.3m vs 72.6m, p=0.02) in T-MT. PFS (15.6m vs 39.2 m, p=0.33) and OS (NR vs NR, p=0.83) were not of discrepancy in L-MT. In patients with any HRCA, T-MT resulted in shorter PFS (12.1m vs 22.8m, p=0.06) and OS (53.1m vs NR, p<0.01). While both were comparable in L-MT or B-MT, with HRCA or not. The main reason of MT withdrawal was disease progression. Discontinuation related to adverse events was seen in

5.1%, 5.8% and 0 patients in T-MT, L-MT and B-MT, respectively. **Conclusion:** In this multi-centered real-world study, thalidomide, a response of CR or better predicts superior PFS in non-transplant NDMM. HRCAs drag down survival in thalidomide, while lenalidomide and bortezomib mostly reverse the negative effects. Though patients on L-MT and B-MT have greater proportion of HRCAs, PFS in three groups are comparable. Clinicians in the real practice prefer lenalidomide or bortezomib as maintenance in high-risk patients.

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Ixazomib versus Lenalidomide or Ixazomib and Lenalidomide combination as maintenance regimen for patients with multiple myeloma: interim analysis of a multi-center prospective study in China

Zhe Zhuang[1], Hong Yu[2], Qinhua Liu[3], Dongmei Zou[4], Lei Shi[5], Ying Tian[6], Fei Dong[7], Yanping Ma[8], Wei-wei Tian[9], Ru Feng[10], Shuangjiao Liu[1], Hui Liu[10], Liang-Ming Ma[8], Hongmei Jing[7], Wenming Chen[6], Yin Wu[6], Li Bao[5], Wanling Sun[4], Rong Fu[2], Junling Zhuang[1]

[1]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; [2]Department of Hematology, Tianjin Medical University General Hospital, Tianjin,China; [3]Department of Hematology, The First Affiliated Hospital of Anhui Medical University, Hefei, China; [4]Department of Hematology, Xuanwu Hospital of Capital Medical University, China; [5]Department of Hematology, Beijing Jishuitan Hospital, China; [6]Department of Hematology, Beijing Chao-Yang Hospital of Capital Medical University, Beijing, China; [7]Department of Hematology, Peking University Third Hospital, Beijing, China; [8]Department of Hematology,The second Hospital of Shanxi Medical University, Taiyuan, China; [9]Department of Hematology, Shanxi Bethune Hospital of Shanxi Medical University, Taiyuan, China; [10]Department of Hematology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Science, China

Background: Maintenance therapy (MT) deepens response and prolongs progression free survival (PFS) in patients with newly diagnosed multiple myeloma (NDMM) after frontline regimens. Ixazomib, a 2nd generation oral proteasome inhibitor, has been approved for MT because of the convenience and tolerability. We conducted this prospective multi-center study to compare the efficacy and safety of Ixazomib (I-MT) or Ixazomib plus Lenalidomide (IL-MT) to Lenalidomide (L-MT) as maintenance regimen in NDMM patients. **Method:** This study was approved by the Institutional Review Board of Peking Union Medical College Hospital and registered (NCT04217967). NDMM patients were enrolled from 10 centers of North China MM Registry, since September 2019. After 4 cycles of front-line induction therapy, patients reached partial response (PR) would receive autologous stem cell transplantation (ASCT) if eligible, or keep up to 5 cycles of front regimens if ineligible, then start MT. Patients did not reach PR would switch to 2nd-line induction for 2-5 cycles and start MT once PR was achieved. For MT, 4mg of Ixazomib was given on day 1,8,15, and 25mg of Lenalidomide every other day on days 1–21 of 28day cycles. Patients in dual drug group were administrated with both Ixazomib and Lenalidomide. The primary endpoint was PFS from MT. **Results:** A total of 111 patients were enrolled, including 45 in I-MT, 41 in L-MT and 25 in IL-MT. The demographic and clinical characteristics were comparable among three groups at baseline, including gender ratio, age, paraprotein isotype, ISS, R-ISS, response status before MT, and ASCT rate. Patients on IL-MT were slightly younger. The proportions of patients with high-risk cytogenetic abnormalities (HRCAs), defined as amplification 1q21, deletion 17p, t(4,14) and t(14,16), were comparable. The median follow-up duration since MT was 5.9, 13.5 and 5.3 months in I-MT, L-MT and IL-MT group, respectively. Disease progression rate was 4.4%, 12.2% and 8%. Mortality rate was 2.2%, 2.4% and 0. There were 84%, 88.8% and 80% of the patients reached VGPR or better before MT, while the rates improved to 95%, 84% and 92% during follow-up. The prevalence of peripheral neuropathy with grade 1 was 20% on I-MT, 36% on IL-MT and 4.9% on L-MT. No grade 2 PN or higher was recorded. The incidence of gastrointestinal events was 11.1%, 24% and 0, respectively. All hematologic toxicities were lower than 8%. Infection rates were 8.9%, 4% and 7.3%. Skin rashes were more common in lenalidomide containing regimens (2.2%, 8% and 7.3%). No drug withdrawal was related to adverse events. **Conclusion:** Due to inadequate access to melphalan and low rate of ASCT in China, there is still a gap of PFS in NDMM patients with those in western countries. We herein design this multi-centered prospective study to evaluate if dual drug MT will further strengthen response and make up the gap. Though the primary endpoint--PFS has not been reached in all treatment groups, dual MT improves response most and is quite tolerable.

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Breakthrough – a designated pharmacist in the hemato-oncology department improves both quality and sequence of drug treatment and reduces ADR in Multiple Myeloma patients during Covid-19 pandemic

areen Alabbasi[1], Shai Cohen[2], manfred green[3], Shuli Brammli[4], Meir Preis[2], Rasmieh Khalaily[1]

[1]Clalit health service; [2]Carmel medical center; [3]University of Haifa; [4]Hebrew University School of Public Health

Background: In March 2020, COVID19 break out and since then the world has been facing a new reality. Multiple Myeloma patients due to their disease and chemotherapy were considered as a high-risk group for infection. Since then, in an attempt to avoid multiple exposures, encounters between patients and caregivers have diminished negatively affecting the sequence and quality of drug treatment. **Objectives:** Improving Quality, Sequence of Drug Treatment and reducing adverse drug reactions(ADR) in MM patients during Covid-19 pandemic. **Methods:** This study is part

of a broader randomized controlled trial. It included 44 MM adult patients, who received chemotherapy or biological therapy at Carmel Medical Center in Isreal. Once they sign a consent form, they were randomized into two groups (23 Intervention, 21 Control). In the intervention group, the pharmacist examined the patient's entire medical treatment and sent recommendations to the family physician and hematoocologist. On the day of the treatment, the pharmacist has met with the patient and provided him/her with a discharge counseling in addition to close supervision for 4 months during the treatment period. The control group was treated without increased pharmacological intervention. The data collection phase had ended one month after intervention period. The control group data was examined after the end of treatment to prevent ethical dilemmas. The variables that were examined are compliance, ADR and balancing medical incidences. **Results:** Intervention group: it was found that 65.2% of the patients did not take their medication according to the manufacturer's instructions, 8.7% took medication that were not registered in their medical file, 30.4% took medication at a different dose than recommended, 56% of patients had poor compliance to one or more prophylactic treatments. 90 recommendations were sent to the hemato-oncologist - 79 (87.7%) were accepted. 57 recommendations were sent to the family physicians and 40 (70%) of them were accepted. During the follow-up period, an improvement of 100% in adherence to the manufacturer's instructions, 100% of the medications were registered in the patient's file and the response to prophylactic treatment increased to 96%. Among the patients in the intervention group, there was an improvement in the indices of diabetes balance (13%), LDL (34%), vitamin D (30%) and GFR (34%). This is in comparison with an improvement of 4.7%, 9.5%, 23% and a 14% in the control group. During the follow-up period in the intervention group 7 cases of ADR were reported compared to 19 cases in the control group. **Conclusion:** We found that integrating of a designated pharmacist as part of the hemato-oncology department during the Covid-19 pandemic had high positive effect on the quality and sequence of drug treatment and reduced the incidence of ADR "Crisis is also an opportunity" – integrating a designated pharmacist should be considered even in routine days.

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Response to SARS-CoV-2 vaccination in patients with Multiple Myeloma using a 12-week spaced dosing strategy

Sarah Bird[1], Aikaterini Panopoulou[1], Robyn Shea[2], Micky Tsui[2], Radovan Saso[2], Amit Sud[1], Sharon West[2], Katy Smith[2], John Barwood[2], Ewa Kaczmarek[2], Carmela Panlaqui[2], Martin Kaiser[1], Simon Stern[3], Kevin Boyd[4], Charlotte Pawlyn[1]

[1]Institute of Cancer Research; [2]Royal Marsden; [3]Epsom & St Helier University Hospitals NHS Trust, UK; [4]The Royal Marsden Hospital, London

Background: Evaluating the degree of protection afforded to multiple myeloma (MM) patients by vaccination against SARS-CoV-2 is of critical importance due to the high morbidity and mortality associated with infection and the immunosuppression associated with MM and its treatment. We have previously reported antibody results after first vaccine dose in the UK (which adopted a 12-week spacing strategy between doses); 52 of 93 patients (55.9% [95% CI 45.8, 66.0%]) tested positive for SARS-CoV-2 IgG antibodies (Lancet Haematol 2021). Here we report results after the second dose. **Methods:** Patients who had received two doses of vaccine and had a documented SARS-CoV-2 anti-S IgG antibody test (Ortho Clinical Diagnostics, USA) ≥10 days after the second vaccination were included. Baseline data included disease characteristics, baseline blood tests, MM assessments and treatments (closest prior to first vaccination), vaccination type and antibody status (prior to vaccination, after first vaccination and after second vaccination). **Results:** Sixty-nine patients had documented antibody status after second vaccination. The median age of patients was 67 years (range 47-87) and 41/69 (59.4%) were male. Patients had received a median of 1 prior line of therapy (range 0-8) and 49/69 (71.0%) were on therapy at the time of first vaccination. Of the 69 patients, 58 (84.1% [95% CI 75.5, 92.7%]) tested positive for SARS-CoV-2 IgG post second vaccine (median days between second vaccine and antibody test 26, range 10-85). The 11 patients negative for antibodies after second vaccine dose had all been negative after first vaccine dose. Of the 58 patients positive after second vaccine dose 38 had been positive and 20 negative after first dose. After second vaccination there was no difference in the percentage of patients with a positive result between those who received the Pfizer (30/35, 85.7%) and AstraZeneca (28/34, 82.4%) vaccine, nor was there a difference with sex or age. Patients who had fewer prior lines of therapy were more likely to have a positive antibody result (0-1 prior lines 41/45, 91.1% vs >1 prior line 17/24, 70.8%, p=0.04). There was no significant difference between antibody status for patients on any current therapy or different individual therapies (including anti-CD38 antibodies), although some subgroups were small. Of note, all six patients who had been transplanted ≤12 months ago were antibody positive after the second vaccine dose. **Conclusion:** The majority of patients (84.1%) were positive for SARS-CoV-2 IgG antibodies after second vaccine dose, although the degree and duration of protection from infection afforded by this requires further study. A subset of patients had no measurable response and this was significantly associated with heavily pre-treated MM. It is critical that these patients are closely monitored as they may remain vulnerable to severe infection with SARS-CoV-2 and require additional protective or therapeutic strategies.

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The effect of a 6-week Nordic walking training cycle on myeloma-related blood parameters, vitamin 25(OH)D3 serum concentration and peripheral polyneuropathy symptoms in patients with multiple myeloma

Olga Czerwińska-Ledwig[1], Joanna Gradek[2], Jakub Deląg[3], Artur Jurczyszyn[4]

[1]Department of Chemistry and Biochemistry, Faculty of Motor Rehabilitation, University of Physical Education in Krakow, Poland; [2]Department of Athletics, Faculty of Physical Education and Sport, University of Physical Education in Krakow, Poland; [3]Faculty of Physical Education and Sport, University of Physical Education in Krakow, Poland; [4]Plasma Cell Dyscrasia Center, Department of Hematology, Jagiellonian University Medical College, Faculty of Medicine, Kraków, Poland

Background: Due to the use of new therapeutic strategies, patients with multiple myeloma (MM) live much longer, hence skeletal and neurological dysfunctions related to MM and advancing age are clinically significant. Properly selected training can bring bone health benefits, both in terms of fitness and blood parameters, as well as contribute to the improvement in the severity of peripheral polyneuropathy symptoms. **Method:** The study involved 28 MM patients after therapy in remission were divided into 2 groups: participating in exercise training (NW, n=15) and control group (CG, n=13). Subjects from the NW group participated in moderate intensity Nordic walking training sessions (60-70% of estimated HRmax) for 1 hour, 3 times a week, for 6 weeks. The intensity of performed exercises was monitored in all subjects individually with the use of a heart rate monitor. Venous blood was collected twice in all participants: at baseline before the beginning of the training cycle and after 6 weeks (at the end of training cycle). Myeloma-related parameters and vitamin 25(OH)D3 concentration were analyzed. After completing the training cycle patients were also asked for determination of changes in the severity of symptoms of peripheral polyneuropathy. The research was approved by a local bioethics committee and all subjects voluntarily signed informed consent prior to participation. **Results:** The applied training cycle (NW group) significantly increased the number of white blood cells (median by 0.56 103/µl, p=0.01), including neutrophils (by 0.62 103/µl, p=0.05). However, no significant impact of NW training on red cell and platelet parameters was observed. Participation in trainings was associated with a decrease in the serum levels of IgA, IgG and IgM, but only the changes in IgG concentration were statistically significant (by 1 g/l, p=0.017). The training contributed to the decrease in the concentrations of k[ED] free light chains in the blood (by 2.2 mg/l, p=0.001) and the k[ED]/l[ED] ratio (by 0.7, p=0.005). However, no significant changes were observed for the concentrations of l[ED] free light chains, beta-2-microglobulin, or monoclonal protein in serum. Serum 25(OH)D3 concentrations were significantly increased in all patients in the NW group (by 10.1 ng/ml, p<0.001). There were no significant changes in the control group. Additionally, patients with a higher initial 25(OH)D3 serum concentration resulted in an improvement in the peripheral polyneuropathy symptoms which was not observed in control group. **Conclusions:** Nordic walking has proven to be a safe form of health training for patients with MM. NW has a positive effect on IgG levels, serum free kappa light chain concentration and k[ED]/l[ED] ratio and the concentration of 25(OH)D3. High initial vitamin 25(OH)D3 serum concentration leads to an improvement in symptoms of peripheral polyneuropathy as a result of participation in Nordic walking training.

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A prospective study of conventional skeletal survey versus Whole-body CT for osteolytic lesions in Multiple Myeloma

Michael Gundesen[1], Jon Thor Asmussen[1], Einar Haukås[2], Michael Schubert[3], Niels Abildgaard[4], Fredrik Schjesvold[5], Thomas Lund[4]

[1]Odense University Hospital; [2]Department of hematology Stavanger University Hospital; [3]Stavanger University Hospital; [4]Department of hematology, Odense University hospital; [5]Oslo Myeloma Center, Department of Hematology, Oslo University Hospital and KG Jebsen Center for B Cell Malignancies, University of Oslo

Background: Multiple Myeloma (MM) is a bone marrow cancer with high prevalence of osteolytic disease. Evaluating bone involvement is essential as it is an important criterion for starting treatment. For many years conventional skeletal survey (CSS) has been used but based on retrospective data .The International Myeloma Working Group now recommends using Whole Body CT (WBCT). This study compares CSS to WBCT at baseline and prospectively for up to 4 years for finding progression of bone involvement. **Methods:** 96 MM patients from the cooperating hospitals were followed for up to 4 years. Patients were scanned every year for the first 2 years and every 6 months thereafter or if suspicion of bone disease was raised. Progressive bone disease was defined as new lesions of at least 5 mm or growth of lesions by at least 5 mm. For evaluation paired t-test for numeric analysis of lesions and McNemars exact test for comparison of proportions of paired observations were used. **Results:** 534 investigations (267 pairs) were evaluated. WBCT consistently found more bone lesions per patient 8.2 (CI 6.8;9.6) vs CSS 3.6 (CI 2.7;4.5). The additional lesions found by WBCT were primarily in the axial skeleton while there was no difference in the skull. In the extremities a few more lesions were found on CSS 0.40 (CI 0.2-0.5) vs WBCT 1.80 (CI 1.1;2.4). In total 23.6% (CI 20.6;26.6) of patients had a negative CSS and a positive WBCT (P<0.0001). Over the period a total of 19 cases of progressive bone disease (PBD) was found with 20 new lesions and 3 growing lesions found on WBCT vs 8 cases with 8 new lesions on CSS (P<0.001). The cases not found on CSS were primarily in the spine, sternum, and pelvic region. There were no cases of PBD on CSS not found on WBCT. Of the 19 cases of progressive bone disease, 5 cases were "bone only" progressors with no biochemical signs of progression. **Conclusions:** WBCT consistently outperformed CSS for finding osteolytic lesions. This supports the current recommendation for using WBCT for skeletal evaluations. Significantly more new lesions were found during follow-up by WBCT compared to CSS suggesting that using only CSS is likely to underestimate progression rates.

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COVID-19, impact of vaccination in myeloma patients

Ellen Hoornaert[1], François Dachy[1], Amandine Hansenne[1], Eugénie Lagneaux[1], Damien Gruson[2], Sarah Bailly[1], Marie Vekemans[1]
[1]Department of Hematology; [2]Department of Clinical Biology

Background: The worldwide COVID-19 pandemic represents an unprecedented crisis that affects the entire medical community, and appears to be a devastating infection in patients with hematological disorders, including myeloma (MM). Vaccination is therefore crucial in this population. Seroconversion after COVID-19 has been shown to be lower in MM patients compared to the general population. The same is expected after vaccination, as different reports have already revealed a lower antibody response after anti-SARS-CoV-2 vaccination in this group. We investigated the role of anti-SARS-CoV-2 vaccination in our MM patients. **Method:** We collected data on the occurrence and outcome of COVID-19, and impact of anti-SARS-CoV-2 vaccination in patients with MM or related disorders, excluding MGUS. Diagnosis of COVID-19 relied on a positive RT-PCR nasopharyngeal swab, while immunization was assessed after two shots of either a mRNA (Pfizer®/Moderna®) or a viral vector (Astra Zeneca®) vaccine, using the Elecsys immunoassay (Roche®) that measures anti-SARS-CoV-2 antibodies including IgG. **Results:** From March 2020 to date, 219 patients with plasma cell dyscrasias were seen on a regular basis at our outpatient facility. Only 15 of them were diagnosed with COVID-19 (median age 71, range 55-85), with an adverse outcome occurring in 3 patients with an advanced disease. We then collected the serological status at day 30, of the first 129 patients that completed vaccination. 97 were affected by MM, 19 by SMM, 3 by MGRS, 10 by AL amyloidosis. 118 developed regular antibodies confirmed by the presence of the receptor binding domain of the spike protein (RBD) antibodies, while 7 presented nucleocapsid protein (N) antibodies, suggesting a previous contact with the virus in the absence of any clinical manifestation. 11 patients failed to develop any immunization, all had received immunosuppressive therapies (renal transplantation in 1, long-term corticosteroid in 1, cyclophosphamide in 7, anti-CD20 monoclonal antibodies in 2) or multiple previous lines of therapies. We could not identify any link with immunoparesis or CD4/CD8 levels, additional tests are pending. With a 3 month median follow up, only 1 patient experienced a mild form of COVID-19 after vaccination despite high levels of neutralizing antibodies. **Conclusion:** So far, SARS-CoV-2 vaccination provides an adequate coverage in our MM population since only one case of COVID-19 occurred after vaccination. Extended follow-up will however be needed to confirm this, particularly with the appearance of new variants, and to know how long this protection will last over time. Whether non responding patients will eventually develop T-cell protection against COVID-19 remains also to be answered, as well as the positivity cutoff that measures neutralizing antibodies, optimal timing of vaccination, particularly in the context of immunodeficiency and diverse anti-MM therapies, and the role of a third shot in specific situations.

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Real-life analysis of the multiple myeloma patient's survival in a third-level hospital

Nieves López-Muñoz[1], Rodrigo Íñiguez García[1], Rafael Alberto Alonso Fernández[1], Jose M Sánchez-Pina[1], Clara Cuéllar[1], Ana Jiménez Ubieto[1], María Calbacho[1], Rosa Ayala[1], M Liz Paciello[1], M Pilar Martínez Sánchez[1], Elena Vera Guerrero[1], Marta Hidalgo Soto[1], María Poza[1], Irene Zamanillo[2], Joaquín Martínez-López[1]
[1]Hospital 12 de Octubre, Madrid; [2]Hospital 12 de Octubre

Background: Multiple myeloma (MM) constitutes approximately 10% of haematological malignancies, with a median age at diagnosis of 65 years. Patient survival has improved considerably over the last 20 years with the introduction of new drugs. In 1999, the first immunomodulatory drug, thalidomide, was approved, followed by lenalidomide in 2005 and pomalidomide in 2013. In 2003, proteosome inhibitors such as bortezomib were introduced and carfilzomib in 2014. In 2015, anti-CD38 monoclonal antibodies such as daratumumab were added to the treatment schemes. We have analyzed the impact on the outcome of the introduction new drugs for MM in the last 20 years in our institution. **Methods:** A total of 862 patients diagnosed with symptomatic multiple myeloma between 1999 and 2020 in a tertiary care hospital in Spain, Hospital 12 de Octubre in Madrid, were retrospectively analysed. Survival by age was evaluated over the years, establishing three groups: 1999-2005, 2005-2015 and 2015-2020. Kaplan-Meier analysis was used for analyzing overall survival, and differences between groups were tested for statistical significance using the log-rank test. **Results:** A total of 862 patients were included in the study. There were 409 men (47.45%) and 453 women (52.55%). The median age at diagnosis was 69 years. Among the group of patients younger than 65 years, the median survival among patients treated between the period 1999 to 2005 was 49.28 months (16.86-81.70; 95%); 78.42 months (49.83-107.01; 95%) between the years 2005 to 2015 and the median is not reached between the years 2015 to 2020 (p=0.001). Equally significantly, patients younger than 75 years have improved survival over the years. Median survival among patients treated between 1999 and 2005 was 43.43 months (23.86. 63.00; 95%); 58.80 months (43.38-74.23; 95%) between 2005 and 2015 and the median is not reached between 2015 and 2020 (p<0.001). However, among patients aged 65 and 75 years and older, no statistically significant differences were found. **Conclusion:** The introduction of new agents in the treatment of multiple myeloma has transformed the natural history of the disease, achieving long survival times in younger patients. Thus, it is essential to continue to advance and develop new therapies, as has been the case in recent years with the emergence of antiBCMA therapies.

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Immunogenicity of SARS-CoV-2 vaccine in patients with multiple myeloma

Florent Malard[1], Béatrice Gaugler[2], Joel Gozlan[1], Lucie Bouquet[3], Djeneba Fofana[1], Zoe Van De Wyngaert[1], Souhila Ikhlef[4], Zora Marjanovitch[4], Laurence Morand-Joubert[1], Mohamad Mohty[4]

[1]Hôpital Saint-Antoine, AP-HP; [2]Centre de Recherche Saint-Antoine; [3]Université de Bourgogne Franche Comté; [4]Hématologie clinique et thérapie cellulaire, Hôpital Saint Antoine, APHP, Sorbonne Université, INSERM UMRs 938, Paris, France

We evaluated the safety and immunogenicity of the BNT162b2 vaccine in 52 patients with multiple myeloma (MM). Median age was 71.3 (range, 39.6-90.8) years. 26 (50%) patients had received active treatment including an immunomodulatory drug (IMiD) (n=21), an anti-CD38 monoclonal antibody (n=11) and/or a proteasome inhibitor (n=4). 21 had received previous treatment interrupted at a median of 27.5 (range, 3.5-169.3) months before first vaccine inoculum. 5 patients had indolent untreated MM. 35 patients had a history of autologous hematopoietic cell transplantation (HSCT) performed at a median of 44.4 (range, 3.5-169.3) months before first vaccine inoculum. The vaccination was well tolerated with few non-severe adverse events. Immune efficacy evaluated by antibody seroconversion showed a significant increase of anti-Spike (S) IgG antibodies between day (d)28 and d42 (p<0.0001). However, anti-S IgG at d42 was significantly lower in patients compared to healthy controls (p=0.0035). Neutralizing antibodies (NAb) correlated with anti-S IgG d42 titers (Spearman r=0.832, p<0.0001). An anti-S IgG d42 level ≥3100 UA/mL was predictive of NAb ≥30%, the positivity cut-off for NAb (p<0.0001). Only 44% (n=23) of the patients achieved an anti-S IgG d42 level ≥3100 UA/mL after the two BNT162b2 inocula, compared to 87% of healthy controls. We then performed a multivariable logistic regression to identify parameters parameters associated with achievement of protective anti-S IgG d42 level (>= 3100 UA/mL). We found that patients' age (>=71 years versus 25 versus = 120/L) had no impact on achievement of a protective anti-S IgG level after two BNT162b2 inocula. In contrast, male gender, and ongoing chemotherapy were associated with a significantly decreased probability of achieving the defined protective anti-S IgG level after two BNT162b2 inocula [odds ratio (OR) 0.126, 95% confidence interval (95% CI) 0.022-0.709, p=0.02; OR 0.146, 95%CI 0.025-0.866, p=0.03, respectively]. Finally, using the IFN-g ELISPOT assay in 12 patients, we found a significant increase in T cell response in 12 MM patients against the S protein, with 7 patients (58%) having an anti-S IgG positive ELISPOT after the second BNT162b2 inoculum. **Conclusion:** These findings suggest that vaccination with two BNT162b2 inocula translates into a significant increase in humoral and cellular response in patients with MM, but only around half of the patients are likely to achieve effective immune protection against COVID-19.

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Quality of life, psychological distress, and prognostic awareness in patients with Multiple Myeloma

Elizabeth O'Donnell[1], Yael Shapiro[1], Omar Nadeem[2], Andrew J. Yee[1], Jacob Laubach[3], Andrew Branagan[1], Kenneth Anderson[4], Clifton Mo[2], Nikhil C. Munshi[4], Irene Ghobrial[3], Adam Sperling[2], Emerentia Agyemang[1], Jill Burke[1], Cynthia Harrington[1], Paul G. Richardson[3], Noopur Raje[5], Areej El-Jawahri[1]

[1]Massachusetts General Hospital; [2]Dana-Farber Cancer Institute; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [5]Massachusetts General Hospital Cancer Center

Background: Multiple myeloma (MM) is an incurable hematologic malignancy requiring long-term, continuous therapy. Despite its chronic and unrelenting course, studies examining quality of life (QOL), psychological distress, and prognostic awareness by line of therapy are lacking. **Methods:** We conducted a cross-sectional, multi-site study of patients undergoing treatment for MM (excluding maintenance therapy) between 6/2020-1/2021. To capture the full spectrum of treatment, we conducted purposeful sampling and recruited patients to 3 cohorts based on lines of therapy: 1) newly diagnosed receiving first-line therapy; 2) 2-3 lines; and 3) ≥ 4 lines. Patients completed validated questionnaires to assess their QOL, symptom burden, fatigue, psychological distress, and perceptions of prognosis. We used multivariate linear regression models to examine the association between lines of therapy, QOL, psychological distress, with patient's perception of their prognosis. **Results:** We enrolled 180 patients with MM (newly diagnosed (n=60), 2-3 lines (n=60), and ≥4 lines of therapy (n=60)). QOL, symptom burden, mood, and fatigue scores did not differ by lines of therapy. The rate of clinically significant depression, anxiety, and PTSD symptoms were 23.9% (43/180), 23.9% (43/180), and 24.4% (44/180), respectively. Overall, 84% (147/175) of patients reported that it is "extremely" or "very" important to know about their prognosis, and the majority (66.1%, 117/177) stated that they had received adequate information regarding their prognosis. Most patients, 84.7% (149/176) reported that their oncologist told them their cancer was incurable but only 30.6% (53/173) acknowledged that they were terminally ill and only 42.0% (73/174) reported that they thought their cancer was incurable. Patients receiving 2-3 lines of therapy were more likely to acknowledge their terminal illness (36.7% vs. 19.6%, p=0.045) and that their MM was incurable (90.0% vs. 75.9%, p=0.047) compared to those receiving first-line therapy. QOL and psychological distress were not associated with patient's perception that their MM was incurable. However, patients who acknowledged their terminal illness reported higher depression (B=1.52, P = 0.009), anxiety (B=1.52, P=0.0037), symptom burden (B=7.42, P=0.007), and lower QOL (B=-14.78, p=0.001). **Conclusions:** MM patients undergoing treatment experience impaired QOL and elevated psychological distress across the disease continuum, irrespective of their line of therapy. Although

the majority reported that their oncologist has told them that their cancer is incurable, a substantial proportion still have significant misperceptions of their prognosis. Interventions are needed to improve patients' QOL, reduce their psychological distress, and enhance patients' perceptions of their prognosis to facilitate informed decision-making.

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Incidence of adverse events in patients with Multiple Myeloma who continued with Denosumab after receiving Denosumab or Zoledronic acid: an open-label extension study

Noopur Raje[1], Wolfgang Willenbacher[2], Kazuyuki Shimizu[3], Ramon Garcia-Sanz[4], Ying Zhou[5], Vamsi Kurra[5], Anthony Glennane[5], Jitesh Rana[5], Evangelos Terpos[6]

[1]Massachusetts General Hospital Cancer Center; [2]Innsbruck University Hospital and Oncotyrol, Center for Personalized Cancer Medicine; [3]National Hospital Organization Higashi Nagoya National Hospital; [4]Hospital Universitario de Salamanca; [5]Amgen Inc; [6]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece

Background: In a randomized phase 3 study of denosumab (XG) vs zoledronic acid (ZA) in patients with newly diagnosed multiple myeloma (MM) (Raje et al. Lancet Oncol 2018), XG was shown to be non-inferior to ZA and had a safety profile comparable to that of ZA with less renal toxicity. The mean treatment duration was 17.5 months for XG, and interest remains on the long-term safety profile of XG. Here, we report safety in the open-label extension (OLE) phase of this study of further XG treatment in patients with newly diagnosed MM. **Methods:** This was an international, phase 3, randomized, double-blind, active-controlled study comparing XG with ZA in patients with newly diagnosed MM (NCT01345019). Due to the positive benefit-risk profile of XG, patients were offered open-label XG for up to 2 years. In the OLE phase, eligible patients receiving XG or ZA from the double-blind phase continued with or switched to XG that was administered subcutaneously at 120 mg every 4 weeks. Patients who received XG in the double-blind phase are designated as XG/XG (n = 426), while those receiving ZA are designated as ZA/XG (n = 418). All patients were strongly recommended to receive vitamin D and calcium supplementation, necessary to treat or prevent hypocalcemia. **Results:** The cumulative mean exposure to XG for the entire study period consisting of double-blind and OLE phases was 29.2 months. The cumulative mean exposure to XG in the OLE phase was 17.5 months for XG/XG and 17.6 months for ZA/XG patients. Among 844 patients who received open-label XG, 443 (52.5%) were male, 401 (47.5%) were female, and the median age was 62 years. At diagnosis, 303 (35.9%) patients were at ISS stage I, 315 (37.3%) at stage II, and 208 (24.6%) at stage III. At study entry, 557 (66.0%) patients had a history of skeletal-related events. During the OLE phase, 361 (84.7%) XG/XG and 366 (87.6%) ZA/XG patients had treatment-emergent adverse events (AEs). Treatment-emergent AEs led to discontinuation of the investigational product in 99 (23.2%) XG/XG and 81 (19.4%) ZA/XG patients. The treatment-emergent AEs of interest for XG/XG and ZA/XG patients, respectively, in the OLE phase included hypocalcemia (7.0%, 7.2%), AEs potentially associated with hypersensitivity (12.0%, 11.5%), musculoskeletal pain (32.4%, 33.7%), and infections and infestations (55.9%, 58.1%). The incidence of positively adjudicated osteonecrosis of the jaw (ONJ) that occurred during the OLE phase was 7.7% for XG/XG (grade 3: 2.3%) and 6.2% for ZA/XG (grade 3: 2.4%). No adjudicated positive atypical femur fracture events were reported. As of October 25, 2019, a notably higher number of ONJ events resolved in XG/XG patients (14 [42%]) than in ZA/XG patients (6 [23%]). **Conclusions:** The safety results were comparable to those of previous skeletal-related event studies. XG has an acceptable safety profile when administered for >2 years in patients with MM.

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Providing nutritional guidance for patients with plasma cell disorders – a missed opportunity for hematologists and oncologists?

Nathan Sweeney[1], Maria Malik[2], Mohammad Jafri[3], Andriy Derkach[4], Cynthia Chmielewski[1], Peter Adintori[4], Sham Mailankody[4], Neha Korde[4], Carlyn Tan[4], Hani Hassoun[4], Malin Hultcrantz[4], Jens Hillengass[5], Susan McCann[6], Neil Iyengar[4], Sergio Giralt[4], Ola Landgren[4], Marcel van den Brink[4], Jenny Ahlstrom[1], Alexander Lesokhin[4], Anita D'Souza[7], Susan Chimonas[4], Urvi Shah[4]

[1]HealthTree Foundation; [2]Geisel School of Medicine at Dartmouth; [3]Touro College of Osteopathic Medicine; [4]Memorial Sloan Kettering Cancer Center; [5]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [6]Roswell Park Cancer Institute; [7]Medical College of Wisconsin

Background: Plasma cell disorders (PCDs) are chronic incurable conditions with an opportunity to positively impact outcomes with nutritional changes. Epidemiologic studies show that inflammatory/insulinemic diets are linked to PCDs (Lee IJC 2020), while vegetarians/vegans have a reduced risk (Key AJCN 2014). MGUS/SMM present a unique opportunity for early intervention, given the standard of care is observation. Though patients often inquire about the role of nutrition and whether they should alter habits to eat healthfully, their oncologists are frequently not prepared to address these concerns. The purpose of this survey was to provide insights into patient nutrition perceptions/practices and identify areas for further research. **Methods:** We utilized HealthTree® Cure Hub (HealthTree® Foundation, Lehi, Utah, USA) and invited participants with PCDs to answer questions pertaining to their diet/nutrition and related experience with their oncologist in an online survey. De-identified aggregated responses were reviewed. **Results:** Of 421 participants, 82% reported having dietary questions post-diagnosis, yet 23% stated this was not addressed by their oncologists despite asking. Among those who discussed it with their oncologist,

50% received no specific advice or were recommended a 'balanced diet' lacking details. Of the participants that received clear guidance from their oncologists, 88% attempted to follow it, reflecting the positive influence their oncologists can have. Lack of knowledge/ conflicting advice were barriers to change for 23%. Although the American Institute of Cancer Research (AICR) has published dietary guidelines, only 34% were aware of them. Patients also more frequently reported following a healthier diet after diagnosis – 75% pre-diagnosis vs 88% post-diagnosis. 78% patients with unhealthy diets pre-diagnosis improved their diet post-diagnosis and 7% with healthy diets pre-diagnosis worsened their diet post-diagnosis. Post-diagnosis, more patients reported consuming whole fruits and vegetables ≥1 times/day and whole grains and seafood ≥3 times/week. Post-diagnosis dietary changes were based on online/ media information and advice from non-medical friends in 47%, compared to advice from PCPs/oncologists/nutritionists in 22%. **Conclusions:** Patients with PCDs are interested in dietary advice and make dietary changes when faced with a cancer diagnosis. Most patients currently receive this advice from non-medical sources and report barriers related to lack of consistent information. Oncologists who provide clear guidance can positively impact dietary changes among patients. Our results reflect a missed opportunity between patients' need for dietary advice and the potential for oncologists to provide helpful counsel. Our findings highlight a need for further research into standardized guideline (AICR) implementation as well as for the development of PCD-specific guidelines. Further disease focused dietary studies are needed to fill this gap.

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Is it time for a more holistic approach to the treatment of Multiple Myeloma?

Faye Sharpley[1], Roxanne Spencer[1], Hannah Miller[1], Dane Bradwell[1], Janet Parkinson[1], Yvette Ibbotson[1], Jowitt Simon[1]

[1]East Cheshire Hospital

Background: Significant advances in the treatment of MM have resulted in improved overall survival. The challenge now is how to ensure quality of life keeps pace with improved survival. Supportive and holistic care is vital to this end. The problem is how to practically integrate supportive care into increasingly busy MM clinics. This abstract advocates for centres to utilise the expertise of every individual in the multidisciplinary team (MDT). The specialist nurse practitioner (SNP) is a constant figure throughout the MM patients' journey. Through the holistic needs' assessment, the SNP has an in-depth understanding of the patients' wishes and concerns. They are the patients advocate and life-line and patients often confide more in the SNP than the myeloma specialist, or members of their own family. The role is a privileged position and the role is evolving. The huge demands on the MM specialist have led to the development of nurse-led clinics. The advanced nurse practitioner (ANP) role has been developed to assist the SNP, and to ensure that the SNP can still be there in a supportive capacity. The ANP role bridges medical and nursing and is becoming increasingly valued. The ANP can assist with bone marrow biopsies, patient consent and pre-chemotherapy and consent clinics, where the ANP can spend more time with the patient, carefully reviewing treatment tolerability, toxicities and patient understanding. Specialist cancer pharmacists are an increasingly utilised resource in the care of MM patients. Anti-myeloma treatment is complex with subcutaneous, intravenous, and oral agents in single agent, duplet and triplet regimens. Extensive supportive drugs can also be overwhelming when added to a patients' established medication. The specialist pharmacist can conduct clinics for MM patients on long-term immunomodulatory (IMID) therapy, in addition to providing medication counselling, compliance charts and blister-packs to aid concordance. Their expertise can allow intervention to help with side effects preventing dose modifications or interruptions to treatment. MM can be both physically and emotionally demanding and the Macmillan Support Team offer psychological support and alternative therapies to help. This includes reflexology, Indian head massage and light touch body massage to help with pain, fatigue, sleep and enhance general wellbeing. Physical activity is encouraged through gentle walking groups. Professional person-centred counselling is also available in a non-clinical safe space to help alleviate emotional suffering. MM diagnosis and treatment was historically solely the remit of the MM specialist. A shake-up of our rigid clinician led approach to care is required, given the number and complexity of modern-day MM patients. An effective MM service needs to recruit the diverse expertise of the ANP, SNP, cancer pharmacist and Macmillan cancer specialist into a clinic model focusing on providing high-quality, holistic, patient-centred care.

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Cytatin C: a new biomarker in Multiple Myeloma?

Francisco Javier Cepeda-Piorno[1], Esther González-Garcia[1], Alba Mendez-Gallego[1], Juan Torres-Varona[1], Vanessa García-Moreira[1], Alfonso Pobes-Martinez[2], Jose-Emilio Sánchez-Alvarez[1], Rubén Fernández-Alvarez[1], Cristina Alberdi-García[1], Elene Astobieta-Madariaga[1], Noelia Andrés-Hernández[1], Christian Sordo-Vahamonde[3], Segundo González-Rodríguez[4], María-Victoria Mateos[5]

[1]Hospital Universitario de Cabueñes; [2]Hospital Valle del Nalón; [3]Universidad de Oviedo; [4]Universidad de Oviedo- ISPA; [5]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca

Background: Renal impairment in patients with multiple myeloma (MM), according with the International Myeloma Working Group (IMWG), is based on serum creatinine (sCrea) ≥ 2mg/dL or creatinine clearance < 40 ml/minute. The aim of this study was to determine whether the different equations used for the evaluation of glomerular filtration rate estimation (GFRe) could also define kidney disease in MM. We also compared the equations with a single parameter (CKD-EPI crea, CKD-EPI cystatin C (CC) and CAPA equation) against the reference method that includes the

two parameters (CKD-EPI crea-CC) to know the most sensitive equation for detection of kidney disease and to identify patients with more risk factors. **Methods:** In this epidemiologic cross-sectional study, 61 consecutives newly diagnosed MM patients (24 women/37 men) from December 2018 to April 2021 were included. In order to compare CKD-EPI and CAPA equations, Cohen´s Kappa statistic was employed. Mann-Whitney T-test and chi-square or Fischer´s exact test were used to evaluate parameters associated to decreased eGFR according to Crea o CC (statistical significance p-value <0.05). Correlation between GFRe CC and GFRe Crea and poor prognosis factors was determined by univariate and multivariate analysis. Statistical analysis were performed using Med.Calc v9.2.1.0 y SPSS v.24 (Armony,NY). **Results:** A total of 61 newly diagnosed patients with MM (24 women/37 men) with a mean age of 68 years (±11) were included. According to IMWG criteria, kidney disease with increased sCrea was found on 20% of patients (1 woman/11 men), compared to 26% (3 women/13 men) or 39% (7 women/17 men) when CKD-EPI Crea or CKD-EPI CC equations were used, respectively. The degree of agreement between the different equations and the reference method was very good for the CKD-EPI crea equation (Kappa: 0.958 (0.88 - 1.00, 95% CI) and good for the CKD-EPI CC and CAPA equations (Kappa: 0.747 (0.577-0.917, 95% CI), Kappa: 0.779 (0.619 - 0.939, 95% CI). Patients with decreased GFRe CC showed higher risk factors in comparison with those identified by GFRe Crea, including: age, b[ED]2-microglobulin, serum urate, increased monoclonal component in urine, 24 hours urine proteinuria and decreased hemoglobin and albumin. Importantly, GFRe CC methods detected more patients with renal impairment and worse prognosis according to R-ISS-3 criteria by univariate and multivariate analysis (Exp (B) 14,73; rango 1,78- 122,23; 95%CI, P=0,013). **Conclusions:** IMWG criteria may underestimate kidney disease in patients with MM, mostly in women, which could affect to the dose received as well as to its toxicity. Altogether, our data suggest that equations that include CC (CKD-EPI and CAPA) are more accurate to detect hidden kidney disease as well as patients with more and worse prognostic factors.

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Incidence, mitigation, and management of neurologic adverse events in CARTITUDE-2, a phase 2 study of ciltacabtagene autoleucel (cilta-cel) in patients with Multiple Myeloma

Hermann Einsele[1], Samir Parekh[2], Deepu Madduri[2], Bianca Santomasso[3], Jaime Gállego Pérez-Larraya[4], Niels W.C.J. van de Donk[5], Bertrand Arnulf[6], María-Victoria Mateos[7], Kevin C. De Braganca[8], Helen Varsos[8], Marlene J. Carrasco-Alfonso[9], Muhammad Akram[9], Nikoletta Lendvai[8], Carolyn C. Jackson[8], Yunsi Olyslager[10], Enrique Zudaire[11], Claire Li[11], Dong Geng[9], Andrzej Jakubowiak[12], Adam Cohen[13]

[1]University Hospital of Würzburg; [2]Mount Sinai Medical Center, New York, NY, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Clínica Universidad de Navarra, Pamplona, Spain; [5]Amsterdam University Medical Center, VU Amsterdam, Department of Hematology, Cancer Center Amsterdam; [6]Saint-Louis University Hospital AP-HP, Paris, France; [7]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca; [8]Janssen R&D, Raritan, NJ, USA; [9]Legend Biotech USA, Inc., Piscataway, NJ, USA; [10]Janssen R&D, Beerse, Belgium; [11]Janssen R&D, Spring House, PA, USA; [12]University of Chicago, Chicago, IL, USA; [13]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

Background: CARTITUDE-2 (NCT04133636) is a phase 2, multicohort, open-label study assessing the efficacy and safety of cilta-cel, a chimeric antigen receptor T (CAR-T) cell therapy with two B-cell maturation antigen (BCMA)-targeting single-domain antibodies, in patients (pts) with multiple myeloma (MM) in various clinical settings. This report describes the mitigation and management strategies implemented to identify and reduce the risk for neurologic adverse events (AEs) in pts with progressive MM after 1–3 prior lines of therapy (Cohort A). **Methods:** Eligible pts (≥18 years) had MM, measurable disease, Eastern Cooperative Oncology Group performance status ≤1, progressive disease after 1–3 prior lines of therapy including a proteasome inhibitor and immunomodulatory drug, and were lenalidomide refractory (no prior BCMA-targeting agent). Cilta-cel was given as a single infusion at the targeted dose of 0.75×10^6 (range $0.5–1.0\times10^6$) CAR+ viable T cells/kg 5–7 days after start of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 daily for 3 days). Monitoring and mitigation strategies for neurologic AEs included providing more effective bridging therapy to reduce tumor burden prior to lymphodepletion, frequent assessment of CAR-T-related immune effector cell-associated neurotoxicity syndrome (ICANS) using the ICE tool, handwriting assessments to detect micrographia, and brain MRI and electroencephalogram for pts with prior neurologic disease. Management strategies included evaluating infectious and paraneoplastic etiologies upon observation of ICANS ≥grade 1, administration of tocilizumab (if concurrent with cytokine release syndrome [CRS], all grades of ICANS) and/or dexamethasone (grade 2/3) or methylprednisolone (grade 4). ICANS and CRS were graded by American Society for Transplantation and Cellular Therapy criteria; non-ICANS neurotoxicities were graded per Common Terminology Criteria for Adverse Events, v5.0. **Results:** As of 15 Jan 2021 (median follow-up: 5.8 months [2.5–9.8]), 20 pts (65% male, median age 60 years [38–75]) in Cohort A received cilta-cel. Four pts (20%) had neurotoxicities. Three pts had ICANS (grade 1/2) with median time to onset of symptoms of 8 days (7–11) and median duration of 2 days (1–2). Supportive measures to treat ICANS were received by 2/3 pts, including levetiracetam and steroids; 3/3 had concurrent CRS and all recovered. One pt developed isolated facial paralysis (grade 2); onset: Day 29 after cilta-cel infusion, recovered: 51 days after the onset following treatment with dexamethasone for 28 days. No movement or neurocognitive disorders were reported. **Conclusion:** In pts with MM, neurologic AEs were generally manageable following treatment with cilta-cel. With a median of 5.8 months of follow-up, no movement or neurocognitive disorders were reported in pts from Cohort A. These

findings suggest that early detection and management of neurologic AEs can lead to better treatment outcomes.

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Bortezomib plasma concentration in multiple myeloma patients using highly sensitive LC-MS/MS method and its correlation with treatment response and peripheral neuropathy

Lavisha Goel[1], Ujjalkumar Subhash Das[1], Pooja Gupta[1], Lalit Kumar[2], Thirumurthy Velpandian[1], Kalpana Luthra[1], Yogendra Gupta[1]

[1]All India Institute of Medical Sciences, Delhi; [2]Medical Oncology, Dr BRAIRCH, AIIMS, New Delhi

Background: Bortezomib is a proteasome inhibitor used for the treatment of multiple myeloma but nearly 10-30% patients either do not respond to or are resistant to the treatment. In addition, 44% patients experience peripheral neuropathy which is one of the most commonly reported adverse event of bortezomib based regimen. The dosing schedule and route of administration of bortezomib has changed after the drug's approval but there is scarcity of data on bortezomib levels with the new dosing schedule. **Methods:** A total of 86 patients, who were attending multiple myeloma OPD were screened. Out of these, 36 patients who were on bortezomib-based induction treatment were recruited and blood samples were collected at different time points during 1st to 6th cycle. The demographic details, stage and type of disease, treatment regimen, response and adverse events were recorded in predesigned case record form. The plasma levels of bortezomib were estimated using highly sensitive LC-ESI-MS/MS method which was developed and validated inhouse with a lower limit of quantification of 0.19 ng/mL. At the end of four to six cycles of induction treatment, response was assessed as per International Myeloma Working Group Uniform Response Criteria. Adverse effects were graded as per Common Terminology Criteria for Adverse Events version 5.0. **Results:** Out of 36 patients, 2 were excluded from the final analysis as bortezomib levels were below the lower limit of detection. For the remaining 34 patients, the median age was 55 years (range 39 – 75 years) and there were 52.9% males. Of these, 5.9%, 32.3% & 61.8% patients were in ISS stage I, II & III respectively, while 23.5%, 58.8% & 17.6% patients were in R-ISS stage I, II & III respectively. For myeloma subtype, 61.8%, 17.6% and 20.6% patients had IgG, IgA and light chain myeloma type respectively. There were 91.1% responders and 8.8% non-responders. The mean plasma levels of bortezomib among non-responders (0.361 ± 0.186 ng/mL) were lower as compared to responders (0.649 ± 0.74 ng/mL). However, the association was not statistically significant (p=0.45). Peripheral neuropathy was seen in 14.7% patients which was of grade I in 8.8% and grade II in 5.8%. The mean plasma level of bortezomib in patients with peripheral neuropathy was 0.509 ng/mL in grade I and 0.19 ng/mL in grade II. **Conclusion:** The bortezomib responders achieve higher drug concentration compared to the non-responders. However, the bortezomib levels were lower in patients with more severe peripheral neuropathy, suggesting the role of bortezomib metabolites such as carbinolamides and peroxycarbinolamide.

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The safety and efficacy of Apixaban in patients with Multiple Myeloma on immunomodulatory therapy: real-world, single centre experience

Sarah Hartley[1], Manoja Abhayawickrama[2], Ian Amott[1], Caroline Harvey[1], Christine Skeet[1], Susan Robb[1], Firas Al-Kaisi[1]

[1]University Hospitals of Derby and Burton; [2]Bristol Royal Infirmary

Background: Multiple myeloma (MM) is an incurable haematological malignancy associated with a high risk of venous thromboembolism (VTE). Studies have shown a significantly higher risk of VTE in MM patients compared to the general population. Moreover, it was shown that VTE in MM patients is an independent risk factor for increased mortality. Immunomodulatory agents (IMiDs) form an integral part in the treatment of MM but can be associated with a further increased risk of thrombosis especially with the addition of steroids. The incidence of VTE was quoted to be as high as 26% in one study with lenalidomide and dexamethasone combination. The IMWG recommends risk stratifying VTE thromboprophylaxis for patient treated with IMiDs to receive aspirin, low molecular weight heparin or warfarin. However, data from myeloma XI trial showed patients receiving VTE prophylaxis based on IMWG recommendations still experienced high rates of thrombosis. Since the publication of IMWG criteria, direct oral anticoagulants (DOACs) have been used as safe and effective alternatives to enoxaparin and warfarin for the treatment and prevention of VTE. Their use for VTE prophylaxis in myeloma lacks randomised comparisons with conventional approaches. **Methods:** We present our experience on the use of apixaban for VTE prophylaxis in MM patients treated with IMiDs as an alternative to standard thromboprophylaxis. We conducted a retrospective observational analysis of VTE prophylaxis for all myeloma patients treated with IMiDs at the Royal Derby Hospital between October 2019-October 2020. Data were collected from electronic patient records. We analysed 115 episodes of IMiDs use in 109 patients (72 males and 44 females). The median age was 73 (range 42-89). Apixaban was used in 63 patients (54.8%). The remainder received enoxaparin (4,3.4%), antiplatelets (40, 34.8%), enoxaparin and antiplatelets (7 , 6%) or warfarin (1, 0.8%). 44 (42%) patients were treated with IMiDs at 1st line whilst 72 (68%) were treated at relapse. The median number of lines of therapy was 2 (range 1-6). **Results:** The number of thrombotic events on treatment was 6 (5.2%); 4 VTEs (2 PEs and 2 DVTs) and 2 arterial events (1 stroke and 1 NSTEMI) with one patient in each group on apixaban. The incidence of thrombotic events with apixaban was 1.7% vs. 3.4% with non-DOAC prophylaxis. Patients developed venous and arterial thrombotic events after a median of 2 (range 1-3) and 2.5 (range 1-4) lines of therapy respectively. VTE occurred on VTD and on lenaldiomide and dexamethasone chemotherapy in 1 and 3 patients respectively. Both arterial events occurred on lenalidomide

and dexamethasone. There were no major haemorrhagic events. **Conclusion:** Although this is a retrospective comparison of apixaban against a heterogenous non-DOAC prophylaxis arm, apixaban showed lower rates of thrombosis with no increased bleeding. Our analysis supports apixaban as a safe and effective alternative to conventional thromboprophylaxis.

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Carfilzomib-induced acute cardiotoxicity is mediated through angiotensin and caused by cardiomyocyte energy depletion

Max Mendez[1], Besse Andrej[2], Bogdan Florea[3], Zuppinger Christian[4], Hermen Overkleeft[5], Besse Lenka[2], Christoph Driessen[6]

[1]Kantonsspital St. Gallen/Universität Zürich; [2]Laboratory of Experimental Oncology, Clinics for Medical Oncology and Hematology, Cantonal Hospital St Gallen, Switzerland; [3]Leiden Institute of Chemistry; [4]DBMR Bern; [5]Leiden Institute or Organic Chemistry; [6]Clinics for Medical Oncology and Hematology, Cantonal Hospital St Gallen, Switzerland

Background: Carfilzomib (CFZ) treatment increases the survival of patients with relapsed/refractory MM, but it is associated with a higher incidence of cardiovascular adverse events not commonly observed after bortezomib (BTZ). Both CFZ and BTZ inhibit the rate-limiting proteasome beta 5 subunit activity at lower concentrations. However, only CFZ co-inhibits the activity of proteasome beta 5 and beta 2 subunits at higher doses, in contrast to the beta 5 and beta 1 co-inhibition provided by high dose BTZ. We hypothesized that the unique beta 5 and beta 2 subunit inhibition pattern explains the CFZ-related acute cardiotoxicity. **Methods:** Isolated primary murine cardiomyocytes treated with BTZ, CFZ or specific inhibitors for the beta 5, beta 2 and beta 1 proteasome subunits were used as in vitro model to assess cardiomyocyte contractility by time lapse video-microscopy in conjunction with motion vector image analysis. The effects of acute proteasome inhibition after CFZ or BTZ treatment was studied in vivo in the heart and bone marrow 1 hour post treatment with a multi-omics approach at the single cell-genomic, proteomic and metabolomic level. Selectivity of proteasome subunit inhibition was confirmed with the activity based chemical probes. All data was evaluated with R v.3.5.1 (2018-07-02) and Matlab 2020a. **Results:** CFZ resulted in co-inhibition of beta 5 and beta 2 proteasome subunit activity in cardiomyocytes, in contrast to beta 5 and beta 1 inhibition by BTZ. CFZ, or the combination of beta 5 and beta 2 specific proteasome inhibitors induced acute impairment of cardiomyocyte contractility, in contrast to BTZ or the combination of beta 5 and beta 1 inhibitors. CFZ caused significant quantitative proteomic changes related to cardiomyocyte metabolism that differed from BTZ-related proteomic changes. Single-cell RNA sequencing of murine hearts revealed that CFZ impairs ATP synthesis in cardiomyocytes. Metabolomic analysis of murine hearts revealed increased levels of angiotensin after CFZ treatment, in contrast to BTZ treatment. Co-treatment of cardiomyocytes with CFZ and valsartan prevented CFZ-induced cardiomyocyte toxicity. Thus, our results suggest a key role of the renin-angiotensin system in the pathogenesis of CFZ-induced acute cardiac toxicity. **Conclusion:** Our data suggest that CFZ specifically impairs cardiac contractility in a dose-dependent manner through its unique proteasome beta 5 and beta 2 subunit co-inhibition pattern, in contrast to BTZ. CFZ leads to more efficient functional proteasome inhibition in cardiomyocytes, impairs cardiomyocyte metabolism and activates the local renin-angiotensin-system, inducing acute cardiotoxicity. Inhibition of the renin-angiotensin system pathway with valsartan mitigated cardiomyocyte contractile impairment, providing a rational strategy to prevent CFZ-induced acute cardiac toxicity.

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Increased risk of second primary malignancy and mortality at ten years after stem cell transplant for Multiple Myeloma: an analysis of 14,532 Patients.

Brittany Miles[1], James Mackey[2]

[1]UT Medical Branch at Galveston; [2]Genesis Medical Group

Background: The landscape for patients with multiple myeloma has improved dramatically over the last 15 years. Immunomodulatory imide drugs (IMiDs) have shown great efficacy, in both the setting of initial therapy and as maintenance after autologous stem cell transplant (ASCT). Concern has been raised, however, regarding the risk of second primary malignancies (SPMs) that appear to be associated with the use of IMiD agents. SPMs are a known sequela of multiple myeloma treatment, particularly as a consequence of maintenance lenalidomide status-post stem cell transplant (SCT). The benefit of SCT has become less clear with the utilization of newer, more effective initial therapies. **Objectives:** To determine the effect of SCT on SPM risk and overall survival in multiple myeloma patients at 5 and 10 years after treatment initiation. **Methods:** We used TriNetX, a global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 58 Million patients in 49 large Healthcare Organizations. We created two patient cohorts who had all received treatment with thalidomide, lenalidomide, or pomalidomide. One cohort had received SCT while the other had not. Both cohorts were then analyzed for the development of all non-myeloma malignancies which occurred at least one year after treatment initiation. **Results:** At 5 years, SPMs were 5.8% more likely in patients who received stem cell transplant (22.4% vs 16.6%, RR 0.741, p value <0.0001). 5-year survival favored transplanted patients by 2.38% (64.85% vs 62.474%, p value 0.0044) but 10-year survival favored patients who did not receive transplant by 1.44% (42.279% vs 40.838%, p value 0.0279). The Kaplan-Meier curves cross at year 6. **Conclusions:** With use of newer treatment regimens, the small 5-year survival benefit derived from stem cell transplant in multiple myeloma patients is completely eliminated in year six by mortality that may be attributed to increased second primary malignancies. Survival in transplanted patients is inferior by year 10. Stem cell transplants in

these patients should only be performed in selective cases and guided by life expectancy.

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Efficacy and safety of induction therapy with IAd versus IRd regimen in fragile elderly patients with newly diagnosed multiple myeloma: results of a prospective multicenter clinical trail

Li Bao[1], Minqiu Lu[2], Peng Liu[3], Junling Zhuang[4], Mei Zhang[5], Zhongjun Xia[6], Zhenling Li[7], Hongmei Jing[8], Yin Wu[9], Wen ming Chen[9], Hebing Zhou[10], Yuping Gong[11], Rong Fu[12], Zhenyu Yan[13], Wenrong Huang[14], Bin Chu[16], Yutong Wang[2], Yongqing Zhang[15]

[1]Department of Hematology, Beijing Jishuitan Hospital, China; [2]Department of Hematology, Beijing Jishuitan Hospital, the Fourth Medical College of Peking University, Beijing, China; [3]Department of Hematology, Zhongshan Hospital, Fudan University, Shanghai, China.; [4]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.; [5]Department of Hematology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China.; [6]Sun Yat-sen University Cancer Center, Department of Hematologic Oncology; [7]Department of Hematology, China-Japan Friendship Hospital, Beijing, China.; [8]Peking University Third Hospital; [9]Department of Hematology, Beijing Chao-Yang Hospital of Capital Medical University, Beijing, China; [10]Department of Hematology, Beijing Luhe Hospital, Capital Medical University, Beijing, China.; [11]Department of Hematology, West China Hospital, Sichuan University, Chengdu, China.; [12]Department of Hematology, Tianjin Medical University General Hospital, Tianjin, China.; [13]Department of Hematology, North China University of Science and Technology Affiliated Hospital, Tangshan, China.; [14]Department of Hematology, Chinese PLA General Hospital, Medical School of Chinese PLA, Beijing, China.; [15]Department of Hematology, The Eighth Medical Center of Chinese PLA General Hospital, Beijing, China.

Background: Fragile elderly patients with multiple myeloma (MM) have low survival rate due to complications, poor tolerance and complianceand lack of effective treatment.This prospective multicenter non-randomized controlled study designed to assessment the efficacy and safety of IAd versus IRd in fragile elderly NDMM. **Methods:** This ongoing trial is conducted at 14 hospitals.Inclusion criteria was aged ≥ 65 years, IMWG GA score ≥ 2 or Mayo geriatric vulnerability scoring system defined as vulnerable.Patients with acute cardiovascular and cerebrovascular events were excluded. Schemes included IAd (ixazomib 4mg d1,8,15, liposome doxorubicin 40mg d1,dex 20mg d1,8,15,22), IRd (ixazomib 4mg d1,8,15, lenalidomide 25mg d1-14, dex 20mg d1,8,15,22), in 4-week cycles. For patients with effective response (≥ PR) after 6 to 8 cycles, Id maintenance initiated until progression.The study was powered for a primary endpoint of ORR,with PFS,OS,toxicity,health-related Qol as secondary endpoints. This study planned to enroll 120 patients, 60 in each group (chiCTR1900024917). **Results:** From Oct 2019 to May 2021, 95 patients were enrolled, median age 71(65-88) yrs, 29.5% of patients ≥75 yrs,18.9% of patients with renal insufficiency(eGFR < 30ml/min, n=13).Efficacy was evaluated in 89 patients,6 were not evaluated, of them,1 had not completed first cycle,2 had dropped out after first cycle,and 3 died in the first course.All patients with renal insufficiency (except for one case), paraplegia, or bedridden were enrolled in IAd group.At a median follow-up of 10 mons (1-20), total ORR was 80.9% , with 80.9% (38/47) in IAd and 81.0% (34/42) in IRd.Median PFS was 16 mons in IAd and was not achieved in IRd.Median OS was not achieved in both two groups,with 12 mon-OS at 81.0%. Cytogenetic high-risk was defined by t(4;14),t(14;16),t(14;20),del(17p) or 1q21 amplification.64.2% of patients stratified as high-risk, 21.0% of patients had ≥ 2 high-risk cytogenetic, median OS was 14 mons, while the median OS of patients with 1 or none high-risk genetic was not achieved (p=0.05).9.5% patients developed hematological grade 3 or above,13.7% patients developed gastrointestinal AE above grade 3 (IAd, n=10; IRd, n=3),13.7% patients with pneumonia(IAd, n=9; IRd,n=4). IRd regimen saw more serious neurotoxicity,5 patients had delirium, mental disorder or cerebral infarction.Fragile elderly patients are relatively vulnerable to death.16 patients died, included 7 deaths due to progression, 4 early deaths (≤60 days),4 treatment abandonment, and 1 unexplained sudden death. **Conclusion:** Overall efficacy and safety results support the use of IAD or IRD as frontline therapy for fragile elderly MM patients.Both regimenswere effective, with an overall response rate of 80.9% and 12-month OS of 81.0%. AE were tolerable.Mortality rate are comparably high in fragile elderly MM patients,it is still a challenge for treatment.

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Ultra-high-risk prognostic significance of double and triple hit myeloma

Jelena Bila[1], Marko Mitrovic[2], Zoran Bukumiric[3], Jelica Jovanovic[2], Marija Dencic Fekete[4], Aleksandra Sretenovic[1], Jelena Jelicic[2], Teodora Peric[1], Biljana Mihaljevic[1], Darko Antic[5]

[1]Clinic of Hematology, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade; [2]Clinic of Hematology, University Clinical Center of Serbia; [3]Institute of Medical Statistics, Faculty of Medicine, University of Belgrade; [4]Institute of Pathology, Faculty of Medicine, University of Belgrade; [5]Clinical Center of Serbia, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade

Background: Association of any of 2 or ≥3 specific high-risk chromosomal abnormalities (HR-CA: t(4;14), t(14;16), t(14;20) and +1q21) in multiple myeloma (MM) characterizes double or triple hit MM. **Aims:** The aim of study was to evaluate prognostic significance of iFISH findings of double and triple hit MM on the course of disease. **Methods:** The study analysed iFISH findings, clinical and laboratory characteristics of 502 newly diagnosed, transplant ineligible patients (pts, 259 male; 243 female, mean age 62yrs, range 35-85yrs) during period 2009-2021. According

to the MM type, IgG MM was found in 297pts (60.4%), IgA in 100 (20.3%), BJ in 88 (17.9%), IgD in 5pts (1.0%) and IgM and non-secretory disease was found at 1pts each (0.2%). The clinical stage (CS, Durie-Salmon) III was confirmed in 397pts (79.6%); II 73pts (14.6%); and I with symptomatic disease 29pts (5.8%). The ISS score 1 had 135pts (28.7%), ISS2 112pts (23.8%), and 224pts (47.6%) had ISS3. Revised ISS score 1 (R-ISS1) was found in 100pts (21.8 %); R-ISS2 in 254pts (55.5%), and R-ISS3 in 104pts (22.7%). Renal impairment had 160pts (32%). Treatment with thalidomide (Thal) based chemotherapy (HT) was applied in 254pts (50.7%); bortezomib (Bz) based HT in 186pts (37.1%), while 56pts (11.2%) were treated with conventional HT. **Results:** Finding of double and triple hit MM was identified in 21pts (6.8%): 17pts with double; 4pts with triple hit MM (12 male, 9 female, mean age 65yrs, range 44-81yrs). The IgG MM was present in 11pts, IgA in 5pts, and BJ in 5pt. Majority, 17pts were in III CS, and 4pts in II CS. The ISS3 score had 14pts, ISS2 5pts, ISS1 2pts, while R-ISS3 was found in 12pts, and R-ISS2 in 9pts. The overall treatment response (ORR, ≥PR) was significantly lower in pts with double and triple hit MM in comparison to the other MM patients (61.9% vs. 78.2%, p=0.018). The average PFS of patients with double and triple hit MM was significantly shorter in comparison to other MM patients, (17.0m vs. 48.0m; Log Rank=12.471, p<0.01); as well as the average OS of patients with double and triple hit MM (18.0m vs. 64.0m; Log Rank=10.593, p<0.01). Univariate Cox regression analysis pointed out the age (p<0.01), elevated LDH (p<0.01), R-ISS score (p<0.01) and presence of double and triple hit MM (p<0.01), as the major prognostic factors with impact on the OS of myeloma patients. Furthermore, the multivariate analysis confirmed major prognostic significance of age (p=0.02) and double and triple hit myeloma (p<0.01) for the OS. **Conclusion:** Presence of double and triple hit myeloma indicates ultra high-risk course of disease, consequently indicating necessity of intensive treatment approach with new treatment modalities.

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Compass: a prospective study comparing clinical evaluation with different geriatric screening methods in newly diagnosed elderly multiple myeloma patients

Michel Delforge[1], Jolien Raddoux[2], Cindy Kenis[2], Anneleen Vanhellemont[2], Philippe Mineur[3], Ellen Hoornaert[4], Ka Lung Wu[5], Jo Caers[6], Koen Van Eygen[7], Alain Kentos[8], Julien Depaus[9], Natalie Put[10], Ann Van De Velde[11], Géraldine Claes[12], Philip Vlummens[13], Vincent Maertens[14], Nathalie Meuleman[15], Isabelle Vande Broek[16], Mélanie Vaes[17], Karel Fostier[18], Hilde Demuynck[19], Stef Meers[20]

[1]University Hospital Leuven, Leuven, Belgium; [2]UZ Leuven Gasthuisberg; [3]GHdC Charlerloi; [4]Department of Hematology; [5]ZNA Stuivenberg; [6]Department of Hematology, Liège University Hospital Center, Liège, Belgium; [7]AZ Groeninge; [8]Hôpital de Jolimont; [9]CHU Dinant Mont-Godinne; [10]ZOL Genk; [11]UZA; [12]Centre Hospitalier EpiCURA; [13]UZ Gent; [14]Imelda; [15]Institut Jules Bordet; [16]AZ Nikolaas; [17]CHU Tivoli; [18]UZ Brussel; [19]Jan Yperman; [20]AZ Klina

Background: Multiple myeloma (MM) affects primarily older patients. Frail older MM patients benefit from a less intensive therapeutic approach to prevent severe drug-related toxicities. To diagnose frailty, several geriatric risk scores have been developed. However, comprehensive geriatric assessment (cGA) is not widely adopted in daily practice and many physicians still prefer to rely on their clinical skills to judge if a patient is fit or frail. **Methods:** The Compass trial is a prospective study in newly diagnosed MM patients ≥ 70 y comparing frailty assessed by clinical assessment (CA) and geriatric screening (GA) at diagnosis and after 3 months of treatment. Initial geriatric screening was performed by the G8 score followed by cGA if the G8 score was ≤14/17, and by IMWG score calculation. CA was performed by the treating physician and G8 independently by a trained health care worker. **Results:** Between 04/2017 and 10/2019 200 patients were enrolled from 20 Belgian hematological sites. 74% of patients were ≥ 75y at enrollment. By CA 43% of patients were scored as frail whereas 69% had a geriatric risk profile by independently performed G8. Compared with patients who scored fit both by CA and G8 (fit-fit), patients who scored fit by CA but frail by G8 (fit-frail) were older (p=0,002), had reduced nutritional status (p<0,001), more recent weight loss (p<0,001), received more polypharmacy (p<0,001) and considered their own health status as poorer (p<0,001). In this fit-frail cohort, 23% of physicians modified the upfront treatment regimen based on the information from the G8 compared to 8% in the fit-fit group (p=0.04). During treatment, additional dose reductions were performed in 45% of the fit-frail vs 33% of the fit-fit cohort (p=ns). In all patients with a G8≤ 14/17, full cGA was performed. CA fit but G8 frail patients were more independent on ADL (63% vs 30,3%; p <0,001), iADL (56,5% vs 26,3%; p <0.001) and had less cognitive impairment (8,4% vs 30,7%; p=0,004) compared with patients scored frail by both CA and G8. The patient subgroup fit by CA but frail by G8 score were primarily categorized into intermediate fitness (31%) and frail (57%) subgroups of the IMWG score. After 3 months of treatment, the majority of evaluable patients remained in the same category (fit or frail) by CA and by G8 (respectively 82% and 80%) and only a small proportion of frail patients were reclassified as fit by CA (5%) and by G8 (6%) reinforcing that frailty status at diagnosis is not driven by myeloma-related symptoms. **Conclusion:** Treatment optimization in elderly MM patients requires a frailty adapted approach. We demonstrated that clinical judgment alone underestimates the geriatric risk profile in 25% of newly diagnosed elderly MM patients requiring more reactive modifications in the treatment regimen. Based on our study results minimal geriatric screening tools like G8 are recommended in all elderly MM patients before treatment initiation.

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Efficacy and safety of Daratumumab, Bortezomib, Melphalan, and Prednisone (D-VMP) versus Bortezomib, Melphalan, and Prednisone (VMP) in Chinese patients with newly diagnosed Multiple Myeloma: OCTANS

Weijun Fu[1], Honghui Huang[2], Wei Li[3], Gang An[4], Zhen Cai[5], Jie Jin[5], Yafei Wang[6], Chor Sang Chim[7], Ming Qi[8], Jianping Wang[9], Yang Song[10], Bin Jia[11], Xue Yang[11], Wenyu Liu[10], Yunan Li[12], Renyi Zhang[13], Jian Hou[17], Jianxiang Wang[4]

[1]Shanghai Changzheng Hospital, Shanghai, China; [2]Department of Hematology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [3]Department of Hematology at the Oncology Center, The First Hospital of Jilin University, Changchun, China; [4]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [5]The First Affiliated Hospital of Zhejiang University, College of Medicine, Hangzhou, Zhejiang, China; [6]Tianjin Cancer Hospital, Tianjin, China; [7]Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong; [8]Janssen Research & Development, LLC, Spring House, PA, USA; [9]Janssen Research & Development, LLC, Raritan, NJ, USA; [10]Janssen Research & Development, LLC, Beijing, China; [11]Janssen Research & Development, LLC, Shanghai, China; [12]Medical Affairs, Xian Janssen Pharmaceutical Ltd., Beijing, China; [13]Medical Affairs, Xian Janssen Pharmaceutical Ltd., Shanghai, China; [17]Department of Hematology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Background: Daratumumab (DARA), a human IgGk[ED] monoclonal antibody targeting CD38, is approved by the FDA and EMA for the treatment of newly diagnosed multiple myeloma (NDMM) in combination with standard-of-care regimens. DARA in combination with VMP (D-VMP) was approved based on results of the phase 3 ALCYONE trial. The phase 3 OCTANS study investigated the efficacy and safety of D-VMP in Asian NDMM patients (NCT03217812). Here, we present a subgroup analysis of D-VMP in Chinese patients in OCTANS. **Methods:** Asian patients with NDMM who were ineligible for ASCT were randomized (2:1) to D-VMP or VMP. Patients received 9 (42-day) cycles of bortezomib (1.3 mg/m2 SC) twice weekly in Cycle 1 (Weeks 1, 2, 4, 5) then once weekly (QW) in Cycles 2-9 (Weeks 1, 2, 4, 5); melphalan (9 mg/m2 PO) and prednisone (60 mg/m2 PO) once daily on Days 1-4 of each cycle. DARA (16 mg/kg IV) was administered to patients in the D-VMP arm QW in Cycle 1, Q3W in Cycles 2-9, and Q4W thereafter until disease progression or unacceptable toxicity. The primary endpoint was the very good partial response or better (≥VGPR) rate. Key secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety. Minimal residual disease (MRD) negativity (10–5) rate was an exploratory endpoint. **Results:** A total of 167 Chinese patients were enrolled (D-VMP [n=114]; VMP [n=53]). Baseline characteristics were balanced between arms; median age was 69 (range, 57-81) years and 35 (21.0%) patients had high-risk cytogenetics. At the time of data analysis (clinical cutoff 2 July 2020), 31 (27.2%) patients in the D-VMP arm had discontinued treatment vs 19 (36.5%) patients in the VMP arm. At a median follow-up of 12.3 (range, 0-29.3) months for the overall study population, ≥VGPR rate was significantly improved with D-VMP vs VMP (74.6% vs 45.3%; odds ratio, 3.51; 95% CI 1.76-7.00; P=0.0003). ORR was 90.4% with D-VMP and 83.0% with VMP. Patients in the D-VMP arm achieved significantly higher MRD-negativity rates (29.8% vs 5.7%; P=0.0003). Median PFS was not reached with D-VMP vs 18.2 months with VMP (HR 0.41; 95% CI 0.21-0.78; P=0.0049); the estimated 12-month PFS rate was 83.4% vs 62.6%, respectively. The most frequent (≥10%) grade 3/4 treatment-emergent adverse events (TEAEs) for the D-VMP/VMP arms were thrombocytopenia (47.4%/44.2%), leukopenia (39.5%/48.1%), lymphopenia (38.6%/28.8%), neutropenia (37.7%/51.9%), pneumonia (32.5%/17.3%), anemia (26.3%/25.0%), hypokalemia (16.7%/3.8%), and hypertension (10.5%/11.5%). Infusion-related reactions occurred in 36 (31.6%) patients, the majority of which were mild. A total of 5 TEAE-related deaths (D-VMP, n=3; VMP, n=2) were reported. **Conclusion:** The addition of DARA to VMP significantly improved efficacy in Chinese NDMM patients and showed a safety profile consistent with the global ALCYONE trial. No new safety concerns were identified. These data support the use of D-VMP for the treatment of Chinese NDMM patients.

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Safety of lenalidomide (LEN)-based therapy vs non–LEN-based therapy for transplant-ineligible newly diagnosed multiple myeloma (TNE NDMM): update from the post-authorization study MM-034

Barbara Gamberi[1], Valerio De Stefano[2], Angel Ramirez Payer[3], Martin Wiesholzer[4], Yvonne Tromp[5], Meegahage Ratnakanthi Perera[6], Valentine Richez-Olivier[7], Sujith Dhanasiri[8], Barbara Rosettani[8], Jelena York[8], Michele Cavo[9]

[1]Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; [2]Fondazione Policlinico A. Gemelli IRCCS, Hematology, Rome, Italy; [3]Hospital Universitario Central de Asturias, Oviedo, Spain; [4]University Hospital St. Pölten, Karl Landsteiner University of Health Sciences, Pölten, Austria; [5]Röpcke-Zweers Hospital, Saxenburgh Groep, Hardenberg, The Netherlands; [6]Midland Regional Hospital at Tullamore, Offaly, Ireland; [7]CHU de Nice Hospital de L'Archet II, Nice, France; [8]Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; [9]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Università di Bologna

Background: LEN-based therapy (tx) until progression is a standard approach for treating TNE NDMM. Several phase 3 trials including FIRST and SWOG S0777 have shown the safety and efficacy of LEN-based tx in this setting. This updated analysis

from the ongoing, non-interventional, post-authorization study MM-034 (NCT03106324) further assessed the safety of LEN-based tx (including LEN + dexamethasone [Rd] and Rd + bortezomib [RVd]) vs non–LEN-based tx (including bortezomib + melphalan/prednisone [VMP]) in patients (pts) with TNE NDMM. **Methods:** Pts in MM-034 had TNE NDMM and were initiating first-line tx or had received <2 cycles of tx. Tx was determined before enrollment per routine clinical practice. Pts were observed while on tx for ≤3 y, with 5 y of total follow-up. Primary endpoint was incidence of cardiovascular events. Secondary endpoints included incidence of infections and second primary malignancies, and further safety characterization. **Results:** As of data cutoff (May 19, 2021), 451 pts who received LEN (Rd, n=378; RVd, n=49) and 439 who received non-LEN (VMP, n=277) were enrolled. Median (range) follow-up was 15.7 mo (0.3–44.3) for LEN (Rd 15.7 mo [0.3–44.3], RVd 15.2 mo [1.0–43.3]) and 15.2 mo (0.2–48.6) for non-LEN (VMP 15.9 mo [0.8–39.4]). Median age was 79 y (LEN) and 76 y (non-LEN); 52% and 62% of pts were male. More pts remained on tx with LEN (45% [Rd 44%, RVd 45%]) than non-LEN (21% [VMP 22%]). Rates of discontinuation of LEN vs non-LEN due to adverse events (AEs; 18% [Rd 19%, RVd 16%] vs 14% [VMP 12%]) and disease progression (9% [Rd 9%, RVd 10%] vs 9% [VMP 10%]) were similar. Among pts with ≥2 y of follow-up, median tx duration was longer with LEN (23.0 mo [Rd 23.5 mo, RVd 19.8 mo]) vs non-LEN (10.4 mo [VMP 10.8 mo]). Similar proportions of pts had cardiac AEs in the LEN (13% [Rd 13%, RVd 10%]) and non-LEN (11% [VMP 10%]) cohorts, including atrial fibrillation (4% vs 4%) and cardiac failure (3% vs 2%). Grade 3/4 tx-emergent AEs (TEAEs) were reported in 52% of pts with LEN (Rd 52%, RVd 59%) and 45% with non-LEN (VMP 42%). The most frequent grade 3/4 hematologic TEAEs (LEN [Rd, RVd] vs non-LEN [VMP]) were neutropenia (10% [11%, 8%] vs 9% [10%]), anemia (6% [6%, 4%] vs 5% [4%]), and thrombocytopenia (5% [5%, 4%] vs 7% [8%]). Grade 3/4 infections occurred in 14% of pts with LEN (Rd 12%, RVd 20%) vs 10% of pts with non-LEN (VMP 8%), including pneumonia (3% vs 3%). Grade 3/4 thromboembolic events occurred in 1% (LEN) and 0% (non-LEN) of pts. Incidence of any-grade peripheral neuropathy was 4% with LEN (Rd 2%, RVd 18%) vs 6% with non-LEN (VMP 8%). **Conclusions:** Updated results of this ongoing non-interventional study continue to show that the safety profile of LEN-based tx in pts with TNE NDMM is similar to those from randomized controlled trials. Duration of tx was twice as long in LEN than non-LEN cohorts, but incidences of grade 3/4 TEAEs were similar. No new safety signals for LEN-based tx, including Rd and RVd, were identified.

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Chronological age as a prognostic factor in transplant-ineligible patients with newly diagnosed Multiple Myeloma

Raquel García Ruiz[1], Elena Meseguer Martínez[2], Irene Navarro Vicente, María Jiménez Castillo[2], María Consejo Ortí Verdet[1], Eva Francés Aracil[2], Mario Arnao Herraiz[1], Omara Samantha Cortés Ortega[2], Pilar Solves Alcaina[1], María José Cejalvo Andújar[2], Rafael Andreu de la Piedra[1], Ana García Feria[2], María Paz Ribas García[2], Javier de la Rubia[1]

[1]Hematology Department, University Hospital La Fe, Valencia, Spain; [2]Hematology Department, University Hospital Doctor Peset, Valencia, Spain

Background: Myeloma Multiple (MM) is a hematological malignancy that affects elderly patients mainly. Due to the heterogeneity of this population, a geriatric evaluation is recommended to decide first-line therapy. However, its application is laborious, and its use in clinical practice is not widespread, being therapeutic decisions usually made according to chronological age. The aim of this study is to evaluate the clinical characteristics and evolution of a series of 148 newly diagnosed transplant-ineligible MM patients according to different age group. **Methods:** Retrospective study of patients with newly diagnosed MM, diagnosed in two tertiary hospitals in Spain, between 2015-2020. According to age at diagnosis, patients were grouped in ≤79 (Group 1; n=90) and ≥80 (Group 2; n=58) years. The International Myeloma Working Group criteria were used to evaluate treatment response. **Results:** The median (range) age of patients in Group 1 and 2 was 74 (70-79) and 83 (80-92) years, respectively. There were more patients with ECOG >2 (5.6 vs 17.2%; p=0.01) and ISS 3 (38.9 vs 53.4%; p=0.013) in Group 2. Remaining characteristics at diagnosis were similar in both groups. The most frequently administered treatments were bortezomib-based (43 patients in Group 1 and 22 in Group 2), followed by regimens with lenalidomide (18 patients in Group 1 and 20 in Group 2). Overall, 66 (73.3%) patients in Group 1 and 40 (71.4%) in Group 2 achieved partial response or better after treatment. The rate of very good partial response or better was 53.3% and 50% in Groups 1 and 2, respectively. Finally, 24 (26.6%) patients achieved complete response in Group 1 and 9 (16.1%) in Group 2 (p = 0.1). Nine (37.5%) out of 24 patients in Group 1 and 3 (33.3%) out of 9 patients in Group 2 achieved minimal residual disease negativity by flow cytometry, with a sensitivity of 10-5. With a median follow-up of 23.5 months, the progression-free survival (95%CI) of Group 1 and 2 was 33.13 (25.9-40.4) and 26.43 (16.6-36.2) months, respectively (p = 0.680). Median overall survival was 50.4 (33.4-67.4) months in ≤79 years and 28.1 (22.5-33.6) months in ≥80 years (p = 0.014). Overall, 38 patients from Group 1 and 33 from Group 2 have died, being infections the leading cause of death in both groups. It should be noted that 22 patients (24%) of Group 1 and 24 (41%) of Group 2 did not reach second line of therapy. **Conclusions:** Patients aged ≥80 years often have a worse general condition at diagnosis, but the rest of the baseline clinical characteristics are similar to those of patients aged ≤79. There were no differences in terms of the rate and quality of responses between both groups of patients. There was a high attrition rate, particularly among patients ≥80 years, highlighting the need to design specific therapeutic strategies for this fragile group of patients.

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Prognostic impact of response-adjusted ISS score in Multiple Myeloma

Marko Mitrovic[1], Zoran Bukumiric[2], Aleksandra Sretenovic[3], Ivana Miketic[3], Jelena Bila[3]

[1]Clinic of Hematology, University Clinical Center of Serbia; [2]Institute of medical Statistics, Faculty of Medicine, University of belgrade; [3]Clinic of Hematology, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade

Background: One of the most powerful prognostic indicators in patients (pts) with multiple myeloma (MM), along with International Staging System (ISS) and recently adapted Revised ISS score (R-ISS), is achievement of complete remission (CR). **Aim:** The aim of study was to analyze prognostic significance of Response-adjusted ISS (RaISS) in transplant ineligible MM pts. **Method:** The study included 257 newly diagnosed, transplant ineligible MM pts, diagnosed during period 2012-2020 (129 male; 128 female, mean age 66 yrs, range 35-85 yrs). The IgG MM existed in 155pts (60.3%), IgA in 50 (19.5%), BJ in 43 (16.7%), IgD in 3 (1.2%) and IgM in 1pt (0.4%). According to the clinical stage (CS, Durie-Salmon), III CS was present in 207pts (80.5%); II in 38pts (14.8%); and I CS in 10pts (3.9%). Renal impairment was present in 82pts (31.9%) and elevated LDH in 58pts (22.6%). The ISS score 1 had 55pts (21.4%), ISS2 65pts (25.3%) and 137pts (53.3%) had ISS3. According to the Revised ISS (R-ISS) score, R-ISS1 was found in 40pts (15.6%), R-ISS2 in 164pts (63.8%), while R-ISS3 was present in 53pts (20.6%). Treatment with triple thalidomide (Thal) based chemotherapy (HT) was applied in 129pts (50.2%) with standard risk features (R-ISS1), while bortezomib (Bz) based triplets were applied in 95pts (37%) with high risk features (R-ISS2 and R-ISS3). Standard HT was applied in 33pts (12.9%). **Results:** Considering RaISS score, the group of pts treated with Thal-based HT consisted of: 15pts (11.6%) with low risk (RaISS 0-1); 65pts (50.4%) with intermediate risk (RaISS 2-3); and high risk (RaISS 4) in 49pts (40.3%). There was significant difference in PFS (Log Rank 7.197; p=0.027), and, even more pronounced, in OS (log Rank 22.192; p=0.000) between low risk pts (RaISS 0-1), and intermediate or high risk pts (RaISS 2-3; RaISS 4), treated with Thal-based HT. The distribution according the RaISS score in patients treated with Bz-based combos was as follows: low risk - 11pts (11.6%); intermediate - risk 36pts (37.9%); high risk- 48pts (50.5%). Although there was no difference in PFS (Log Rank 3.307; p=0.191), pts of low risk, with RaISS score 0-1, had significantly longer OS (Log Rank 13.894; p=0.001) in comparison to the pts of intermediate and high risk (RaISS ≥2), treated with Bz-based triplets. There was no difference in PFS (Log Rank 0.008; p=0.930) or OS (Log Rank 0.502; p=0.479) between pts with RaISS 4, and pts with R-ISS 3 (Log Rank 0.008; p=0.930) treated with Thal-based HT. Likewise, no difference was found considering PFS (Log Rank 0.168; p=0.682) and OS (Log Rank 0.923; p=0.337) in patients treated with Bz-based triplets with RaISS 4 in comparison to the pts with R-ISS3. **Conclusion:** RaISS score is simple and powerful prognostic index, indicating necessity of tailored treatment in accordance to the R-ISS score with final goal to overcome high-risk features in patients with multiple myeloma.

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Real-world elderly myeloma patients: improved survival despite more adverse risk factors than younger patients and RCT populations. A study on behalf of the Nordic Myeloma Study Group

Kari Lenita Falck Moore[1], Cecilie Hveding Blimark[2], Annette Juul Vangsted[3], Ingemar Turesson[4], Tobias Klausen[5], Louise Redder[6], Dorota Knut-Bojanowska[7], Ingigerdur Sverrisdottir[2], Anna Genell[8]

[1]KG Jebsen Centre for B cell malignancies, Institute of Clinical Medicine, University of Oslo; [2]Sahlgrenska University Hospital; [3]Rigshospitalet København; [4]Lund University; [5]Herlev University Hospital; [6]Odense University Hospital; [7]Uddevalla hospital; [8]Regional Cancer Center West

Background: Elderly multiple myeloma (MM) patients are underrepresented in randomized clinical trials (RCTs). Prospective registries provide insight into real-world patient characteristics, treatment and outcome. The Danish Multiple Myeloma Registry (DMMR) and the Swedish Myeloma Registry (SMR), established in 2005 and 2008 respectively, are nationwide prospective registries with near 100% coverage. **Methods:** We describe baseline characteristics, treatment and survival for patients diagnosed with active myeloma in the DMMR January 1st 2005-February 18th 2020, and the SMR January 1st 2008-December 31st 2019. We performed a retrospective comparison of patients aged ≥75 years at diagnosis to MM patients <75 years. Further, we compared our cohort to the populations in pivotal RCTs guiding the treatment of elderly myeloma patients. **Results:** In total, we report on 4647 Swedish and Danish MM patients ≥75 years at diagnosis compared with MM patients <75 years (n=7378). Out of 4691 newly diagnosed MM patients in the DMMR, 36% (n=1688) were ≥75 years. Among 7334 MM patients in the SMR, 40% (n=2959) were ≥75 years. The elderly cohort presented with more advanced disease (46% ISS III in both registries vs 30.3% (SMR) and 34.6% (DMMR) among the younger cohorts). The proportion of patients with anemia and/or renal failure was higher in the older cohort. In comparison, important RCTs underpinning current treatment guidelines included a lower proportion of elderly patients and patients with ISS III. 30% of patients in the VISTA-trial (VMP vs MP) and the ALCYONE-trial (Dara-VMP vs VMP) were ≥75 years. In the FIRST trial (Rd continuously vs Rd 18 months vs MPT) 35% of patients were >75 years, while the MAIA trial (Dara-Rd vs Rd) has the largest proportion of elderly patients among these studies (43.6%). However, in the MAIA trial only 29% of patients presented with ISS III, compared to 46% of patients ≥75 years in our real-world population. Similarly, 35% of patients in VISTA and 38% in ALCYONE had ISS III. The FIRST trial had a composition more similar to the Swedish and Danish registry population with 35% of patients >75 years, and 48% of these patients with ISS stage III. The treatment strategies in the elderly were similar in Denmark and Sweden. Melphalan and prednisolone (MP) were replaced by bortezomib-based regimes from around 2012, while lenalidomide-

based treatment increased in recent years. Median relative survival (RS) for patients ≥75 years in Denmark increased from 25 months to 36 months for patients diagnosed 2005-2007 and 2015-2016, respectively. Similarly, in Sweden the median RS increased from 24 months to 42 months for patients ≥75 years diagnosed 2008-2009 and 2016-2017, respectively. **Conclusion:** The real-world MM population is older and has a higher proportion of patients with ISS III disease than patients included in the pivotal RCTs, and compared to the younger patient cohort. Future studies in MM patients should take this into account.

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A single centre retrospective analysis on the ability to identify transplant-ineligible patients with Multiple Myeloma (MM) who are not likely to benefit from new standard therapies

Massimo Offidani[1], Sonia Morè[2], Laura Corvatta[3], Valentina Maria Manieri[1], Attilio Olivieri[1]

[1]AOU Ospedali Riuniti di Ancona, Ancona, Italy; European Myeloma Network, Italy; [2]Clinica di Ematologia, AOU Ospedali Riuniti di Ancona, Ancona, Italy; [3]UOC Medicina Fabriano, Italy

Background: Daratumumab has recently become the cornerstone of initial therapy of patients not eligible for autologous stem cell transplantation (NTE) after phase III trials assessed the efficacy of D-VMP vs VPM (ALCYONE) and DRd vs Rd (MAIA) in this population. However, it is an expensive drug and has to be administered indefinitely until progression. Moreover, NTE patients, mainly elderly, represent a very heterogeneous group, particularly in term of frailty status affecting compliance to treatment, toxicities and early mortality (EM) (death within 6 months). Due to all these reasons, it would be extremely important to identify patients who may not benefit from new standard but high-cost regimens. **Method:** In this analysis we considered NTE MM patients recorded in our database from 2010 to 2020 and we retrospectively calculated simplified frailty scores, proposed by Facon et al (Leukemia 2000) using data from FIRST trial and based on age, ECOG PS and CCI with the aim to evaluate its applicability in a real-world setting. Secondly, using logistic analysis and Cox regression analysis we tried to search factors affecting EM to increase discriminating power of Facon score. **Results:** Overall, 189 patients, among whom 44 (23%) older than 80 years, were included in the analysis. As regard disease characteristics, R-ISS stage 2-3 was detected in 81% and renal failure in 23% of patients. Forty percent of patients had CCI >1 and 33% PS ≥2. As induction therapies all patients were given IMiDs- and PIs-based regimes and EM occurred in 23 (12.2%). Overall, 132 patients (70%) were classified as frail and 57 (30%) non-frail as per Facon scale, being EM 12% and 0, respectively (p=0.02), a value comparable with published data. Exploring all potential variables affecting EM to improve the predictive value of Facon score, binary logistic analysis selected CCI>1, PS ≥2 and albumin level ≤ 3g/dL whereas age was not found a factor affecting EM. Using albumin level ≤3 g/dL instead of age > 80, present in the Facon scale, the new score was able to stratify patients in frail (score 3-5, n= 55, 29.5%) and non-frail (score 0-2, n=155, 70.5%). Although univariate Cox analysis found CCI>1, PS ≥2, albumin level ≤3 g/d, Facon frailty score and our new frailty score as factors significantly affecting EM, stepwise regression analysis selected only our score with which EM resulted 23% in frail and 6% in non-frail patients (p=0.002). **Conclusion:** As the number of effective and costly therapies is increasing, it is mandatory to identify patients at highest risk of EM who may not benefit from any treatment. Our analysis suggests that, overestimating the number of frail patients in the real life setting, simplified frailty score by Facon et al not allows to identify true frail individuals. This score could be improved using simple parameter as albumin level so as to increase the ability to detect patients with the highest risk of EM, to personalize treatments and to save cost of treatments in NTE MM patients.

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Outcome of non-transplant eligible patients with newly diagnosed multiple myeloma depending on the eligibility for clinical trials: a single institution experience

Natalia Tovar[1], Luis Gerardo Rodríguez-Lobato[1], Raquel Jiménez[1], Daniel Esteban[1], Ana Triguero[1], MT Cibeira[2], C Fernández De Larrea[2], Laura Rosiñol[2], Arturo Pereira[1], J Bladé[2]

[1]Hospital Clinic de Barcelona; [2]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain

Background: Patient participation in clinical trials forms the backbone of cancer clinical research as they represent a key step in the development of new treatment strategies to improve the outcome of incurable diseases such as multiple myeloma (MM). Although the results obtained from them will determine the future therapeutic approaches due to several reasons, the vast majority of patients with MM do not participate in clinical trials. **Methods:** To determine the reasons they were or weren't recruited into prospective clinical trials and evaluate their outcome in one group or the other, we retrospectively reviewed from our database all consecutive patients with newly diagnosed MM, non-candidate to autologous stem cell transplantation, who received first line treatment at our institution from 2003 to 2017. We thoroughly reviewed their characteristics and their outcome after first line treatment only. We analyzed the reasons why they were or not included in a trial and compared the outcome of those included in a clinical trial versus those who did not meet the eligibility criteria and who received standard therapy. Patients who didn't have a clinical trial available at the time of diagnosis were excluded from the analysis. **Results:** Between January 2003 and December 2017 we analyzed 211 patients diagnosed and treated at our institution; 105 entered a clinical trial and 106 did not meet the eligibility criteria. The causes for not entering in a clinical trial were as: 1) Didn't fulfill inclusion criteria due to comorbidities (26.7%), other previous malignancies (16.2%) or renal insufficiency (13.3%); 2) Didn't have measurable disease (1.9%); 3) The urgency to start

treatment didn't allow the delay of a screening period (8.6%); 4) Very advanced age (10.5%), cognitive impairment (1.9%) or performance status (4.85%); 5) Patient refusal (10.5%). Finally 1.9% were screen failures and 3.8% did not participate for unknown reasons. Patients included in clinical trials were significantly younger (median 71 vs. 78 p<0.001) and had better ECOG (0/1 78.4% vs. 35.6 p<0.001). No differences regarding immunological subtype or bone marrow plasma cells infiltration were found. ISS stage was slightly lower in the clinical trial group although not statistically significant. The ORR was 79 vs.46 p<0.001 and the CR rate was 17% vs. 3% p<0.001 both significantly higher in the clinical trial group. Patients included in clinical trial had a significantly longer OS than those who were not (median 62.5 vs.31.8 p<0.001). **Conclusion:** Patients included in clinical trials have a significantly higher response rate and OS than those who do not meet the eligibility criteria. Only half of the elderly patients at our institution fulfill the inclusion criteria to enter a clinical trial. This questions the extrapolation of the results of clinical studies to broader populations.

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Transplant related morbidities with Melphalan as conditioning regimen for myeloma autotransplants

Joel Andrews[1], Charise Gleason[1], Madhav V. Dhodapkar[2], Sagar Lonial[1], Jonathan Kaufman[3], Ajay Nooka[4]

[1]Winship Cancer Institute of Emory University; [2]Emory University School of Medicine; [3]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Emory University Hospital/Winship Cancer Institute, Atlanta, GA, USA

Background: Melphalan as high dose therapy (HDT) is a proven effective conditioning regimen for patients undergoing myeloma autotransplants and is associated with known peri-transplant toxicities that warrant a discussion with patients. Efforts to optimize supportive care have resulted in significant decline in transplant related morbidities and mortality. In this context, we have reviewed the observed toxicities among patients receiving autotransplants in the recent years with an intent to deliver consistency in informing patients of the known toxicities. **Methods:** We conducted a retrospective analysis of myeloma patients undergoing autologous stem cell transplant over a two-year period. Demographic and outcomes data for the patients were obtained from our IRB approved myeloma database and responses were evaluated per IMWG Uniform Response Criteria. Fisher's exact and Cochran-Mante-Haenszel tests were used when groups were compared. **Results:** Of the 395 patients that underwent autotransplants 308 patients received a dose of 200 mg/m2 (Mel200) and 87 received 140 mg/m2 (Mel140). Median age of the patients was 62 years (range, 17-78). Impressively, African American patients comprised of 41.5% of the entire cohort. Relevant comorbidities prior to transplant include hypertension (62%), renal failure (5%), coronary artery disease (5%) and h/o atrial fibrillation (4%). 11% of patients had KPS ≤70, median pretransplant EF was 55% (30-86%), and DLCO corrected was 87% (30-156). Median time for neutrophil engraftment, platelet engraftment and LOS were 14 (12-24), 14 (11-21), 15 (7-53) days respectively. While peri-transplant, neutropenic fevers were seen in 67% of the patients, majority were of non-infectious nature. Documented bacteremia was seen in 13% of patients, clostridium difficile infection in 8%, respiratory infections in 5%, and other infections were seen in 2% (cellulitis- 1% and UTI -1%). Any grade mucositis was seen in 31% and grade 3 mucositis in 7%. Atrial fibrillation was seen in 5% and renal failure in 4%. Readmission rates were 5%, median time to readmission was 4 days (range, 1-20). Transplant related mortality at the 30-day mark was 0.25% (1 incident due to a intracranial aneurysm rupture) and at 100-day mark was 0.75% (1 death due to septic shock and 1 due to cardiac failure). Unfortunately, 2 patients succumbed to aggressive myeloma during the same period. **Conclusion:** While we are able to offer HDT to patients with advanced age, cardiac toxicities and renal insufficiency, an explicit conversation regarding known peri-transplant toxicities is necessary to make an informed decision. Very interestingly, 93% of this cohort received risk-adapted maintenance initiating at a median time of 105 days from autotransplants, a surrogate to suggest adequate recovery from transplant related morbidities. Outcomes regarding AA patients and additional progression free and overall survival data by cytogenetic risk will be presented at the meeting.

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Multistate models provide complementary insights into outcomes for patients treated in the UK NCRI Myeloma XI randomised trial

Zoe Craig[1], Christopher Parrish[2], Martin Kaiser[3], Charlotte Pawlyn[3], Catherine Oliver[1], John Jones[3], Mark Drayson[4], Roger Owen[5], Matthew Jenner[6], Gordon Cook[7], Walter Gregory[1], Faith Davies[8], Gareth Morgan[8], David Cairns[1], Graham Jackson[9]

[1]Leeds Institute of Clinical Trials Research, University of Leeds; [2]Leeds Teaching Hospitals NHS Trust; [3]The Institute of Cancer Research; [4]Institute of Immunology and Immunotherapy, University of Birmingham, Edgbaston, Birmingham, UK; [5]St James' Institute of Oncology; [6]Southampton University Hospital, UK; [7]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK; [8]The Myeloma Institute, Institute of Clinical Trials Research, University of Leeds; [9]Newcastle Hospitals NHS Trust

Background: Multistate models (MSMs) are an alternative to traditional survival analysis methods. MSMs describe the life history of an individual who at any time can be in any one of the states specified within the model. MSMs allow multiple events to be modelled simultaneously and patient prognosis can be predicted based on treatment and prognostic factors, offering benefit over traditional survival analysis methods. **Method:** In the NCRI Myeloma XI trial, newly diagnosed myeloma patients eligible for ASCT (TE) were randomised to induction therapy with CTD (cyclophosphamide, thalidomide and dexamethasone) or CRD (C, lenalidomide, D). Further randomisations occurred following induction as described elsewhere. Co-primary endpoints were

progression-free survival (PFS) and overall survival (OS). An MSM was used for an exploratory analysis of 2042 TE patients. Patients transitioned between 3 irreversible states (alive and progression-free (PF) ®[ED] alive with progressive disease (PD), alive and PF ®[ED] died, and alive with PD ®[ED] died). Key prognostic factors were combined to define low (ISS1 & 0 cytogenetic abnormalities), medium (ISS2 & 1 abnormality) and high (ISS3 & 2+ abnormalities) risk groups. **Results:** MSM analysis found CRD was associated with a reduced risk of PD vs CTD (hazard ratio (HR) 0.86; 95% confidence interval (CI) 0.77-0.96). This reflects the primary analysis of the trial, by Cox regression, where CRD was associated with significantly longer PFS vs CTD (median 36 vs 33 months; HR 0.85; 95% CI 0.75-0.96). The MSM also showed that patients randomised to CRD had a 51% (95%CI 48-54%) chance of being alive and PF at 3 years post-randomisation vs 46% (95%CI 43-49%) for CTD. Primary trial analysis found that CRD was also associated with significantly longer OS vs CTD (3-year OS 82.9% vs 77.0%; HR 0.77; 95%CI 0.63-0.93). However, the MSM found CRD was not significantly associated with reduced risk of death following PD (HR 0.89; 95%CI 0.76-1.05) or death without PD (HR 0.89; 95%CI 0.63-1.27). This suggests the main treatment benefit is occurring prior to PD. Patients in the high-risk group had the poorest prognosis, regardless of treatment, with a 17% (95%CI 11-23%) chance of being alive and PF at 3-years, vs 57% (95%CI 53-61%) and 45% (95%CI 39-51%) in low and medium risk groups. Furthermore, high-risk patients had a 45% (95%CI 33-57%) chance of death following PD at 3 years-post randomisation, vs 9% (95%CI 7-11%) and 17% (95%CI 11-23%) for low and medium risk patients. These factors strongly influence the expected duration for patients in the alive and PF state (low, 55m; medium, 43m; high 23m), but have a less dramatic effect on duration in the alive with PD state (28m, 26m and 19m). **Conclusion:** MSMs can explore the myeloma disease pathway and identify transitions most associated with treatment and prognostic factors. Moreover, they provide interpretable estimates for the probability of PD and death for any treatment/prognostic factors combination at any point in the disease course.

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Daratumumab (Dara), Cyclophosphamide, Thalidomide and Dexamethasone: a quadruplet intensified treatment for transplant eligible newly diagnosed Multiple Myeloma (TE NDMM) patients final results

Edvan Crusoe[1], Juliana santos[2], JOanna Leal[3], Herbert Santos[4], Allan santos[4], Alessandro Almeida[5], Mariane Santos[4], Larissa Lucas[3], Sarah Queiroz[3], Cleverson Fonseca[6], Elisangela Adorno[6], Lucas Vieira[7], Vania Hungria[8], Marco Salvino[9], Maria da Gloria Arruda[9]

[1]Rede D'or Oncologia and Federal University of Bahia; [2]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil and Federal University of Bahia; [3]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil; [4]Federal University of Bahia- Cytometry and Immunology laboratory; [5]Federal University of Bahia; [6]Federal University of Bahia- Pharmacy School; [7]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil - HOspital Sao Rafael; [8]Department of Hematology and Oncology, Clínica São Germano, São Paulo, Brazil; [9]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Federal University of Bahia; [15]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil

Background: Newly drugs access for MM treatment still a challenge. One of the available inductions for TE NDMM patients (pts) worldwide is cyclophosphamide (C), thalidomide (T) and dexamethasone (d)- (CTd). We hypothesized that the Daratumumab and CTd combo could be safe and allow deeper activity as an alternative protocol. Primary endpoint was to evaluate the VGPR after two consolidation cycles post-ASCT. Secondary endpoints were the ORR during all treatment phases and MRD, based on the IMWG criteria that includes the NGF by the EuroFlow® and PET-CT and the safety profile. **Method:** This is a phase II, open-label single-center clinical trial. The main inclusion criteria were: TE NDMM, CrCl > 30 ml/min, normal cardiac, renal and liver function and the ECOG performance status = 0 - 2. The protocol was Dara-CTd for up to four 28-day induction cycles: C-500mg PO on days 1,8 and 15, T at 100-200mg PO on days 1 to 28, (d) at 40mg PO on days 1,8,15 and 22 and Dara at 16mg/Kg/dose IV- QW during cycles 1 - 2 and every other week in cycles 3 – 4, followed by ASCT. All pts received up to four 28-day consolidation cycles that was started at D+30 after ASCT: Dara and (d) at 40mg every other week, associated with T at 100mg PO on days 1 - 28. Dara was used monthly as maintenance until progression or limiting toxicity. G-CSF was used for stem cell (SC) mobilization and plerixafor if needed. All pts received anti(viral, pneumocystis and thrombotic) prophylaxis. **Results:** A total of 21 pts were included, the median age being 56 (range 37 – 67 years), 19 (90%) were non-white, 3 (14%) had an R-ISS = 1, 12 (57%) had an R-ISS = 2 and 3 (14%), an R-ISS = 3. Five (24%) pts had HR [del17p, t(4;14) or t(14;16)]. To date, all pts have completed induction, 19 have received transplant and 17 have completed D+90 post-transplant assessment. No SC mobilization failure was observed, and five (26%) pts needed plerixafor use. In an ITT analysis, after the end of induction (cycle 4), 19 (90%) of the pts obtained > PR and 8 (38%) obtained >VGPR, including three MRD negativity by NGF. 17 pts have completed two consolidation cycles after transplant and 94% obtained > VGPR, 12 (70%) obtained MRD negativity by NGF and nine (53%) had negative PET-CT. Seven (41%) pts had both flow and PET-CT negativity. Three pts died from infection, one before transplant because of Covid, one on post-transplant, considered not related to the investigational agent, and another after consolidation, related to the investigational agent. The most common nonhematological AEs grades 3 and 4 before ASCT were neuropathy (n = 6), infusion reaction (n = 7), infection (n = 2), hypertension (n = 1) and rash (n = 1). **Conclusion:** This is the first study that combined Dara with CTd as induction for TE NDMM pts. This present data has shown that the association of Dara-CTd achieved the primary end point once > 90% of the pts

achieved VGPR after two consolidations cycles, and safety profile was acceptable. **Clinical trial information:** NCT03792620.

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Impact of Daratumumab (DARA) administration during transplant-eligible newly diagnosed Multiple Myeloma (TE NDMM) induction on stem cell (SC) mobilization count and post-transplant engraftment

Edvan Crusoe[1], Alessandro Almeida[2], Marcos Chaves[2], Marco Salvino[3], Jamile Nicanor[2], JOanna Leal[4], Herbert Santos[5], Allan Santos[5], Victor Guimaraes[2], Daniela Dourado[2], Larissa Lucas[4], Mariane Santos[5], Juliana santos[6], Maria da Gloria Arruda[7]

[1]Rede D'or Oncologia and Federal University of Bahia; [2]Federal University of Bahia; [3]Federal University of Bahia and IDOR-Instituto D'or Oncologia; [4]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil; [5]Federal University of Bahia- Cytometry and Immunology laboratory; [6]Instituto D'or de pesquisa e ensino (IDOR), Salvador, Brazil and Clinica CEHON, Salvador, Brazil and Federal University of Bahia; [7]Hematology, Instituto D'or de pesquisa e ensino (IDOR), Clinica CEHON

In the MAX Dara study, Dara-CTd was used sequentially close to the pre- and post-ASCT (D-30 and D + 30), in order to take advantage of the Dara as an in vivo purge. However, dara could interfer in the SC collection and bone marrow engraftment. In this analysis, we examine the impact of the number of Dara doses administered pre-mobilization on CD34 cell count, SC apheresis yield, and post-ASCT engraftment. This is a phase II, open-label single-center clinical trial. The original protocol was Dara-CTd for up to four 28- day induction cycles and Dara-Td for up to four 28 days consolidation cycles. C-1500mg PO per cycle, during cycles 1 to 4, T at 100-200mg PO on days 1 to 28, during cycles 1-8, (d) at 160mg PO per cycle, during cycles 1 - 8 and Dara at 16mg/Kg/dose IV QW during cycles 1 - 2 and QOW in cycles 3 – 8. Because of the COVID pandemic we had to adapted the protocol and moving 5-6 consolidation cycles to be used as induction, increasing the total dose of Dara from 12 to 16 and the number of cycles from 4 to 6 before ASCT. G-CSF was administered alone for SC mobilization and plerixafor added based on day 4 preharvest PB CD34 counts. The target of SC collection was (>2,5×10^6/kg). PMN and platelet engraftment post-ASCT was defined as the first day with sustained PMN count >1000×10^6/L and independence from platelet transfusion in the preceding 7 days with a count >20×10^9/L, respectively. From a total of 21 included pts, 19 pts completed mobilization. 12 pts received 12 and 7 pts received 16 induction Dara doses, respectively. The median number (range) of days between the last dose of Dara infusion and SC harvest was 23 (16-63) days. A total of five (26%) pts received plerixafor during mobilization. More pts from Dara 16 doses needed plerixafor comparing with Dara 12 doses (42% vs 16%), but without statistic difference. Pts underwent a median (range) of 1 (1-2) days of apheresis. The median number of CD34+ cells collected in the total group was 3.94×10^6/kg, and no difference was found between Dara 12 vs 16 doses (3.61×10^6/kg vs 4.01×10^6/kg), p=0.27. There was no difference in the number of SC collected considering the response rate after induction > or or 1000 cells/mm^3, and a median (range) of 12.0 (9-14) vs 11.0 (8-16) days was required to achieve sustained platelets >20,000 cells/mm^3 without transfusion, respectively. In summary, SC mobilization was feasible with Dara-CTd induction. Despite the more doses of Dara use before mobilization increases the need of plerixafor use, the SC number difference was not significant comparing Dara 12 vs 16 doses (p=0.3). The infusion of Dara close to harvest didn't interfere with SC collection. Adding DARA to CTd allowed successful transplantation in pts with TENDMM.

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Clinical study of bortezomib-based regimens of BCD, PAD and VDD for newly diagnosed multiple myeloma – an analysis of 400 cases in a single center of China

Shuhui Deng[1], Yan Xu[1], Weiwei Sui[1], Dehui Zou[1], Gang An[2], Lugui Qiu[3]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; [2]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [3]Institute of Hematology and Blood Diseases Hospital

Background: Objective To investigate the clinical efficacy and safety of bortezomib-based regimens of BCD (bortezomib, cyclophosphamide and dexamethasone), PAD (bortezomib, doxorubicin and dexamethasone) and VDD (bortezomib, pegylated liposomal doxorubicin and dexamethasone). **Methods:** 400 newly diagnosed multiple myeloma (MM) patients enrolled in two prospective non-randomized cohort studies in a single center were retrospectively analyzed from April 2008 to August 2017. **Results:** Among all the patients, 194 cases (48.5%) received BCD, 84 cases (21.0%) received PAD, and 122 cases (30.5%) received VDD. 1) Analysis of clinical features: Serum albumin (ALB) level was lower in the BCD group than the other two (P<0.001), and the proportion of patients in the International Stage System (ISS) stage III was higher in the BCD and VDD groups than the PAD group (P=0.002). Patients younger than 65 years were much more in the PAD group than the other two. Correspondingly, the proportion of patients receiving autologous hematopoietic stem cell transplantation (ASCT) was significantly higher in the PAD group. 2) The overall response rates (ORR) of the patients in BCD, PAD and VDD groups were 87.5%, 83.6% and 83.0% respectively, and there was no significant difference between the three groups. More patients attained complete response (CR) in the VDD group than the other two (P=0.049).The rate of minimal residual disease (MRD) negativity was slightly higher

(60%) in PAD group which may be related to the higher ASCT proportion in this group, but the difference was not statistically significant (P=0.272). 3) Whether combined with alkylating agents (BCD) or combined with anthracyclines (PAD and VDD), there was no significant difference of the median progression-free survival (PFS) and the median overall survival (OS). Also there was no significant difference in PFS and OS between BCD, PAD and VDD groups. 4) In the safety aspect, there was no significant difference in non-hematologic toxicities such as peripheral neuropathies, cardiac events, gastrointestinal reactions, thrombus and bleeding events between the three groups. The incidence of hand-foot syndrome in VDD group was 5.8%, all of which were grade 1/2. In terms of hematologic toxicity, the incidence of grade 3/4 neutropenia and thrombocytopenia was significantly higher in the PAD group than the other two groups. There was no significant difference between the BCD and VDD group. **Conclusion:** As the bortezomib-based three-drug regimens combined with traditional chemotherapeutic agents, BCD, PAD and VDD can all achieve remission in more than 80% newly diagnosed MM patients as induction therapy. The efficacy and long-term outcomes are comparable between the three regimens. In the aspects of safety, the BCD and VDD groups had a lower risk of grade 3/4 hematological toxicity.

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Outcomes of autologous-allogeneic vs autologous tandem approach followed by thalidomide maintenance for transplant-eligible patients with newly diagnosed multiple myeloma: a prospective phase II-study

Nico Gagelmann[1], Ute Hegenbart[2], Matthias Stelljes[3], Martin Kaufmann[4], Lutz Müller[5], Arnold Ganser[6], Christoph Schmid[7], Guido Kobbe[8], Eva Wagner[9], Martin Bornhäuser[10], Michael Kiehl[11], Gerald Wulf[12], Wolfgang Bethge[13], Andreas Burchert[14], Dominik Wolf[15], Thomas Heinicke[14], Marion Heinzelmann[1], Christine Wolschke[1], Andreas Völp[16], Stefan Schönland[17], Nicolaus Kröger[1]

[1]University Medical Center Hamburg-Eppendorf; [2]2University Hospital Heidelberg, Heidelberg, Germany; [3]University Hospital Münster, Münster, Germany; [4]Robert Bosch Hospital, Stuttgart, Germany; [5]University Hospital Halle, Halle, Germany; [6]Medical School Hannover, Hannover, Germany; [7]University Hospital Augsburg, Augsburg, Germany; [8]University Hospital Düsseldorf, Düsseldorf, Germany; [9]University Hospital Mainz, Mainz, Germany; [10]University Hospital Dresden, Dresden, Germany; [11]Hospital Frankfurt/Oder, Frankfurt/Oder, Germany; [12]University Hospital Göttingen, Göttingen, Germany; [13]13University Hospital Tübingen, Tübingen, Germany; [14]University Hospital Marburg, Marburg, Germany; [15]University Hospital Innsbruck, Innsbruck, Austria; [16]psy consult scientific services; [17]Universitätsklinikum Heidelberg Medizinische Klinik V

Background: The aim of this phase 2 study (NCT00777998) was to compare autologous-allogeneic tandem stem cell transplantation (auto-allo) and tandem autologous transplantation (auto-auto), both followed by maintenance therapy in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). **Methods:** Between 2008 and 2014 a total of 210 MM patients ≤60 years of age were included from 23 German Centers within an open-label, parallel-group, multicenter clinical trial to investigate whether auto-allo versus auto-auto followed by a 2-year maintenance therapy with thalidomide (100mg/daily), respectively, has benefit on outcome. Patients received autologous peripheral blood stem cell transplantation followed by allogeneic transplant when a matched related or unrelated donor would be available; otherwise, or if they declined allogeneic transplant, they received two autologous transplants. The primary endpoints were 4-year progression-free survival (PFS) and overall survival (OS). **Results:** 178 patients underwent second transplant, of whom auto-allo received 132 and auto-auto 46 patients. The median age was 51 years (range 26-61), respectively. 32 patients in the auto-allo group and 8 patients in the auto-auto group did not receive thalidomide maintenance. The 4-year PFS was 47%(95% CI, 38-55%) for auto-allo and 35% (95% CI, 21-49%) for auto-auto, with median survival times of 40 and of 30 months (P=0.26). The 4-year OS was 66% (95% CI, 57-73%) for auto-allo and 66% (95% CI, 50-78%) for auto-auto (P=0.91). 53 (40%) patients in the auto-allo group and 28 (61%) in the auto-auto group showed progression or relapse of MM. Estimated cumulative incidence of relapse/progression was 40% (95% CI, 33-50%) for auto-allo and 63% (95% CI, 50-79%) for auto-auto (P=0.01). The estimated cumulative incidence of 4-year non-relapse mortality was 13% (95% CI, 8-20%) for auto-allo and 2% (0.3-2) for auto-auto (p=0.04). With long-term follow-up of patients, 8-year PFS was 43% (95% CI, 34-52%) for auto-allo versus 21% (95% CI, 7-35%) for auto-auto (P=0.10). Furthermore, 8-year OS was 55% (95% CI, 45-65%) for auto-allo and 50% (95% CI, 32-68%) for auto-auto (P=0.87). Median OS was not reached in both groups. Multivariate analysis on PFS at last follow-up (median, 8 years) showed a hazard ratio of 0.67 (95% CI, 0.44-1.02; P=0.06) for auto-allo (with auto-auto as reference). Other factors for improved outcome were absence of del(17p) or t(4;14), CR after induction and thalidomide maintenance. Subgroup analysis for patients with present high-risk cytogenetic features including del(17p) or t(4;14) showed a hazard ratio of 0.55 (95% CI, 0.22-1.39; P=0.21) for auto-allo (with auto-auto as reference). **Conclusion:** This prospective phase 2 study of auto-allo transplant versus auto-auto showed reduced rates of MM recurrence or progression. At long-term follow-up, auto-allo appeared to improve PFS, while OS was comparable.

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Effect of induction regimen in survival in newly diagnosed multiple myeloma patients receiving consolidation with autologous stem cell transplantation

David Garrido[1], Alana von Glassenap[2], Camila Peña[3], Humberto Martínez-Cordero[4], Aline Ramírez-Alvarado[5], Luz Tarín-Arzaga[6], Natalia Schütz[7], Virginia Bove[8], Claudia Sossa[9], Sebastián Yantorno[10], Paola Ochoa[11], Sergio Orlando[12], Washington Ladines-Castro[13],

Patricio Duarte[14], Guillermina Remaggi[15], Claudia Shanley[16], Guillermo Ruiz-Argüelles[17], Dorotea Fantl[7], Eloisa Riva[1]

[1]Hospital de Clínicas "Dr. Manuel Quintela"; [2]Instituto de Previsión Social, Asuncion, Paraguay; [3]Hospital Del Salvador, Santiago, Chile; [4]Instituto Nacional de Cancerología ESE de Colombia, Bogotá, Colombia; [5]Centro Médico Nacional La Raza, Instituto Mexicano del Seguro Social, Ciudad de México, Hospital, Mexico; [6]ervicio de Hematología, Hospital Universitario y Facultad de Medicina, UANL, Monterrey, Nuevo León, México.; [7]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. Ariel Corzo. Hospital de Clínicas, Buenos Aires, Argentina.; [8]Hospital Central de las FFAA, Montevideo, Uruguay.; [9]Clinica Carlos Ardila Lulle, Bucaramanga, Colombia; [10]Hospital San Martín de La Plata; [11]Instituto Alexander Fleming, Buenos Aires, Argentina.; [12]Hospital Rossi, La Plata, Argentina; [13]SOLCA – Instituto Oncológico Nacional – Guayaquil; [14]Unidad de trasplante Hematopoyético en CEMIC.; [15]FUNDALEU; [16]Hospital Británico Buenos Aires; [17]Mexico. Clinica Ruiz. Puebla, Mexico

Background: Novel therapies improved the survival of newly diagnosed multiple myeloma patients (NDMM) during the last decades. Nevertheless, autologous stem cell transplantation (ASCT) remains a standard consolidation strategy. How induction therapy affects the outcomes in NDMM patients receiving consolidation with ASCT has not been explored in our region. **Objective:** To analyze the impact of different induction therapies in NDMM patients receiving consolidation with ASCT in overall survival (OS) and progression-free survival (PFS). **Method:** This is a retrospective survival analysis study based on the Grupo de Estudio Latinoamericano de Mieloma Múltiple (GELAMM) registry. We included adults patients with NDMM who received ASCT as frontline consolidation therapy from 6 countries. The induction regimens compared were VCD (Bortezomib, cyclophosphamide, dexamethasone), VTD (Bortezomib, thalidomide, dexamethasone), CTD (Cyclophosphamide, thalidomide, dexamethasone), or VRD (Bortezomib, lenalidomide, dexamethasone). OS and PFS were defined as the time from MM diagnosis until the death/last control or disease progression, respectively. We used SPSSv.25 for statistical analysis. Survival was analyzed using the Kaplan-Meier model with Log-rank test. **Results:** Five hundred eighty-five patients were included, with a median age at diagnosis of 55 years (IQR 10), 54% males, 58.6% IgG, 17.8% IgA, 17.8% Light Chain, and 5.8% other subtype. Risk stratification at diagnosis (n=534) showed 30.7% ISS-I, 34.3% ISS-II, and 35% ISS-III. Two-thirds (66.8%) received maintenance therapy. Induction regimen were 55% VCD, 25% VTD, 16.1% CTD, and 3.9% VRD. The proportion of patients by ISS group was similar among all the regimens (p=0.97). Also, the median age was equivalent among the groups included (p=0.23). At end of induction, the rate of very good partial response or better was 51.3% VCD, 56.7% VTD, 48.9% CTD, and 85% VRD. The 5-year OS for the whole group was 82.7%, and the 5-year OS per induction regimen were 82.9% VCD, 83.6% VTD, 80.1% CTD, and 89.5% VRD (Log-Rank, p=0.70). The median OS was not reached in any of the induction regimens. The 5-year PFS (n=368) for the whole group was 27%, and the 5-year PFS per induction regimen were 27.4% VCD, 20.3% VTD, 30% CTD, and 74% VRD (Log-Rank, p=0.23). The median PFS was 42 months for both VCD and VTD, 48 months for CTD, and not reached for VRD. Maintenance therapy was associated with a 5-year OS of 86.60% vs. 80.60% (p>0.05) for patients not receiving maintenance. The 5-years PFS was 30.3% for maintenance vs. 21.2% (p>0.05) in non maintenance. **Conclusions:** in this real-world cohort, VRD as induction therapy was associated with deeper response rates and longer PFS and OS. Regardless of the frontline therapy, ASCT achieves a long PFS and OS in NDMM. There is a trend for longer PFS and OS in patients receiving maintenance. Larger number of patients may be needed to allow more robust conclusions.

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Predictive factors for severe infections and early death during novel agent-based induction therapy in newly diagnosed, transplant-eligible myeloma: a multicohort analysis from phase III trials

Elias Mai[1], Thomas Hielscher[2], Uta Bertsch[1], Hans J. Salwender[3], Markus Munder[4], Peter Brossart[5], Igor W. Blau[6], Marc Raab[7], Jan Duerig[8], Nicola Giesen[1], Britta Besemer[9], Roland Fenk[10], Mohammed Wattad[12], Mathias Haenel[13], Ivana von Metzler[14], Ullrich Graeven[15], Christoph Scheid[15], Katja Weisel[16], Hartmut Goldschmidt[17]

[1]Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany; [2]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Tumorzentrum Asklepios Hamburg, AK Altona and AK St. Georg, Hamburg, Germany; [4]Department of Internal Medicine III, University Medical Center Mainz, Mainz, Germany; [5]University Hospital Bonn, Bonn, Germany; [6]Medical Clinic, Charité University Medicine Berlin, Berlin, Germany; [7]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/ Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [8]Department of Hematology, University Clinic Essen, Essen, Germany; [9]Department of Hematology, Oncology and Immunology, University Hospital Tübingen, Tübingen, Germany; [10]Department of Hematology, Oncology and Clinical Immunology, University Hospital Düsseldorf, Düsseldorf, Germany; [12]Klinik für Hämatologie, Onkologie, Palliativmedizin, Stammzelltransplantation, Klinikum Hochsauerland GmbH, Meschede, Germany; [13]Department of Internal Medicine III, Klinikum Chemnitz, Chemnitz, Germany; [14]5 of Internal Medicine I, Hospital Maria Hilf GmbH, Mönchengladbach, Germany; [15]Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany; [16]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [17]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT)

Background: At initial diagnosis of multiple myeloma (MM), about 25% of patients develop severe infections and up to 10% decease during induction therapy (IT) due to immunosuppression from MM and antineoplastic therapy3. The present analysis aims at characterization and identification of predictive factors for severe infections (SI) and deaths during IT. **Methods:** Between 07/2005 and 01/2018, 1333 patients from three subsequent multicenter phase III trials, HD4, MM5 and HD6 from the German-speaking Myeloma Multicenter Group (GMMG), received a novel agent-based IT with either bortezomib (BTZ) / doxorubicine / dexamethasone (DEX; PAD: n=192, HD4; PAd: n=296, MM5), BTZ / cyclophosphamide / DEX (VCD: n=300, MM5), BTZ / lenalidomide / DEX (VRD: n=272, HD6) or elotuzumab / VRD (ELO-VRD: n=273, HD6). SI were defined as any infection ≥ grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE). Uni- and multivariate logistic regression models were used to assess predictive factors accounting for trial effects. **Results:** SI occurred in HD4-PAD: 27.1%, MM5-PAd: 10.8%, MM5-VCD: 9.3%, HD6-VRD: 7.3% and HD6-ELO-VRD: 9.9% of patients (overall rate of severe infections of 11.9%). Death from any cause occurred overall in 1.8% (n=24) of patients during IT with 62.5% (n=15) of deaths being infection-related. Multivariate analyses identified three major factors, besides trial effects, to predict an increasing risk for SI during IT: age >60 years (odds ratio, OR=1.81,p<0.001), International Staging System (ISS) stage III (OR=1.79,p<0.016) and low platelets (<150/nl; OR=2.07,p<0.001) at initial diagnosis. An additive score based on these three factors (one risk factor=one point) was built and included n=559, n=559 and n=203 patients with a score of 0, 1 and ≥2 points, respectively. A higher score gradually predicted an increasing risk for both, SI and early death during IT: 0 points: 7.9% / 0.9%, 1 point: 11.8% / 1.8% and ≥2 points: 22.2% / 4.4%. **Conclusions:** Our present analysis highlights the association between SI and early deaths in newly diagnosed MM treated with novel agent-based IT. Our proposed easy-to-use scoring system allows the identification of a subgroup of patients at high risk for SI and early death during IT in clinical routine. This enables close monitoring of patients at risk and might guide preventive anti-infective strategies in clinical routine and future prospective trials. Validation of the score is being planned.

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Impact of t(11;14) according to induction regimen in newly diagnosed transplant-eligible multiple myeloma patients: long term follow-up of GEM05MENOS65 and GEM2012 PETHEMA/GEM studies

David Moreno[1], A Oriol[2], Javier de la Rubia[3], Miguel Teodoro Hernández[4], Belen Iñigo[5], Luis Palomera[6], Felipe de Arriba[7], Yolanda González[8], Ana Isabel Teruel[9], Miquel Granell[10], Ana López de la Guía[11], Antonia Sampol Mayol[12], Rafael Ríos[13], A Sureda[14], Norma C. Gutierrez[15], María José Calasanz[16], María Luisa Martin Ramos[17], María-Victoria Mateos[18], Jesús F. San-Miguel[19], Juan José Lahuerta[20], J Bladé[21], Laura Rosiñol[21]

[1]Hospital Clinic de Barcelona, IDIBAPS; [2]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol; [3]Hematology Department, University Hospital La Fe, Valencia, Spain; [4]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [5]Hospital Clínico San Carlos, Madrid, Spain; [6]Hospital Clínico Lozano Blesa, Zaragoza, Spain; [7]Hospital Morales Meseguer, IMIB-Arrixaca, Universidad de Murcia, Murcia, Spain; [8]Hospital Universitario Dr Josep Trueta, Girona, Spain; [9]Hospital Clínico Universitario de Valencia, Valencia, Spain; [10]Hospital Sant Pau, Barcelona, Spain; [11]Hospital Universitario La Paz, Madrid, Spain; [12]Hospital Son Espases, Palma de Mallorca, Spain; [13]Hospital Universitario Virgen de las Nieves, Instituto de Investigación Biosanitaria, Granada, Spain; [14]Instituto Catalán de Oncología Hospitalet de Llobregat, Barcelona, Spain; [15]Hospital Universitario de Salamanca Hematología. Instituto de investigación biomédica de Salamanca (IBSAL); [16]Clinica Universidad de Navarra, Centro de Investigacion Medica Aplicada (CIMA), Instituto de Investigacion Sanitaria de Navarra (IDISNA), CIBER-ONC number CB16/12/00369; [17]Hospital Universitario 12 de Octubre; [18]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca; [19]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA; [20]Hospital Universitario 12 de Octubre, Madrid, Spain; [21]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain

Background: t(11;14) is the most frequently IgH rearrengement in newly diagnosed multiple myeloma (NDMM) with a 15-20% prevalence and is considered a standard-risk cytogenetic abnormality (SR). However, t(11;14) is controversial since recent reports describe inferior outcomes in contrast to other SR patients. We analyze the long-term outcome of t(11;14) compared to the remaining SR population in transplant-eligible patients included in GEM05MENOS65 and GEM2012 spanish trials for NDMM. **Methods:** 386 patients included in GEM05MENOS65 trial were randomized to receive induction with 6 cycles of thalidomide and dexamethasone (TD) vs. 6 cycles of VTD vs. 4 cycles of alternating chemotherapy (VBMCP/VBAD) plus 2 cycles of bortezomib (VBMCP/VBAD/B). 458 patients included in GEM2012 trial received induction with 6 cycles of VRD. **Results:** From a total of 414 SR patients, 84 (20%) were positive for t(11;14) and 328 (80%) were SR non-t(11;14). There were no differences in baseline characteristics among groups. In the VBMCP/VBAD/B arm, there were no significant differences in ORR or CR rate after induction between patients with t(11;14) or other SR (ORR 93 vs. 85%, p=0.4; CR 21 vs. 16%, p=0.6). However, patients with t(11;14) treated with VTD had lower ORR and CR rates after induction than SR patients (ORR 85 vs. 97%, p=0.04; CR 15 vs. 38%, p=0.1). Patients with t(11;14) treated with TD had lower ORR and CR rates although the differences were not statistically significant (ORR 63 vs. 78%, p=0.2, CR 5 vs. 11%, p=0.4). In the VRD arm, patients with t(11;14) had similar ORR and CR compared to other SR (ORR 87 vs. 89%, p=0.8; CR 24 vs. 32%, p=0.3). With a median follow-up of 54.2 months, no differences in median PFS were observed in the VBMCP/VBAD/B arm (44 vs. 46 months; p=0.7). However,

shorter PFS was observed in patients with t(11;14) in the TD (30 vs. 46 months; p=0.03) and VTD arms (28 vs. 72 months; p=0.003). With VRD, median PFS was not reached for patients with t(11;14) and SR non-t(11;14) (p=0.8). Among patients with t(11;14), VTD showed shorter median PFS compared to VRD (28 months vs. not reached, p<0.01). Patients with t(11;14) treated in the VBMCP/VBAD/B arm showed shorter median OS than SR patients (66 months vs. not reached; p=0.03). In contrast, median OS was not reached in patients with t(11;14) or SR in neither TD, VTD and VRD arms. **Conclusion:** Thalidomide-based induction regimens (VTD/TD) are suboptimal in patients with t(11;14) concerning response rates and PFS than SR patients, although this does not impact on OS. In contrast, VRD showed similar ORR and PFS in patients with t(11;14) and SR. Despite this is a non-randomized comparison, VRD appears to be more effective than VTD in this subset of patients. Patients with t(11;14) receiving induction with chemotherapy have the same response and PFS than SR patients but display a shorter OS. These results should be confirmed in larger series.

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Immunoparesis remains a negative prognostic factor in newly diagnosed Multiple Myeloma by competing risk analysis

David Moreno[1], Ignacio Isola[1], Raquel Jiménez[2], Aina Oliver Caldés[2], Luis Gerardo Rodríguez-Lobato[2], Natalia Tovar[2], MT Cibeira[3], J Bladé[3], Laura Rosiñol[3], C Fernández De Larrea[3]

[1]Hospital Clinic de Barcelona, IDIBAPS; [2]Hospital Clinic de Barcelona; [3]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain

Background: Recent reports describe worst outcome in patients with multiple myeloma (MM) and immunoparesis (IP). However, infections can be considered a competing event when analyzing the impact of IP on overall survival (OS). Here, we analyzed the prognostic impact of IP in newly diagnosed MM (NDMM) with a different approach. **Methods:** This is a single-center retrospective study of NDMM patients diagnosed between 2000 to 2018. We defined IP as suppression of both uninvolved polyclonal immunoglobulins in IgG and IgA MM or three uninvolved polyclonal immunoglobulins in light-chain MM. **Results:** A total of 651 patients with NDMM were diagnosed and treated at our institution. Median age at diagnosis was 65 years old (56 – 74). The M-protein isotype was IgG in 355 (55%) patients, IgA in 184 (28%), light – chain in 98 (15%) and IgD in 14 (2%). At diagnosis, IP was present in 318 (47%) patients, and increased with each ISS stage (37% in ISS-1, 54% in ISS-2 and 63% in ISS-3; p<0.01). 347 (53%) patients were fit for autologous stem cell transplant (ASCT). With a median follow-up of 5 years, median PFS in patients with IP was shorter compared to those without IP (22 vs. 27 months; p<0.01). Cox univariate analysis for known risk factors of progression showed that high b[ED]2-microglobulin (≥3.5 mg/L, HR 1.4; p<0.01), low serum albumin (< 35 g/L, HR 1.2; p=0.1), high LDH (≥ 450 U/L, HR 1.6; p<0.01) and IP (HR 1.3; p<0.01) had similar negative impact on PFS. Multivariate analysis showed that high b[ED]2-microglobulin, high LDH and IP were the main risk factors with independent negative impact on PFS. Given this data, we aimed to create a prediction model on PFS by two different approaches. The first one consisted of evaluating all possible equations (Stata 16.0. College Station, TX) with AIC and C-Harrell as main criteria, and the second used backward stepwise elimination process. Both resulted in a parsimonious model that contained high b[ED]2-microglobulin, high LDH and IP. At the time of this analysis, 45% patients were still alive. Severe infection as a cause of death was seen in 7% patients. Cox univariate analysis showed that patients with IP at diagnosis had negative impact on OS (HR 1.2; p=0.04). To evaluate the impact of IP on OS, we included severe infections deaths as competing events. With this approach, risk of death among patients with or without IP did not change significantly, maintaining its prognostic value both in eligible and non-eligible patients for ASCT (Peppe and Mori test; p=0.12 and p=0.08 respectively). These results suggest that severe infections do not play a major role in OS of patients with NDMM and IP. **Conclusion:** In patients with NDMM, IP is an important negative biomarker with shorter median PFS. Its prognostic impact was similar to other known potent risk factors of progression. Regarding OS, IP kept its negative impact even in the presence of severe infections deaths as competing events.

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Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in newly diagnosed Multiple Myeloma (NDMM): analysis of vascular thrombotic events (VTEs) in the GRIFFIN study

Douglas Sborov[1], Muhamed Baljevic[2], Brandi Reeves[3], Jacob Laubach[4], Yvonne Efebera[5], Cesar Rodriguez[6], Luciano Costa[7], Ajai Chari[8], Rebecca Silbermann[9], Sarah Holstein[1], Larry D. Anderson, Jr[10], Jonathan Kaufman[11], Nina Shah[12], Huiling Pei[13], Sharmila Patel[14], Annelore Cortoos[14], Blake Bartlett[15], Jessica Vermeulen[16], Thomas Lin[14], Peter Voorhees[17], Paul G. Richardson[4]

[1]Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; [2]Division of Oncology & Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; [3]University of North Carolina – Chapel Hill, Chapel Hill, NC, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]OhioHealth, Columbus OH, USA; [6]Mount Sinai Tisch Cancer Institute; [7]University of Alabama at Birmingham, Birmingham, AL, USA; [8]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [9]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [10]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center; [11]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [12]Department of Medicine, University of California San Francisco; [13]Janssen Research & Development, LLC, Titusville, NJ, USA; [14]Janssen Scientific Affairs, LLC,

Horsham, PA, USA; [15]Janssen Research & Development, LLC, Raritan, NJ, USA; [16]Janssen Research & Development, LLC, Leiden, The Netherlands; [17]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

Background: DARA is approved across lines of therapy for multiple myeloma (MM). The phase 2 GRIFFIN study (NCT02874742) investigated DARA+RVd (D-RVd) in transplant-eligible NDMM; at the primary analysis, D-RVd improved efficacy, and safety was consistent with prior reports for DARA and RVd. We conducted a post-hoc analysis of GRIFFIN to evaluate anti-thrombosis prophylaxis use, in concordance with IMWG guidelines, and the incidence of VTEs, given a historical risk of VTEs with lenalidomide plus dexamethasone occurring in 10-25% of MM patients (pts). **Methods:** Pts with NDMM eligible for autologous stem cell transplant (ASCT) were randomized 1:1 to receive 4 cycles of D-RVd/RVd induction, high-dose therapy, ASCT, 2 cycles of D-RVd/RVd consolidation, and maintenance with DARA-R/R for 24 months. During induction and consolidation (21-day cycles), pts received R (25 mg PO on Days 1-14); V (1.3 mg/m2 SC on Days 1, 4, 8, 11); and d (40 mg QW). DARA (16 mg/kg IV) was given on Days 1, 8, 15 of Cycles 1-4 and Day 1 of Cycles 5-6. During maintenance (Cycles 7-32; 28-day cycles), pts received R (10 mg PO on Days 1-21; if tolerated, 15 mg in Cycles 10+)±DARA (16 mg/kg IV Q8W or Q4W per protocol amendment 2). VTE prophylaxis was recommended for all pts (aspirin, ≥162 mg) with alternative prophylaxis for pts at increased VTE risk, based on medical history. VTEs were identified through standardized MedDRA queries, and treatment group comparisons were by descriptive analyses. **Results:** VTEs occurred in 10% (10/99) of D-RVd pts and 15% (15/102) of RVd pts. Grade 3/4 VTEs occurred in 4% of D-RVd pts and 6% of RVd pts, with grade 3 pulmonary embolism in 1% of D-RVd pts and 4% of RVd pts. The median (range) time to VTE was 379 (6-810) and 232 (21-511) days in the D-RVd and RVd groups, respectively. Anti-thrombosis prophylaxis use was reported in 83% of D-RVd pts and 83% of RVd pts, including heparin derivates in 14% and 19% of pts, respectively (majority of pts on LMWH). Among pts who developed a VTE, 80% (8/10) of D-RVd pts and 93% (14/15) of RVd pts received anti-thrombosis medication, including LMWH in 30% and 27% of pts, respectively. However, only 60% (6/10) of D-RVd pts and 67% (10/15) of RVd pts were on anti-thrombosis prophylaxis at the time of the VTE, including aspirin in 40% and 60% of pts and LMWH in 10% and 7% of pts, respectively. One D-RVd pt received DOAC (rivaroxaban). Bone marrow involvement ≥60% plasma cells was seen in 50% of D-RVd pts and 60% of RVd pts developing VTEs, compared with 43% of all D-RVd pts and 41% of all RVd pts. **Conclusion:** In this descriptive analysis, the use of daratumumab did not increase the VTE rate, and the median time to VTE was longer for D-RVd. Although no formal conclusion can be drawn, these observations indicate additional and larger investigations may be warranted to understand optimal VTE prophylaxis in NDMM pts, as current data show VTE prophylactic therapy adherence may be suboptimal.

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Treatment outcome and prognostic factors of newly diagnosed Multiple Myeloma receiving Bortezomib-based induction in Hong Kong: an analysis of 448 patients

Hoi Ki Karen Tang[1], Chi Yeung Fung[1], Yu Yan Hwang[1], Harold Lee[2], Sze Fai Yip[3], Howard Wong[4], Chi Kuen Lau[5], Kwan Hung Leung[6], Elaine Au[1], Bonnie Kho[4], Eric Tse[1], Joycelyn Sim[1], Yok Lam Kwong[1], Chor Sang Chim[1]

[1]Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong; [2]Department of Medicine, Princess Margaret Hospital, Hong Kong; [3]Department of Medicine, Tuen Mun Hospital, Hong Kong; [4]Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong; [5]Department of Medicine, Tseung Kwan O Hospital, Hong Kong; [6]Department of Medicine, United Christian Hospital, Hong Kong

Background: Autologous stem cell transplant (ASCT) is the standard of care for eligible patients with newly diagnosed multiple myeloma (NDMM). In Hong Kong, NDMM received bortezomib-based triplet induction. NDMM ≤65 years of age were considered transplant-eligible (TE), and >65 years transplant-ineligible (TIE). Therefore, upfront ASCT is offered to all TE patients ≤65 years, unless considered medically unfit (TE-unfit) or ASCT refused (TE-refused). The outcome and risk factors were analysed herein. Data was retrieved from the HKSOM database from 2006 to Jan 2021 for 448 NDMM patients treated with bortezomib-based induction therapy, with bortezomib-based triplet in the majority (n=425; 94.9% were triplets). For the entire cohort, apart from being TIE, additional adverse factors for both event free survival (EFS) and overall survival (OS) male gender, advance ISS, R-ISS stage 3, high LDH, failure of post- induction CR, and high-risk FISH. Multivariate analysis excluding high-risk cytogenetics (incomplete data in many) showed that male gender (p=0.026), advance ISS (p=0.000357), high LDH (p=0.000129), CR induction (p=0.003) and ASCT (p=0.001) were negative predictors for OS. In the TE group, upfront ASCT were conducted in 252 (76.1%). Among the TE patients, ASCT was not performed in 63, due to being medically unfit (TE-unfit) (N=41; 12.4%) or patient refusal (TE-refusal) (N=22; 6.6%). Compared with transplanted MM, failure to undergo ASCT rendered a much inferior OS in TE-unfit and TE-refusal (p=1.03x10-8) and EFS (p=0.000043), with survivals comparable to that of TIE patients (median OS 48 months p=0.576, median EFS 31 months p=0.614). Among TE patients who had undergone ASCT, adverse risk factors for OS and EFS included advance ISS (p=0.000293), RISS stage 3 (p=8.5x10-9) and high LDH (p=0.000019). Multivariate analysis excluding high-risk cytogenetics (incomplete data in many) showed age (p=0.012), ISS (p=0.000353) and high LDH (p=0.002) were adverse predictors OS. Post-induction CR predicted superior EFS (median 83 months vs 45 months p=0.006) but not OS. The presence of high-risk FISH (median OS 131 months vs 86 months p=0.022) negatively impacted on OS despite ASCT. Our data reaffirmed the favourable impact of ASCT. **Conclusion:** Among transplanted patients, adverse risk factors for both OS and EFS

included ISS, LDH, HR FISH and post-induction CR status. Moreover, while ASCT was offered to those MM patients ≤65 years, advanced age remained an adverse risk factor. Importantly, among TE patients, refusal of ASCT rendered an inferior EFS and OS comparable to TIE MM that requires due consideration when providing counselling on ASCT in TE MM.

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Comparison of lenalidomide, bortezomib, dexamethasone vs bortezomib, cyclophosphamide, dexamethasone as an induction regimen in newly diagnosed myeloma patients eligible for intensive chemotherapy

Zoe Van de Wyngaert[1], Florent Malard[1], Zora Marjanovitch[1], Tamim Alsuliman[1], Souhila Ikhlef[1], Mohamad Mohty[1]

[1]*Hématologie clinique et thérapie cellulaire, Hôpital Saint Antoine, APHP, Sorbonne Université, INSERM UMRs 938, Paris, France*

Background: Induction with lenalidomide, bortezomib and dexamethasone (VRD) is a standard of care for newly diagnosed multiple myeloma patients (NDMM). However, lenalidomide might be difficult to manage, for example if acute kidney failure or thromboembolic events are present at diagnosis. In these cases, induction with bortezomib, cyclophosphamide and dexamethasone (VCD), might be more easily manageable. We conducted a retrospective study to assess efficacy of VCD and VRD as induction regimens, in NDMM, eligible for intensive treatment, treated between 2010 and 2020. Overall, 110 patients were treated, 62 received VCD and 48 VRD. Median age was 64 (range, 36-72) years in the VCD group and 59 (33-71) in the VRD group. There was no difference in ISS stage III status [VCD n=21 (34%) vs VRD n=17 (35%), p=.5470], although there were more high-risk cytogenetics patients in the VRD group [VCD n=4 (7%) vs VRD n=10 (16%), p=.248]. Patients received a median number of 4 (3-9) cycles of VCD and 4 (3-8) cycles of VRD. Of note, in the VCD group, 5 (8%) patients switched to VRD, mostly because of renal function improvement. All patients completed the induction phase and underwent high dose melphalan (HDM) at 200 mg/m2: VCD, n=24 and VRD, n=40; or 140 mg/m2: VCD, n=37 and VRD, n=8, and autologous stem cell transplant (ACST). After ACST, 45 (63%) and 32 (67%) patients received consolidation treatment; 9 patients in the VCD group received VRD as consolidation. Among the 5 patients who switched from VCD to VRD, 1 also received VRD consolidation, 1 received RD without bortezomib, and 3 did not received consolidation. Then, 20 (32%) and 34 (71%) received maintenance with lenalidomide in the VCD and VRD group, respectively. Median follow-up was 3.75 years. Overall response rate (ORR) was similar in the two groups, whatever the time point: 98 vs 98% ORR was seen before HDM and ACST, 100 vs 98% after 3 months, 92 vs 93% after 6 months and 73 vs 73% after 1 year, for VCD and VRD groups, respectively. However, faster and deeper responses were achieved with VRD compared to VCD, with VGPR or more achieved in 79 vs 60% patients before ACST, 90 vs 77% after 3 months, 85 vs 77% after 6 months and 73 vs 65% after 1 year, respectively. There were no significant differences in survival data between groups. Progression-free survival was 3.2 years in the VCD group and 4.75 years in the VRD group (p=ns). Overall survival was not reached in the VCD group and 8.9 years in the VRD group (p=ns). **Conclusion:** VRD yielded faster and deeper responses compared to VCD in our series, but this did not translate into significant differences of PFS nor OS. Even if VRD remains the standard induction regimen today for NDMM eligible for ACST, VCD remains a good alternative to VRD, with similar ORR and no significant differences in survival. We believe that these data are relevant and useful for clinicians who deal with multiple myeloma patients in daily practice. Multivariate analysis will be updated for IMW congress.

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Clinical characteristics and outcomes in Multiple Myeloma patients younger than 40 years in a non-Caucasian population.

Jule Vasquez[1], Shirley Quintana[1], Tatiana Vidaurre[1]

[1]*Instituto Nacional de Enfermedades Neoplasicas*

Background: Multiple Myeloma has a median age at diagnosis of 65 years old. The percentage of patients diagnosed under 40 years old is relatively rare (2,2%) (1, 2). Clinical characteristics about this age group of patients was studied mainly in Caucasian population and recently in a Latin-America cooperative group that included Caucasian population. However, there is no data about an only non-Caucasian population. **Objective:** To determine the clinical characteristics, response to treatment and survival. **Methods:** We reviewed the medical records of patients diagnosed with Multiple Myeloma diagnosed at the National Institute of Neoplastic Diseases from 2000 to 2020 in Lima, Peru. Stratification was made based of age group, year of diagnosis and eligibility for hematopoietic stem cell transplant. Tables of relative and accumulative frequency were made. **Results:** Twenty-three patients were analyzed. The median age was 35 years old (range 25-39), and 82% were male. The most frequent monoclonal component type was IgG (60.8%) followed by Ig A and light chain MM (both 17.4%). International Score System (ISS) 3 was the most frequent with 56.5%. Median hemoglobin was 11g/dl (range 4.3-16.3). 59% had anemia. 96% had lytic lesions 70%. LDH elevated was present only in two patients (9.5%). Plasmacytomas were present in 30% of cases. 11 patients (48%) received cyclophosphamide, thalidomide and dexamethasone followed by bortezomib, thalidomide and dexamethasone (26%). The overall response rate was 78%, and complete response was 30%. Nine patients (39%) received high dose therapy and autologous stem cell transplantation. Only 8% received post-transplant consolidation, and 45% received maintenance therapy. After a median of 20-month follow-up (range 1-108) the median progression-free survival (PFS) was not reached. The 5-year PFS was 88.8% (95% CI, 62.07-97.09). The median overall survival (OS) was not reached, and the 5-year OS was not 81.8% (95% CI, 52.69-93.93). **Conclusion:**

Peruvian patients with multiple myeloma younger than 40 years old have some features of high-risk disease as predominance of ISS score 3 and a higher prevalence of plasmacytoma compared to studies in elderly patients. The overall response rate was high, although complete response was low. Less than half of patients underwent autologous stem cell transplantation. Both the PFS and the OS are longer than previous reported in Peruvian patients although the time of follow-up was shorter due to loss to follow-up.

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Regional differences in treatment and outcome for myeloma patients in Sweden: a population based Swedish Myeloma Register study

Göran Wålinder[1], Anna Genell[2], Gunnar Juliusson[3], Ronald Svensson[4], Antonio Santamaria[5], Jacob Crafoord[6], Kristina Carlson[7], Dorota Knut-Bojanowska[8], Ljupco Veskovski[9], Birgitta Lauri[10], Johan Lund[11], Ingemar Turesson[3], Markus Hansson[12], Cecilie Hveding Blimark[12], Hareth Nahi[1]

[1]Karolinska Institutet. Karolinska University hospital.; [2]Regional Cancer Center West; [3]University of Lund; [4]Linköping University hospital; [5]Umeå University hospital; [6]Örebro University hospital; [7]Uppsala University hospital; [8]Uddevalla hospital; [9]Södra Älvsborg hospital; [10]Sunderby Hospital; [11]Karolinska University hospital; [12]Sahlgrenska University hospital

Background: The objective of this study was to investigate if there are differences in survival for Multiple myeloma (MM) patients in Sweden depending on health care region and early use of modern therapies. **Method:** Cohorts (labelled A-F) were defined by the six healthcare regions in Sweden. Modern initial therapies were defined as bortezomib in combination with melphalan, cyclophosphamide or thalidomide or as therapy including lenalidomide, pomalidomide, carfilzomib or daratumumab. Only therapies started within a year from diagnosis were considered. Data from patients with MM in the Swedish Myeloma Register diagnosed during 2008-2017 was used. Overall, 5326 patients with MM were analyzed after 250 patients who did not receive any treatment were excluded. A one year follow up report was required to evaluate treatment. To adjust for time to treatment bias, separate analyses were performed for patients alive 6 months after diagnosis. **Results:** In all treated MM patients, we observed a significant superior overall survival (OS) for region A compared to all other regions ($p<0.01$ for all respectively). After adjusting for time to treatment bias there was also a superior survival for patients with high use of modern initial therapy compared to intermediate and low use ($p<0.01$ for both). Initial modern therapy appeared to increase in regions over time. Age adjusted incidence for region A, B, C, D, E and F was 6.3, 6.1, 6.0, 5.9, 6.4 and 7.3 per 100 000, respectively. Coverage of one-year follow up was less frequent in region A (82.6 %) compared to other regions (95.2-99.2%). In patients treated with autologous stem cell transplantation (ASCT) a significantly superior survival was observed for region A compared to all regions besides region B. When adjusting for time to treatment bias, results were similar. In patients not treated with ASCT, 75 years or older, a superior survival was observed for region A when compared to region B, E and F (log rank $p=0.02$, $p=0.04$, $p=0.02$). After adjusting for time to treatment bias, a difference was noted only between region A and E (log rank $p=0.04$, HR 1.2, CI 1.00-1.44, $p=0.06$). In patients not receiving ASCT younger than 75 years of age we saw no differences in OS. When adjusting for age, ISS stage and time period of diagnosis, a difference remained in survival for patients treated with ASCT when comparing region A vs C, D, E and F ($p=0.01$, $p<0.01$, $p<0.01$, $p=0.03$). In patients not treated with ASCT, 75 years or older, no differences remained between the regions in multivariate analysis. **Conclusion:** In conclusion we observed a superior survival in region A for patients treated with ASCT. Possible explanations may be higher usage of modern initial therapy, different number in cycles of pretreatment or regional residual confounding. In patients not receiving ASCT younger than 75 years of age no difference in survival was observed. For patients not receiving ASCT, 75 years or older the small differences in survival could be adjusted for.

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Impact of the changing landscape of induction therapy prior to autologous stem cell transplantation in 540 myeloma patients: a retrospective real-world study

Song-Yau Wang[1], Tanja Holzhey[1], Simone Heyn[1], Thomas Zehrfeld[2], Susann Fricke[2], Franz Albert Hoffmann[3], Cornelia Becker[3], Leanthe Braunert[3], Thomas Edelmann[3], Inessa Paulenz[4], Markus Hitzschke[5], Franziska Flade[3], Andreas Schwarzer[3], Klaus Fenchel[3], Georg-Nikolaus Franke[1], Vladan Vucinic[1], Madlen Jentzsch[1], Sebastian Schwind[1], Thoralf Lange[6], Dietger Niederwieser[1], Uwe Platzbecker[1], Wolfram Pönisch[1]

[1]University of Leipzig; [2]Krankenhaus Torgau; [3]Gemeinschafspraxis Hämatologie Onkologie; [4]Krankenhaus Dessau; [5]Krankenhaus Borna; [6]Krankenhaus Weib[ED]enfels

Background: High-dose therapy followed by autologous stem cell transplantation (ASCT) is the standard first line treatment for younger patients (pts) (<70 years) with multiple myeloma (MM). However, due to restrictive inclusion and exclusion criteria, more than half of MM pts were excluded from randomized phase 2/3 studies with ASCT. To overcome this and to better reflect clinical practice, we conducted a retrospective study to determine the efficacy and tolerability for all myeloma pts transplanted at the university hospital of Leipzig without trial-specific selection criteria. **Methods:** This analysis included all consecutive pts with newly diagnosed MM who received first line induction therapy followed by high-dose therapy and ASCT between 1996 and 2019. **Results:** 540 pts were enrolled in the study. The median age at diagnosis was 59 (range 29-75) years. In the first period up to 2005, induction therapy consisted mainly of conventional chemotherapies, e.g. vincristine/adriamycin/

dexamethasone (VAD) (n=95). In the following years, the triple-combinations based on bortezomib coupled with anthracycline/dexamethasone (n=29), cyclophposphamide/dexamethasone (n=70) or bendamustine/prednisolone (n=169) became the most popular treatment options. After completion of induction therapy, the ORR in pts treated with VAD was only 66% with a ≥VGPR rate of 14% and ≥CR rate of 2%. The implementation of various bortezomib-containing therapy regimens significantly improved the ORR to 77-86% (p<0.005), with a ≥VGPR rate between 29-41% (p<0.001) and a ≥CR rate between 3-11% (p=0.07). 522 pts (96.7%) responded after the first ASCT with 75 sCR (13.8%), 40 CR (7.4%), 87 nCR (16.1%), 169 VGPR (31.3%) and 151 PR (28.0%). The ORR was no different following initial treatment with VAD (96%) or with bortezomib-containing therapies (97%). TRM was 0.6% (n=3). With the median follow-up of 45 months of the surviving pts, median PFS was 39 and median OS 79 months. Comparing the group of pts treated before 2006 with those treated after 2015, the use of the novel drugs improved the 48-months PFS from 33 to 47% and the 48-months OS from 61 to 85%. **Conclusions:** The introduction post 2005 of modern three-drug induction regimens including bortezomib has improved the prognosis in younger MM pts undergoing first line ASCT. Our real world data in unselected pts also stress the substantial value of ASCT during the first line treatment of younger MM pts.

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Toxicity and survival outcomes of autologous stem cell transplant in Multiple Myeloma patients with renal impairment

Samuel Wang[1], Melinda Tan[2], Nurul Aidah Abdul Halim[2], Cinnie Soekojo[3], Yunxin Chen[2], Wee Joo Chng[3], Chandramouli Nagarajan[2]

[1]Ministry of Health Holdings; [2]Singapore General Hospital Department of Haematology; [3]National University Cancer Institute

Background: High dose therapy followed by autologous stem cell transplant (ASCT) remains a standard of care for eligible patients with multiple myeloma(MM) as it has been shown to deepen responses and prolong progression-free survival (PFS). There is some evidence to support the use of ASCT in patients with renal impairment and is recommended by IMWG for the management of MM in renally impaired patients. Some of the studies however, have shown increased risks associated with ASCT, coupled with somewhat poorer outcomes in this group of patients. Through this multi-centre retrospective study, we demonstrate the feasibility of ASCT in patients with renal impairment (creatinine clearance <60ml/min) and document the safety, PFS and overall survival (OS) of this cohort, in comparison to patients who did not have renal impairment immediately prior to ASCT (CrCl≥60ml/min). **Methods:** Patients with MM who had renal impairment at diagnosis who underwent ASCT between 2010-2018 were identified from the institutional disease registries. They were then stratified into 2 groups – the first cohort had renal impairment at diagnosis and at ASCT while the second cohort had renal impairment at diagnosis but with normal renal function prior to ASCT. The patient characteristics, safety and survival outcomes were collected and the data was analysed using STATA. A total of 50 patients were identified, 38 patients had renal impairment and 12 patients had normal renal function prior to ASCT. There was no difference in the baseline characteristics between both groups, including age, sex, prognostic scores (ISS, R-ISS), first line induction therapy, best response to first line therapy and mean peripheral blood stem cells collected. **Results:** There was increased incidence of grade 3 or 4 neutropenia during ASCT (100% vs 83.3%, p=0.00) in the cohort of patients with renal impairment. However, this did not translate to increased febrile neutropenia episodes (73.7% vs 91.7%, p=0.19), or prolonged admission (20.7 vs 22.7 days, p=0.97). The incidences of serious grade 3 or 4 adverse events such as anaemia, thrombocytopenia, diarrhoea and vomiting were not different between both cohorts. The dose of melphalan used for ASCT was attenuated in patients with renal impairment (133mg VS 197mg, p= 0.02). Despite this difference, the mean number of days taken for neutrophil and platelet engraftment were similar (11.0 vs 12.1 days p=0.02 and 14.1 vs 13.1days, p=0.97 respectively). Overall outcomes also did not differ between patients with renal impairment vs normal renal function, with comparable 3-year PFS (60.5% VS 58.3%, p=0.849) and 3- year OS (78.9% VS 83.3%, p=0.86). **Conclusion:** Taken together, our cohort of patients with renal impairment had comparable toxicity profiles and overall outcomes as compared to patients with normal renal function. As such, ASCT should be considered in patients who present with renal impairment in line with the international recommendations so as to optimise their long-term outcomes.

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Expert elicitation of long-term survival (LTS) for patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with idecabtagene vicleucel (ide-cel, bb2121) in the KarMMa phase 2 trial

Dieter Ayers[1], Shannon Cope[1], Devender S. Dhanda[2], Kevin Towle[1], Ali Mojebi[1], Michel Delforge[3], Paula Rodríguez-Otero[4], Suzanne Trudel[5], Katja Weisel[6], Elena Zamagni[7], Parameswaran Hari[8]

[1]Evidence Synthesis & Decision Modeling, PRECISIONheor, Vancouver, BC, Canada; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]University Hospital Leuven, Leuven, Belgium; [4]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]European Myeloma Network, Italy; [8]Division of Hematology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

Background: Cost-effectiveness analyses (CEA) of new treatments often need LTS extrapolations, but models can lack clinical expert evaluation. A systematic process can integrate expert

opinion (EO) in an unbiased way. In the global multicenter, single-arm phase 2 KarMMa trial (NCT03361748), ide-cel, a B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T cell therapy, showed deep, durable responses in triple-class exposed (TCE) pts with RRMM, with survival data reported up to 12 months (Munshi NC, et al. NEJM 2021;384:705-716). Without EO, predicted LTS varies with the extrapolation model. This study estimated expected survival rates at 3, 5, and 10 years for pts treated with ide-cel, based on integrating observed trial data with EO. **Methods:** This prospective qualitative study incorporated semi-structured interviews, adapted from the Sheffield Elicitation Framework. Oncologists and hematologists with experience in treating pts with RRMM with BCMA-targeted therapies including CAR T cell therapies participated in the elicitation exercise (n=6). Evidence on pts in the KarMMa clinical trial from the Jan 2020 data cut (median follow-up 13.3 months) and conventional care (CC) for TCE pts with RRMM were summarized to give a common baseline data set for EO. In a facilitator-guided web-based application, experts gave upper and lower plausible limits and likely survival values at 3, 5, and 10 years. Experts were given the blinded, individual estimates and collectively gave consensus estimates from a 'rationale impartial observer' perspective. To assess the impact of incorporating EO, separate models were based on observed data with or without EO. Exponential, Weibull, Gompertz, generalized gamma (GG), lognormal, and log-logistic survival distributions were used to assess model fit. Analyses used a Frequentist framework and the Akaike information criterion compared the goodness-of-fit in survival models. This process estimated LTS for CC from the observational studies KarMMa-RW (Jagannath S, et al. JCO 2020;38;8525) and MAMMOTH (Gandhi UH, et al. Leukemia 2019;33:2266-2275). **Results:** The best-fitting distributions for models using observed ide-cel (KarMMa) data only vs observed data and EO were Gompertz and GG, respectively. Survival estimates were 11% (without EO) to 35% (with EO) at 3 years; 0% (without) to 15% (with) at 5 years; and 0% (without) to 2% (with) at 10 years. In comparison, for the real-world CC cohort in KarMMa-RW survival estimates (with EO) were 16%, 6%, and 1% at 3, 5, and 10 years, respectively, for the best-fitting (GG) model. For the MAMMOTH CC cohort, survival estimates (with EO) were 5%, 0%, and 0% at 3, 5, and 10 years for the best-fitting (GG) model. **Conclusion:** These findings suggest when observed data and EO are integrated, ide-cel treatment provides extended estimated survival rates vs CC. This study indicates that including EO is informative in assisting decision-making processes.

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Carfilzomib, lenalidomide, and dexamethasone followed by salvage autologous stem cell transplant with or without maintenance for relapsed or refractory multiple myeloma

Marc-A. Baertsch[1], Mathilde Fougereau[2], Thomas Hielscher[3], Sandra Sauer[4], Iris Breitkreutz[5], Karin Jordan[2], Carsten Müller-Tidow[2], Hartmut Goldschmidt[6], Marc Raab[7], Jens Hillengass[8], Nicola Giesen[9]

[1]Heidelberg University Hospital and Stanford University School of Medicine; [2]Heidelberg University Hospital; [3]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany; [4]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; [5]Heidelberg University Hospital; [6]Multiple Myeloma Section, Department of Medicine V, University Hospital Heidelberg; and National Center for Tumor Diseases (NCT); [7]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [8]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [9]Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany

Background: Salvage high dose chemotherapy followed by autologous stem cell transplantation (HDCT/ASCT) is a treatment option in patients with relapsed and/or refractory multiple myeloma (RRMM) after prolonged remissions with frontline transplantation. The role of salvage HDCT/ASCT following re-induction treatment with state-of-the-art triplet regimens has not been defined. The present analysis therefore aims to investigate the efficacy and toxicity of salvage HDCT/ASCT after carfilzomib (CFZ)/lenalidomide (LEN)/dexamethasone (KRd) re-induction with or without post-transplant maintenance treatment. **Methods:** We retrospectively assessed efficacy and toxicity in 44 patients receiving salvage HDCT/ASCT following re-induction with carfilzomib/lenalidomide/dexamethasone (KRd). All patients had received frontline HDCT/ASCT with median time to progression (TTP1) of 2.9 (1.2-13.5) years, allowing for paired comparison of frontline and salvage HDCT/ASCT. Median age at time of re-induction was 58.9 years (range 40-71) and n=38/44 patients (86%) had only 1 prior line of therapy (range 1-3). Sixteen of 44 patients (36%) were LEN pretreated and all patients were CFZ-naive. Maintenance treatment was administered in n=22/44 patients (50%) after frontline HDCT/ASCT and in n=17/44 patients (39%) after salvage HDCT/ASCT. **Results:** After a median of 3 re-induction cycles (range 3-9), 25/44 patients (57%) attained at least very good partial response (VGPR), which increased to 34/44 (77%) at best response after salvage HDCT/ASCT. Patients achieving deep remissions during frontline treatment were more likely to re-achieve deep remissions in the salvage setting at each individual timepoint: after (re-)induction (≥VGPR: odds ratio [OR] 6.22; 95% confidence interval [95%-CI] 1.33-29.01; p=0.02), after (salvage) HDCT/ASCT (≥nCR: OR 5.71; 95%-CI 1.44-22.62; p=0.01) and at best response (≥nCR: OR 4.50; 95%-CI 1.12-18.13; p=0.03). After a median follow up of 23.9 months, median progression-free survival (PFS) was 23.3 months from salvage HDCT/ASCT. Patients at least in VGPR at the time of salvage HDCT/ASCT and those receiving maintenance treatment post salvage HDCT/ASCT had significantly superior PFS (hazard ratio [HR] 0.19, p=0.001 and HR 0.20, p=0.009). In patients achieving at least an equal depth of response before salvage HDCT/ASCT as before frontline HDCT/ASCT, PFS after salvage HDCT/ASCT was comparable to the frontline situation (p=0.3). **Conclusion:** Despite higher comorbidity scores at salvage HDCT/

ASCT, no significant increase in relevant toxicity parameters including infections and intensive care unit admission was observed and no transplant-related mortality occurred after salvage HDCT/ASCT. This is the first report of state-of-the-art triplet re-induction and salvage HDCT/ASCT for RRMM after frontline transplantation. Deep remissions achieved with KRd translate into prolonged PFS following salvage HDCT/ASCT and are enhanced by maintenance treatment.

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Pomalidomide, dexamethasone, and daratumumab in relapsed refractory multiple myeloma (MM-014 phase 2 trial): a subanalysis of patients previously treated with lenalidomide and a proteasome inhibitor

Nizar J. Bahlis[1], Gary J. Schiller[2], Michael Sebag[3], Jesus G. Berdeja[4], Siddhartha Ganguly[5], Jeffrey V. Matous[6], Kevin Song[7], Christopher Seet[2], Mirelis Acosta-Rivera[8], Michael Bar[9], Donald Quick[10], Bertrand M. Anz[11], Gustavo Fonseca[12], Donna E. Reece[13], Prisca Vogel[14], Kim Lee[15], Weiyuan Chung[15], Amit Agarwal[15], David S. Siegel[16]

[1]Tom Baker Cancer Centre; [2]David Geffen School of Medicine at University of California; [3]Cedars Cancer Center, McGill University Health Centre; [4]Sarah Cannon Research Institute and Tennessee Oncology; [5]The University of Kansas Cancer Center; [6]Colorado Blood Cancer Institute, Sarah Cannon Research Institute; [7]Vancouver General Hospital; [8]Fundación de Investigación; [9]Stamford Hospital; [10]Joe Arrington Cancer Research and Treatment Center; [11]Tennessee Oncology; [12]Florida Cancer Specialists; [13]Princess Margaret Cancer Centre; [14]Celgene International Sàrl, a Bristol Myers Squibb Company; [15]Bristol Myers Squibb; [16]John Theurer Cancer Center, Hackensack University Medical Center

Background: Lenalidomide (LEN) with or without a proteasome inhibitor (PI) administered until disease progression is a standard treatment (Tx) approach for patients (pts) with newly diagnosed multiple myeloma (MM). Clinical trials investigating triplet therapies included few pts whose disease was relapsed/refractory to LEN after early-line Tx. The phase 2 MM-014 trial (NCT01946477) was designed to investigate outcomes with pomalidomide (POM)-based therapy immediately after first- or second-line LEN-based Tx failure in pts with relapsed/refractory MM (RRMM). In cohort B (n=112) of this trial, POM + dexamethasone (DEX) + daratumumab (DARA) demonstrated promising efficacy and safety with an overall response rate (ORR) of 78% and median progression-free survival (PFS) of 30.8 mo. Efficacy and safety in a subgroup of pts in cohort B previously exposed to LEN+PI are reported. **Methods:** Pts with RRMM (1–2 prior Tx lines), LEN-based Tx for ≥2 consecutive cycles as most recent regimen, and disease progression during/after last line of Tx received POM+DEX+DARA (28-d cycles) until disease progression. POM 4 mg/d was given orally (PO) on d1–21; DEX 40 mg/d (20 mg/d in pts aged >75 y) PO on d1, 8, 15, and 22; and DARA 16 mg/kg IV on d1, 8, 15, and 22 of cycles 1–2, d1 and 15 for cycles 3–6, and d1 for cycles 7+. The primary endpoint was ORR; secondary endpoints included PFS and safety. **Results:** In cohort B, 89/112 pts (79%; median age, 65 y) received prior LEN+PI. In this subgroup, 67 pts (75%) had LEN-refractory MM and 22 (25%) had LEN-relapsed MM; most pts (52 [58%]) received 1 vs 2 (37 [42%]) prior Tx lines. Median duration of Tx with POM, DEX, and DARA was 15.9, 14.0, and 16.1 mo, respectively. At a median follow-up of 28.4 mo (data cutoff Mar 2020), the ORR was 79% (≥very good partial response [VGPR], 55%). The ORR was 81% (≥VGPR, 63%) and 76% (≥VGPR, 43%) in pts with 1 vs 2 prior lines of Tx, respectively. Median duration of response and median PFS were not yet reached (1-y PFS rate, 74%). Infusion-related reactions occurred in 28% of pts and were primarily low grade (Gr). Overall, 98% of pts had ≥1 Gr 3/4 Tx-emergent adverse event. The most common Gr 3/4 hematologic events were neutropenia (64%; febrile, 12%), anemia (19%), and thrombocytopenia (13%). Gr 3/4 infections occurred in 40% of pts, including 16% with pneumonia. **Conclusion:** POM+DEX+DARA administered immediately after LEN failure in a subgroup of pts previously treated with LEN+PI demonstrated a high response rate and a safety profile consistent with that in the overall cohort B population. Results support the use of POM-based therapy, integrating the monoclonal antibody DARA, as early as second line in pts with RRMM, potentially immediately after LEN Tx failure. Furthermore, the data support subsequent Tx with the same immunomodulatory agent class in a pt population with LEN-relapsed or -refractory MM. **Previous presentation:** Bahlis NJ, et al. HemaSphere 2021;5:e482–483. EP1019.

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A systematic literature review and indirect treatment comparison among randomized clinical trials to estimate the relative efficacy of treatments for relapsed/refractory multiple myeloma

Rachel Bhak[1], Holly Cranmer[2], Jonathan Dabora[2], Iryna Bocharova[1], Dasha Cherepanov[2], Mu Cheng[1], Maral DerSarkissian[1], Mei Sheng Duh[1]

[1]Analysis Group; [2]Takeda Pharmaceuticals International Co.

Background: The spectrum of treatment options available for relapsed/refractory multiple myeloma (RRMM) has dramatically broadened over the past 10 years, including the approval of ixazomib, the first and only oral proteasome inhibitor (PI). Ixazomib+lenalidomide+dexamethasone (IRd) compared to placebo plus lenalidomide+dexamethasone (Rd) was associated with significantly longer progression-free survival (PFS) in patients with RRMM in the Phase III TOURMALINE-MM1 trial. Due to the lack of head-to-head randomized controlled trials (RCTs) comparing IRd to other key treatments in RRMM, network meta-analyses (NMAs) were conducted to evaluate the relative efficacy of IRd compared to these therapies. **Methods:** A systematic literature review (SLR) was conducted to identify studies assessing the efficacy of IRd and other selected regimens for the treatment of RRMM to June 2020. Targeted literature searches supplemented the SLR

results. Eligible studies consisted of multi-arm RCTs (base case) and observational studies (sensitivity analysis). All analyses were conducted using Bayesian fixed effect NMA models. The posterior median hazard ratios (HRs) for PFS and the corresponding 95% credible intervals (CrI) were reported for IRd as compared to other regimens. **Results:** A total of 9 RCTs reported PFS results and were included in the base case NMA. The extended network in the sensitivity analysis included 21 studies evaluating 17 treatments. The following 8 treatments were evaluated in the base case NMA: IRd, Rd, elotuzumab+lenalidomide+dexamethasone (ERd), carfilzomib+lenalidomide+dexamethasone (KRd), daratumumab+lenalidomide+dexamethasone (DRd), dexamethasone (Dex), pomalidomide+dexamethasone (Pom-dex), and bortezomib monotherapy (V). In the base case PFS analysis, IRd was not associated with any significant differences in PFS compared to ERd (HR 1.097; 95% CrI 0.843, 1.428) or KRd (HR 1.194; 95% CrI 0.929, 1.547). However, IRd was associated with statistically significantly longer PFS as compared to Rd (HR 0.789, 95% CrI 0.656, 0.953), V (HR 0.501; 95% CrI 0.351, 0.714), Dex (HR 0.276; 95% CrI 0.210, 0.362), and Pom-dex (HR 0.563; 95% CrI 0.399, 0.795), but statistically significantly shorter PFS as compared to DRd (HR 1.795; 95% CrI 1.345, 2.393). Results from the extended network in the sensitivity analysis were consistent with the base case NMA. **Conclusion:** Results of the NMA provide a comprehensive treatment network of evidence-based results in the RRMM setting using the most up-to-date RCT data. The NMA demonstrated that the efficacy profile of IRd was more favorable than the monotherapies and doublet regimens (Rd, V, Dex and Pom-dex), and comparable relative to Rd-based triplet regimens (ERd and KRd) except for DRd. These findings suggest that the all-oral IRd triplet regimen could be a preferable treatment option for many patients with RRMM, particularly those seeking an efficacious, tolerable and convenient therapeutic option for management of MM.

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Comparison of efficacy outcomes for Carfilzomib plus Dexamethasone and Daratumumab (KdD) versus Pomalidomide plus Bortezomib and Dexamethasone (PVd) and D-Pd in relapsed or refractory Multiple Myeloma

Ajai Chari[1], Meletios-Athanasios Dimopoulos[2], Meral Beksac[3], Xavier Leleu[4], Katja Weisel[5], Joshua Richter[6], Franziska Dirnberger[7], Karim Iskander[7], Akeem Yusuf[7], Joseph Mikhael[8]

[1]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital; [3]Ankara University; [4]Service d'Hématologie et Thérapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France; [5]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [6]Icahn School of Medicine at Mount Sinai Hospital; [7]Amgen Inc; [8]Translational Genomics Research Institute (TGen), City of Hope Cancer Center

Background: With increasing utilization of immunomodulatory agents (particularly lenalidomide) for the management of newly diagnosed multiple myeloma, there is an emerging need for efficacious lenalidomide-free options at relapse. In the CANDOR trial, carfilzomib plus dexamethasone and daratumumab (KdD) demonstrated improved efficacy over Kd for the management of relapsed or refractory multiple myeloma (RRMM) and has a tolerable safety profile. Two pomalidomide-containing triplet regimens with bortezomib (PVd) or daratumumab (D-Pd) plus dexamethasone have demonstrated improved efficacy over Vd or Pd alone in randomized clinical trials (OPTIMISSM and APOLLO, respectively). Herein, naive comparisons and matching-adjusted indirect comparisons (MAIC) of progression-free survival (PFS) were performed for KdD versus PVd and KdD versus D-Pd in lenalidomide-exposed patients. **Methods:** These analyses used baseline characteristics and PFS data from the CANDOR, OPTIMISSM, and APOLLO trials. For each analysis, a naive comparison (without adjustments) and MAIC were performed. For MAIC, KdD patients in CANDOR who were previously exposed to lenalidomide (based on propensity scores) were matched to published summary baseline characteristics of PVd patients in OPTIMMISM and D-Pd patients in APOLLO. Weighted PFS outcomes were calculated. Variables included in the matching analysis were age, disease stage (International Staging System), lenalidomide refractoriness, and number of prior lines of treatment. For the comparison of KdD versus D-PD, bortezomib refractoriness was also included as a matching variable. Scenario and subgroup analyses were conducted to assess the robustness of results. **Results:** Overall, 123 lenalidomide-exposed KdD patients in CANDOR, 281 PVd patients in OPTIMISSM, and 151 D-Pd patients in APOLLO received treatment. There were no notable differences in baseline characteristics considered for the matching procedure. Naive comparisons for PFS significantly favored KdD versus PVd (median PFS, 25.9 months vs 11.5 months; hazard ratio [HR]: 0.545 [0.397–0.747]) and KdD versus D-Pd (median PFS, 25.9 months vs 12.8 months; HR: 0.629 [0.445–0.890]). After matching, PFS also significantly favored KdD versus PVd (median PFS, 25.0 months vs 11.5 months) and KdD versus D-Pd (median PFS, 25.0 months vs 12.8 months). The HR for PFS in the MAIC was 0.539 (0.395–0.736) for KdD versus PVd and 0.677 (0.474–0.966) for KdD versus D-Pd. **Conclusion:** This analysis showed that KdD extended PFS compared with PVd and D-Pd in patients with RRMM and previous lenalidomide exposure. A comparison of overall survival was not considered due to immature data in the studies considered for this analysis. These results suggest KdD offers clinically meaningful improvements over pomalidomide-based triplet regimens for patients with RRMM.

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Circularly permuted TRAIL (CPT) combined with Thalidomide and Dexamethasone in patients with relapsed/refractory Multiple Myeloma: a randomized, double-blind, placebo-controlled phase 3 study

Wenming Chen[1], Zhongjun Xia[2], Baijun Fang[3], Chengcheng Fu[4], Wei Li[5], Linhua Yang[6], Xiaoyan Ke[7], Hua Jiang[8], Jianyu Weng[9], Li Liu[10], Yaozhong Zhao[11], Xuejun Zhang[6], Aichun Liu[12], Zhongxia Huang[1], Qingzhi Shi[13], Yuhuan Gao[14], Xiequn Chen[15], Ling Pan[16], Zhen Cai[17], Zhao Wang[18], Yafei Wang[19], Yizhuo Zhang[19], Yaqun fan[20], Ming Hou[21], Shifang Yang[22]

[1]Beijing Chaoyang Hospital, Capital Medical University, Beijing, China, Department of Hematology; [2]Sun Yat-sen University Cancer Center, Department of Hematologic Oncology; [3]Henan Cancer Hospital, Henan Cancer Hospital Affiliated to Zhengzhou University, Department of Hematologic Oncology; [4]The First Affiliated Hospital of Soochow University, Jiangsu Institute of Hematology, National Clinical Research Center for Hematologic Diseases, Department of Hematology; [5]Department of Hematology at the Oncology Center, The First Hospital of Jilin University, Changchun, China; [6]The Second Hospital of Shanxi Medical University, Department of Hematology; [7]Peking University, Third Hospital, Department of Hematology and Lymphoma Research Center; [8]Chang Zheng Hospital, Second Military Medical University, Department of Hematology; [9]Guangdong General Hospital, Guangdong Academy of Medical Sciences, Department of Hematology; [10]Tangdu Hospital, The Fourth Military Medical University, Department of Hematology; [11]Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Department of Lymphoma Center; [12]Harbin Medical University Cancer Hospital, Department of Hematology and Lymphology; [13]The Second Affiliated Hospital of Nanchang University, Department of Hematology; [14]The Fourth Hospital of Hebei Medical University, Department of Hematology; [15]Xijing Hospital, Fourth Military Medical University, Department of Hematology; [16]West China Hospital, Sichuan University, Department of Hematology; [17]The First Affiliated Hospital of Zhejiang University, College of Medicine, Hangzhou, Zhejiang, China; [18]Beijing Friendship Hospital, Capital Medical University, Department of Hematology; [19]Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Department of Hematology; [20]The First Affiliated Hospital of Xiamen University and Institute of Hematology, Medical College of Xiamen University, Department of Hematology; [21]Qilu Hospital, Shandong University, Department of Hematology; [22]Beijing Sunbio Biotech Co., Ltd.*

Background: CPT, a recombinant permuted human TNF-related apoptosis-inducing ligand (TRAIL), is a 1rst-in-human anti-myeloma drug targeting death receptor 4/5. In order to verify the effectiveness and safety of CPT, we have conducted this multi-center, double-blind, placebo-controlled phase 3 study. **Methods:** In this study, 417 RRMM patients previously treated with two or more lines of therapies were randomly assigned (2:1) to receive CPT+TD (CPT group) vs. placebo+TD (control group). CPT or placebo at a dose of 10 mg/kg was intravenously administered on days 1 to 5, both groups receive dexamethasone 40 mg orally on days 1 to 4, and thalidomide 150mg daily, 28 days per cycle until to disease progressions or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), and the key secondary endpoints overall survival (OS), overall response rate (ORR), and safety. **Results:** Of the 417 patients enrolled, 415 patients received CPT+TD (n=276) or placebo+TD (n=139) treatment. The demographic, baseline disease and clinical characteristic of the two groups were comparable. The median age of the patients was 59 years, and the median time from the initial diagnosis of multiple myeloma (MM) to participating this trial was 2.6 years. The median number of lines of prior therapies was 3. Proteasome inhibitors (PI) and immunomodulators (IMiD) were previously used in 74% and 86.5% of patients, respectively. At date cutoff, the primary endpoint of PFS was significantly longer in the CPT group than in the control group (median 5.5 vs. 3.1 months; hazard ratio [HR] 0.619; P3 lines of prior therapies. PFS and ORR were also significantly improved in the patients with PI and IMiD double-refractory MM. The serious adverse events (SAE) rates were similar in the CPT group and the control group (40.6% vs. 37.4%), as were the death rates during the treatments (7.6% vs. 8.6%). Treatment-emergent adverse events (TEAEs) with at least a 10% greater frequency in the CPT group vs. the control group were elevated alanine transaminase (ALT), elevated aspartate transaminase (AST), elevated lactate dehydrogenase (LDH), increased monocyte counts, hypocalcaemia and upper respiratory tract infections. **Conclusions:** The combination of CPT with TD significantly prolonged the PFS and OS, increased the ORR. CPT combined with TD was well tolerated, the adverse events were mild, transient and reversible.

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Elotuzumab plus pomalidomide/dexamethasone for relapsed/refractory multiple myeloma: final overall survival from the phase 2 ELOQUENT-3 trial

Meletios-Athanasios Dimopoulos[1], Dominik Dytfeld[2], Sebastian Grosicki[3], Philippe Moreau[4], Naoki Takezako[5], Mitsuo Hori[6], Xavier Leleu[7], Richard LeBlanc[8], Kenshi Suzuki[9], Marc Raab[10], Paul G. Richardson[11], Mihaela Popa McKiver[12], Ying-Ming Jou[12], David Yao[12], Prianka Das[12], Jesús F. San-Miguel[13]

[1]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital; [2]Department of Hematology and Bone Marrow Transplantation, Karol Marcinkowski University of Medical Sciences, Poznań, Poland; [3]Medical University of Silesia, Katowice, Poland; [4]University Hospital Hôtel-Dieu; [5]Department of Hematology, Disaster Medical Center of Japan, Tokyo, Japan;

[6]Department of Hematology, Ibaraki Prefectural Central Hospital, Kasama, Japan; [7]Service d'Hématologie et Thérapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France; [8]Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, QC, Canada; [9]Myeloma/Amyloidosis Center, Japanese Red Cross Medical Center, Tokyo, Japan; [10]Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [11]Dana-Farber Cancer Institute, Boston, MA, USA; [12]Bristol Myers Squibb, Princeton, NJ, USA; [13]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA

Background: In the randomized phase 2 ELOQUENT-3 trial (NCT02654132), elotuzumab in combination with pomalidomide/dexamethasone (EPd) significantly improved progression-free survival (PFS) versus pomalidomide/dexamethasone (Pd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) (Dimopoulos MA et al. N Engl J Med 2018). A preliminary analysis of overall survival (OS) (minimum follow-up of 9.1 mo) showed a trend favoring EPd over Pd (hazard ratio [HR] 0.62; 95% CI, 0.30–1.28). Here we present the final OS analysis from ELOQUENT-3. **Methods:** 117 pts with RRMM, ≥2 prior lines of therapy (LoTs), and disease refractory to last therapy, and either refractory or relapsed and refractory to lenalidomide and a proteasome inhibitor (PI), were randomized (1:1) to receive EPd or Pd in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was PFS. OS was a secondary endpoint. Final OS analysis was pre-specified to occur after 78 deaths, giving the study 75% power at an a[ED]=0.2 level to show a statistically significant difference when the true HR is 0.64. OS was also analyzed within patient subgroups. **Results:** At the January 11, 2021 data cutoff (minimum follow-up of 45 mo), 3 pts remained on treatment (2 on EPd and 1 on Pd). Pts received a median of 9.0 cycles of EPd or 5.0 cycles of Pd. In all, 76.9% of pts (EPd 70.0%, Pd 84.2%) discontinued from the study mainly due to death (EPd 61.7%, Pd 71.9%). At final analysis, there were 37 (61.7%) deaths in the EPd group and 41 (74.5%) in the Pd group, most commonly due to disease progression (EPd 41.7%, Pd 49.1%). The median (95% CI) OS was significantly improved with EPd (29.8 mo [22.9–45.7]) versus Pd (17.4 mo [13.8–27.7]), with an HR of 0.59 (95% CI, 0.37–0.93; 2-sided stratified log-rank P=0.0217). The OS benefit of EPd was consistently observed across key subgroups. In pts with lenalidomide as their most recent prior LoT (n=65), HR for OS was 0.55 (95% CI, 0.29–1.04) in favor of EPd. Overall, 70.0% (EPd) and 68.4% (Pd) of pts received subsequent systemic therapy; the most common in both groups (other than dexamethasone) was daratumumab (EPd 43.3%, Pd 43.9%). The safety profile of EPd was consistent with prior reports and no new safety signals were detected. Anemia, neutropenia, and thrombocytopenia were less common with EPd (28.3%, 26.7%, 16.7%) versus Pd (38.2%, 30.9%, 20.0%). Grade 3/4 infections occurred in 25.0% (EPd) and 21.8% (Pd) of pts; grade 5 infections occurred in 6.7% (EPd) and 5.5% (Pd). Adverse events led to discontinuation in 18.3% (EPd) and 23.6% (Pd) of pts. **Conclusion:** EPd demonstrated a statistically significant and clinically meaningful reduction (41%) in the risk of death versus Pd in pts with RRMM previously treated with lenalidomide and a PI. ELOQUENT-3 is the first randomized controlled study of a triplet regimen incorporating a monoclonal antibody and Pd in this setting to show both significant PFS and OS benefits.

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Pomalidomide-based therapy in Relapsed/Refractory Multiple Myeloma: a real-world single-center experience.

Ludovica Fucci[1], Luciano Fiori[2], Ugo Coppetelli[2], Giuseppe Cimino[3]

[1]La Sapienza University of Rome; [2]S.M. Goretti Hospital of Latina; [3]La Sapienza University of Rome - Polo Pontino

Background: Several new drugs, now available for patients affected from relapsed/refractory Multiple Myeloma (RRMM), improved outcomes. In this study, we focused on the 3rd generation IMiD drug Pomalidomide, administered in combination with dexamethasone (PD) for RRMM patients who received at least 2 prior regimens, including Bortezomib and Lenalidomide. In the past few years, adding cyclophosphamide to PD has been tried in order to deepen responses and increase duration of response (DOR), but solid data about the outcomes of this specific combination are lacking. The aim of our study is to add useful information about Pomalidomide administration in the real-life setting, and to assess the possible benefit of the three-drug combination approach. **Method:** We retrospectively evaluated a total of 23 RRMM patients, who received a Pomalidomide based therapy between November 2015 and July 2021. Among the study cohort, there were 12 (52%) females and 11 (48%) males, with a median age of 75 years. 14 patients (61%) received 3 or more prior treatment lines, and 19 (83%) were refractory to lenalidomide. The most common comorbidities were chronic kidney failure (61%) and diabetes (35%). Two study group were defined, 10 (44%) patients received PD, 13 (56%) received PCD. In the PD group, oral Pomalidomide (4 mg D1-D21) and oral dexamethasone (20 mg on D1, 8, 15, 22) were administered in a 28-day cycle. In PCD, oral cyclophosphamide (50 mg/die D1-D21) was added from the beginning. All patients were evaluable for response, having received at least two cycles of PD. **Results:** Overall response rate (ORR) was 87%, with 3/23 (13%) patients experiencing PD within the first 3 mths of therapy. After a median follow up of 13 mths, 12/23 (52%) patients were alive, median progression free survival (mPFS) was 11 mths for the entire population, whereas 2y PFS and OS were 13% and 17%, respectively. No statistically significant difference emerged in terms of PFS and OS between PD and PCD subgroups (mPFS 13 vs 10 mths, p=0,57); mOS 13 vs 11 mths, p=0,5). Best response was VGPR in 7/23 (30%), PR in 11/23 (48%), SD in 2/23 (9%) patients. Grade 3 hematological AEs occurred in 5/23 (22%) of patients, 1/10 (10%) in PD and 4/13 (31%) in PCD group resulting in drug dose reduction up to 2 mg. Grade 1-2 hematological AEs occurred in 7/23 (35%) of patients, 5/10 (50%) in PD and 3/13 (23%) in PCD group. Grade 1-2 non-hematological AEs occurred in 4/23 (17%) of patients, 1/10 (10%) in PD and 3/13 (23%) in PCD group. Grade 4 hematological and 3-4 non-hematological AEs were not observed. **Conclusion:** In our

experience, the addition of cyclophosphamide to the conventional PD didn't give any advantage in terms of PFS and OS, still providing an overall increase in toxicity, both hematological and not. In conclusion, our single-institution series suggests that PD could still be a safe and effective oral therapy for RRMM, even in older patients. The PCD combination should not be routinely used.

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Salvage autologous stem cells transplantation and maintenance therapy in relapsed refractory multiple myeloma

David Garrido[1], Virginia Bove[2], Eloisa Riva[2]

[1]Hospital de Clínicas "Dr. Manuel Quintela"; [2]Hospital Central de las FFAA, Montevideo, Uruguay

Background: Multiple myeloma (MM) is an incurable hematological neoplasm. However, new therapies have improved overall survival (OS). In relapsed/refractory MM (RRMM) and a resource-limited environment, optimizing treatment options is essential. Autologous hematopoietic stem cell transplantation (ASCT) is an available strategy, frontline and at relapse. **Objective:** to analyze overall survival (OS2) and progression-free survival (PFS2) in RRMM patients comparing second-line consolidation strategies. **Methods:** This retrospective survival analysis study, based on the Uruguayan Multiple Myeloma Registry, included all RRMM adult patients <66 years diagnosed in 2010-2020 who received second-line therapy. RRMM was defined according to international criteria. OS2 and PFS2 were measured from the identification of relapse until death/last control and progression, respectively. We used SPSSv.25 for statistical analysis. Survival was analyzed using Kaplan-Meier model with Log-Rank test, and Cox regression model along with hazard ratios (HR) **Results:** Fifty-nine patients were included, with a median age at diagnosis of 56 years (IQR 12), 49.1% were male, 70.10% IgG, 84.75% were Durie-Salmon stage (DS) III and 37.3% ISS-III, 27.1% ISS-II, and 30.5% ISS-I. Age, ISS, and DS were not statistically different between therapeutic groups. Most (69.5%) patients had received a first ASCT, and 35.6% received maintenance as first-line therapy. Maintenance therapy was lenalidomide in 20.3%, thalidomide in 6.8%, and 8.5% other options. Eleven patients (18.6%) received salvage ASCT and maintenance, 18.6% received only ASCT, 16.9% received only maintenance and 45.8% neither ASCT nor maintenance. The median OS2 was 34 months, and PFS2 was 26 months. The 3-year OS2 and 3-year PFS2 were 47.2% and 32.2% for the entire cohort, respectively. The combination of ASCT and maintenance achieved a 3-year OS2 of 75.0% whereas OS2 in the non-combined therapy (NCT)(ASCT or maintenance) was 50.7% (HR 0.1, CI95% 0.01 to 0.6, p=0.01). ASCT and maintenance achieved a 3-year PFS2 of 43.1% whereas PFS2 was 37.6% for the NCT (HR 0.2, CI95% 0.1 to 0.7, p=0.01). The 3-year OS2 was 50.7% for those who received ASCT or maintenance vs. 28.4% for those without second-line consolidation (HR 0.3, CI95% 0.2 to 0.9, p=0.02). The 3-year PFS2 was 37.6% for patients who received any of the consolidative strategies vs 19.1% (HR 0.4, CI95% 0.2 to 0.9, p=0.02) in those who did not receive salvage ASCT or maintenance **Conclusion:** ASCT has been recommended for patients relapsing after primary therapy, including an ASCT with an initial remission duration of >18 months. The role of salvage ASCT in patients who received lenalidomide maintenance has not been determined. In our analysis, the combination of ASCT and maintenance improved the OS2 and PFS2 compared to those treated with only ASCT or maintenance. Not receiving second-line consolidation was associated with inferior PFS2 and OS2.

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Isatuximab plus Carfilzomib and Dexamethasone in patients with relapsed Multiple Myeloma and soft-tissue Plasmacytomas: IKEMA subgroup analysis

Roman Hájek[1], Tomas Jelinek[2], Philippe Moreau[3], Thomas Martin[4], Luděk Pour[5], Gábor Mikala[6], Argiris Symeonidis[7], Sara Bringhen[8], Andreea Rawlings[9], Marie-Laure Risse[10], Helgi van de Velde[9], Ivan Špička[11]

[1]Department of Hemato-oncology, University Hospital Ostrava and University of Ostrava; [2]Department of Haematooncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [3]University Hospital Hôtel-Dieu; [4]Department of Hematology, University of California at San Francisco, San Francisco, CA, USA; [5]Department of Internal Medicine, University Hospital Brno; [6]National Institute for Hematology and Infectious Diseases; [7]Hematology Division, Department of Internal Medicine, University of Patras Medical School, Patras, Greece; [8]Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; [9]Sanofi, Cambridge, MA, USA; [10]Sanofi Research & Development, Vitry-sur-Seine, France; [11]Charles University and General Hospital

Background: Isatuximab (Isa) is an approved IgG1 monoclonal antibody that targets a specific epitope of CD38 and kills multiple myeloma (MM) cells via multiple mechanisms. The Phase 3 IKEMA study (NCT03275285) demonstrated that Isa plus carfilzomib (K) and dexamethasone (d) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed MM (hazard ratio [HR], 0.531; 99% CI, 0.32–0.89; P=0.0007), leading to the approval of Isa-Kd in the US for adults with MM with 1–3 prior lines and in the EU for those with ≥1 prior therapy. The presence of soft-tissue plasmacytomas is associated with poor prognosis, and newer therapies are urgently needed. In this post hoc analysis, we evaluated the efficacy and safety of Isa-Kd vs Kd in pts with relapsed MM and pre-existing soft-tissue plasmacytomas. **Methods:** Pts (N=302) were randomized (3:2) to Isa-Kd (n=179) or Kd (n=123). Isa (10 mg/kg IV) was given weekly for 4 weeks, then every 2 weeks. K (20 mg/m² days 1–2, then 56 mg/m²) was given twice-weekly 3 of 4 weeks, and d (20 mg) twice-weekly. The independent review committee assessed response based on central radiology review and central lab M-protein using the International Myeloma Working Group criteria. **Results:** At study entry, 19

(6.3%) pts had soft-tissue plasmacytomas:12/179 (6.7%) had Isa-Kd and 7/123 (5.7%) had Kd. Overall median (range) duration of exposure in these pts was 41.9 (2–87) weeks for Isa-Kd vs 29.9 (4–83) for Kd, with 41.7% pts still on treatment at cycle 20 in Isa-Kd vs 14.3% pts in Kd. Baseline characteristics in the plasmacytomas subgroup were similar to those in the overall IKEMA intent-to-treat (ITT) population with the exception of ISS stages II (42.1% vs 31.1%) and III (31.6% vs 15.2%), and renal function impairment (38.9% vs 22.1%) which were more prevalent in the plasmacytomas subgroup vs ITT. PFS was improved with Isa-Kd vs Kd: HR, 0.574; 95% CI, 0.125–2.640. Median PFS was 18.76 (95% CI, 4.435–not calculable [NC]) months with Isa-Kd vs NC (0.986–NC) months with Kd. Overall response rate (50.0% vs 28.6%), very good partial response or better (33.3% vs 14.3%), and complete response (25.0% vs 0%, all with minimal residual disease negativity) rates were also improved with Isa-Kd vs Kd. Grade ≥3 TEAE occurred in 12 (100%) pts with Isa-Kd vs 4 (57.1%) with Kd. Grade 5 TEAEs during study treatment occurred in 2 (16.7%) vs 1 (14.3%) pt; serious TEAEs in 9 (75.0%) vs 4 (57.1%); TEAEs leading to discontinuations were 0 (0%) vs 1 (14.3%). Grade 5 events were pneumonia (1 [8.3%], Isa-Kd) and progressive disease (1 [8.3%], Isa-Kd; 1 [14.3%], Kd). **Conclusions:** In pts with relapsed MM and soft-tissue plasmacytomas, Isa-Kd improved PFS and depth of response compared with Kd alone, with a manageable safety profile, consistent with the benefit observed in the IKEMA study overall population. Isa-Kd is a new treatment option for pts with relapsed MM and soft-tissue plasmacytomas. **Funding:** Sanofi.

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Central nervous system Multiple Myeloma (CNS-MM), presentation and outcomes in an Era of anti-CD38 and pomalidomide inclusive therapies

Maliha Khan[1], Shehab Mohamed[1], Melody Becnel[1], Sheeba Thomas[1], Elisabet Manasanch[2], Hans Lee[3], Swami Iyer[1], Muzaffar Qazilbash[1], Qaiser Bashir[1], Samer Srour[1], Susan Wu[1], Penny Fang[1], Jillian Gunther[1], Chelsea Pinnix[1], Behrang Amini[1], Pei Lin[1], Bouthaina Dabaja[1], Krina Patel[1], Donna Weber[1], Robert Z. Orlowski[4], Gregory Kaufman[1]

[1]MD Anderson Cancer Center; [2]The Unversity of Texas MD Anderson Cancer Center Department of Lymphoma Myeloma; [3]MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: CNS-MM is a rare extramedullary manifestation of MM characterized by infiltration of the CNS parenchyma or meninges and often cerebrospinal fluid (CSF) with malignant plasma cells. Historically, patient (pt) outcomes have been poor, with reported OS of 2-7 months (m). However, the landscape for treating MM has changed, with regulatory approval and availability of anti-CD38 targeting antibodies daratumumab (DARA) and isatuximab, pomalidomide (POM) based combinations, and other novel agents (selinexor, BCMA targeting). Despite isolated case reports of durable responses in CNS-MM with these new therapies, most larger case series of CNS-MM do not include pts treated in this more current therapeutic era. We sought to analyze pt presentation and outcomes with CNS-MM in a more recent era. **Methods:** Pts treated at MD Anderson with CNS-MM confirmed by CSF pathology, or MRI findings were retrospectively identified. Pts who received follow up at MDACC between 2015 and 2020 were included. The study was approved by the MDACC IRB and conducted in accordance with the Declaration of Helskinki. Descriptive statistics were used and time to event analysis was conducted using JMP Pro v15 (Cary, North Carolina). **Results:** Twenty-one (n=21) pts met criteria for analysis. Fourteen pts (67%) had CNS-MM confirmed by both CSF and MRI, five pts (24%) by CSF, and two pts by MRI alone. At CNS-MM diagnosis, ten pts (48%) were in 1st-2nd relapse, 9 pts (43%) had ≥3 prior lines of therapy, and two had newly diagnosed MM. Of 19 pts with prior therapy at CNS-MM dx, eight (42%) were POM exposed/refractory, and seven (37%) were DARA exposed/refractory. Fourteen (67%) pts had 1q gain/amplification on FISH, and 5 of these additional HR-FISH with del(17p), t(4;14) or t(14;16). Median time from MM dx to CNS-MM was 37 m (0-103). Initial treatment post CNS-MM included XRT, intrathecal therapy (IT) with cytarabine, and systemic therapy in 8 pts, 6 pts had XRT and systemic therapy, 4 pts had IT with systemic therapy, 2 pts had XRT alone, and 1 pt had systemic therapy alone. Median overall survival (OS) from MM dx for the cohort was 40 m (11-123), and 4 m (1-59) post diagnosis of CNS-MM. Median OS from CNS-MM for DARA exposed/refractory pts was 3 m (1-7). Median OS from CNS-MM for POM exposed/refractory pts was 4.5 m (1-31). DARA and POM based combinations (9 pts each) were the most common systemic therapies given initially after CNS-MM dx. Of 7 pts with greater than 12 m OS post CNS-MM, all were DARA naive at CNS-MM dx and five were POM naive. All 7 pts cleared CSF, though therapy varied, with 6 pts receiving multi-modality therapy (XRT/IT in combination with systemic therapy). **Conclusions:** Despite occasional success in DARA/POM naive pts using multi-modality therapy, our CNS-MM outcomes remain poor. Understanding the incidence of CNS-MM in the context of the changing biology and longer lifespan of RRMM pts may help guide strategies to prevent or treat CNS-MM.

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Isatuximab plus Carfilzomib and Dexamethasone in East Asian patients with relapsed Multiple Myeloma: IKEMA subgroup analysis

Kihyun Kim[1], Chang-Ki Min[2], Youngil Koh[3], Kenichi Ishizawa[4], Sung-Hyun Kim[5], Shigeki Ito[6], Junji Tanaka[7], Michihiro Uchiyama[8], Yawara Kawano[9], Jin Seok Kim[10], Philippe Moreau[11], Thomas Martin[12], Yvonne Dong[13], Marie-Laure Risse[14], Kenshi Suzuki[15]

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Hematology, Seoul St Mary's Hospital, Seoul, Republic of Korea; [3]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of

Korea; [4]Department of Hematology and Cell Therapy, Yamagata University, Yamagata, Japan; [5]Department of Internal Medicine, Dong-A University College of Medicine, Busan, Republic of Korea; [6]Division of Hematology & Oncology, Department of Internal Medicine, Iwate Medical University School of Medicine, Yahaba, Japan; [7]Department of Hematology, Tokyo Women's Medical University, Tokyo, Japan; [8]Department of Hematology, Japanese Red Cross Society, Suwa Hospital, Suwa, Japan; [9]Department of Hematology, Kumamoto University Hospital, Kumamoto, Japan; [10]Department of Hematology, Severance Hospital, Seoul, Republic of Korea; [11]University Hospital Hôtel-Dieu; [12]Department of Hematology, University of California at San Francisco, San Francisco, CA, USA; [13]Sanofi R&D, Beijing, China; [14]Sanofi Research & Development, Vitry-sur-Seine, France; [15]Myeloma/Amyloidosis Center, Japanese Red Cross Medical Center, Tokyo, Japan

Background: Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib and dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (hazard ratio [HR] 0.53; 99% confidence interval [CI] 0.32–0.89; P=0.0007). We evaluated efficacy and safety of Isa-Kd in East Asian pts (19 Japanese, 27 Korean) from IKEMA study. **Methods:** RMM pts who received 1–3 prior lines of therapy were stratified to receive Isa-Kd or Kd. Isa-Kd arm received Isa (10 mg/kg intravenously) weekly for 4 weeks, then every 2 weeks. Both arms received K (20 mg/m² Days 1–2, 56 mg/m² thereafter) twice-weekly for 3 of 4 weeks, and d (20 mg) twice-weekly. Treatment continued until disease progression or unacceptable adverse events (AEs). The primary endpoint was PFS. Key secondary endpoints were overall response rate (ORR), very good partial response or better (≥VGPR), minimal residual disease negativity (MRD–), and complete response (CR) rates. Complete renal response (CRr, increase in eGFR from <50 mL/min/1.73 m² at baseline to ≥60 mL/min/1.73 m² in at least one post-baseline assessment) was also measured. **Results:** East Asian pts (25 Isa-Kd, 21 Kd) were randomized. Pt characteristics were similar in the East Asian subgroup and the intent to treat (ITT) population (N=302). Median age (Isa-Kd 64.0 [range 45–83] years vs Kd 60.0 [33–73] years); median prior lines Isa-Kd 2.0 (1–3) vs Kd 1.0 (1–3); refractory to lenalidomide 16.0% Isa-Kd vs 47.6% Kd; refractory to proteasome inhibitor 20.0% Isa-Kd vs 33.3% Kd; high-risk cytogenetics 48.0% Isa-Kd vs 42.9% Kd. After a median follow-up of 20.7 months, PFS HR (0.64; 95% CI: 0.23–1.76) favored Isa-Kd, consistent with the HR in ITT population. ORR was high in both arms (Isa-Kd 88.0% vs Kd 81.0%); however, addition of Isa to Kd improved ≥VGPR (Isa-Kd 80.0% vs Kd 52.4%), MRD– (Isa-Kd 44.0% vs Kd 9.5%), and CR (Isa-Kd 44.0% vs Kd 23.8%) rates in East Asian pts, consistent with the ITT population (Isa-Kd vs Kd) (≥VGPR: 72.6% vs 56.9%; MRD–: 29.6% vs 13.0%; CR: 39.7% vs 27.6%). Renal response (CRr) was 100% (3/3 pts) in Isa-Kd vs 0% (0/2 pts) in Kd arm. Safety profile of Isa-Kd in East Asian pts was similar to the ITT population: Grade ≥3 AEs were observed in 79.2% Isa-Kd vs 55.0% Kd pts, serious TEAEs in 45.8% Isa-Kd vs 50.0% Kd pts, TEAEs fatal during study treatment in 0% Isa-Kd vs 5.0% Kd pts, and TEAEs leading to treatment discontinuation in 4.2% Isa-Kd vs 10.0% Kd pts. Overall, 64.0% Isa-Kd vs 42.9% Kd pts were still on treatment. **Conclusions:** Efficacy and safety results of Isa-Kd in East Asian pts are consistent with overall IKEMA population; similar treatment effect for PFS, ≥VGPR, MRD–, and CR rates was reported in favor of Isa-Kd without an increase in the number of pts with serious TEAEs, TEAEs fatal during study treatment, or leading to discontinuations. Isa-Kd is a potential new treatment option for East Asian pts with RMM.

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Real-world toxicity and efficacy of ixazomib, lenalidomide and dexamethasone in Asian RRMM patients supported by the patient assistance program

Ji Hyun Lee[1], Sung-Hyun Kim[2], Joon Ho Moon[3], Chang-Ki Min[4], Je-Jung Lee[5], Ho-Jin Shin[6], Jae-Cheol Jo[7], Kihyun Kim[8]

[1]Dong-A University College of Medicine; [2]Department of Internal Medicine, Dong-A University College of Medicine, Busan, Republic of Korea; [3]Division of Hematology-Oncology, Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; [4]Department of Hematology, Seoul St Mary's Hospital, Seoul, Republic of Korea; [5]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [6]Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea; [7]Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea; [8]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: The all-oral triplet therapy, ixazomib, lenalidomide, and dexamethasone (IRd), has shown superior progression-free survival (PFS) with excellent safety profile compared with Rd doublet therapy in relapsed and refractory multiple myeloma (RRMM) both in the prospective and retrospective studies. Still, there is limited report of IRd regimen in the real-world Asian RRMM population in terms of the safety and the efficacy. **Method:** Sixty RRMM patients treated with ixazomib, which was supported by the patient assistance program, in combination with Rd were retrospectively analyzed by the meticulous electronic medical record review. **Results:** The median age was 68 years. Trial-ineligible patients due to ECOG performance status ≥ 3, platelet count <75,000/μL, creatinine clearance <30 mL/min, underlying heart or chronic active hepatitis B, unmeasurable disease, primary refractoriness to bortezomib, and remaining peripheral neuropathy after previous therapy were included in 35%. Patients had received a median 1 prior line of therapy. The overall response rate and the clinical benefit rate were 80% and 90%, respectively, and the PFS and overall survival was not reached after a median follow-up of 9.2

months. Thalidomide non-refractoriness and thalidomide response duration of ≥ 12 months in thalidomide responders significantly reduced the risk of progression. Non-hematologic adverse events (AEs) were more common than hematologic AEs, most commonly skin rash followed by gastrointestinal toxicities, and infections, and peripheral neuropathies. Grade 3 or higher AEs were observed but mostly in less than 5%. **Conclusion:** Ixazomib and Rd combination therapy showed a comparable efficacy with a favorable toxicity profile especially in the early relapse of Asian RRMM patients.

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Pomalidomide-based chemotherapy in plasmacytoma at relapse

Ji Hyun Lee[1], Sung-Hyun Kim[2], Kihyun Kim[3], Chang-Ki Min[4], Sung-Soo Park[5], Sung-Soo Yoon[6], Ja Min Byun[6], Je-Jung Lee[7], Sung-Hoon Jung[8], Ho-Jin Shin[9], Jae-Yong Kwak[10], Ho-Young Yhim[10]

[1]Dong-A University College of Medicine; [2]Department of Internal Medicine, Dong-A University College of Medicine, Busan, Republic of Korea; [3]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Department of Hematology, Seoul St Mary's Hospital, Seoul, Republic of Korea; [5]"Division of Hematology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea"; [6]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [7]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [8]Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [9]Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea; [10]Department of Internal Medicine Chonbuk National University Medical School, Jeonju, Republic of Korea

Background: Plasmacytoma at the time of relapse of multiple myeloma is associated with poor response and survival. However, data on the activity of the recently available new drug or drug combinations in RRMM with plasmacytoma in the real-world clinical practice is limited. Pomalidomide and dexamethasone (Pd) with or without cyclophosphamide is an active therapeutic combination in relapsed and refractory multiple myeloma (RRMM) after 2 lines of previous line of therapy. **Method:** This study aimed to analyze the clinical outcome of the pomalidomide-based regimen in RRMM with plasmacytoma. Clinical data of 221 patients who were treated with Pd with or without cyclophosphamide from 7 hospitals participating in the Korean multiple myeloma working party were retrospectively analyzed by electronic medical chart review. All the of patients were previously treated with at least 2 lines of therapies including bortezomib and lenalidomide in most of the patients. Plasmacytoma was diagnosed by the computed tomography, magnetic resonance imaging or FDG-PET scan. **Result:** Twenty-nine patients among the 221 patients analyzed (13.1%) had plasmacytoma at the time of pomalidomide-based chemotherapy. Patients were previously treated with a median 4 lines of therapy (range, 2-14), including bortezomib, lenalidomide, autologous stem cell transplantation in 97%,100%, and 52% of the patients, respectively. 14 patients were treated with Pd and 15 patients had been treated with Pd and cyclophosphamide (PCd). Median number of sites of plasmacytoma involvement was 2 (range, 1-9), including paraskeletal and soft tissue involvement in 83% and 52% of the patients. Sites of soft tissue involvement were: 5 pleura, 4 lymph nodes, 4 subcutaneous, 3 liver, 3 muscle, 2 pancreas, 1 kidney, 1 pericardium, 1 peritoneum, 1 adrenal gland, and 1 stomach. 50% patients (13 among the 26 response evaluable patients) had responded to Pd with or without Cy: 2 complete response, 2 very good partial response, 9 partial response, 1 stable disease, 2 minimal response, and 10 progressive disease. Patients who were treated with PCd showed a better response compared with Pd therapy (53% versus 29%, P=0.264). After a median follow-up of 9.33 months (range, 0.30-52months), patients with plasmacytoma versus no plasmacytoma showed a progression-free survival of 3.57 (95% CI, 0.35-6.78 months) versus 8.40 months (95% CI, 7.00-9.80 months) (P=0.002) and an overall survival of 3.33 (95% CI, 0.00-7.82 months) versus 19.67 months (95% CI, 13.39-25.95 months) (P=0.001). **Conclusion:** RRMM patients with plasmacytoma was responsive after pomalidomide-based chemotherapies. The addition of cyclophosphamide to Pd seemed to result in a better response compared with Pd only. However, RRMM patients with plasmacytoma had poorer survival compared with patients without plasmacytoma even after Pd with or without cyclophosphamide.

P-201

Triple-class refractory disease as a modern therapeutic benchmark for clinical trials testing new agents for relapsed refractory Multiple Myeloma

Ehsan Malek[1], Ankit Kansagra[2], Luciano Costa[3], Saad Z. Usmani[4], Ravi Vij[5], Shaji Kumar[6], Kelly Godby[3], Susan Bal[3], Robert Cornell[7], Yubin Kang[8], Elvira Umyarova[9], Smith Giri[10], Saurabh Chhabra[11], Natalie S. Callander[12], Parameswaran Hari[13], Michaela Liedtke[14]

[1]UH Cleveland Medical Center; [2]University of Texas Southwestern Medical Center; [3]University of Alabama at Birmingham, Birmingham, AL, USA; [4]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [5]Washington University in St. Louis; [6]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [7]Vanderbilt Univeristy; [8]Duke; [9]University of Vermont; [10]University of Alabama; [11]Medical College of Wisconsin; [12]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [13]Division of Hematology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [14]Stanford University

Background: Despite high efficacy of three main classes of anti-myeloma agents, i.e., proteasome inhibitors (PI), immunomodulatory agents (IMiD) and anti-CD38 monoclonal antibodies (CD38MoAb), Multiple Myeloma (MM) remains incurable; therefore clinical trials

testing new agents in the relapsed setting are crucial to open new therapeutic avenues. Where to best position these clinical trials in the trajectory of a MM patient (pt) is highly debatable, mostly due to uncertainty around clinical outcomes after exhausting agents from each main class. This study aims to delineate outcomes of pts with triple-class refractory (TCR) MM treated outside of clinical trials. **Methods:** MAMMOTH represents real world data (RWD) collected from 2016-18 evaluating outcomes of MM pts refractory to CD38MoAB from 14 academic US institutions. This RWD was used to identify pts with TCR MM who received subsequent therapy. Refractoriness was defined as no response and/or progression on or within 60 days of therapy. The reference point for analysis was initiation of next therapy after MM became TCR. TCR MM that was also exposed to two PIs, two IMiDs and a CD38MoAb was considered penta-exposed, and if refractory to those was considered penta-refractory. **Results:** Of 275 pts in the MAMMOTH study, 177 were included in this analysis based on eligibility criteria above. Median age was 65 years and 29% had high risk cytogenetics [t(4;14), t(14;16) or del(17p)]. Median number of prior therapies was 5, median time from diagnosis to TCR was 4.8 years; 58% of pts were penta-exposed and 30% penta-refractory. The first regimen after MM became TCR included cytotoxic chemotherapy in 45%, CD38MoAb in 25%, SLAMF7 MoAb in 7%, carfilzomib in 24%, and pomalidomide in 34% of cases. Overall response rate (ORR) was 30%. Median progression-free survival (PFS) was 2.8 mo (95% C.I. 2.3-3.2) and overall survival (OS) 8.6 mo (95% C.I. 6.8-10.3). For pts with penta-exposed MM (N=102), ORR was 30%, median PFS 2.7 mo (95% C.I 2.1-3.2), and median OS 7.7 mo (95% C.I. 6.0-9.4). For pts with penta-refractory MM (N=53), ORR was 32%, median PFS 2.5 mo (95% C.I. 1.7-3.3), and median OS 6.9 mo (95% C.I. 4.9-8.9). PFS or OS was similar among pts who were TCR but not penta-exposed, TCR plus penta-exposed but not penta-refractory or TCR plus penta-refractory. In multivariable analysis, no factor was predictive of PFS while refractoriness to carfilzomib (HR 2.2, 95% C.I. 1.5-3.3), high-risk cytogenetics (HR 1.5, 95% C.I. 1.0-2.2) and short interval from diagnosis to TCR (HR 0.92, 95% C.I 0.85-0.99) were predictors of shorter OS. **Conclusions:** Taken together we demonstrate that pts with TCR MM have poor ORR to subsequent therapy and inferior survival regardless of being penta-exposed or penta-refractory. Our RWD analysis suggests that triple-class refractoriness represents an important therapeutic milestone that requires novel anti-myeloma therapies to improve outcome and should be considered a benchmark for future drug approval.

P-202

Characterization of ocular adverse events in patients receiving Belantamab Mafadotin for ≥12 months: post-hoc analysis of DREAMM-2 study in relapsed/ refractory Multiple Myeloma

Sagar Lonial[1], Ajay Nooka[2], Praneetha Thulasi[3], Ashraf Z. Badros[4], Bennie Jeng[5], Natalie S. Callander[6], Douglas Sborov[7], Brian E. Zaugg[8], Rakesh Popat[9], Simona Degli Esposti[10], January Baron[11], Allison Doherty[11], Eric Lewis[11], Joanna Opalinska[11], Prani Paka[11], Trisha Piontek[11], Ira Gupta[12], Asim V. Farooq[13], Andrzej Jakubowiak[14]

[1]Winship Cancer Institute, Emory University; [2]Emory University Hospital/Winship Cancer Institute, Atlanta, GA, USA; [3]Emory University, Emory Eye Center; [4]The University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland Medical Center, Baltimore, MD, USA; [5]University of Maryland School of Medicine; [6]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [7]Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; [8]Moran Eye Center, University of Utah; [9]University College London Hospitals NHS Foundation Trust; [10]NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology; [11]GlaxoSmithKline; [12]GlaxoSmithKline, Upper Providence, PA, USA; [13]University of Chicago Medical Center; [14]University of Chicago, Chicago, IL, USA

Background: The B-cell maturation antigen–targeting antibody–drug conjugate belantamab mafodotin (belamaf; GSK2857916) is approved for the treatment of adult patients with heavily pretreated relapsed or refractory multiple myeloma (RRMM). Ocular symptoms (eg, dry eye, blurred vision), eye examination findings (including keratopathy; superficial punctate keratopathy and/or microcyst-like epithelial changes), and visual acuity changes are common with belamaf. This post-hoc analysis characterizes the safety profile of belamaf 2.5 mg/kg Q3W in patients treated for ≥12 months in the DREAMM-2 study. **Methods:** Patients with RRMM who had ≥3 prior therapies, including an immunomodulatory agent and proteasome inhibitor, refractory and/or intolerant to an anti-CD38 monoclonal antibody, received single-agent belamaf. Eye examinations were conducted at baseline and prior to each dose. Dose modifications were based on the most severe Keratopathy and Visual Acuity scale grading, which considers corneal exam findings and best corrected visual acuity (BCVA) changes from baseline. Recovery was defined as Grade 1 exam finding/no exam finding, and ≤1-line decline in BCVA vs baseline. Patient-reported ocular symptoms were graded per Common Terminology Criteria for Adverse Events version 4.03. **Results:** At 13-month follow-up, the clinical benefit rate (≥minimal response) in patients receiving belamaf 2.5 mg/kg (n=97) was 36%; 14 patients (15%) had received ≥12 months of treatment. All 14 patients experienced ≥1 ocular event (maximum grade: 2 [14%]; 3 [79%]; 4 [7%]), and required ≥2 dose delays, with dose reduction to 1.92 mg/kg in 12 patients (86%). Dose modifications permitted ocular event recovery, so belamaf was resumed in all 14 patients. Patients had a mean of 3.6 dose delays (median: 3.5; range: 2–6). Median duration of dose delays was 41 days (range: 4–212); 10 patients (71%) had dose delays >63 days. Long delays did not appear to negatively impact clinical response to belamaf: 12 (86%) had a clinical response (≥partial response; 11 [79%] for ≥6 months). All 14 patients had keratopathy. Ocular symptoms occurred in 13 patients (93%); blurred vision 57%, dry eye 36%, visual acuity reduced 21%, and photophobia 21%. No patients had permanent complete vision loss. **Conclusions:** In this subset of patients receiving belamaf treatment for ≥12 months, dose modification was effective in managing ocular symptoms and

decreasing findings at eye examination, and allowed patients the clinical benefit gained from continuing treatment with belamaf. The safety profile of belamaf will be further characterized in ongoing analyses and studies. **Funding:** GlaxoSmithKline (Study 205678, NCT03525678). Drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa.

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EXCALIBER: a phase 3 study comparing iberdomide, daratumumab, and dexamethasone (IberDd) with daratumumab, bortezomib, and dexamethasone (DVd) in patients with relapsed or refractory multiple myeloma

Sagar Lonial[1], Jesus G. Berdeja[2], Meletios-Athanasios Dimopoulos[3], Sundar Jagannath[4], Stefan Knop[5], Hang Quach[6], Paula Rodríguez-Otero[7], Paul G. Richardson[8], April Sorrell[9], Min Chen[9], Elisabeth Kueenburg[10], Tuong Vi Nguyen[9], Kevin Hong[9], Teresa Peluso[11], Niels W.C.J. van de Donk[12]

[1]Winship Cancer Institute, Emory University; [2]Sarah Cannon Research Institute and Tennessee Oncology; [3]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital; [4]The Mount Sinai Hospital; [5]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; [6]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [7]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [8]Dana-Farber Cancer Institute, Boston, MA, USA; [9]Bristol Myers Squibb, Princeton, NJ, USA; [10]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [11]Celgene International Sàrl, a Bristol Myers Squibb Company; [12]Amsterdam University Medical Center, VU Amsterdam, Department of Hematology, Cancer Center Amsterdam

Background: Despite recent advances, new therapies are needed to deepen and extend remissions in early-line relapsed/refractory multiple myeloma (RRMM). Iberdomide (IBER) is a novel, potent oral cereblon E3 ligase modulator (CELMoD®) compound with enhanced tumoricidal and immune-stimulatory effects when compared with IMiD® agents. Preclinically, IBER overcomes IMiD resistance and has synergy with dexamethasone (DEX), daratumumab (DARA), and bortezomib (BORT). In a phase 1/2 trial in patients (pts) with RRMM, IberDd showed efficacy with favorable tolerability, and pharmacodynamic data demonstrated increased NK and T cell proliferation (Lonial S, et al. HemaSphere 2021; 5(S2):49). The EXCALIBER trial was initiated to compare efficacy and safety of IberDd with that of DVd, a globally approved regimen, in pts with early-line RRMM. **Methods:** In this multicenter, open-label, phase 3 study ≈742 pts will be randomized 1:1 to receive IberDd or DVd. Pts will be stratified within each cohort by number of prior lines of therapy (1 vs 2), age (≤70 years vs >70 years), and ISS staging at study entry (I–II vs III). Key eligibility criteria include age (≥18 years), measurable disease treated with 1–2 prior lines of antimyeloma therapy where a partial response or better to ≥1 prior therapy was achieved, and disease progression during or after the last regimen. Prior treatment with anti-CD38 monoclonal antibodies and/or BORT is permitted under stringent conditions. Treatment in the IberDd arm will consist of 28-day (D) cycles (C) with 1.6 mg IBER on D1–21; 1,800 mg subcutaneous (SC) DARA on D1, 8, 15, and 22 of C1–2, D1 and 15 of C3–6, and D1 of ≥C7; and 40 mg oral DEX (20 mg if ≥75 years) on D1, 8, 15, and 22. Treatment in the DVd arm will consist of 21-D cycles for C1–8 and 28-D cycles for ≥C9; 1,800 mg SC DARA on D1, 8, and 15 for C1–3, D1 for C4–8, and D1 for ≥C9; 1.3 mg/m2 SC BORT on D1, 4, 8, and 11 for C1–8; and 20 mg oral DEX (10 mg if ≥75 years) on D1, 2, 4, 5, 8, 9, 11, and 12 for C1–8. Treatment will continue until confirmed progressive disease, unacceptable toxicity, or consent withdrawal. Primary efficacy endpoint is PFS, calculated as the time from randomization to progressive disease, or death. Assuming a decrease in the PFS risk by 25% (HR=0.75) with IberDd, under exponential distribution assumption of PFS (one-sided a[ED]=0.025) and adjusted for the 2 interim analyses, 441 PFS events will have 85% power to detect an improvement in treatment effect. Secondary efficacy endpoints include OS, duration of response, time to progression, overall response rate, measurable residual disease, and quality of life. Safety evaluations include treatment-emergent adverse events, laboratory parameters, and vital signs. Two interim analyses are planned for PFS, when ≈134 (30%) and ≈334 (75%) events have been accumulated, to examine futility and superiority, respectively. Enrollment is expected to begin in Q3, 2021. NCT number is pending.

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Carfilzomib, Dexamethasone, and Daratumumab (KdD) vs Kd: subgroup analysis of the CANDOR study by prior autologous stem cell transplantation, Lenalidomide exposure, or Lenalidomide refractory disease

María-Victoria Mateos[1], Saad Z. Usmani[2], Hang Quach[3], Meletios-Athanasios Dimopoulos[4], Rafael Fonseca[5], Ian McFadden[6], Akeem Yusuf[6], Monica Khurana[6], Mihaela Obreja[6], Andrew Spencer[7]

[1]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca; [2]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [3]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [4]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital; [5]Mayo Clinic; [6]Amgen Inc.; [7]Alfred Health-Monash University

Background: Widespread use of lenalidomide (Len) as standard first-line therapy for patients (pts) with multiple myeloma (MM) has resulted in a need for Len-sparing treatments in relapsed/refractory

(RR) MM. The CANDOR study (NCT03158688) demonstrated prolonged median progression-free survival (PFS) with carfilzomib, dexamethasone, and daratumumab (KdD) versus Kd alone in pts with RRMM (28.6 vs 15.2 mo; Hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.45–0.78) that was consistent across clinically relevant subgroups (Dimopoulos Blood 2020). Autologous stem cell transplantation (ASCT) is frontline standard of care for MM, particularly for younger pts without severe comorbidities. Therapies that work consistently in pts with and without prior ASCT are needed, as many pts may defer or forego ASCT either due to ineligibility or alternatively selected therapy. This subgroup analysis of CANDOR reports overall efficacy and safety of KdD in RRMM pts with and without prior ASCT subdivided by Len-refractory and/or Len-exposed status. **Methods:** Pts with RRMM (1–3 prior therapies) were randomized 2:1 to KdD or Kd (Dimopoulos Lancet Onc 2020). HR and corresponding 95% CI were estimated using a stratified Cox proportional hazard model. **Results:** 62% (194/312) of pts in the KdD arm and 49% (75/154) of pts in the Kd arm received prior ASCT. With a median follow-up of 27 months, subgroup analyses of PFS were consistent with the primary analysis, suggesting PFS favorability of KdD vs Kd. In pts with prior ASCT, the PFS HR (95% CI) was 0.54 (0.37–0.77) overall, 0.35 (0.20–0.61) for Len-exposed, and 0.30 (0.15–0.59) for Len-refractory. In pts without prior ASCT, the PFS HR (95% CI) was 0.68 (0.44–1.05) overall, 0.62 (0.33–1.15) for Len-exposed, and 0.62 (0.31–1.22) for Len-refractory. Median PFS was estimable for some, but not all subgroups. In pts with prior ASCT, 2-year PFS rates for KdD and Kd were 55% vs 31% overall, 57% vs 15% for Len-exposed, and 57% vs 12% for Len-refractory. In pts without prior ASCT, 2-year PFS rates for KdD and Kd were 55% vs 44% overall, 53% vs 41% for Len-exposed, and 54% vs 39% for Len-refractory. Overall response rates, complete responses (CR), and minimal residual disease-negative CR rates favored KdD vs Kd consistently across all subgroups. Grade ≥3 adverse events (AE) were reported in 89.6% and 78.7% of pts receiving KdD and Kd in the ASCT subgroup and in 82.8% and 73.1% of pts without prior ASCT, with consistent rates across Len subgroups. Rates of treatment-emergent AEs leading to discontinuation of any study drug were 28.6% vs 21.3% for pts with prior ASCT and 25.9% vs 28.2% without ASCT for KdD vs Kd, respectively. **Conclusion:** These findings further support the consistent clinical efficacy and safety of KdD among pts with RRMM with or without prior ASCT, including in the high unmet need group of pts with Len-refractory disease. The KdD regimen should be considered for all these pts beginning at first relapse.

P-205

PORT (OP-109): Phase 2, randomised, Pharmacokinetic (PK), cross-over study of peripheral vs central intravenous administration of Melflufen in patients with Relapsed/ Refractory Multiple Myeloma (RRMM)

Jiri Minarik[1], Ilina Micheva[2], Ganna Usenko[3], Gábor Mikala[4], Tamas Masszi[5], Kameliya Simeonova[6], Birgitta Andersson[7], Markus Jerling[7], Hanjing Xie[7], Luděk Pour[8]

[1]Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic; [2]Multiprofile Hospital for Active Treatment "Sveta Marina", Varna, Bulgaria; [3]City Clinical Hospital 4 of Dnipro City Council, City Hematology Center, Dnipro, Ukraine; [4]National Institute for Hematology and Infectious Diseases; [5]Department of Internal Medicine and Haematology, Semmelweis University, Budapest, Hungary; [6]Specialized Hospital for Active Treatment of Hematological Diseases, Sofia, Bulgaria; [7]Oncopeptides AB, Stockholm, Sweden; [8]Department of Internal Medicine, University Hospital Brno

Background: Melphalan flufenamide (melflufen) is a peptide–drug conjugate with unique PK properties that rapidly penetrates cells, where it is metabolised to melphalan either directly or through an intermediate metabolite, desethyl-melflufen. Melflufen has only been administered via central venous catheter (CVC); however, peripheral venous catheter (PVC) administration may be preferred by patients if safety and tolerability are acceptable. The ongoing PORT study aims to assess the PK, safety, tolerability and efficacy of melflufen CVC vs PVC administration in patients with RRMM (NCT04412707). **Methods:** Patients (following ≥2 lines of prior therapy) were randomised (1:1) to melflufen 40 mg (with oral dexamethasone 40 mg [20 mg for patients aged ≥75 years] weekly on Days 1, 8, 15 and 22) either via PVC in cycle 1 then CVC in cycle 2 (Arm A) or via CVC in cycle 1 and then PVC in cycle 2 (Arm B). From cycle 2 (Arm A) or cycle 3 (Arm B) onwards, patients received melflufen via CVC. PK sampling was performed frequently during and after the 30-minute melflufen infusion. Primary endpoints were maximum observed concentration (Cmax), area under the concentration–time profile from start of infusion to both last measurable concentration (AUC0–t) and to infinity (AUC0–inf) for melphalan, and frequency and severity of PVC-related local infusion-site reactions. Secondary endpoints included PK variables for melflufen and desethyl-melflufen and general safety and tolerability. PK parameters after CVC and PVC administration were compared using bioequivalence methods. **Results:** At data cutoff (2 June 2021), 27 patients had received melflufen (median age 67 years; 48.1% male), of whom 19 patients received at least two doses and were evaluable for PK analysis. Melphalan Cmax, AUC0–t, and AUC0–inf were all bioequivalent for CVC and PVC administration, as demonstrated by a 90% confidence interval (CI) for the ratio of means within 80–125%. For melflufen, the ratio of means was 107–117% for the PK parameters, with all upper 90% CIs above 125%. For desethyl-melflufen, AUC0–t and AUC0–inf were bioequivalent and the 90% CI for Cmax was marginally above the upper limit (127%). Melflufen disappeared rapidly from plasma after the end of infusion, with an average half-life of 5–7 minutes. Melphalan Cmax was observed on average 7–9 minutes after the end of melflufen infusion for both routes of administration, which reflects the delay in distribution of melphalan from tissues to plasma. No PVC-related local reactions were reported. The overall melflufen safety profile was in line with previous studies. **Conclusion:** Systemic melphalan exposure is similar after melflufen PVC and CVC administration. Differences between PVC- and CVC-related PK parameters for

melflufen and desethyl-melflufen are considered to have no clinical consequences as their plasma-exposure duration is short. There were no local reactions after melflufen PVC administration.

P-206

SELECT Trial in Progress: an open-label, phase 2 study of Carfilzomib, Pomalidomide, and Dexamethasone in patients with first or second relapse of Multiple Myeloma

Philippe Moreau[1], Sosana Delimpasi[2], Eirini Katodritou[3], Angelo Belotti[4], Jason Melear[5], Ulf Frolund[6], Laura Rosiñol[7], Britta Besemer[8], Akeem Yusuf[9], Monica Khurana[9], Zhao Yang[10], Meletios-Athanasios Dimopoulos[11]

[1]University Hospital Hôtel-Dieu; [2]General Hospital Evangelismos; [3]Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece; [4]Hematology Division, ASST Spedali Civili Brescia, Brescia, Italy; European Myeloma Network, Italy; [5]US Oncology Research, Texas Oncology - Austin Midtown, Austin, TX, USA; [6]Department of Haematology, Zealand University Hospital, Roskilde, Denmark; [7]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [8]Department of Hematology, Oncology and Immunology, University Hospital Tübingen, Tübingen, Germany; [9]Amgen Inc.; [10]Amgen Inc., Thousand Oaks, CA, USA; [11]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital

Background: Combination therapies comprised of proteasome inhibitors (PI), immunomodulatory drugs (IMiD), and monoclonal antibodies +/- autologous stem cell transplant have significantly improved outcomes for patients (pts) with multiple myeloma (MM). However, many pts relapse despite achieving complete response (CR). Lenalidomide (R) is part of standard of care in newly diagnosed MM, resulting in many pts being refractory at first relapse. There is an emerging unmet need for effective regimens that induce deep responses in the early (first or second) relapsed setting. Minimal residual disease (MRD) is a sensitive measure with deep prognostic value for clinical outcomes, with results influencing subsequent treatment decisions. The IMiD pomalidomide (P) has synergistic activity when combined with a PI plus dexamethasone (d) in pts with relapsed MM refractory to R (Richardson 2019). Carfilzomib (K), a second-generation PI, is approved in combination with d, and as a triplet with daratumumab (KdD) or R (KRd) for pts with MM and 1–3 prior therapies. Phase 1/2 studies have shown that adding K to Pd is well tolerated and effective in heavily pre-treated pts, including those refractory to R (Bringhen 2018). The SELECT trial will evaluate the novel primary endpoint of MRD-negative CR to assess efficacy of KPd in pts with 1 or 2 relapses of MM. **Methods:** This ongoing, open-label phase 2 study (NCT04191616) will enroll ~85 adult pts with MM who have received 1 or 2 prior lines of therapy and are refractory to R. Pts will be treated until disease progression. Prior exposure to PI or anti-CD38 antibody is allowed. Pts previously exposed to K must have responded with at least partial response, must not have discontinued due to toxicity, may not have relapsed while receiving or within 60 days of the last dose of K, and not had K in the last 6 months. Patients with prior P exposure are excluded. K will be given intravenously (IV) (20 mg/m2 on Cycle 1, Day 1; 56 mg/m2 thereafter) on Days 1, 8, and 15 of each 28-day cycle for Cycles 1–12 and on Days 1 and 15 from Cycle 13 until progression or end of study. P (4 mg) will be given orally on Days 1–21 of all cycles. Oral or IV d will be given prior to K at a dose of 40 mg (20 mg for pts ≥75 years of age) on Days 1, 8, 15, and 22 of Cycles 1–12, and at 20 mg (10 mg for pts ≥75 years of age) on Days 1 and 15 of Cycles 13 onwards. The primary endpoint is MRD–negative CR in bone marrow at 12 months by next generation sequencing (sensitivity of 10-5). Secondary endpoints include overall response rate, best MRD-negative response at any time, sustained MRD-negative CR, duration of response, time to response, progression-free survival, overall survival, and safety. SELECT is actively enrolling at ~40 sites in Denmark, France, Germany, Greece, Italy, Spain, and the United States, with expansion to more countries planned. 26 pts are currently enrolled; the target for enrollment completion is January 2022.

P-207

A multi-center, phase 1b study to assess the safety, Pharmacokinetics and efficacy of subcutaneous Isatuximab plus Pomalidomide and Dexamethasone, in patients with Relapsed/Refractory Multiple Myeloma

Philippe Moreau[1], Gurdeep Parmar[2], Miles Prince[3], Enrique Ocio[4], Chatchada Karenes[5], Sumit Madan[6], A Oriol[7], Pierre Bories[8], Michel Delforge[9], Nashat Galbrail[10], Dorothee Semiond[11], Nan Jia[11], Sandrine Macé[12], Florence Suzan[11], Helgi van de Velde[13]

[1]University Hospital Hôtel-Dieu; [2]Illawarra Cancer Care Centre, Wollongong, NSW, Australia; [3]Epworth Healthcare and University of Melbourne; [4]University of Cantabria; [5]City of Hope National Medical Center; [6]Banner MD Anderson Cancer Center; [7]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol; [8]Réseau Régional de Cancérologie Onco-Occitanie; [9]University Hospital Leuven, Leuven, Belgium; [10]Gabrail Cancer Center; [11]Sanofi; [12]Sanofi, Vitry-sur-Seine, France; [13]Sanofi, Cambridge, MA, USA

Background: Intravenous (IV) isatuximab (Isa) + pomalidomide and dexamethasone (Pd) is an approved regimen for the treatment of adults with relapsed/refractory multiple myeloma (RRMM). Subcutaneous (SC) delivery would optimize convenience of administration. **Methods:** This multicenter, open-label, Phase 1b study evaluated the safety, pharmacokinetics (PK), and efficacy of SC vs IV Isa + Pd in patients (pts) with RRMM who had received ≥2 lines including lenalidomide and a proteasome inhibitor. Pts were

randomized 2:1 to Cohorts 1a (SC–1000 mg) or 1b (IV–10 mg/kg) and, after evaluation of Isa SC safety, PK and CD38 Receptor Occupancy (RO), randomized to Cohorts 2a (SC–1400 mg) or 2b (IV). SC was delivered through a syringe pump. Primary endpoints assessed safety including dose-limiting toxicity (DLT), injection site reactions (ISR), and PK parameters. Key secondary endpoints were overall response rate (ORR), progression-free survival (PFS), and CD38 RO. **Results:** 34 pts were randomized and treated: 12 pts Isa IV 10 mg/kg + Pd, 12 pts Isa SC1000 + Pd, 10 pts Isa SC1400 + Pd. On March 31, 2021, 7 pts (58%) IV, 4 pts (33%) SC1000, and 7 pts (70%) SC1400 remained on study treatment. At study entry, International Staging System (ISS) stage II–III was 58% in IV, 33% in SC1000 and 60% in SC1400 pts. Due to sequential accrual, the median follow-up was longer in IV (15.1 months [mos]) and SC1000 (14.8 mos) cohorts than SC1400 (8.8 mos). Infusion reactions were infrequent (≤10% across cohorts, all Grade (G) 2), and only at first injection. Local tolerability of SC injection was very good with only a single episode of G2 ISR in SC1400 cohort. Similar occurrence of ≥G3 treatment emergent adverse events (TEAE), treatment-related TEAE, and neutropenia occurred across cohorts. One DLT was reported in each SC cohort: G4 neutropenia (SC1000) and G3 pulmonary infection (SC1400). No maximum tolerated dose was identified. ORR, ≥VGPR, and complete response were 67%, 33%, and 17% in the IV cohort; 67%, 42%, and 25% in the SC1000 cohort and 80%, 40%, and 20% in the SC1400 cohort, respectively. 8 mos PFS-free rate was 73% in the IV and SC1000 cohorts and 89% in the SC1400 cohort. Mean Ctrough after the 4th weekly administration was higher in the SC cohorts (339 µg/mL for SC1000, 338 µg/mL for SC1400) vs 235 µg/mL for IV cohort. High CD38 receptor saturation by Isa on bone marrow plasma cells was reached for both SC doses; mean CD38 RO was 76% in IV, 80% in SC1000, and 81% in SC1400. **Conclusions:** The safety of Isa SC at 1000 mg and 1400 mg + Pd was consistent with the known safety profile associated with IV administration, with no new safety signals identified. Local tolerability of SC Isa was very good. Efficacy results were comparable with the Phase 3 ICARIA study. Higher Ctrough at 4 weeks (PK best predictor of Isa efficacy) was achieved following SC administration compared with IV. Isa SC administration appears to be a promising and convenient option. Funded by Sanofi.

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Ongoing trials investigating *in*-class transition (*i*CT) from parenteral to oral proteasome inhibitor (PI)-based treatment with ixazomib in multiple myeloma (MM)

Stephen Noga[1], Hans Lee[2], Presley Whidden[1], Ajay Nooka[3], Wenming Chen[4], Kenshi Suzuki[5], Renda Ferrari[1], Ruth Williams[1], Robert Rifkin[6]

[1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Emory University Hospital/Winship Cancer Institute, Atlanta, GA, USA; [4]Beijing Chaoyang Hospital, Capital Medical University, Beijing, China, Department of Hematology; [5]Myeloma/Amyloidosis Center, Japanese Red Cross Medical Center, Tokyo, Japan; [6]Rocky Mountain Cancer Centers, US Oncology Research, Denver, CO, USA

Objective: Several clinical trials in MM are investigating iCT from parenteral PI-based induction with bortezomib (V) or carfilzomib (K) to oral PI-based therapy with ixazomib as part of a triplet regimen. This novel iCT approach aims to prolong the duration of PI-based therapy while maintaining quality of life (QoL) (Manda, CLML, 2020). Here we describe five ongoing iCT trials: the phase IV US MM-6 study (NCT03173092), phase IV Japan MM-6 study (NCT03416374), phase IV MODIFY study in China, & two phase II US collaborative studies, one at the MD Anderson Cancer Center (MDACC study; NCT03763162) & the DeRIVE study (NCT03942224). **Studies:** These are open-label, single-arm iCT studies, except for the DeRIVE randomized study. US MM-6 is a community-based, multicenter study (enrolled, N=141 patients; pts); the population includes US racial & ethnic groups that are typically under-represented in global trials, including African-American & Hispanic pts (Manda, CLML, 2020; Girnius, ASH, 2020). The MDACC study (target enrolment, N=60) & DeRIVE (target, N=76) are single-center US studies. Pts in Japan & China have been/will be enrolled in the Japan MM-6 (enrolled, N=45) & MODIFY (target, N=320) studies, respectively. Across the trials, populations include pts with newly diagnosed (US MM-6, MODIFY, & DeRIVE) & relapsed/refractory (Japan MM-6 & MDACC study) MM. Various induction regimens are being used, but all include parenteral V or K. At iCT, pts transition from the parenteral PI to oral ixazomib from cycle 4 (cycle ≥4 in MODIFY) onwards as part of a triplet regimen. In US MM-6, Japan MM 6, & MODIFY, pts meeting defined response criteria following induction (V-based in US MM-6 & MODIFY; V or K + lenalidomide [R] + dexamethasone [d] in Japan MM-6) go on to receive the all-oral triplet of ixazomib + Rd (IRd) after iCT. Pts transition from daratumumab (D) + Vd (DVd) to D + ixazomib + d (DId) in the MDACC study & DeRIVE. In DeRIVE, the iCT approach is being compared with DId induction alone. Primary endpoints are progression-free survival (US MM-6, Japan MM-6, MODIFY, & MDACC study) or response rate (very good partial response or better; ≥VGPR; DeRIVE); secondary endpoints include time to progression (MDACC study & DeRIVE), duration of treatment (DOT; US MM-6, Japan MM-6, & MODIFY), & QoL measures (US MM-6, Japan MM-6, MODIFY, & MDACC study). To date, the only available data are from US MM-6; the first 101 pts were mostly elderly & comorbid, & the data describe community pt demographics & indicate the tolerability, prolonged DOT (mean duration of IRd after iCT, 9.2 months), & encouraging efficacy (≥VGPR after iCT, 53.5%) of iCT to ixazomib (Girnius, ASH, 2020). **Conclusions:** iCT to all-oral IRd after parenteral V- or K-based induction may prolong DOT & improve outcomes for real-world pts with MM. This approach could also help to prevent treatment interruptions for pts who cannot/prefer not to travel due to travel restrictions or other factors.

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High response rates with IMiD retreatment post anti-CD38 exposure in patients with Multiple Myeloma

Ioannis Ntanasis-Stathopoulos[1], Maria Gavriatopoulou[2], Panagiotis Malandrakis[2], Despina Fotiou[1], Magdalini Migkou[1], Nikolaos Kanellias[1], Evangelos Eleutherakis-Papaiakovou[1], Foteini Theodorakakou[1], Maria Roussou[1], Evangelos Terpos[2], Efstathios Kastritis[2], Meletios-Athanasios Dimopoulos[2]

[1]National and Kapodistrian University of Athens; [2]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital, 11528, Athens, Greece

Background: Anti-CD38 antibodies can alter myeloma pathobiology, and can potentially overcome refractoriness to IMIDs. The aim of the study was to evaluate the efficacy of re-treatment with IMiD-based therapy in patients refractory both to IMiDs and anti-CD38 antibodies. **Patients and Methods:** The study included 38 patients who were refractory to anti-CD38-based therapy and to at least one IMiD. Overall, 26 (68%) patients had received lenalidomide, 11 (29%) pomalidomide and 1 (3%) thalidomide before anti-CD38 treatment. **Results:** Median number of prior lines before IMiD retreatment was 4 (range 2 to 13). The patient distribution per R-ISS was: R-ISS 1: 8, R-ISS 2: 9, R-ISS 3: 4. Overall, 4 (11%) patients received lenalidomide-, 33 (86.5%) pomalidomide-, and 1 (2.5%) thalidomide-based regimens post anti-CD38. The majority of patients were treated with pomalidomide-cyclophosphamide-dexamethasone (PCD) (n=13) and pomalidomide-dexamethasone (PomD) (n=11). The remaining 14 patients were treated with other IMiD-based triplets. Importantly, 10 (26%) patients received the same IMiD as prior to anti-CD38 exposure (lenalidomide n=2, pomalidomide n=8). Median time from diagnosis to IMiD re-treatment was 61.5 months. Overall, 20 patients (53%) achieved a response during IMiD retreatment, including CR=1, VGPR=5, PR=10 and MR=4; 11 patients achieved SD, whereas 7 patients progressed. The disease control rate (DCR=SD+PR+VGPR+CR) was 82%. Among the patients re-exposed to the same IMiD, 5 responded, 3 progressed and 2 remained stable. Among the responders, 1 achieved VGPR with PCD, 2 PR with PCD and DaraPomDex, whereas 2 showed MR with PCD and PCD with Bortezomib. 79% (22/28) of the patients received pomalidomide following previous exposure to lenalidomide; among them, 15/22 (68%) patients responded (1 CR, 4 VGPR, 8 PR, 2 MR), 3 remained stable and 4 progressed. Interestingly, 10 out of 13 (77%) patients who received PCD responded. Median PFS for all patients was 4 months (range 2.9-4.8). Median time to next treatment (TtNT) for the whole study cohort as well as for those who received the same IMiD pre- and post-exposure to anti-CD38 was 4.2 months as well. Median duration of response (DoR) for the responders was 7 months. Median TtNT for those who received pomalidomide after previous exposure to lenalidomide (n=22) was 3.9 months; median DoR among the responders was 6.6 months. Median OS 5.3 range 0.5-35.5. **Conclusion:** IMiD retreatment in patients refractory to both an IMiD and an anti-CD38 antibody can induce significant response rates, even among patients re-exposed to the same IMiD. This indicates that after anti-CD38 therapy a long lasting, probably immunomodulatory effect may be associated with some degree of re-sensitization to IMiDs. The subgroup of patients receiving PCD derived the most benefit. In this context, a prospective study evaluating the role of PCD in this population is currently ongoing.

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Oral ixazomib (Ixa), IV daratumumab (Dara), and dexamethasone (dex; IDd) in relapsed/refractory multiple myeloma (RRMM) patients (pts) with 1–3 prior therapies: phase 2 study interim analysis (IA)

Robert Orlowski[1], Sosana Delimpasi[2], Jan Straub[3], Argiris Symeonidis[4], Luděk Pour[5], Roman Hájek[6], Cyrille Touzeau[7], Viralkumar Bhanderi[8], Petr Pavlíček[9], Pawel Robak[10], Jesus G. Berdeja[11], Jeffrey V. Matous[12], Lionel Karlin[13], Sonja Zweegman[14], Sebastian Grosicki[15], Andrzej Pluta[16], Suman Kambhampati[17], Kaveri Suryanarayan[18], Philip Twumasi-Ankrah[18], Ajeeta Dash[18], Richard Labotka[18], Meletios-Athanasios Dimopoulos[19]

[1]The University of Texas MD Anderson Cancer Center; [2]General Hospital Evangelismos; [3]Department of Internal Medicine - Hematology, University Hospital, Prague, Czech Republic; [4]Hematology Division, Department of Internal Medicine, University of Patras Medical School, Patras, Greece; [5]Department of Internal Medicine, University Hospital Brno; [6]Department of Hemato-oncology, University Hospital Ostrava and University of Ostrava; [7]CHU Nantes Hôtel Dieu, Nantes, France; [8]Florida Cancer Specialists, Tallahassee Cancer Center, Tallahassee, FL, USA; [9]Department of Internal Medicine and Hematology, University Hospital Kralovske Vinohrady, Prague, Czech Republic; [10]Department of Hematology, Medical University of Lodz and Copernicus Memorial Hospital, Lodz, Poland; [11]Sarah Cannon Research Institute and Tennessee Oncology; [12]Colorado Blood Cancer Institute, Sarah Cannon Research Institute; [13]Service d'Hématologie Clinique, Centre Hospitalier Lyon Sud, Pierre-Bénite, France; [14]Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands; [15]Medical University of Silesia, Katowice, Poland; [16]Oncology Specialist Hospital, Brzozow, Poland; [17]Sarah Cannon Research Medical Center, Kansas City, MO, USA; [18]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [19]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital

Background: Proteasome inhibitors (PIs) & monoclonal antibodies are backbones of RRMM treatment; Ixa is approved with lenalidomide-dex for pts with ≥1 prior therapy, & Dara is approved in various regimens, including with bortezomib-dex (DVd).

In CASTOR (DVd vs Vd), Vd was limited to 8 cycles; however, prolonged PI therapy is associated with improved outcomes. The IDd regimen with oral Ixa may enable longer-term PI therapy than with DVd. We evaluate IDd using a treat-to-progression approach. **Methods:** Ixa/Dara-naive RRMM pts receive Ixa 4 mg (days 1, 8, 15), Dara 16 mg/kg (days 1, 8, 15, 22, cycles 1–2; days 1, 15, cycles 3–6; day 1, cycles 7+), & dex 20 mg (days 1, 2, 8, 9, 15, 16, 22, 23) in 28-day cycles. The primary endpoint is ≥ very good partial response (VGPR) rate; secondary endpoints include overall response rate (ORR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), & safety. We report data from the 2nd IA, conducted after ~50% of PFS events had occurred (data cutoff: 1/1/2021). **Results:** 61 pts were enrolled (median age 69 y, 19.7% aged ≥75 y; 19.7% International Staging System stage III; 26.2% high-risk cytogenetics [del(17p), t(4;14), t(14;16)], 42.6% expanded high-risk cytogenetics [high-risk &/or amp1q21]); 59.0/26.2/14.8% of pts had received 1/2/3 prior lines. At data cutoff, pts had received a median of 16 IDd cycles; 37.7% were ongoing. Relative dose intensity (RDI) of Ixa, Dara, & dex was 20%) TEAEs were diarrhea (39.3%), anemia (27.9%), thrombocytopenia (26.2%), & fatigue (21.3%); common (>5%) G≥3 TEAEs were pneumonia (11.5%), thrombocytopenia (11.5%), & anemia (8.2%). Infections & Infestations TEAEs were seen in 57.4% of pts (G≥3 24.6%) and were serious in 26.2%, including pneumonia (9.8%) and COVID-19/pneumonia (4.9%). Rate of peripheral neuropathy (PN) was 18.0% (1.6% G≥3). PN was 28.6% & 12.5% in pts with & without history of PN, respectively. Study drug dose modifications, reductions & discontinuations due to TEAEs were required in 57.4% (Ixa 36.1%, Dara 34.4%, dex 41.0%), 32.8%, & 9.8% of pts, respectively. Four pts died on study due to sudden death, COVID-19 pneumonia, septic shock, & COVID-19 (none were considered study drug-related). **Conclusion:** These IA data suggest IDd has a positive risk-benefit profile in RRMM pts, with a ≥VGPR rate of 30.5%, median PFS of 17.0 m, & a low rate of discontinuation due to TEAEs. The final analysis of this ongoing study is expected in 2022.

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Phase 2 MARCH study: ATG-010 plus Dexamethasone in Chinese relapsed/refractory Multiple Myeloma (RRMM) patients previously treated with an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI)

Lugui Qiu[1], Weijun Fu[2], Chengcheng Fu[3], Wenming Chen[4], Chunkang Chang[5], Baijun Fang[6], Gang An[7], Yongqiang Wei[8], Zhen Cai[9], Sujun Gao[10], Jianyu Weng[11], Lijun Chen[12], Hongmei Jing[13], Fei Li[14], Zhuogang Liu[15], Xiequn Chen[16], Jing Liu[17], Ling Li[18], Yang Yu[19], Aihua Wang[19], Yijun Yang[19], Zhinuan Yu[19], Zhongjun Xia[20]

[1]Institute of Hematology and Blood Diseases Hospital; [2]Shangai Changzheng Hospital; [3]The First Affiliated Hospital of Soochow University, Jiangsu Institute of Hematology, National Clinical Research Center for Hematologic Diseases, Department of Hematology; [4]Department of Hematology, Beijing Chao-Yang Hospital of Capital Medical University, Beijing, China; [5]Shanghai Jiao Tong University Affiliated Sixth People's Hospital; [6]Henan Cancer Hospital, Henan Cancer Hospital Affiliated to Zhengzhou University, Department of Hematologic Oncology; [7]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [8]Nanfang Hospital, Southern Medical University; [9]The First Affiliated Hospital of Zhejiang University, College of Medicine, Hangzhou, Zhejiang, China; [10]the First Affiliated Hospital of Jilin University; [11]Guangdong Provincial People's Hospital; [12]Jiangsu Province Hospital, First Affiliated Hospital of Nanjing Medical University; [13]Peking University Third Hospital; [14]the First Affiliated Hospital of Nanchang University; [15]Shengjing Hospital of China Medical University; [16]Xi Jing Hospital affiliated to the Fourth Military Medical University; [17]the Third Xiangya Hospital of Central South University; [18]Antengene Cooperation; [19]Antengene; [20]Sun Yat-sen University Cancer Center

Background: ATG-010 (selinexor), a novel, oral selective inhibitor of nuclear export, inhibits exportin1. In preclinical and clinical studies, ATG-010 has demonstrated activity against multiple myeloma (MM). ATG-010 (80 mg biweekly) plus dexamethasone (20 mg biweekly) (Sd) has been approved by US FDA for treatment of patients (pts) with penta-refractory MM based on the STORM study. MARCH is a single arm, Phase 2 study to assess efficacy and safety of Sd in Chinese pts with RRMM. **Methods:** Enrolled Chinese pts were previously treated with and refractory to PI, IMiD, and the last line of therapy. Sd was administered in 4-week cycles. The primary endpoint was overall response rate (ORR) per independent review committee. The total planned 82 pts provide ~80% power to test against H0 of 15% ORR at one-sided a[ED] of 0.025. This abstract includes data from the first 60 treated pts. **Results:** As of 13 Oct 2020, 18 (30%) of the 60 pts were on treatment. Median follow-up was 9.5 months (mo) (range: 1.9-12.8). Median age was 61 years (range 43-82; 42% > 65). Pts had received a median of 5 (range 1-16) prior MM regimens, with the following baseline risk factors: 72% R-ISS II/III, 70% cytogenetic abnormalities, 22% del (17p13),20% renal impairment, 15% prior CAR-T therapy, and 25% pre-treated with daratumumab (considered 'triple-class exposed'). ORR was 26.7% (95% CI: 16.1, 39.7). Median duration of response (DOR) was 4.6 mo (95% CI: 1.42, NE). Median progression free survival was 3.7 mo (95% CI: 1.92, 4.66). Median overall survival (OS) was not reached; 9-mo OS rate was 68.5%. ORR was 33.3% in triple-class-exposed pts. Nine pts had prior CAR-T therapy with a median of 9 prior regimens (range 5-12). Among them, ORR was 44.4%, and median DOR was 3 mo (95% CI; 0.96, 4.63). Common treatment emergent adverse events (TEAEs) of any grade included: thrombocytopenia (87%), nausea (87%), leukopenia (85%), anemia (85%), lymphopenia (78%), neutropenia (73%), weight loss (72%), hyponatremia (65%), decreased appetite (63%), asthenia (62%)/fatigue (17%), hyperglycemia (53%), vomiting (52%), hypocalcemia (38%), hypokalemia (30%), diarrhea (30%), and pneumonia (27%). Common TEAEs of Grade ≥ 3 included: anemia (60%), thrombocytopenia (55%), leukopenia (42%), lymphopenia (42%), neutropenia (38%), hyponatremia (28%), and pneumonia (23%). Thirty pts (50%) had TESAEs, including (>3%):

thrombocytopenia (15%), pneumonia (15%), anemia (6.7%), and hyponatremia (3.3%). Eight pts (13.3%) had TEAEs leading to treatment discontinuation, including (>2%): thrombocytopenia (5%) and pneumonia (3%). There were three fatal TEAEs: pneumonia, intracranial hemorrhage, and sudden death (1 each). **Conclusions:** MM pts refractory to both IMiD and PI remain a high unmet medical need. The MARCH study confirms the efficacy of Sd in Chinese patients with a manageable safety profile. These data are consistent with the STORM trial and offer a new, oral therapeutic option for MM patients.

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DREAMM-5 platform trial: Belantamab mafodotin (belamaf; GSK2857916) in combination with five different novel agents in patients with relapsed/refractory multiple myeloma (RRMM)

Paul G. Richardson[1], Suzanne Trudel[2], Natalie S. Callander[3], Ajay Nooka[4], Kevin Song[5], Katarina Uttervall[6], Monique C. Minnema[7], Paula Rodríguez-Otero[8], Herbert Struemper[9], Anne Yeakey[10], Rocio Montes de Oca[11], L. Mary Smith[12], Nicola Jackson[13], Morrys Kaisermann[10], Ellie Im[11], Frank G. Basile[14], Christoph M. Ahlers[11], Beata Holkova[11], Ira Gupta[11], Brandon E. Kremer[11], Hang Quach[15]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Princess Margaret Cancer Centre, Toronto, Canada; [3]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [4]Emory University Hospital/Winship Cancer Institute, Atlanta, GA, USA; [5]Vancouver General Hospital; [6]Karolinska University Hospital, Stockholm, Sweden; [7]UMC Utrecht Cancer Center, Utrecht, the Netherlands; [8]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [9]GlaxoSmithKline, Chapel Hill, NC, USA; [10]GlaxoSmithKline, Research Triangle Park, NC, USA; [11]GlaxoSmithKline, Upper Providence, PA, USA; [12]SpringWorks Therapeutics Inc, Stamford, CT, USA; [13]GlaxoSmithKline, Brentford, UK; [14]Sanofi Genzyme, Cambridge, MA, USA; [15]University of Melbourne, St Vincent's Hospital, Melbourne, Australia

Background: Single-agent belamaf, a B-cell maturation antigen-targeting antibody-drug conjugate, induced durable responses with a manageable safety profile in patients with RRMM at 13 months of follow-up (DREAMM-2; NCT03525678). The unique multimodal mechanisms of action (MoAs) of belamaf, in combination with MoAs of selected agents, have the potential to achieve synergistic effects in RRMM to further enhance the benefit-risk profile. Belamaf is being evaluated in DREAMM-5 in various lines of treatment, as monotherapy or in combination with other agents. **Methods:** DREAMM-5 (NCT04126200) is a phase 1/2 platform study that utilizes a master protocol with separate sub-studies comprised of sequential dose-exploration (DE) and cohort-expansion (CE) phases to identify effective belamaf combinations compared with a shared single-agent belamaf control arm (CE phase only). In the DE phase, patients will be assigned to one of the multiple belamaf dosing combination cohorts by a predetermined algorithm (N≤10 per cohort). A recommended phase 2 dose (RP2D) for each combination will be identified based on safety and preliminary efficacy in the DE phase. An interim analysis of safety, pharmacokinetic, biomarker, and efficacy data will be performed for each combination to determine if it should move forward to the CE phase. Patients in the CE phase (N≥35 per cohort) will be randomized to a sub-study, and within a sub-study, to either the combination arm or belamaf control arm. Patients will also be stratified by number of prior therapies; eligible patients will have received ≥3 prior lines, including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 antibody. All patients will provide informed consent for participation. Primary objectives of the study are to identify the RP2D (DE phase), the overall response rate (≥partial response, CE phase), and safety and tolerability for each combination. Sub-study 1 (combination with GSK3174998, OX40 agonist antibody) is no longer open to enrollment. Sub-studies 2 (combination with GSK3359609, feladilimab, anti-ICOS agonist), 3 (combination with nirogacestat [PF-03084014; SpringWorks Therapeutics], gamma-secretase inhibitor), and 4 (combination with dostarlimab, PD-1 antagonist antibody) are currently open to enrollment. Sub-study 5 (combination with isatuximab [Sanofi], CD38 antagonist antibody) will be open to enrollment soon. Additional sub-studies will be explored based on scientific rationale and/or available preclinical combination data. **Funding:** GSK (208887; NCT04126200). Belamaf drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa. Nirogacestat and isatuximab produced by and used in collaboration with SpringWorks Therapeutics and Sanofi, respectively.

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A matching-adjusted indirect comparison of isatuximab plus carfilzomib and dexamethasone versus daratumumab plus lenalidomide and dexamethasone for relapsed multiple myeloma

Joshua Richter[1], Peggy Lin[2], Viviana Garcia-Horton[3], Patricia Guyot[2], Erin Singh[2], Zheng-Yi Zhou[3], Mark Sievert[2]

[1]Icahn School of Medicine at Mount Sinai Hospital; [2]Sanofi; [3]Analysis Group

Background: The phase 3 IKEMA trial evaluated isatuximab plus carfilzomib and dexamethasone (IsaKd) for relapsed multiple myeloma after 1–3 therapy lines. As no head-to-head comparison exists, we compared IsaKd vs daratumumab plus lenalidomide and dexamethasone (DaraRd) via matching-adjusted indirect comparison (MAIC). **Methods:** Individual patient data from IKEMA (IsaKd arm, NCT03275285) were matched to aggregate data from the phase 3 POLLUX trial (DaraRd arm) by a two-step

process. First, POLLUX inclusion criteria (creatinine clearance >30 mL/min; hemoglobin >7.5 g/dL; platelet count >75×10^9/L; non-lenalidomide-refractory) were applied to the IKEMA IsaKd arm. Second, data for remaining IsaKd patients were re-weighted by their odds of enrolment in POLLUX so that key baseline characteristics were matched with the DaraRd arm. Matched-on characteristics were age (≤64; 65–74; ≥75), Eastern Cooperative Oncology Group performance status (0; 1–2), number of prior therapy lines (1; ≥2), disease stage at entry (I or II; III), cytogenetic risk (standard; high; unknown), prior treatment (proteasome inhibitor [PI]; lenalidomide; immunomodulatory drug [IMiD]), and refractory status (PI-refractory only; IMiD-refractory only). Matching-adjusted progression-free survival (PFS), overall survival (OS) and depth of response rate were compared for IsaKd vs DaraRd. Hazard ratios (HR) and 95% confidence intervals (CI) for PFS and OS were generated by Cox proportional hazard models. Odds ratios (OR) for ≥Very Good Partial Response rate (VGPR) were calculated as the proportion of patients with complete response (CR), stringent CR, and VGPR as best overall response; 95% CI and p values were calculated by Wald tests. **Results:** After applying POLLUX inclusion criteria (before matching), significant (p3 prior therapy lines (0 vs 4.9%), high cytogenetic risk (24.1% vs 12.2%), and who were IMiD-refractory (9.8% vs 3.5%). After matching, there were no significant differences for IsaKd vs DaraRd except for patients with >3 prior lines (0% vs 4.9%). PFS was significantly better with IsaKd vs DaraRd (HR [95% CI]: 0.46 [0.24–0.86]; p=0.0155). There was a numeric, non-significant, improvement favoring IsaKd for OS (HR [95% CI]: 0.47 [0.20–1.09]; p=0.0798) and VGPR (OR [95% CI]: 1.53 [0.89–2.64]; p=0.1252). **Conclusion:** Lenalidomide-based regimens are frequently used in non-lenalidomide-refractory patients until progression. After adjusting for differences in inclusion criteria and baseline characteristics, this MAIC showed significantly better PFS with IsaKd vs DaraRd, the current gold standard in early relapse. In addition, a non-significant numeric trend in favor of IsaKd was observed for OS and VGPR rate. These data suggest that switching to IsaKd vs DaraRd in early relapse in non-lenalidomide-refractory patients may provide superior outcomes. This study was funded by Sanofi.

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Sequencing of treatment regimens after lenalidomide (LEN) in patients with multiple myeloma (MM) in a US community oncology setting

Robert Rifkin[1], Alisha Monnette[2], Chuck Wentworth[2], Arianna Kee[3]

[1]Rocky Mountain Cancer Centers, US Oncology Research, Denver, CO, USA; [2]Ontada, Woodlands, TX, USA; [3]Bristol Myers Squibb, Princeton, NJ, USA

Background: Choice of treatment and sequencing of MM therapies is complex with multiple therapeutic options. LEN-containing regimens are a standard of care at induction, but there is a lack of consensus on the most appropriate therapy for patients (pts) after LEN treatment. Recent evidence describes the importance of continuous immune stimulation and suggests that use of immunomodulatory imide drugs (IMiD® agents) sequentially (LEN to pomalidomide [POM]-containing regimens) vs class switching (LEN to non-POM containing regimens) may improve clinical outcomes. To assess if IMiD sequencing is used in real-world practice, this study aimed to characterize treatment sequences in pts with MM post-LEN in community oncology settings where most pts receive treatment. **Methods:** A retrospective observational study was conducted to identify adult pts with MM in the US Oncology Network (USON) who initiated a post-LEN treatment (index) within 90 days of LEN discontinuation between Jan 1, 2016 and May 1, 2019. Data were sourced from structured and unstructured data in USON's iKnowMed electronic health records. Descriptive analyses were performed to assess demographic and clinical characteristics. Treatment sequences were presented in Sankey plots for pts with MM who initiated POM or non-POM containing regimens post-LEN. Treatment regimens were classified by drug class. **Results:** In total, 257 pts were included in this study, mean age was 68 years (SD=10.7), 184 (72%) pts were White, 136 (53%) were male, and 163 (63%) had an ECOG performance score of 0/1. Overall, 83/257 (32%) pts initiated a POM-containing regimen and 174 (68%) initiated a non-POM containing regimen. Clinical and demographic characteristics were consistent in both cohorts. The most common LEN-containing regimen prior to index was LEN+proteasome inhibitor (PI)+/-dexamethasone (DEX) (n=139/257, 54%), more specifically, LEN+bortezomib+DEX (n=116). The most common index regimens in the POM cohort were POM+monoclonal antibody+/-DEX (n=32/83, 39%), most often POM+daratumumab+DEX (n=29), and POM+PI+/-DEX (n=32/86, 39%), most often POM+carfilzomib (CFZ)+DEX (n=19). The most common index regimen in the non-POM cohort was PI+/-DEX (n=81/174, 47%), most often CFZ+DEX (n=30). In total, 84 pts did not receive treatment after index: 25 (30%) in POM and 59 (34%) in the non-POM cohort. When assessing retreatment with IMiD agents in subsequent lines, 17/83 (20%) pts in the POM cohort had retreatment with LEN and/or POM after a POM-containing regimen vs 15/174 (9%) non-POM pts who had retreatment with LEN. **Conclusions:** This real-world study provides insights into the heterogeneity of treatment sequences for pts with MM in a community oncology setting where approximately one-third of pts were sequenced on IMiD agents. Given recent data suggesting the benefit of using IMiD agents sequentially, further exploration and guidance is warranted to optimize treatment sequencing in MM and maximize therapeutic benefits.

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A phase I/II study of Pomalidomide, Ixazomib, Clarithromycin and Dexamethasone (PICd) in patients with relapsed or refractory Multiple Myeloma (RRMM)

Aaron Rosenberg[1], Meilen Muñoz[2], Caitlin Costello[3], Elizabeth Brem[4], Erin Reid[5], Emanual Maverakis[6], Paul Kaesberg[1], Lisa Lee[7], Mehrdad Abedi, Joseph Tuscano[1]

[1]UC Davis Comprehensive Cancer Center; [2]UC Davis Internal Medicine; [3]Moores Cancer Center, University of California San Diego, La Jolla, CA; [4]University of California, Irvine; [5]UC San Diego Moores Cancer Center; [6]University of California, Davis; [7]Chao Family Comprehensive Cancer Center

Background: Clarithromycin (CL) is a macrolide antibiotic with anti-MM activity when combined with dexamethasone (dex), and imids. Immunomodulatory activity and altered dex metabolism are proposed mechanisms of CL activity, though concerns over toxicity remain. We designed a phase I/II study of pomalidomide (pom), ixazomib (ix), CL and dex (PICd) to assess the tolerability and efficacy of CL in RRMM. **Methods:** The primary endpoints were the maximal tolerated and recommended phase 2 dose of PICd. Secondary endpoints were overall response rate (ORR)(≥ PR), disease control rate (DCR)(≥ SD), duration of response (DOR) and progression free (PFS) and overall survival (OS). Cycles were 28 days. CL 250 mg PO BID was given c1 d15-21 and d1-21 subsequently. Pom 4 mg PO daily for 21 days, ix 4 mg d1, 8, 15 and dex 40 mg (20 mg if age >75 years) d1, 8, 15 and 22 were given for 6 cycles. After C6, maintenance until unacceptable toxicity or PD consisted of reduced pom, ix, dex and CL doses at 2, 2.3, 20 and 250 mg respectively. CL was held during weeks 1-2 of cycle 1 to facilitate correlative studies. **Results:** A total of 32 patients consented to study. Of these, 4 were unevaluable for response/survival due to rapid disease progression (n=2), late screen failure (n=1), and withdrawn consent (n=1). Of these, 3 were included in toxicity data. Median follow up was 20 months (mo). Median age was 68.5 (range 54 – 82), 74% were male. Median number of prior therapies was 2 (1 – 5). All patients had prior lenalidomide and proteasome inhibitor exposure. Of the 26 patients with FISH data, 15 (57%) had high risk cytogenetics. Of these, 9 (35%) had del(17p), 10 (38%) had +1q and 2 (8%) had t(4;14). Four had del(17p) and +1q; 1 each had t(4;14) and del(17p) or +1q. At least 1 grade 3-4 adverse event (AE) was experienced by 17 (55%) patients. Grade 3-4 hematologic AEs were seen in 8 (26%), of which 5 (16%) had neutropenia. Ten (31%) experienced grade 3-4 non-hematologic AEs, of which infections were the most common [4 (13%) patients]. Grade 3-4 neuropathy was not seen. ORR was 75%, DCR was 100%; 13 patients (56%) achieved ≥VGPR while 4 (14%) achieved CR/sCR. High risk cytogenetics were not associated with ORR (Fisher exact test P=1) or ≥VGPR rates (Fisher exact test P=0.42). Median DOR was 23.2 mo (95% Confidence interval: 12.2 – not reached); median PFS was 24.7 mo (13.4 – NR). There was no difference in median PFS in patients with or without del(17p): 24.7 mo (7.5 – NR) vs 22.2 mo (11.0 – NR) respectively (log rank P=0.4). Patients with +1q had a median PFS of 13.4 mo (11 – NR) vs to 39.6 mo (25 – NR) in those without +1q (log rank P=0.09). Median OS was 37.3 mo (21.5 – NR). Correlative studies examining immune effector subsets before and after the addition of CL will be presented at the meeting. **Conclusions:** Overall, PICd is a promising all PO regimen which combines convenient administration, tolerable side effect profile, and long duration of disease control.

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Daratumumab, Carfilzomib, Lenalidomide, & Dexamethasone for relapsed/refractory Myeloma with salvage autologous hematopoietic cell transplant: interim analysis of the multicenter 2nd chance protocol.

Gunjan Shah[1], Susan Bal[2], Cesar Rodriguez[3], Saurabh Chhabra[4], Ruthee Bayer[5], Luciano Costa[2], Jonathan Lambird[6], Christine Ferrer[1], Allison Parascondola[1], Leeann Marcello[1], Leah Shulman[1], Obadi Obadi[1], Jennifer Acosta[1], Hani Hassoun[1], Malin Hultcrantz[1], Neha Korde[1], Sham Mailankody[1], Carlyn Tan[1], Urvi Shah[1], Alexander Lesokhin[1], Oscar Lahoud[1], Michael Scordo[1], David Chung[1], Heather Landau[24], Sergio Giralt[1]

[1]Memorial Sloan Kettering Cancer Center; [2]University of Alabama at Birmingham; [3]Mount Sinai Tisch Cancer Institute; [4]Medical College of Wisconsin; [5]Northwell Health; [6]Wake Forest Baptist Health

Background: Despite major advances in multiple myeloma (MM) therapy, most patients relapse after primary treatment. We present the interim analysis of a phase II multicenter trial evaluating the efficacy of daratumumab, carfilzomib (27 mg/m2 twice weekly), lenalidomide, & dexamethasone (Dara-KRD) with high-dose melphalan and autologous hematopoietic cell transplantation (AHCT) in patients after 1-3 prior lines to induce a complete response and provide patients a 2nd chance at long term disease control. **Methods:** Patients received 4 cycles of Dara-KRD followed by AHCT and 4 additional cycles of Dara-KRD followed by maintenance at investigator discretion with a primary endpoint of best overall response by the end of cycle 8. Using a Simon's two-stage optimal design, 7/22 patients need to achieve a CR to continue. Patient reported outcomes were monitored monthly using the MDASI-MM and NCI PRO-CTCAE. Data cutoff was 7/15/21. **Results:** Between 7/2018 and 7/2020, 23 patients enrolled with 22 evaluable for interim analysis (one did not complete one cycle of treatment and was replaced). Patients had a median age of 65 (range 29-73), with 68% male, 64% white, and 18% black. Time from initial MM diagnosis to enrollment was a median of 4.4 years (range 0.4 -10.6). At initial diagnosis, 36% of patients had ISS stage I disease and 31% had unknown ISS staging. High risk cytogenetics were seen in 36%, with 2 patients having del17p, 2 t(4;14), 1 t(14;16), and 4 gain 1q. Eight-six percent had 1 line of treatment before enrollment with no patients having prior daratumumab, 14% receiving prior carfilzomib, and 86% having had a prior AHCT a median of 3.6 years (range 0.8-9.3) prior to enrollment. Eighty-two percent underwent AHCT and 59% completed all study treatments. Responses deepened post-AHCT prior to the second 4 cycles of Dara-KRD in most cases. Best overall response on study was a CR in 45% (10/22), >VGPR in 77%, and >PR in 82%. Three patients have died, 1 from infection during the pre-HCT cycles and 2 from disease progression. **Conclusion:** Dara-KRD with salvage AHCT induced high overall response rates, meeting the pre-specified cutoff for promising results. Enrollment is ongoing for the second

stage of the study using subcutaneous daratumumab and weekly carfilzomib. Full interim analysis and patient reported outcomes will be presented.

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Isatuximab plus Carfilzomib and Dexamethasone in relapsed Multiple Myeloma patients with high-risk cytogenetics: IKEMA subgroup analysis

Ivan Špička[1], Philippe Moreau[2], Thomas Martin[3], Thierry Facon[4], Gracia Martinez[5], A Oriol[6], Youngil Koh[7], Andrew Lim[8], Gábor Mikala[9], Laura Rosiñol[10], Münci Yağci[11], Michele Cavo[12], Marie-Laure Risse[13], Gaëlle Asset[14], Sandrine Macé[15], Helgi van de Velde[16], Kwee Yong[17]

[1]Charles University and General Hospital; [2]University Hospital Hôtel-Dieu; [3]Department of Hematology, University of California at San Francisco, San Francisco, CA, USA; [4]University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France; [5]Hospital das Clínicas de São Paulo, São Paolo, Brazil; [6]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol; [7]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [8]Austin Health, Melbourne, Australia; [9]National Institute for Hematology and Infectious Diseases; [10]Amyloidosis and Myeloma Unit. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona. Barcelona, Spain; [11]Gazi University, Ankara, Turkey; [12]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Università di Bologna; [13]Sanofi Research & Development, Vitry-sur-Seine, France; [14]Sanofi R&D, Chilly-Mazarin, France; [15]Sanofi, Vitry-sur-Seine, France; [16]Sanofi, Cambridge, MA, USA; [17]University College London

Background: A prespecified interim efficacy analysis of Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) + carfilzomib (K) and dexamethasone (d) (Isa-Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (HR 0.531; 99% CI, 0.318–0.889; P=0.0007), with a clinically meaningful increase in minimal residual disease negativity (MRD–) (29.6% vs 13.0%) and complete response (CR) (39.7% vs 27.6%) rates, and a manageable safety profile. This subgroup analysis of IKEMA examined efficacy and safety in pts with high-risk cytogenetics [t(4;14), del(17p), and t(14;16)] and/or gain(1q21). **Methods:** Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). High-risk cytogenetics was assessed by central laboratory analysis and patients were classified as high risk if abnormalities were present in ≥1 of the following: del(17p): 50% cutoff; t(4;14) or t(14;16): 30% cutoff. In addition, assessment of gain(1q21) was prespecified as ≥3 copies: 30% cutoff; 1q21 amplification as ≥4 copies: 30% cutoff. **Results:** Of randomized pts, 23.5% (Isa-Kd) and 25.2% (Kd) had ≥1 high-risk cytogenetic abnormality (CA); 41.9% (Isa-Kd) and 42.3% (Kd) had gain(1q21); 26.3% (Isa-Kd) and 25.2% (Kd) had isolated gain(1q21); 17.9% (Isa-Kd) and 12.2% (Kd) had 1q21 amplification. Addition of Isa to Kd improved PFS (HR; 95% CI) for pts with ≥1 high-risk CA (0.724; 0.361–1.451) and standard-risk (0.440; 0.266–0.728); pts with t(4;14) (0.549; 0.232–1.301) had a more pronounced treatment effect than pts with del(17p) (0.837; 0.281–2.496). A clear PFS benefit with Isa-Kd was seen for pts with gain(1q21) (0.569; 0.330–0.981), isolated gain(1q21) (0.462; 0.219–0.972), and 1q21 amplification (0.531; 0.150–1.878). Addition of Isa (Isa-Kd vs Kd) led to an improved depth of response for ≥very good partial response (VGPR) (73.3% vs 51.9%), MRD– (32.0% vs 13.5%), and CR (41.3% vs 25.0%) rates in pts with gain(1q21) while these rates were similar between arms in pts with high-risk CA (≥VGPR: 57.1% vs 54.8%; MRD–: 21.4% vs 22.6%; CR: 23.8% vs 22.6%). Higher percentage of pts with isolated gain(1q21) achieved ≥VGPR (80.9% vs 51.6%), MRD– (36.2% vs 9.7%), and CR (46.8% vs 22.6%) with Isa-Kd vs Kd, similar to that seen in pts with standard-risk and 1q21 amplification. Grade ≥3 treatment-emergent adverse events (TEAEs) were more common with Isa-Kd vs Kd for pts with high-risk (85.7% vs 63.3%) and gain(1q21) (80.8% vs 64.7%); incidence of serious TEAEs and TEAEs fatal during study treatment was similar in both arms for high-risk pts. **Conclusions:** Addition of Isa to Kd improved PFS in pts with high-risk CA, and both PFS and depth of response in pts with 1q21 gain/amplification, with a manageable safety profile, consistent with the benefit noted in overall IKEMA population. Isa-Kd is a new treatment option for difficult-to-treat subgroup of pts with RMM and high-risk cytogenetics.

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Tandem autologous + non-myeloablative allogeneic stem cell transplantation in relapsed multiple myeloma: an Australian joint report from the Alfred and Myeloma and Related Diseases Registry

Aditya Tedjaseputra[1], Tongted Das[1], Cameron Wellard[2], Andrew Spencer[3]

[1]Alfred Health; [2]Transfusion Research Unit, Monash University; [3]Alfred Health-Monash University

Background: Graft-versus-myeloma (GvM) effect from allogeneic-SCT potentially affords long-term disease control in multiple myeloma (MM). A salvage program incorporating chemotherapy followed by tandem autologous + non-myeloablative allogeneic-SCT (TAA-SCT) may offer a survival advantage over chemotherapy alone (ChA). **Method:** Consecutive patients with relapsed MM (R-MM) salvaged with chemotherapy followed by TAA-SCT at the Alfred between Jan-08 and Dec-19 were identified. A 2:1 comparator cohort salvaged with ChA (iMiD agent/PI available) matched for age/sex/ISS-stage, was extracted from the Myeloma and Related Diseases Registry (MRDR). All patients received autologous-SCT as part of their upfront treatment. Survival was assessed by

Kaplan-Meier method and compared using log-rank test. Prognostic variables were adjusted using Cox-regression. **Results:** 48 patients received TAA-SCT following salvage chemotherapy during the study period; 35% met criteria for high-risk myeloma at diagnosis (ISS-III and/or adverse CG/FISH) with a median age at salvage of 57 [range: 32-68] and 2 prior therapy lines [range: 1-7]. Preceding TAA-SCT, salvage chemotherapy yielded ≥ PR in ~95% of cases; iMiD® and/or PI were used in ~85%. 87 matched patients were identified from the MRDR as the ChA cohort. Baseline characteristics were comparable, except that the TAA-SCT cohort was more heavily pre-treated ($p < 0.001$). With a median follow-up of 60 months, the estimated 5-year OS were similar: TAA-SCT 63% (95%CI: 48%-75%) vs. ChA 53% (95%CI: 34%-68%). However, after adjusting for number of prior therapy lines, an OS advantage was observed in the TAA-SCT relative to the ChA cohort (HR 0.33, 95% CI:0.13-0.82, $p = 0.001$). In addition, PFS was also improved in the TAA-SCT cohort (Figure 1, $p < 0.001$), with a 5-year PFS of 25% (95%CI: 14%-38%) vs. 1% (95%CI: 0-6%) for the ChA cohort. **Conclusion:** In the iMiD® and PI era, TAA-SCT following chemotherapy remains an effective salvage strategy in selected patients with R-MM, providing an immunological platform for a GvM effect with OS and PFS advantage over chemotherapy alone.

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Relationship between corneal exam findings, best-corrected visual acuity, and ocular symptoms in patients with relapsed or refractory multiple myeloma receiving belantamab mafodotin

Evangelos Terpos[1], Ashraf Z. Badros[2], Rakesh Popat[3], Paula Rodríguez-Otero[4], Asim V. Farooq[5], Bennie Jeng[6], Simona Degli Esposti[7], Eric Lewis[8], Ira Gupta[9], Joanna Opalinska[8], Antonio Palumbo[10], Suzanne Trudel[11], Vinay Jadhav[8]

[1]National and Kapodistrian University of Athens School of Medicine; [2]The University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland Medical Center, Baltimore, MD, USA; [3]University College London Hospitals NHS Foundation Trust; [4]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [5]University of Chicago Medical Center; [6]University of Maryland School of Medicine; [7]NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology; [8]GlaxoSmithKline; [9]GlaxoSmithKline, Upper Providence, PA, USA; [10]GlaxoSmithKline, Zug, Switzerland; [11]Princess Margaret Cancer Centre, Toronto, Canada

Background: Belantamab mafodotin (belamaf; GSK2857916) is a B-cell maturation antigen (BCMA)-targeting antibody–drug conjugate approved in the United States and European Union as a monotherapy for heavily pretreated adult patients with relapsed or refractory multiple myeloma (RRMM). Ocular events (OEs) during the pivotal DREAMM-2 trial (NCT03525678) included corneal exam findings (superficial punctate keratopathy and/or microcyst-like epithelial changes), decline in best-corrected visual acuity (BCVA), and ocular symptoms. Dose reductions or delays based on corneal exam findings and BCVA were used to manage OEs. Here we performed a post hoc investigation of relationships between corneal exam findings, BCVA changes, and patient-reported ocular symptoms to explore if BCVA decline and symptoms could guide dosing, rather than corneal exams. **Methods:** Eye evaluations (including a corneal exam and BCVA assessment of Snellen visual acuity) were performed on all patients receiving single-agent belamaf (2.5 mg/kg) by ophthalmologists at baseline and prior to each belamaf dose. Changes in the corneal epithelium (keratopathy) and BCVA were both assessed as per protocol-defined criteria and assessment of grade (GR) was based on the worse eye. BCVA grading was relative to baseline. Patient-reported ocular symptoms were reported as per the Common Terminology Criteria for Adverse Events. **Results:** In 12.5% of eye evaluations, GR 3–4 keratopathy was associated with minimal or no (GR ≤1) BCVA changes. When patient-reported ocular symptoms were also considered, GR 3–4 keratopathy with GR ≤1 BCVA changes and no ocular symptoms was observed in only 7.5% of evaluations. Mild or no (GR ≤2) keratopathy was associated with GR ≤1 BCVA changes in 59.5% of evaluations, or in 38.8% of evaluations with no ocular symptoms reported. Overall, GR 3–4 keratopathy was found in 24.9% of evaluations; by contrast, patients had GR 2–4 BCVA changes or ocular symptoms in 53.6% of evaluations. **Conclusions:** These findings suggest that BCVA changes and ocular symptoms should be further investigated to determine if they can be used as potential surrogate markers (eg, frequency of eye examinations based on symptoms) for the management of belamaf dosing to potentially reduce the burden on patients and healthcare professionals. **Funding Source:** GSK (205678; NCT03525678). Drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa.

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Use of Carfilzomib regimens in patients with Multiple Myeloma refractory to CD38 antibodies: a subgroup analysis from a prospective observational study

Evangelos Terpos[1], Jo Caers[2], Sorina N Badelita[3], Renato Zambello[4], Thomas Kuehr[5], Eirini Katodritou[6], Alessandra Brescianini[7], Tony Liang[8], Sally Wetten[9], Xavier Leleu[10]

[1]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Greece; [2]Department of Hematology, Liège University Hospital Center, Liège, Belgium; [3]Fundeni Clinical Institute, Bucharest, Romania; [4]European Myeloma Network, Italy; [5]Department of Internal Medicine IV, Academic Teaching Hospital Wels-Grieskirchen, Wels, Austria; [6]Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece; [7]Amgen (Europe) GmbH,

Rotkreuz, Switzerland; [8]Parexel International, Taipei, Taiwan; [9]Center for Observational Research, Amgen Ltd., Uxbridge, United Kingdom; [10]Service d'Hématologie et Thérapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France

Background: Increasing use of antibodies targeting CD38 in first line (1L) for multiple myeloma (MM) has created a need for treatments for patients who are refractory to anti-CD38. This analysis describes the use of carfilzomib (K) with lenalidomide and dexamethasone (KRd) or with dexamethasone alone (Kd) in anti-CD38 refractory patients. **Methods:** Patients with MM who received ≥ 1 K dose and an anti-CD38 in any prior line were retrieved from a prospective real-world study (NCT03091127) of 701 patients. Patients were deemed refractory if any of these criteria were met for any prior anti-CD38 treatment: the best response was stable or progressive disease; progression was the reason for discontinuation; date of relapse was after the start date and within 60 days after the last anti-CD38 dose. **Results:** Of patients who had previously received anti-CD38 (daratumumab [D] or isatuximab), 33 KRd and 71 Kd patients were anti-CD38 refractory at K initiation. Most received D (97% of KRd and 96% of Kd patients), mainly in the immediate prior line. Patients were heavily pre-treated, with 3 and 4 median prior lines in KRd and Kd groups, respectively. Among KRd patients who were refractory to anti-CD38 in any prior line, 18% received anti-CD38 as maintenance therapy. Anti-CD38 was given as continuous therapy in 85% of KRd and all Kd patients, of whom 33% and 52% received it as monotherapy, respectively. The most common anti-CD38 combinations received in any prior line were triplets: D and a proteasome inhibitor (PI), bortezomib or ixazomib (33%) for KRd patients; DRd (41%) for Kd patients. At K initiation, 64% and 45% of KRd and Kd patients who were anti-CD38-refractory were also refractory to PI or IMiD (including 15% and 18% to lenalidomide), respectively, and 3% and 6% of patients were refractory to a PI and IMiD. All results are from anti-CD38 refractory patients who received KRd and Kd, respectively. In those who had a disease response assessment, overall response rates (ORRs) were 67% (18/27) and 52% (32/62), and 44% and 27% had a very good partial response or better (VGPR+). At 2L or 3L (2L/3L), ORR was 75% (9/12) and 67% (6/9), with 67% and 44% of patients achieving a VGPR+. At 4L+, ORR was 60% (9/15) and 49% (26/53), while 27% and 25% had a VGPR+. The median time to K discontinuation, most commonly due to disease progression, was 7 months overall (2L/3L: 12 months; 4L+: 4 months) in KRd and 5 months overall (2L/3L: 5 months; 4L+: 5 months) in Kd patients. Treatment-related adverse events occurred in 33% and 24% of patients, of which 6% and 10% led to K discontinuation. **Conclusions:** These results expand on initial reports (Ghandi et al. Leukemia 2019) indicating K-based regimens are suitable treatment options for anti-CD38 refractory patients, providing evidence for the use of KRd and Kd from 2L with a consistent safety profile to previous studies. Patients completing 1L anti-CD38 therapy will continue to provide further real-world results.

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Evolution of Dara-based regimen use along treatment lines from 2016 to 2019: a real-life study based on the French national claim database

Cyrille Touzeau[1], Vincent Augusto[2], Marie Pierres[3], Matthieu Javelot[3], Caroline Guilmet[3], Martin Prodel[4], Ludovic Lamarsalle[4], Marie Laurent[4], Helene Denis[4], Isabelle Borget[5], Aurore Perrot[6]

[1]Centre Hospitalier Universitaire de Nantes; [2]Center for Biomedical and Healthcare Engineering Mines; [3]JANSSEN Cilag France; [4]HEVA; [5]Institut Gustave Roussy; [6]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France

Background: The therapeutic management of multiple myeloma (MM) has strongly evolved over the past years with the introduction of innovative agents such as daratumumab. This study, based on the nationwide French National Health Insurance databases called SNDS ("Système National des Données de Santé"), provides an overview of the evolution of daratumumab-based regimen use in real-life settings in France since 2016. **Methods:** This retrospective observational cohort study including all MM treated patients identified from 2014 to 2019 through the SNDS, databases which gather hospital records, primary and secondary care, as well as death records for 66 million people. Patients were detected using a validated algorithm which was expanded to consider recent evolutions of MM therapeutic management. Treatment lines were re-constructed through ATLAS, an artificial intelligence algorithm adapted from the Smith-Waterman alignment sequence. For each year (2016-2019) and for each line, the number and percentage of patients starting a daratumumab-based regimen was assessed and regimen detailed (D mono, DRd, DVd, DPd, DKd, DVMp, DVTd, DVRd). Time To Next Treatment (TTNT) for each line has been estimated with a Kaplan Meier method. **Results:** 40,747 prevalent patients treated for a MM between 2014 and 2019 were included, from which 36,241 had lines identified through ATLAS algorithm. Since 2016 (first daratumumab authorization in France) 3,819 patients have received at least one treatment line with daratumumab. 54% [N=2,077] of these patients had a daratumumab-based regimen in L4+, 26% [N=977] in L3, 24% [N=930] in L2, 2% [N=75] in L1 (6% [N=240] had several lines with daratumumab). In L4+, the number of lines started with a daratumumab-based regimen increased (2016: 23% of the L4+ started this year [N=388], 2019: 31% [N=728]). D mono was the main daratumumab-based regimen in L4+ each year, but the number of patients starting this regimen decreased over years (2016: 21% [N=345], 2019: 14% [N=330]). In L3, the number of patients starting a daratumumab-based regimen drastically increased (2016: 6% [N=77]; 2019: 29% [N=441]). D mono was also the main daratumumab-based regimen in L3 (2016: 5% [N=62], 2019: 13% [N=196]) but the daratumumab-based triplet regimens raised in 2019 (15% [N=244]). In L2, the number of patients starting a daratumumab-based regimen also drastically increased (2016: 2% [N=36]; 2019: 23% [N=551]). In 2019 the main daratumumab-based regimen in L2 was DRd (13% [N=320]). In L1, the percentage of patients starting a daratumumab-based regimen in 2019 is 1%

[N=34]. The median TTNT was 11 months for daratumumab-based regimen given in L4+, 14 months for L3. **Conclusion:** The MYLORD study demonstrates the fast integration of daratumumab in the treatment management of MM patients from late relapse to earlier treatment lines over years. Real-world data appear as a powerful tool to study treatment lines and evolution of therapeutic management at a national scale.

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Extended follow-up safety and efficacy results of Belantamab mafodotin (Belamaf) 1.92 mg/kg or 2.5 mg/kg combined with POM and DEX for the treatment of relapsed/refractory Multiple Myeloma

Suzanne Trudel[1], Arleigh McCurdy[2], Heather Sutherland[3], Martha Louzada[4], Christopher Venner[5], Darrell White[6], Hira Mian[7], Rami Kotb[8], Ibraheem Othman[9], Fernando Camacho[10], Molei Fu[10], Engin Gul[10], Donna Reece[10]

[1]Princess Margaret Cancer Centre, Toronto, ON, Canada; [2]The Ottawa Hospital; [3]Vancouver General Hospital, BC Cancer; [4]London Health Sciences Centre; [5]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [6]Dalhousie University, QEII Health Sciences Centre; [7]Juravinski Cancer Centre; [8]Cancer Care Manitoba; [9]Allan Blair Cancer Centre, University of Saskatchewan; [10]Canadian Myeloma Research Group

Background: Belantamab mafodotin (belamaf) is a first-in-class antibody-drug conjugate (ADC) targeting B-cell maturation antigen (BCMA) that has demonstrated clinically meaningful activity as monotherapy in RRMM. Pre-clinical studies demonstrate that the immune mediated anti-myeloma activities of belamaf are enhanced by immunomodulatory drugs providing the rationale for combining Belamaf with POM. **Methods:** A Phase 1/2 multicenter, dose-escalation study evaluated the maximum tolerated does (MTD), recommended phase 2 dose (RP2D), safety and activity of Belamaf plus POM and DEX (B-Pd) in patients (pts) with RRMM. Eligibility required > 1 prior line of treatment (LoT), exposure to lenalidomide (LEN) and a proteasome inhibitor (PI) and refractoriness to the last LoT. POM was administered at 4 mg days 1-21, with weekly dexamethasone (DEX) and various doses and schedules of IV Belamaf on 28-day cycles. Responses were assessed by IMWG criteria and adverse events (AEs) were graded by CTCAE except for corneal findings which were graded by a pre-specified keratopathy and visual acuity (KVA) scale. To better inform the RP2D for Part 2, up to 12 pts could be enrolled in each dose cohort not exceeding the MTD. **Results:** Here we report the tolerability and efficacy of 32 pts treated at each cycle with Belamaf, 1.92 mg/kg (n=12) or 2.5 mg/kg (n=20) in combination with Pd with a median follow up of 13.6 months. The 2.5 mg/kg B-Pd cohort included pts treated with belamaf Q4W (n=7), a 2.5 mg/kg LOADING dose followed by 1.92 mg/kg Q4W from cycle 2+ (n=5) or 2.5 mg/kg SPLIT equally on days 1 and 8 of each cycle (n=8). The median age was 64 (range 36-81) and median prior LoT 3 (1-5). Prior therapies (exposed/refractory) included stem cell transplant (62.5%), PI (100%/78%), LEN (100%/91%) and daratumamb (DARA) (37.5%/100%). 72% were refractory to LEN and a PI and 31% to LEN, a PI and DARA. Grade 3/4 non-ocular AEs reported in >25% of pts treated in the 1.92 and 2.5 mg/kg cohorts respectively, were neutropenia (50% and 50%), thrombocytopenia (42% and 25%), dyspnea (25 and 15%) and lung infection (25% and 10%). At 12 months of treatment =>G3 keratopathy (an eye exam finding) or =>G3 symptomatic blurred vision were observed in 42.9%/93.3% and 28.6%/13.3% of pts treated in the 1.92mg/kg (n=7)/2.5 mg/kg (n=15) groups, respectively. No patients discontinued treatment for AEs and no grade 5 AEs were observed. The ORR/=>VGPR rates for the 1.92 and 2.5 mg/kg cohorts, were 81.8%/63.6% and 95%/85%, respectively. As of May 20, 2021, the median PFS was 14.2 months for the 1.92 mg/kg cohort and 24.2 months for the 2.5 mg/kg group. **Conclusions:** The safety profile of B-Pd is consistent with that observed for Pd or Belamaf individually. Both dose cohorts demonstrate deep and durable responses however the 2.5 mg/kg dose appears to have better efficacy. Alternative dosing schedules are under evaluation to optimize efficacy and safety.

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Bortezomib-Thalidomide-Dexamethasone (VTD) as salvage treatment in patients with Multiple Myeloma eligible for transplantation in the real world. Long-term follow-up.

Jule Vasquez[1], Shirley Quintana[1], Cindy Alcarraz[1], Marco Villena[1], Tatiana Vidaurre[1]

[1]Instituto Nacional de Enfermedades Neoplasicas

Background: Peru is a middle-income country with limited options to access to novel therapies in multiple myeloma (MM). Bortezomib has been introduced as salvage treatment a few years ago. In this setting, bortezomib, thalidomide, dexamethasone (VTD) became the standard salvage treatment for transplant-eligible patients. **Objectives:** To determine the response to treatment to VTD in patients with relapsed/refractory multiple myeloma eligible to transplant. To determine progression-free survival (PFS) and overall survival (OS) to VTD. **Methods:** We retrospectively assessed the clinical efficacy and toxicity of VTD as salvage treatment in patients with relapsed/refractory MM eligible to autologous stem cell transplantation treated at Instituto Nacional de Enfermedades Neoplasicas in Lima, Peru, between January 2014 and December 2016. The treatment consisted of bortezomib 1.3 mg/m2 subcutaneously on days 1, 4, 8 and 11; thalidomide 100mg orally on days 1 through 21; dexamethasone 40mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 for three-week cycles. Antithrombotic prophylaxis was based on acetylsalicylic acid. Prophylaxis against herpes zoster infection was with acyclovir 400mg twice a day, also trimethoprim/sulfamethoxazole was given each other day. **Results:** Sixteen patients were found to fulfill the selection criteria. The median age was 52 (39-62), fifty-six percent (n=9) were male. International Staging

System III disease was present in 75%.Ig G and IgA MM were 62.5% and 12.5% respectively. For VTd regimen the median number of treatment cycles delivered was four (range 2-5), totally 62 cycles. After a median follow-up of 19 months since patients received VTd (range 6-63), the overall response rate was 81%, stringent complete response (SCR) was 18.8% (n= 3), complete response 37.5%, very good partial response 12,5%. Seven out of 16 patients (43.8%) with VTD treatment who were candidates for transplantation finally were transplanted. Median PFS was 19 months (95% CI,12-NR), for the cohort who received SCT was the median PFS was 40 m (95% CI,16-NR), and for the cohort who did not undergo SCT was 14 m (95% CI, 6 - NR), however, this difference was statistically non-significant (p = 0.10). After a median follow-up of 41 months (range 7-141) since the diagnosis of MM, the median overall survival (OS) for the entire cohort was not reach (95% CI, 41– NR). For the cohort who received ASCT the median was not reached (95% CI, 41 - NR), and for the cohort who did not received was 49 months (95% CI, 22 - NR), however this difference was statistically non-significant (p = 0.20). 3-years OS was 86.7% (95%, CI, 56.4 –96.5), the 5-year OS was 66 m (95%, CI, 31.1 – 86.2). **Conclusion:** VTD is an effective treatment in transplant-eligible patients with multiple myeloma who have relapsed after one previous therapy including thalidomide achieving high response rates and acceptable PFS and OS.

P-224

Pomalidomide, bortezomib, and dexamethasone after 1 prior line of therapy in relapsed or refractory multiple myeloma (RRMM): A safety subanalysis of the phase 3 OPTIMISMM trial

Katja Weisel[1], Meletios-Athanasios Dimopoulos[2], Albert Oriol[3], Meral Beksac[4], Fredrik Dimopoulos[5], Anna Marina Liberati[6], Jindriska Lindsay[7], Darrell White[8], Jesús F. San-Miguel[9], Philippe Moreau[10], Larry D. Anderson, Jr[11], Alessandra Lorocca[12], Paweł Robak[13], Prisca Vogel[14], Ruiyun Jiang[15], Lara Grote[15], Teresa Peluso[16], Paul G. Richardson[17]

[1]Department of Oncology, Hematology and Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital; [3]Institut Català d'Oncologia-Hospital Germans Trias i Pujol, Josep Carreras Leukaemia Research Institute; [4]Ankara University School of Medicine, Department of Hematology; [5]Oslo Myeloma Center, Department of Hematology, Oslo University Hospital and KG Jebsen Center for B Cell Malignancies, University of Oslo; [6]University of Perugia; [7]East Kent Hospitals University NHS Foundation Trust, Kent and Canterbury Hospital; [8]Dalhousie University and Queen Elizabeth II Health Sciences Centre; [9]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA; [10]University Hospital Hôtel-Dieu; [11]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center; [12]A.O.U. Citta Della Salute e della Scienza di Torino; [13]Medical University of Lodz, Nicolaus Copernicus Memorial Hospital; [14]Celgene International Sàrl, a Bristol Myers Squibb Company; [15]Bristol Myers Squibb; [16]Celgene International Sàrl, a Bristol Myers Squibb Company; [17]Dana-Farber Cancer Institute, Boston, MA, USA

Background: Patients (pts) with multiple myeloma (MM) refractory to lenalidomide (LEN) are a growing and clinically relevant patient population with a need for safe and effective therapies. In the OPTIMISMM trial (NCT01734928), pts with LEN RRMM who were treated with pomalidomide (POM), bortezomib (BORT), and dexamethasone (DEX; PVd) at first relapse had significantly improved median PFS (20.7 vs 11.6 mo; HR, 0.54; 95% CI, 0.36–0.82; P=0.0027) vs BORT and DEX (Vd; Richardson PG, et al. Lancet Oncol 2019;20:781–794). Treatment-emergent adverse events (TEAEs) reported with PVd were consistent with safety profiles of POM, BORT, or DEX alone. Here we report a safety analysis of TEAEs in the events of interest (EOI) category for PVd vs Vd administered at first relapse in OPTIMISMM. **Methods:** Patients with RRMM and 1–3 prior lines of therapy were randomized 1:1 to receive PVd or Vd in 21-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Key eligibility criteria included ≥2 cycles of prior LEN (LEN-refractory pts were included). AEs were graded according to the NCI CTCAE (v4.0) and summarized by system organ class and preferred term. **Results:** The safety analysis included 221/559 pts (PVd, n=111; Vd, n=110) who had 1 prior line of therapy and received ≥1 dose of study drug. Baseline characteristics were balanced between Tx arms. All pts had prior LEN (57% were refractory); 59% had prior BORT. Median duration of treatment was longer with PVd (47.4 wk; range 4.7–147.0) vs Vd (27.1 wk; range 0.4–162.0). Grade (Gr) 3/4 TEAE EOI occurred in 57% of pts (PVd, 69%; Vd, 45%). The most common Gr 3/4 TEAE EOI were neutropenia (24%), infections and infestations (22%), and thrombocytopenia (20%). Gr 3/4 TEAE EOI more common with PVd vs Vd included neutropenia (37% vs 12%), infections and infestations (29% vs 15%), and peripheral neuropathy (12% vs 5%). Onset of neutropenia was mostly in the first 3 cycles and mainly Gr 3/4, with a median duration of 8 days with PVd and 5 days with Vd. Onset of infections and infestations commonly occurred during cycles 1–9, were mostly Gr 1/2, with a median duration of 12 days with both PVD and Vd. Among patients with ≥1 TEAE EOI, most were managed with dose reductions (PVd, 59%; Vd, 39%) or interruptions (PVd, 79%; Vd, 55%). POM discontinuations due to ≥1 any-grade TEAE EOI were low (9%), none due to neutropenia. In the PVd arm, 62% (31/50) of pts with any-grade neutropenia received G-CSF support. Infections and infestations were the main cause of PVd dose interruptions (54%). Peripheral neuropathy was the most common TEAE EOI leading to dose reduction (32%) and discontinuation (16%) with PVd. **Conclusion:** The safety profile for PVd at first relapse in pts with RRMM is consistent with previous reports. Most TEAE EOI occurred in early cycles of treatment and were managed with dose modifications or appropriate treatment. **Previous presentation:** Weisel K, et al. HemaSphere 2021;5:e464–465. EP988.

P-225

A first-in-human study of FOR46 in patients with triple refractory Multiple Myeloma

Sandy Wong[1], Philip Imus[2], Tomer Mark[3], Jonathan Kaufman[4], Ajai Imus[5], Jeffrey A. Zonder[6], Zachary Walker[3], Daniel Sherbenou[3], Mark Schroeder[7], Jill Abbey[8], Marc Nasoff[8], Andrew Dorr[8], Bin Liu[9], Thomas Martin[10]

[1]University of California; [2]Johns Hopkins Medical Institute; [3]University of Colorado - Anschutz Medical Center; [4]Emory University - Winship Cancer Institute; [5]Mount Sinai School of Medicine; [6]Karmanos Cancer Institute; [7]Washington University School of Medicine; [8]Fortis Therapeutics; [9]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco; [10]Department of Hematology, University of California at San Francisco, San Francisco, CA, USA

Background: Cluster of differentiation 46 (CD46) is highly expressed in multiple myeloma, especially in patients (pts) with gain of chromosome 1q and in the refractory setting. In vitro studies show upregulation and enhanced cytotoxicity upon treatment with pomalidomide, dexamethasone or lenalidomide. FOR46, an anti-CD46 antibody-drug conjugate with vc-MMAE, recognizes a tumor selective epitope of CD46 and is taken up by malignant cells by macropinocytosis, which is a relatively tumor selective uptake mechanism. **Methods:** Pts with MM were enrolled who had progressed on proteasome inhibitors, immunomodulatory drugs and CD38-targeted therapies. An accelerated titration followed by 3+3 dose escalation design was used. FOR46, at protocol specified doses, was infused intravenously over 30-60 minutes on Day 1 of 21-day cycles. Following excess toxicity (neutropenia and fatigue) in a patient (pt) with high body mass index (BMI), dosing was changed from actual weight (AW) to adjusted body weight (ABW). G-CSF secondary prophylaxis was required for pts experiencing grade (gr) ≥ 3 neutropenia during a previous treatment cycle. The initial protocol had 2.4 mg/kg AW as the highest dose. When the MTD was not defined using ABW dosing, escalation was held pending protocol amendment to allow a higher dose and expansion to 10 patients at 2.4 mg/kg ABW began. Safety was evaluated using CTCAE v5.0 and efficacy was evaluated per IMWG criteria. Dexamethasone was only allowed for infusion reaction prophylaxis. CD46 antigen density was determined on patient MM cells via flow cytometry. **Results:** Fifteen pts were enrolled at 6 pre-defined dose levels from 0.1 to 2.4 mg/kg with 1 patient each at the 0.1, 0.3 and 0.6 mg/kg dose levels, 3 at 1.2 and 1.8 mg/kg and 6 at 2.4 mg/kg. Median age was 68 (range 33 – 79) with 4 females. Gain 1q was present in 9 pts, absent in 5 pts and unknown in 1. The median number of prior lines of therapy was 6 (range 3-17). The only dose-limiting toxicity (DLT) was gr 4 neutropenia in 1 high BMI patient dosed by AW. This was the only DLT among 6 pts at 2.4 mg/kg dosed by a mix of AW (n=3) and ABW (n=3). One of 3 at 2.4 mg/kg ABW had non-dose limiting gr 4 neutropenia. The most common related adverse event was gr 4 neutropenia in 3 pts (20%). One patient (6.7%) had gr 4 thrombocytopenia and 1 each (6.7%) had gr 3 AST elevation, neutropenia, anemia, nausea, and peripheral neuropathy (PN). Of the 6 response-evaluable pts in the 1.8 and 2.4 mg/kg cohorts, 3 had partial responses (PRs) lasting 21, 30, and 15 weeks, respectively. Of the PRs, 1 pt did not have gain of 1q21. In addition to the fifteen pts in dose escalation cohorts, 10 have been enrolled in an expansion cohort at 2.4 mg/kg by ABW. **Conclusion:** FOR46 demonstrates an acceptable toxicity profile using ABW dosing. There is encouraging evidence of efficacy in triple refractory MM. A protocol amendment allowing additional dose escalation to 2.7 mg/kg by ABW has been approved. NCT03650491

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Clinical outcomes of Multiple Myeloma patients after anti-CD38 monoclonal antibodies failure

Irene Zamanillo[1], Rosalia De la Puerta[2], Rodrigo gil[1], Maria Poza[1], Rodrigo De la Puerta[1], Rafael Alonso[3], Teresa Cedena[3], Maria Calbacho[1], Rosa Ayala[1], Joaquín Martínez-López[4]

[1]Hospital 12 de Octubre; [2]Hospital la Fe; [3]Hospital universitario 12 de Octubre; [4]Departamento de Hematología, Hospital 12 de Octubre, Complutense University, CNIO, Madrid, Spain

Background: Anti-CD38 monoclonal antibodies (Mab) have significantly improved the prognosis of patients with multiple myeloma. However, not all patients sustain durable responses. Patients relapsed or refractory (R/R) to anti-CD38 Mab present dismal prognosis and constitute a group for whom therapeutic needs are still not defined. We aimed to describe the natural history of patients relapsed or refractory to CD38 monoclonal antibodies. **Methods:** Unicentric retrospective analysis of 57 MM patients R/R to anti-CD38 Mab. Refractoriness was defined as progression within the first two months of treatment. We used chi-square test to compare categorical variables, the Kaplan-Meier method and log rank test for the survival analysis and multivariable analysis using logistic regression. IBM SPSS (v25.0) was used for the statistical analysis. **Results:** The median age was 66 years, 57.9% were female. The cohort received a median of 2; R(0-11) lines of treatment previous to anti-CD38 Mab. 49% had undergone autologous transplant and 64.9% had received a proteasome inhibitor and an immunomodulatory previously. 21 patients (37%) were refractory and 20 (35%) achieved very good partial response or better response. The most frequent combinations were with lenalidomide (DRd; 11%), bortezomib (DVd; 16%), bortezomib and melphalan (D-VMP; 13%) and with carfilzomib (KDd; 27%). 26% received daratumumab in monotherapy or with corticosteroids. Median time to treatment progression was 7 months and median overall survival (OS) was 12 months for the global cohort. OS was longer in patients who achieved a deeper response (49, 12 and 4 months for patients with complete response, partial response and stable disease or progression respectively; p=0.001). High cytogenetic risk was related to poor outcomes, with an OS of 5 months and more frequent CD38 Mab refractoriness (63% vs 37% for the global cohort; p=0.007). Resistance to daratumumab as a first line treatment was observed in 8 patients. 7 of them were treated within a clinical trial for non eligible AHCT patients Median time to daratumumab progression

within this group was 12 months and median OS was 49 months. 49 (86%) of the patients received at least one line of treatment after anti-CD38 Mab R/R and 47% of them had and objective response to at least one of the subsequent therapies employed, with median progression free survival (PFS) of 5 months. Daratumumab-resistant patients had longer OS when treated with regimens containing pomalidomide compared to other agents (median OS 26 vs 6 months respectively; p= 0.021). **Conclusion:** Patients R/R to CD-38 targeted monoclonal antibodies present dismal prognosis, with a median OS of 12 months. Patients with high cytogenetic risk have worse outcomes, with shorter OS and higher probability to anti-CD38 Mab refractoriness. Treatment with pomalidomide-based regimens may be an interesting option for this population. The authors declare no conflicts of interest.

P-227

Alternate day dosing of pomalidomide in patients with refractory/relapsed multiple myeloma (RRMM): Results of a multicenter, single arm phase 2 trial (SAKK 39/16 OptiPOM Study).

Thilo Zander[1], Thomas Pabst[2], Sämi Schär[3], Stefan Aebi[4], Tobias Pabst[5], Ulrich Mey[6], Urban Novak[7], Erika Lerch[8], Gaëlle Rhyner[9], Jeroen Goede[10], Zuzanna Maniecka[3], Stefanie Hayoz[3], Axel Rüfer[11], Christoph Renner[12], Christoph Driessen[13]

[1]Luzerner Kantonsspital; [2]Inselspital, University of Bern; [3]Swiss Group for Clinical Cancer Research (SAKK) Coordinating Center; [4]Luzerner Kantonsspital & University of Bern; [5]Kantonsspital St. Gallen; [6]Kantonsspital Graubünden; [7]Inselspital, University of Bern; [8]EOC - Istituto Oncologico della Svizzera Italiana, Bellinzona; [9]Hôpital Fribourgeois - Hôpital Cantonal; [10]Kantonspital Winterthur; [11]Luzerner Kantonsspital; [12]Onkozentrum Hirslanden Zürich; [13]Clinics for Medical Oncology and Hematology, Cantonal Hospital St Gallen, Switzerland

Background: Pomalidomide (POM) with dexamethasone (DEX) is approved in patients (pts) with relapsed and refractory (RRMM) myeloma and achieved a progression free survival (PFS) between 4.0 and 4.6 months in two pivotal phase III trials (MM-003 and MM-010). In addition, POM-DEX is a current standard backbone for triplet combinations in RRMM. However, POM-DEX with registered POM dosing (4mg daily, 21/28 day cycle) has significant toxicity with G3/4 neutropenia (48%), anemia (33%), infections (34%) and thrombocytopenia (22%) in MM-003, and up to 85% G3/4 neutropenia in triplets containing CD38 antibodies. The relationship between dose, efficacy and toxicity of POM is poorly established and POM delivered on a 2mg daily continuous schedule was similarly active compared to the standard schedule, but less toxic. Half life time of POM (7.5h) is significantly longer compared to lenalidomide (3h) with a slow decline of the POM plasma concentration at the terminal phase. Alternate day dosing of POM 4mg may therefore maintain efficacy while mitigating toxicity. This multicenter, open label, non-randomized phase II study investigated the activity and toxicity of POM 4mg given continuously every second day in RRMM pts. **Methods:** Inclusion criteria matched MM-003. Pts with RRMM must have had ≥ 2 prior lines including bortezomib (BORT), lenalidomide (LEN), adequate alkylator treatment, and progressive myeloma on or within 60 days of the last MM treatment. Continuous oral POM 4mg on alternate days 1 to 28 was combined with weekly oral DEX 40mg (pts > 75 years 20mg) until intolerance or progression (PD). Pts received prophylaxis with acyclovir/valacyclovir, cotrimoxazole and ASS. Prophylactic G-CSF was not allowed. Primary endpoint was overall response rate (ORR, minimal response (MR) or better by IMWG criteria). Secondary objectives were overall survival (OS), 12 months OS, PFS and adverse events (AE). **Results:** 34 patients were enrolled (median age 75 yrs, range 52-87) with time from diagnosis of 5.1 yrs (range 1.9-16.8). Prior treatments included LEN (100%), BORT (100%), alkylator (100%), carfilzomib (29%) and daratumumab (27%); 14 (41%) pts had high-risk cytogenetic features. Median treatment duration was 3.6 months. G3/4 AE occurred in less than one quarter of patients: (neutropenia 24%; anemia 18%; infections 18%; thrombocytopenia 12%). Neutropenic fever was not observed. ORR was 29 % (95% confidence interval [CI], 16%-50%; 3 (9%) VGPRs, 6 (8%) PRs and 1 (3%) MR; 15 pts (44%) achieved SD. 9 pts (26%) progressed. Median PFS was 4.2 months (95% CI, 1.9-5.5 months). OS at 12 months was 66.5% (95% CI, 47.6-79.9). **Conclusion:** POM 4mg on an alternate day continuous dosing schedule is an active and well-tolerated option to deliver POM-DEX to RRMM pts and is especially reasonable for patients at increased risk of toxicity. This dosing schedule may have comparable efficacy, improved safety and should be explored in triplet combination.

NS-61

Higher EQ-5D-5L utility scores at diagnosis are associated with improved overall survival in Australian patients with multiple myeloma: results from the ANZ Myeloma and Related Diseases Registry

Elizabeth Moore[1], Cameron Wellard[1], Adam Irving[2], Erica Wood[2], Zoe McQuilten[2], Andrew Spencer[3]

[1]Transfusion Research Unit, Monash University; [2]Monash University; [3]Alfred Health-Monash University

Introduction: Multiple myeloma (MM) is an incurable blood cancer with a high disease burden. Early assessment of health-related quality of life (HRQOL) can help to guide therapy planning. EQ-5D-5L (EQ5D) scores are collected in the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR) at diagnosis and follow-up as a non-mandatory item. We describe the use of EQ5D utility scores to assess patients' HRQOL at diagnosis. **Methods:** Utility scores are a measure of HRQOL, from '0' (equal to death) to '1' (full health). Scores were calculated for Australian patients with EQ5D data at diagnosis on the MRDR (Feb 2013 - Mar 2021) using a scoring algorithm developed for Australia1. Kaplan-Meier methods were used for survival analysis. **Results:** Of 2239 Australian patients with MM on the MRDR, 483 had baseline EQ5D within 6m of diagnosis, with data for all 5 dimensions.

Median age was 68y (59-76), 63% were male, and median overall survival was 63.0m (54.1-NR). In self-care, 66% of pts reported no problems at diagnosis, while only 22% were pain-free. Problems with mobility were reported in 55%, anxiety/depression in 56%, and problems with usual activities in 67% of patients at diagnosis. Patient characteristics were compared between EQ5D utility score groups (Q1: <0.25, Q2: 0.25-0.49, Q3: 0.50-0.74, Q4: 0.75-1.0) with no difference in median age, gender or disease stage (ISS) between the 4 groups (p≥0.19). As expected, with increasing utility score (better health), median EQ VAS score (patient-identified health status, 0 to 100, 100=best health, 0=worst) increased, and proportion of patients with ECOG performance status 2-4 (unable to work) decreased (p<0.001). Presence of cardiac disease decreased with higher utility score (p=0.048). Notably, higher utility scores at diagnosis were found to be associated with improved overall survival (OS). **Conclusion:** Pain/discomfort was the most frequently reported health issue in MM, and self-care related problems the least, compared to the other health dimensions. EQ5D utility scores in Australian MRDR patients with MM were independent of age, gender and disease stage (ISS=3), but high scores were associated with higher EQ VAS score, improved ECOG, less cardiac disease, and better overall survival. HRQOL of MM patients at diagnosis has prognostic potential with better EQ5D utility scores associated with longer overall survival. **Reference:** [1] Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Appl Health Econ Health Policy. 2013 Jun;11(3):287-98. doi: 10.1007/s40258-013-0035-z.

NS-62

The Importance of regular disease monitoring for patients with low or low intermediate risk Monoclonal Gammopathy of Undetermined Significance (MGUS)

Beth Faiman[1], Jack Khouri[1], Hamilton Kim[1], Saveta Mathur[1], Cynthia Scott[1], Christy J. Samaras[1], Mazzoni Sandra[1], Koc Omer[1], Jason Valent[1]

[1]Cleveland Clinic

Background: Monoclonal gammopathies encompass a number of disorders characterized by a clone of a normal protein. Although biologically heterogeneous, monoclonal gammopathy of undetermined significance (MGUS) represents the most common of these disorders with the production of a monoclonal protein (Mprotein). This abnormal clone of plasma or other lymphoid cells carries a variable risk of progression to a plasma cell disorders (PCDs) requiring treatment. Few studies report real-world incidence of progression from low risk MGUS to PCDs requiring therapy and with newer risk models. Purpose: To describe characteristics of patients who progress from MGUS to PCD requiring plasma cell directed therapy. **Methods:** A list of all patients with MGUS seen at the Cleveland Clinic from 1/1998 to 6/2021 was obtained from an internal IRB approved data base. Demographic information, the date of antecedent MGUS diagnosis, and disease characteristics were confirmed. Patients were categorized as having low, low-intermediate, high intermediate, or high risk MGUS by assigning a point system as follows: Mprotein with IgA isotype (1point), Mprotein concentration of 1.5g/dL or more (1point), serum FLC ratio less than 0.1 or more than 10 (1point), and immunoparesis (≥1 uninvolved immunoglobulins below lower level of normal; 1-2 points).In the scoring system for light-chain MGUS, serum FLC ratio less than 0.1 or more than 10 (1 point) and immunoparesis (1, 2, or 3 points) were identified as risk factors. Patients were excluded if MGUS was diagnosed prior to 2004, missing sFLC, or MGUS <1 year. **Results:** Included in this study were 3,188 charts of patients with confirmed MGUS. Of these, 209 were excluded as did not meet criteria for analysis. An additional 102 patient charts were excluded due to incomplete baseline disease evaluation, or a diagnosis of MGUS prior to 2004 (when light chain assay was commercially available). A total of 2,853 patients remained without evidence of disease progression according to 2014 IMWG diagnostic criteria. 23 patients (12M;11F) progressed from MGUS:14 progressed to MM, 6 progressed to amyloidosis, 2 progressed to WM and 1 progressed to MGRS. The median days from MGUS diagnosis to PCD diagnosis requiring therapy was 2,018 days (5.53y). Interestingly, 5 patients had 0 risk factors for progression but still progressed (3 MM, 2 Amyloidosis); 11 had 1 risk factor/low intermediate risk (7 MM,4 Amyloidosis); 6 had 2 risk factors (4 MM, 2 WM) while 1 had 3 risk factors (to MM). **Conclusions:** Despite this small sample from a single institution, our findings are consistent with other studies in that the number of patients who progress from MGUS to other PCDs remains low. Routine monitoring can improve the time to diagnosis and minimize the risk of organ damage. Advanced practice providers and nurses are well-suited to monitor and mangage patients with MGUS.These findings support regular blood and urine testing for MGUS and ongoing risk assessment.

NS-63

Adapting and improving a Myeloma Support group during the pandemic

Emma Dowling[1], Margareta Sowton[2], Nuno Correia[1], Darren Simpson[1]

[1]HCA Healthcare UK; [2]Maggies, St Bart's Hospital

Introduction: The COVID-19 pandemic has been extremely challenging for myeloma patients and their families. Avenues of support previously available were closed and our regular Myeloma support group was unable to meet. Patients' anxiety levels higher than ever before, we looked at new methods of contact, communication, information and support. Aims: To transfer our longstanding support group to a virtual platform and to maintain the level of access, provision and quality of care throughout the pandemic. **Methods:** An anonymised patient email group was created with weekly email contact, shielding guidance, webinar and support group invitations. Clinical Nurse Specialists facilitated the virtual support group via Microsoft teams. Prior to engaging in events patients were advised of online safety measures and a consent form was given. At the start of each meeting we explained to patients how to utilise the online platform in a straightforward way, including chat function and hand raising. A survey was created to evaluate patients' experience

in this new virtual format and provide us with both qualitative and quantitative statistics. **Results:** We compared satisfaction ratings of the virtual group to meetings in the previous 2 years . Comparably 100% of attendees indicated that support was beneficial whether in person or virtually. 94% agreed that they felt better supported from attending the face to face group last year in comparison with 100% of patients in the virtual meetings. 89% of attendees agreed they benefited from meeting others living with myeloma during meetings last year compared to 100% of patients in virtual meetings. **Conclusion:** The support group evolved over the course of the pandemic in response to patient need and feedback. Many virtual educational events were created with leading specialists discussing the international impact of COVID19 on Myeloma patients around the world and later the vaccine effect in our patients. We looked at empowering our patients shielding at home by creating separate webinars with a physiotherapist, a psychologist and a pain specialist. Through these webinars they received tools and coping mechanisms. A much needed subgroup for younger Myeloma patients in their 30's and 40's was also created due to the rising numbers of patients in this age-group and their unique issues. There have been many positives to the virtual platform including larger capacity (60+ patients in attendance at some events) and increased frequency (at least monthly). On surveying, there was 100% satisfaction and 66% of patients were indifferent to returning to 'in person' meetings in the future proving that quality is still being attained. It was challenging to provide support over a different medium and we were apprehensive that the change in method would alienate or discourage patients. However as one of our patients stated, 'This is all unchartered territory and your calm expertise is even more welcome than usual'.

NS-64

Lessons learned: patient management and outcomes of Multiple Myeloma patients during the COVID-19 pandemic in New York City

Donna Catamero[1], Oliver Van Oekelen[1], Tarek Mouhieddine[2], Bo Wang[1], Megan Metzger[1], Joshua Richter[3], Ajai Chari[4], Daniel Verina[1]

[1]Mount Sinai Hospital; [2]Icahn School of Medicine at Mount Sinai; [3]School of Medicine at Mount Sinai Hospital; [4]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA

New York City (NYC) was an epicenter of COVID-19 pandemic in the United States during spring 2020. During March–May 2020, approximately 203,000 confirmed COVID-19 cases were reported among NYC residents including 54,211 (26.6%) known to have been hospitalized and 18,679 (9.2%) who died. NYC had a higher confirmed coronavirus case volume than any country in the world, besides the United States. Here, we discuss how advanced practitioners Providers (APPs) and Health Care Support Staff in the Multiple Myeloma (MM) program at Mount Sinai Hospital in NYC modified patient care guidelines during the COVID-19 pandemic in an effort to balance the need for social distancing and optimizing patient care. Cognizant of these key factors during the pandemic, oncology APPs, nurses, physicians, and staff at Mount Sinai convened to determine how patients should be best managed. Important considerations in addition to remission status and type of therapy (IV/SC or oral) included the patient's performance status and chemotherapy oral adherence. Based on these, the group determined: (1) Newly diagnosed patients or relapsed patients with significant cytopenias who need parenteral therapy should continue with the current therapy, but the number of visits should be decreased to limit exposure to other HCPs. If the patient has had a good response to treatment, consider changing to an oral regimen. (2) Patients in remission (complete remission, very good partial remission) should consider switching therapy to an oral regimen (immunomodulatory agents, proteasome inhibitors, dexamethasone, and/or Histone deacetylase inhibitors). (3) Stem cell harvest and stem cell transplant should be delayed if the patient continues to respond to the current therapy. **Outcomes:** During this time we had 58 MM patients diagnosed with COVID-19, 36 were hospitalized and 22 were managed at home. The median age was 67 years; 52% of patients were male and 63% were non-White. Hypertension (64%), hyperlipidemia (62%), obesity (37%), diabetes mellitus (28%), chronic kidney disease (24%), and lung disease (21%) were the most common comorbidities. In the total cohort, 14 patients (24%) died. Older age (>70 years), male sex, cardiovascular risk, and patients not in complete remission (CR) or stringent CR were significantly ($p<0.05$) associated with hospitalization. Although several demographic factors and comorbidities increased the risk of hospitalization and mortality, myeloma therapy did not influence outcomes. In fact, survival was comparable to the overall population of New York during the pandemic. Our data supports the need to maintain proactive management of MM patients by balancing their need for therapy with the increased risk of hospitalization and death in a subset of MM patients with COVID-19.

NS-65

Introducing frailty assessment into a myeloma service – a Quality Improvement Project (QIP)

Catherine Morrow[1], Linda Barton[1], Nicky Hayes[2], Winfield Marc[1], Mamta Garg[3], Sachedina Shelina[1], Asagba Graham[1]

[1]University Hospitals of Leicester NHS Trust; [2]Kings College University, London; [3]Leicester Royal Infirmary, UK

Developments in management and treatment of myeloma have extended survival rates in the myeloma population (Kumar et al, 2008) resulting in older patients living with the effects of myeloma and treatments and also the concurrent problems of ageing. The myeloma multidisciplinary team (MDT) in Leicester UK introduced frailty assessment for newly diagnosed patients over 65 years using QIP methodology as a Clinical Nurse Specialist (CNS) led initiative. The aim being to improve MDT decision making and documentation about treatment attenuation and furthermore to proactively identify frailty to enable enhanced support for frailer patients. This was aimed to be the initial development of an older person's pathway of care. The International Myeloma Working Group (IMWG) frailty

score (Palumbo et al 2015) and Clinical Frailty Score (Rockwood et al, 2005) were used as assessment tools, the latter being widely used throughout UK healthcare settings. Following initial audit and project planning, stakeholder engagement was undertaken using questionnaires, experience surveys and presentations. Interventions were planned using the Plan-Do-Study-Act (PDSA) method. Data was collected via audit of a number of team documentation sources and via patient feedback questionnaires. The aim of the project was surpassed and in both PDSA 2 and 3, 100% of newly diagnosed patients were frailty assessed, results being discussed in MDT, documented and communicated to primary care. The quality of information about patient frailty and function assisted MDT decision-making processes and improved over the QIP. This enabled clear rationales for MDT decisions to be documented in relation to individualised patient treatment options. There were no extra demands on CNS time, in fact consultation time decreased. Patient experience was maintained. The MDT recognised during the project that frailty scores need to be used with caution taking into consideration myeloma burden and presenting complications to avoid the risk of under-treatment (American Society of Haematology, 2019). Frailty scoring is now embedded into practice and assessment. **References:** American Society of Haematology (2019) Staging the Aging. Retrieved from https://www.ashclinicalnews.org/spotlight/feature-article/staging-the-aging [accessed 14/03/2020]. Kumar S. et al (2008) Improving Survival in multiple myeloma: Impact of novel therapies. Blood. Vol 111(5) pp 3594. Palumbo A. et al (2015) Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. vol 125 no.13 pp2068-2074. Rockwood K. et al (2005) Global Clinical Measure of Fitness and Frailty in Elderly People. CMAJ; 173 (5), 489-494.

NS-66

Project to improve volume of treatment and satisfation-PIVOTS, a quality improvement project

Mary Steinbach[1], Kelley Julian[1], Grace Blissell[1], Samuel Shewan[1], Zachary Francom[1], Matt Whooley[1], Carrie Bellerive[1], Amandeep Godara[1], Brian McClune[1], Douglas Sborov[1]

[1]Huntsman Cancer Institute/University of Utah

Background: The Huntsman Cancer Institute Multiple Myeloma (MM) Program is the primary referral center for the Intermountain West. Over the past 5 years, our Program has experienced a 40% increase in patient volumes, an increase to 4 MM physician providers, and significant expansion of the clinical trial portfolio and clinical/trial support staff. Our previous care model was inefficient and did not optimize the independence of our advanced practice clinicians (APC). Previously, we relied on a traditional "resident model" in which APCs staffed every patient with the attending physician. Our provider group hypothesized that utilizing a more contemporary clinical model would improve clinical efficiency and Relative Value Unit (RVU) generation and enhance job satisfaction for all members of our clinical team while maintaining high patient satisfaction scores. This model, called Project to Improve Volume of Treatment and Satisfaction or PIVOTS, is focused on 4 fundamental pillars including: 1) Modifying physician and APC clinic templates to optimize daily clinic volumes; 2) Establish specific "divisions of labor" for patient follow-up; 3) Standardization of post-autologous transplantation follow-up and disease reassessment; and 4) Standardization of new and return patient clinic notes. The main objective of this project is to fundamentally change our care model to better support our patients and optimize the productivity and moral of our team. **Design and implementation:** Physician templates includes seeing all new patients, follow-up visits with disease reassessments and treatment modification, and per patient request. APC templates shifted to the RCO Model (Revlimid maintenance, Cruising patient, and Outpatient transplant) and acute issue and day 1 treatment visits. Clinic note templates for new, return, and acute patient visits were constructed as a team over the 6 months prior to starting the project. **Metrics:** A 12-month period from May 2021 – April 2022 has been specified and the following metrics have been defined pre- and post-PIVOTS implementation. RVU generation will be collected for all providers over this 12-month timeframe and descriptively compared to per provider metrics from the prior 2 years. University Qualtrics and Patient Experience has developed and implemented all job satisfaction surveys that will be completed by all staff (MA, RN, APC, physician) at 3, 6, 9, and 12 months. Patient satisfaction scores and comments are collected per institutional standards. Research productivity for all members of the MM Program will be collected pre- and post-PIVOTS implementation and will include abstract submissions, grant funding, and manuscript production. **Results:** The PIVOTS project will be instrumental in defining a new standard for structuring a dedicated myeloma clinic to improve clinical and academic productivity and job satisfaction without compromising a high-quality patient experience.

NP-108

Improvement in patient experience with successful implementation of a Velcade at Home program in patients with myeloma

Hayley Beer[1], Emma-Jane Furphy[1], Simon Harrison[1], Trish Joyce[1], Nella Combe[1], Catherine Downey[1], David Routledge[1], Allison Drosdowsky[1], Amit Khot[1]

[1]Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Traditionally subcutaneous Velcade is delivered in a day ward environment. To reduce hospital visits for our patients, we introduced a Velcade at Home program (VAH) consisting of two arms; self-injection and general practitioner (GP) delivery. Here we present data on the patient experience outcomes. **Methods:** A Self-Injection Assessment Questionnaire was developed for both GP and self-injection arms, adapted from a previously validated tool (1). The questionnaire elicited respondents' feelings about GP administration or self-injection using a Likert scale format with free text questions used to evaluate time and cost burden. The questionnaire was completed each week during the first cycle in the chemotherapy day unit, prior to cycle 3 (after one full cycle in the community) and at

the end of cycle 4. All data were analysed using descriptive statistics. **Results:** The first 20 patients enrolled onto the VAH Program were consented to the study, with 19 completing the program (15 self-injection, 4 GP). In the self-injection arm 46% (7/15) of patients felt anxious prior to their first dose, this decreased to 0/15 by the end of cycle 4. No participants had difficulty removing the cap, depressing the plunger or administering the injection after their first cycle of training. The time reported to complete the injection was shorter for the self-injection arm when compared to their previous injections at hospital (mean 6 minutes and 280 minutes respectively). Similarly, patients in the self-injection arm reported a reduction in the cost burden associated with attending hospital. Of those who responded, 5/7 reported no costs associated with VAH. **Conclusion:** The VAH program has been very well received with patients appreciating the opportunity to regain some control over their treatment and the potential for significant benefit in time and costs. We have been able to share our resources with 7 sites in Australia and New Zealand to help in the implementation of a similar program. **Reference:** [1] Keininger, D., Coteur, G. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health Qual Life Outcomes 9, 2 (2011). https://doi.org/10.1186/1477-7525-9-2

NP-109

Improving long-term quality of life for patients living with multiple myeloma: a service evaluation

Sarah Henshaw[1]

[1]*Nottingham University Hospitals*

Background: Multiple myeloma (MM) is an incurable malignancy of the bone marrow. With improving survivorship patients are developing late effects and long-term consequences due to the treatments, alongside the disease itself. The 2017 guidance for screening and management of late and long-term consequences does not suggest where in the MM pathway this screening should be. **Methods:** A quantitative, formative service evaluation using audit of the current screening and a correlational design, using one-way MANOVA evaluating the effect the stage of pathway has on symptom burden and distress. Symptom burden is assessed using the palliative outcome score MY-POS and distress using the distress thermometer. **Results:** Patients (N=60) are currently frequently screened for adjusted calcium (96%), urea and electrolytes (96%), liver function tests (90%) and blood pressure (62%). LH/FSH (0%), testosterone (10%), oestrogen (0%), T-SAT (30%), Vitamin D (15%) and BNP (3%) are least likely to be screened. Completed questionnaires (N=223) demonstrated that frequently reported symptoms were pain (76.2%), weakness or lack of energy (86.1%), drowsiness (69.1%), poor mobility (70.1%) and tingling in the hands and feet (65.5%). Distress is perceived higher by those patients on treatment (M=4.01, SD=2.486). Higher levels of distress were demonstrated by patients post first line (M=3.33, SD=2.446) and post third line (M=4.6, SD=2.510). MANOVA analysis demonstrated an effect on overall wellbeing of the patients in relation to position in the treatment pathway (F=13.35, p=<0.005). **Discussion:** Screening and management of late effects and long-term consequence can improve quality of life. This evaluation has demonstrated the need for formal screening and management of these complications from diagnosis. Evaluation of symptoms and distress in the pathway has demonstrated that assessment at diagnosis, at the end of first line treatment or one year after starting a continuous treatment and repeated annually from when patients start third line treatment will improve QOL.

NP-110

Physical activity in multiple myeloma: a review of the literature

Michaela Hillengass[1], *Janine Joseph*[1], *Jens Hillengass*[1], *Jane McCarthy*[1]

[1]*Roswell Park Comprehensive Cancer Center*

Background: One of the major problems Multiple Myeloma (MM) patients suffer from is bone instability and the resulting difficulties that come along with it, such as pain and immobility. Few studies have been performed among this patient group to investigate the effects of physical exercise (PE) on MM patient outcomes like muscle strength, and quality of life, such as fatigue, and pain. **Methods:** A PubMed search was conducted by entering the search terms "Multiple myeloma" + "Exercise" and "Multiple myeloma" + "Physical exercise" and yielded 178 and 218 manuscripts respectively. Limiting the search results to clinical trials left 13 and 14 manuscripts; 7 studies: 1 retrospective chart review, 1 questionnaire study, and 5 prospective clinical trials. The majority of these studies (5) were published in the last decade. **Results:** Due to factors such as small sample size and short time of follow up intervention, the results are mostly unclear. The outcomes of several studies of exercise in MM show that physical exercise is feasible for MM patients preparing for an autologous stem cell transplant. Compared to the control groups, the most active participants show better outcomes, like improvements in their blood counts and in Quality-of-Life parameters such as fatigue, pain, sleep, and mood. In one study, no significant benefits were found for fatigue, muscle strength, and cardiovascular fitness; Investing monetarily in the fitness program for one patient group did not result in less costly treatment afterwards. One trial found that MM patients were in much poorer condition then people in a normative standard group. However, compared to other cancer patients, there were no differences in physical performance tests. **Conclusion:** Some of the reported outcomes of exercise in MM have been promising but need to be substantiated in a broader setting with more diverse participants, for a longer duration and include more endpoints like treatment tolerance, survival, and bone pain amongst others. Due to the disease inherent risk of bone-related complications, an individualized, supervised training protocol could be a preferrable tool.

NP-111

Myeloma Treatment Scheduler (MyeTxScheduler): an online educational tool to help keep patients on track

Tracy King[1], Jenny Hempton[2], Jacqueline Jagger[3], Carmel Woodrow[4], Julija Sipavicius[5], Alicia Snowden[6], Kerin Young[7], Sally Haines[8]

[1]Institute of Haematology, Royal Prince Alfred Hospital; [2]Barwon Health Geelong; [3]Central Coast Local Health District; [4]Princess Alexandra Hospital; [5]Royal North Shore Hospital; [6]Precision Haematology; [7]WA Country Health Service - Great Southern; [8]The Alfred Hospital

Introduction: An increasing number of complex treatment regimens are utilized for the management of multiple myeloma (MM). Treatment schedules include multiple drugs, supportive measures, pathology tests and clinician reviews, however there is no universal scheduling template for Australian use. The Myeloma Specialist Practice Network (M-SPN) of the Haematology Society of Australia and New Zealand (HSANZ) works toward improving quality nursing care and outcomes for individuals with MM. Aim: To develop an online tool for clinicians to create individual MM treatment schedules to be printed and provided to patients to aid understanding, improve adherence and enhance myeloma patient care. **Method:** The M-SPN partnered with a health technology platform, myINTERACT to develop and deliver the online tool MyeTxScheduler. A nurse member working group developed content based on Cancer Institute NSW Cancer Treatments Online (eviQ) and real-world clinical experience. Standard MM protocols are included with ability to amend as clinically indicated. Patient identifiers are not included but added after printing. A recent update improved speed, functionality, added new standard protocols and provides links to additional patient information. 3 Haematologists and 2 oncology pharmacists provided content review. Patients provided input on final schedules. **Results:** MyeTxScheduler is distributed through HSANZ membership but available to all clinicians as free download on iOS / Android tablet devices or online populating through the myINTERACT digital platform. 26 standard protocols provide pre-populated MM schedules. Users can amend each item, save, edit and clone schedules. Capacity to add additional drugs and amend notes allows flexibility for real world clinical application. Access MyeTxScheduler at https://rego.interact.technology/myetx/ **Conclusion:** MyeTxScheduler enables clinicians the ability to create individualized treatment schedules to provide to their patients at the point of care, promoting and enhancing quality patient care and nurse understanding of the complex myeloma treatment journey.

NP-112

Onboarding advanced practice providers to myeloma clinical teams

Danielle Roberts[1], Charise Gleason[1]

[1]Winship Cancer Institute of Emory University

Background: Advanced practice providers (APP), also known as nurse practitioners and physician assistants, are essential members of the multidisciplinary myeloma care team. APP's within our organization train and specialize in myeloma specific clinics practicing at the top of their license with independent schedules collaborating with their physician colleagues. APP's working in clinic have independent schedules, participate in clinical research, and run a malignant hematology procedure clinic. We also have dedicated APPs working on our inpatient service. As our myeloma program continues to grow, we have developed a distinct advanced practice provider orientation and onboarding program to better prepare our new team members. **Methods:** The APP leadership team reviewed the current onboarding process, performed a literature review of onboarding best practices, and developed an onboarding structure for newly hired APPs. All APPs were evaluated at 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months during the first year of employment. Each new APP was assigned a preceptor/mentor, an orientation/onboarding timeline, and competency tools. Employment satisfaction, retention, and productivity were measured during each time frame. **Results:** Over the last three years our institution has onboarded 16 new APPs to our myeloma program in both outpatient and inpatient clinical settings. Our competency tools specifically outlined expected reading materials, number of patients seen each week, and number of procedures to be completed by the end of orientation. At this point we have successfully integrated new advance practice providers into the team and have a retention rate of 81%. One APP did not make it through orientation, one left after 2 years and went to work at another hospital, and one left after a year due to pregnancy. **Conclusion:** Having a dedicated approach to onboarding APPs in the myeloma program, increases productivity and patient access to care. Our myeloma APP providers are integrated into the clinical setting from the beginning and are given a period of training and ramp up allowing them to practice at the top of their license. Having independent schedules has been essential for APP job satisfaction and retention. Collaboration between the APP and myeloma physician is essential as is the relationship of the multidisciplinary team which includes nursing, research, and a clinical pharmacist. We evaluated our competencies on a yearly basis to ensure that our APPs are learning the information as it pertains to the changes in landscape of myeloma diagnosis and treatments. The success of our onboarding process has led to higher retention rates and increased job satisfaction, making our APPs experts in the field of myeloma.

NP-113

Developing a national information and support group program for the carers of people living with myeloma

Narelle Smith[1], Nella Combe[1], Alicia Hopper[1], Jo Gardiner[1], Hayley Beer[1], Rachel McCann[1]

[1]Myeloma Australia

Introduction: Myeloma Australia's support services have always been available to carers of people living with myeloma. However, we recognised a need to offer a space just for carers to help them

cope with the unique issues of a complex disease, treatment side effects, supportive care needs and the impact of each relapse on their loved one. The aim of this project was to understand the needs of carers in the Australian myeloma community to guide development of an appropriate carer-specific national information and support group program. **Methods:** A 14-question survey was emailed to the Myeloma Australia national database to gauge carer interest, priorities and needs. Four pilot information and support groups were held online in two Australian states over a two month period. Each group was facilitated by two myeloma support nurses. Attendees and facilitators evaluated sessions according to content, time of day and length of meeting. Data collection from the survey, feedback from pilot group attendees and a literature review were interpreted using thematic analysis to guide the program development. **Results:** 144 survey responses were received in which 70% expressed interest in attending an information and support group. 17 carers and 6 facilitators evaluated the four pilot online information and support groups. Carers identified feelings of loneliness, helplessness, worry and exhaustion in the survey. Themes emergent from carer engagement in the study and review of local and international literature included priorities of gaining knowledge, developing coping strategies and the desire to share with others in a similar situation. **Conclusion:** There are significant, unmet needs for carers of myeloma patients. Myeloma Australia has now launched carer information and support groups in all states. Future directions include development of resources for carers of people living with myeloma in Australia and collaboration with external organisations to expand national carer service provision.

NP-114

Lesson Learned: Management of patients with Multiple Myeloma (MM) and their response to two doses of COVID-19 RNA vaccine

Daniel Verina[1], Oliver Van Oekelen[2], Charles Gleason[3], Sarita Agte[4], Komal Srivastava[3], Katherine Beach[3], Adolfo Aleman[5], Tarek Mouhieddine[5], Ajai Chari[6], Carlos Cordon-Cardo[7], Florian Krammer[3], Sundar Jagannath[8], Viviana Simon[9], Ania Wajnberg[10], Samir Parekh[11]

[1]Mount Sinai Medical Center; [2]Mount Sinai Hospital; [3]Icahn School of Medicine at Mount Sinai, Department of Microbiology; [4]Icahn School of Medicine at Mount Sinai, Department of Medicine, Hematology and Medical Oncology; [5]Icahn School of Medicine at Mount Sinai; [6]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [7]Icahn School of Medicine at Mount Sinai, Department of Pathology; [8]The Mount Sinai Hospital; [9]Icahn School of Medicine at Mount Sinai, Department of Medicine, Division of Infectious Diseases; [10]Icahn School of Medicine at Mount Sinai, Department of Internal Medicine; [11]Mount Sinai Medical Center, New York, NY, USA

Introduction: COVID-19 has resulted in a global, social and economic disruptions, especially a widespread shortage in supplied and stress on the healthcare system. The global effort to develop an effective vaccine was monumental. The COVID-19 mRNA vaccine is effective in preventing morbidity and mortality in a phase 3 clinical studies. Evidences by Addeo et al, 2021, note that some individuals with underlying comorbidities may mount suboptimal response to the COVID immunization. MM patients are immune-compromised due to a defect in immunity as well as immunosuppressed due to therapy. Cognizant of these key factors during the pandemic, oncology Advance Practice Practitioners (APP's), nurses, physicians, and staff at Mount Sinai convened to explore if MM patient on active treatment were able to mount a response to COVID 19 RNA vaccine and the considerations if patient showed no response. Based on these, the group determined: (1) Continue to practice Social distancing: Social distancing is an essential step in preventing the spread of COVID-19. Social distancing is reducing physical interaction between people and it lowers the chances of spreading illness between people. Practice social distancing by putting space (at least 6 feet) between yourself and others. Inside your home: Avoid close contact with people who are sick. If possible, maintain 6 feet between the person who is sick and other household members. Outside your home: Put 6 feet of distance between yourself and people who don't live in your household. (2) Continue to Wear a Mask: wear a mask in indoor public places. In areas with high incidences of COVID-19 cases, consider wearing a mask in crowded outdoor settings and for activities with close contact with others who are not fully vaccinated. (3) Encourage all family members > 12 years old to be fully vaccinated. **Outcomes:** During this time, we collected 320 MM patient samples who had received 2 doses of the COVID Vaccine. The median age was 68 years; 57.8% of patients were male. Previous treatment lines > 3 lines (26.9%), > 5 lines (14.7%). Treatment regiments containing: Immunomodulatory drugs (46.6%), Proteasome inhibitor (28.4%), Anti-CD38 mAb (43.3%), Anit-SLAMF7 mAb (5.6%), CAR-T therapy (7.2%); BCMA-targeted therapy (11.3%), Previous ASCT (51.6.%). Vaccine type, 69.1% received Pfizer of which 80.5% had an undetectable SARS-CoV-2 antibody spike; Moderna 27.7%, of which 19.5% had an undetectable SARS-CoV-2 antibody spike.

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