Personalized Treatment of Relapsed MM

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Disclosure Information

Marc S. Raab

I have the following financial relationships to disclose:

- Consultant for: Amgen, BMS, GSK, Janssen, Novartis, Pfizer, Sanofi, Takeda
- Speaker's Bureau for: Amgen, BMS, Janssen
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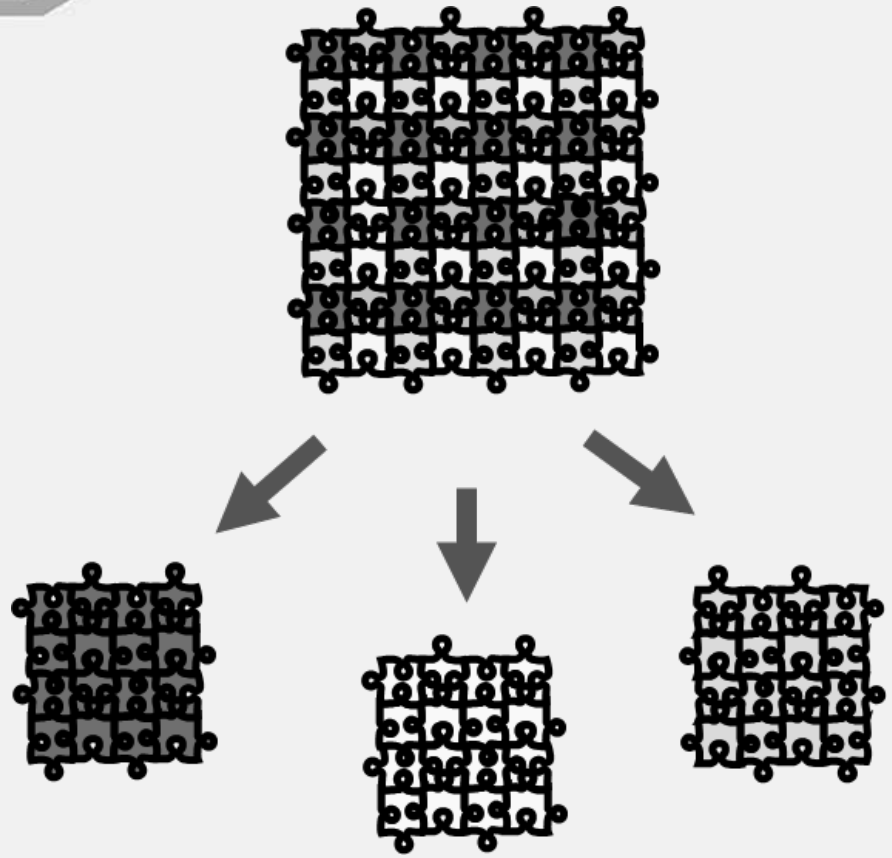
- Stockholder in: none
- Employee of: none

I will discuss the following off label use and/or investigational use in my presentation: *encorafenib, binimetinib*

How to define Personalized Therapy in MM



Immunotherapeutic Targets

- Epitopes: SLAMF7, CD38, BCMA, GPRC5D, FcRH5, …
- Technology: MoABs, ADCs, TCEs, CAR-Ts

Molecular Targets

- Cytogenetics: translocations, gains/deletions
- Genomics: mutations, signatures, molecular mechanisms

Generic Targets

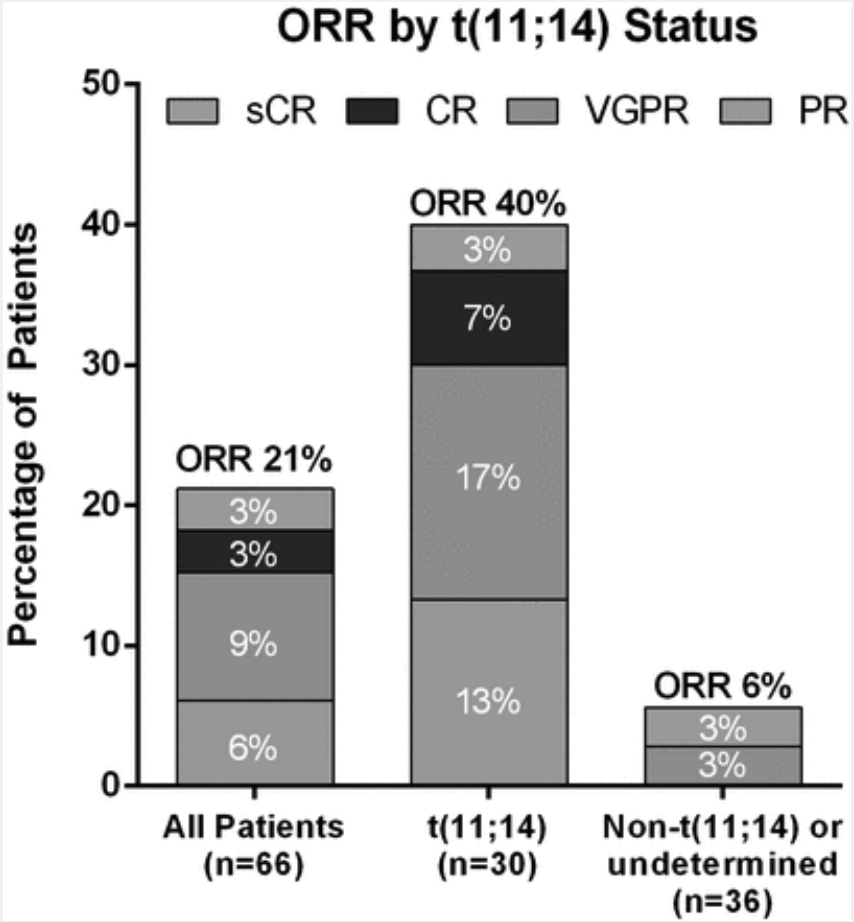
- MRD, residual lesions, …
- Resistance mechanisms
- Activated signaling pathways

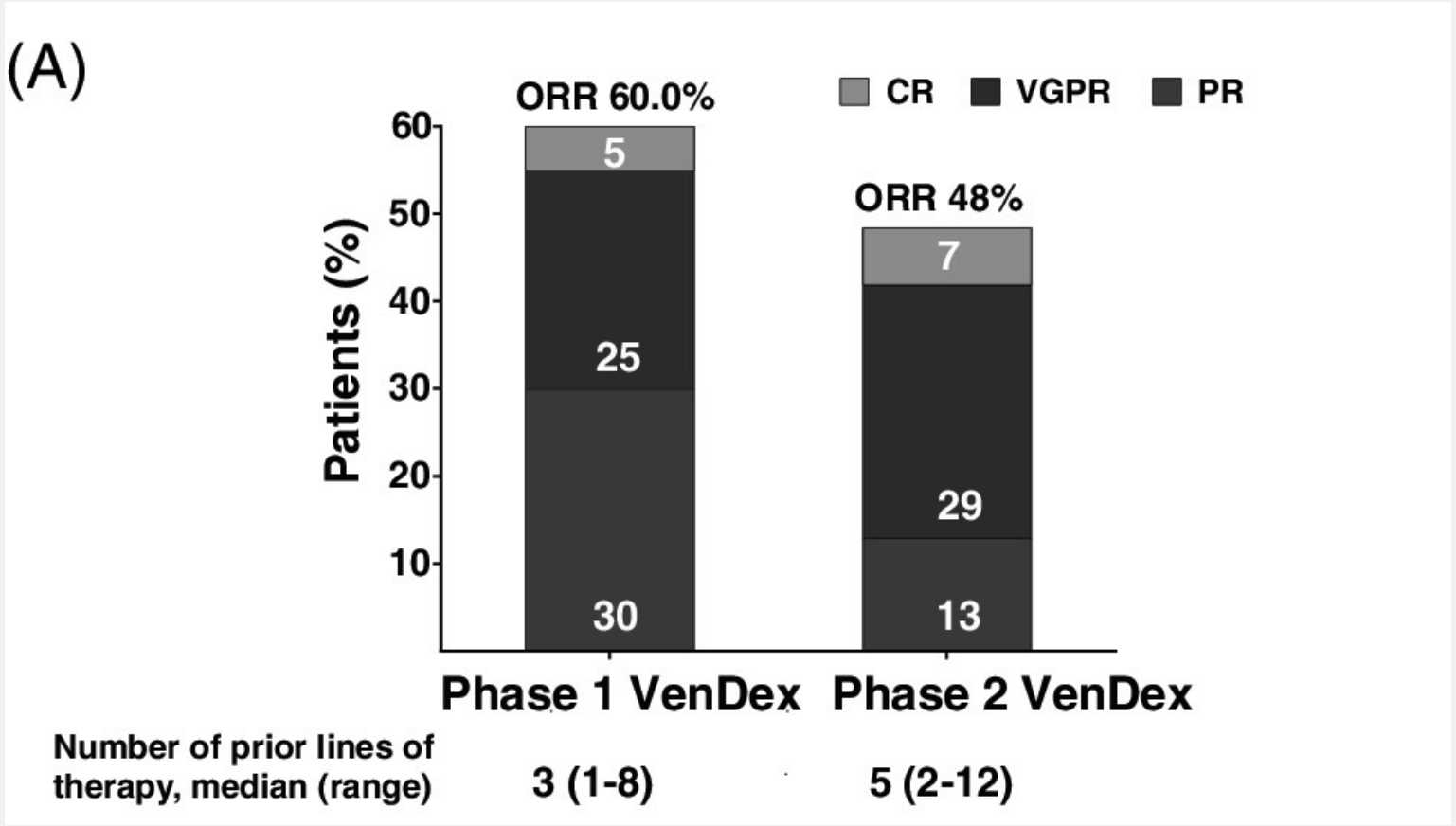
Genomics

- **Well-known hallmark translocations involving IgH locus** t(11;14), t(4;14), t(14;16), t(14;20)
- **Diverse mutational landscape, few recurrently mutated genes:**
  - **KRAS/NRAS:** ∑20-25% each
  - **FAM46C**: ca. 12%
  - **TP53**: ca.8%
  - **BRAF**: 4%
  - **TRAF3 and DIS3**: <3%
- **Mutational clusters within pathways:**
  - **MAPK pathway:** ca. 50%
  - **Akt/NF-κB pathways:** ca.17%

Chapman et al. Nature. 2011. 471: 467-472; Lohr et al. Cancer Cell. 2014. 25(1): 91-101;
Walker et al. JCO. 2015. 33(33):3911-20; Walker et al. Nat. Comm. 2015. 6: 6997-7008

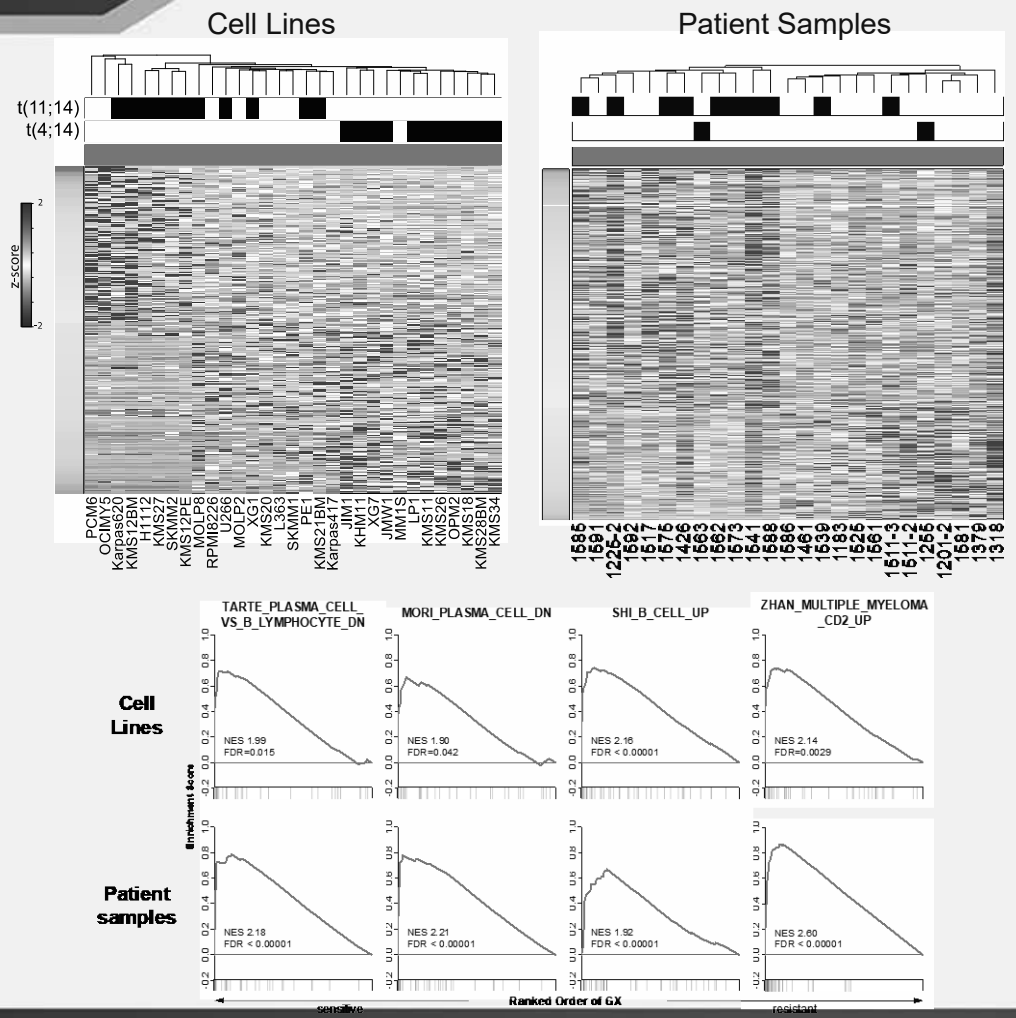
Targeting BCL2 is effective in patients with t(11;14) myeloma

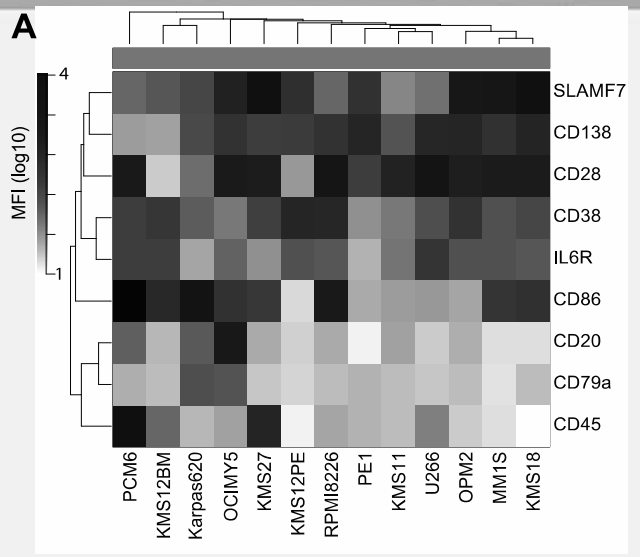




Kumar et al., Blood , 2018
Kaufman et al., Am. J. Hematol., 2021

Enrichment of B cell genes in venetoclax sensitive samples. Flow cytometry of cell surface markers predicts venetoclax sensitivity.

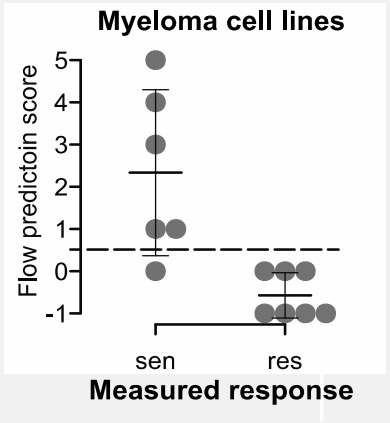


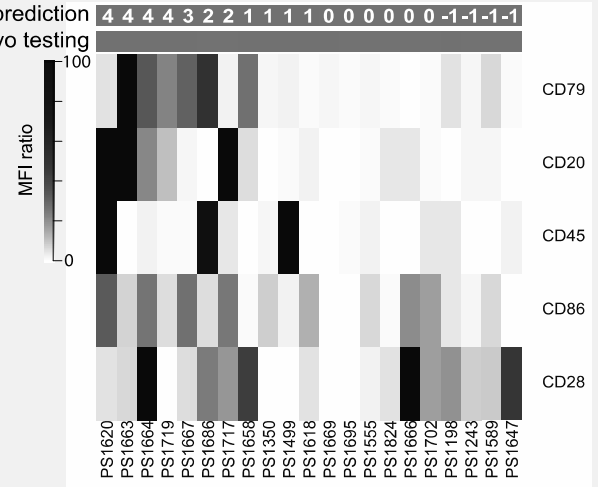


B

Marker	Score
CD79a	+2
CD20	+2
CD45	+1
CD86	+1
CD28	-1

Sensitive	Resistant
≥1	≤0

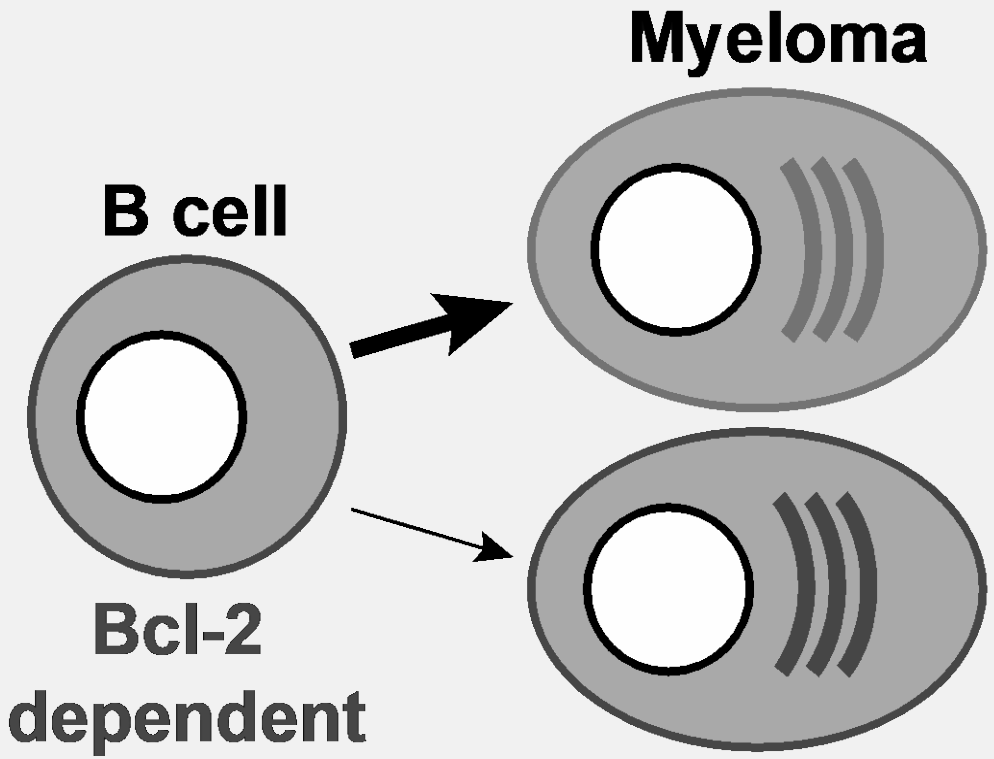




82% Sensitivity
80% Specificity
p=0.0089

Gupta et al., Blood, 2021

BH3-Mimetics require predictive markers for optimal use in MM



Plasma cell biology

Mcl-1 dependent

↑Proteasome Inhibitors

↑Immunomodulatory agents

B cell biology

Bcl-2 dependent

↓Proteasome Inhibitors

↓Immunomodulatory agents

Courtesy of L. Boise

Molecular therapy in Multiple Myeloma: Proof of Concept

Targeting the BRAF V600E Mutation in Multiple Myeloma

Mindaugas Andrulis[1], Nicola Lehners[2,3], David Capper[4], Roland Penzel[2], Christoph Heining[5], Jennifer Huellein[5], Thorsten Zenz[2,5], Andreas von Deimling[4], Peter Schirmacher[1], Anthony D. Ho[2], Hartmut Goldschmidt[2,6], Kai Neben[2], and Marc S. Raab[2,3]

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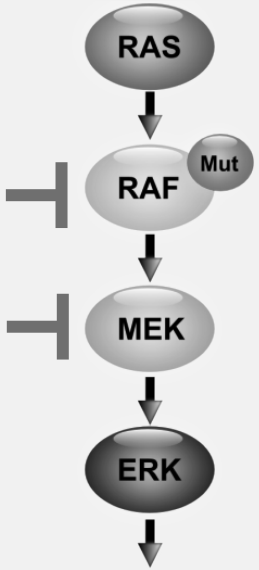
Andrulis et al., Cancer Discovery 2013
Raab et al., Blood 2016

GMMG-BIRMA trial - Overview

BRAF Inhibitor Encorafenib (450 mg. p.o. QD)

MEK Inhibitor Binimetinib (45 mg p.o. BID)



RRMM with mutant BRAF V600E/K in > 50% of MM cells

BRAF/MEK **I**nhibition in **R**elapsed/Refractory **M**ultiple Myeloma: Phase 2 trial

Primary: Overall Response Rate (ORR)

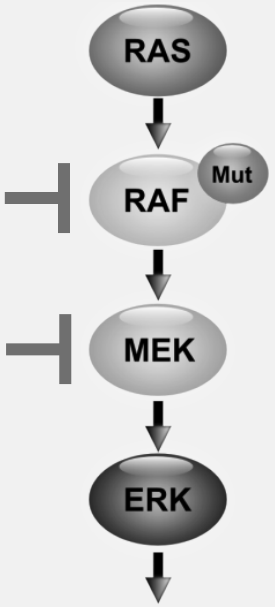
Secondary: Progression-free survival, Overall survival

Exploratory aims:

- Analysis of efficacy and safety parameters
- Effect of study drugs on signaling pathways in multiple myeloma cells derived from bone marrow.
- Investigating the potential mechanism of resistance to combined BRAF/MEK inhibition

Personalized molecular-based therapy in RRMM

BIRMA trial – Safety



Proliferation

Patient characteristics (n=12):

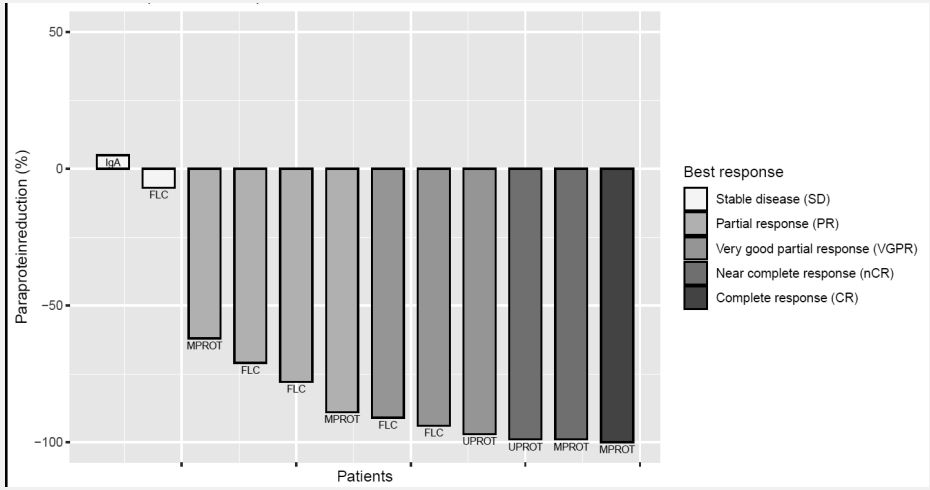
- Prior lines of therapy, median 5 (2-14)
- Prior PI+IMiD 12/12
- Prior anti-CD38-Ab 6/12

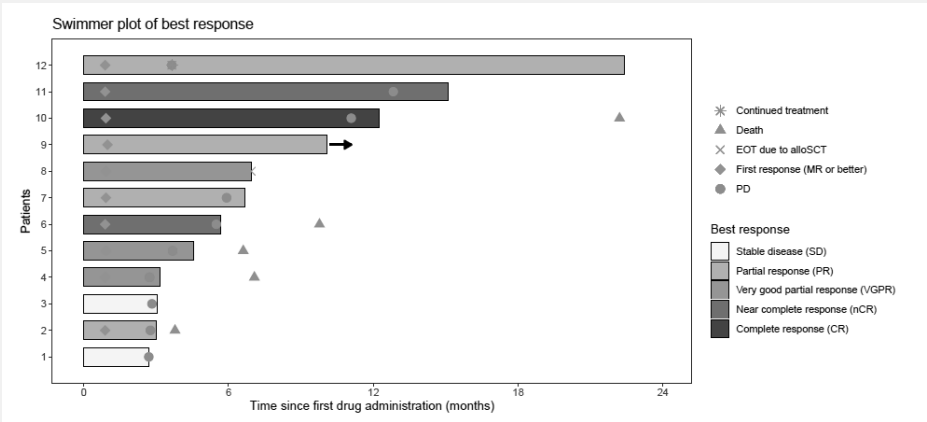
Safety:

- AEs related: 9/12
  - All grade: incl. macula edema, blurred vision, cramps, arthralgia, skin rash, LV function
  - Grade 3/4: anemia, thrombopenia, hypertension
- SAE: pneumonia, tooth extraction (nr) 2/12

Raab et al., ASH 2020

BIRMA trial – Efficacy





Response rates:

Primary endpoint:

- **ORR** **83%** 10/12

  (lower limit of the 95% CI 56.4%, one-sided exact binomial test, p<0.0001)

- ≥VGPR 50% 6/12
- ≥nCR/CR 25% 3/12

Secondary endpoints

- **PFS,** median 6 months (CI 3.4-11.3)
- **Best response,** median 1.8 months
- **OS** at 2 years 55%

Raab et al., ASH 2020, updated

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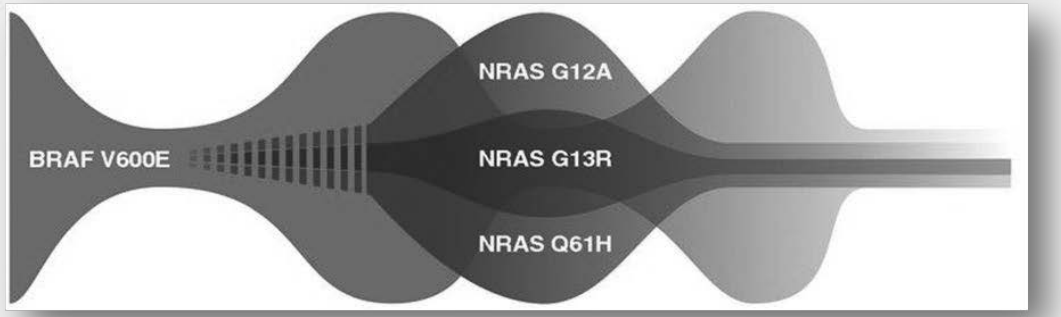
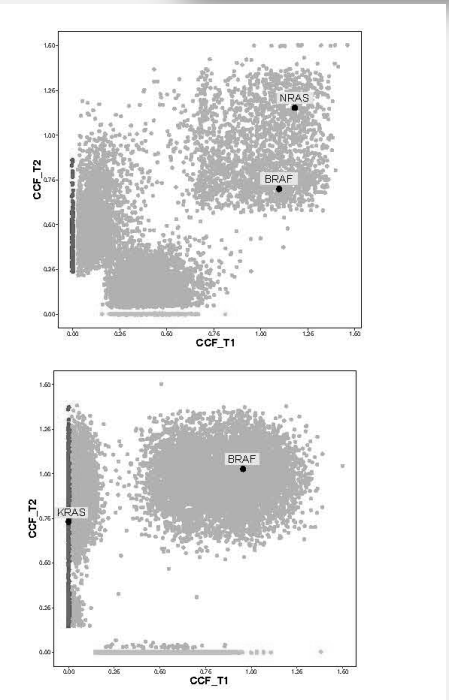
BIRMA trial – Correlative Science



Raab *et al.* Blood (2016)



Identification of resistance mechanisms:

- Samples pre-/post-Tx (T1; T2)
- WGS, RNAseq, IHC pERK

➢**RAF mutation:**

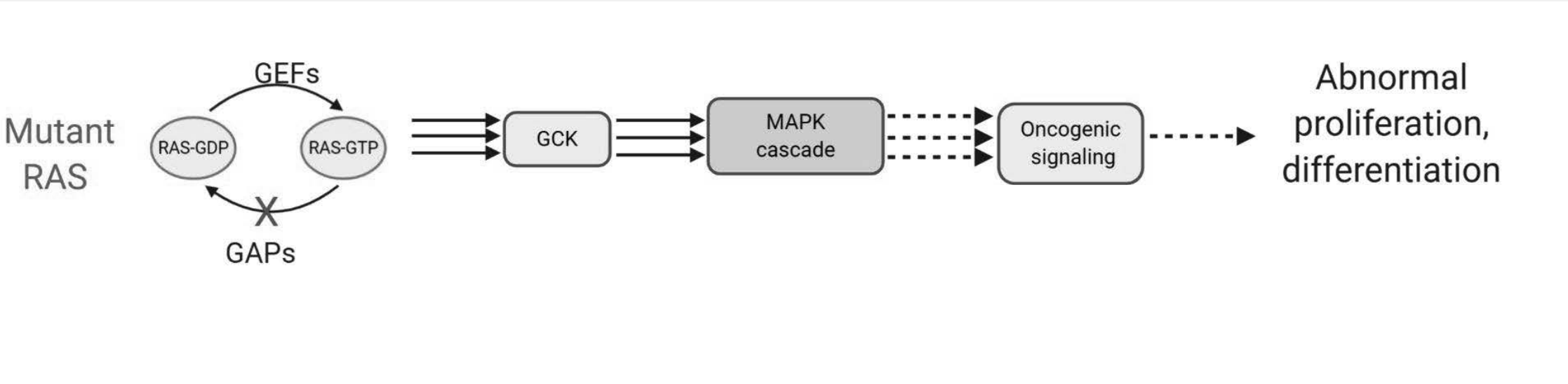
- Pts 1-5: BRAF p.V600E (T1+T2)

➢**RAS mutations:**

- Pts 1+2: KRAS p.G13D <u>new at relapse (T2)</u>
- Pt 3: NRAS p.Q61K and KRAS p.G12V <u>new at relapse (T2)</u>
- Pt 4: NRAS p.Q61R <u>in T1+2</u> (best response stable disease)
- Pt 5: Translocation involving BRAF <u>new at relapse</u> (T2), no RAS^{mut}

Raab et al., ASH 2020, updated

Targeting RAS signaling



- Germinal Center Kinase (GCK), also named MAP4K2, is an upstream activator in the MAPK pathway
- GCK is critical for proliferation and survival of RAS^{Mut} MM cells
- Pharmacological blockage of GCK activity inhibits the growth of RAS^{Mut} multiple myeloma

Shirong Li, et al., ASH 2020

Summary

- Personalized therapies emerge in multiple myeloma
- Immunotherapy (antibody-based, cell-based) to become available in rrMM
- Molecular targets (BCL-2, BRAF) promising for subsets of patients
- Combined BRAF/MEK inhibition induces rapid and deep responses in BRAF V600E-mutant relapsed/refractory MM
- Pre-existing RAS mutations may predict poor response to BRAF/MEK inhibition
- Targeting sequelae of mutant RAS would be major achievement
- Exploiting molecular mechanisms, such as impaired DNA damage response, may hold promise for future generations of targeted therapies in MM

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All Patients and their Families

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