Future of Myeloma Treatment
the roadmap for curing

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Speakers Bureau	NA
Honoraria	Takeda; Janssen; Celgene; Novartis; Amgen, BMS, Sanofi
Scientific Advisory Board	Takeda; Janssen; Celgene; Novartis; Amgen, BMS, Sanofi

How should we treat Multiple Myeloma?

Key points to consider

- ***Currently, Myeloma treatment is highly expensive.***
- ***The cheapest medicine is the one that is able to CURE the patient.***
- ***Not to use the best drugs upfront is an expensive and frustrating approach***

The roadmap to cure patients with multiple myeloma

1) *To Investigate the pathogenesis of MM (identify the signatures of high Risk clones)*

2) *To eradicate all tumour cells: high sensitive techniques to evaluate treatment efficacy.*

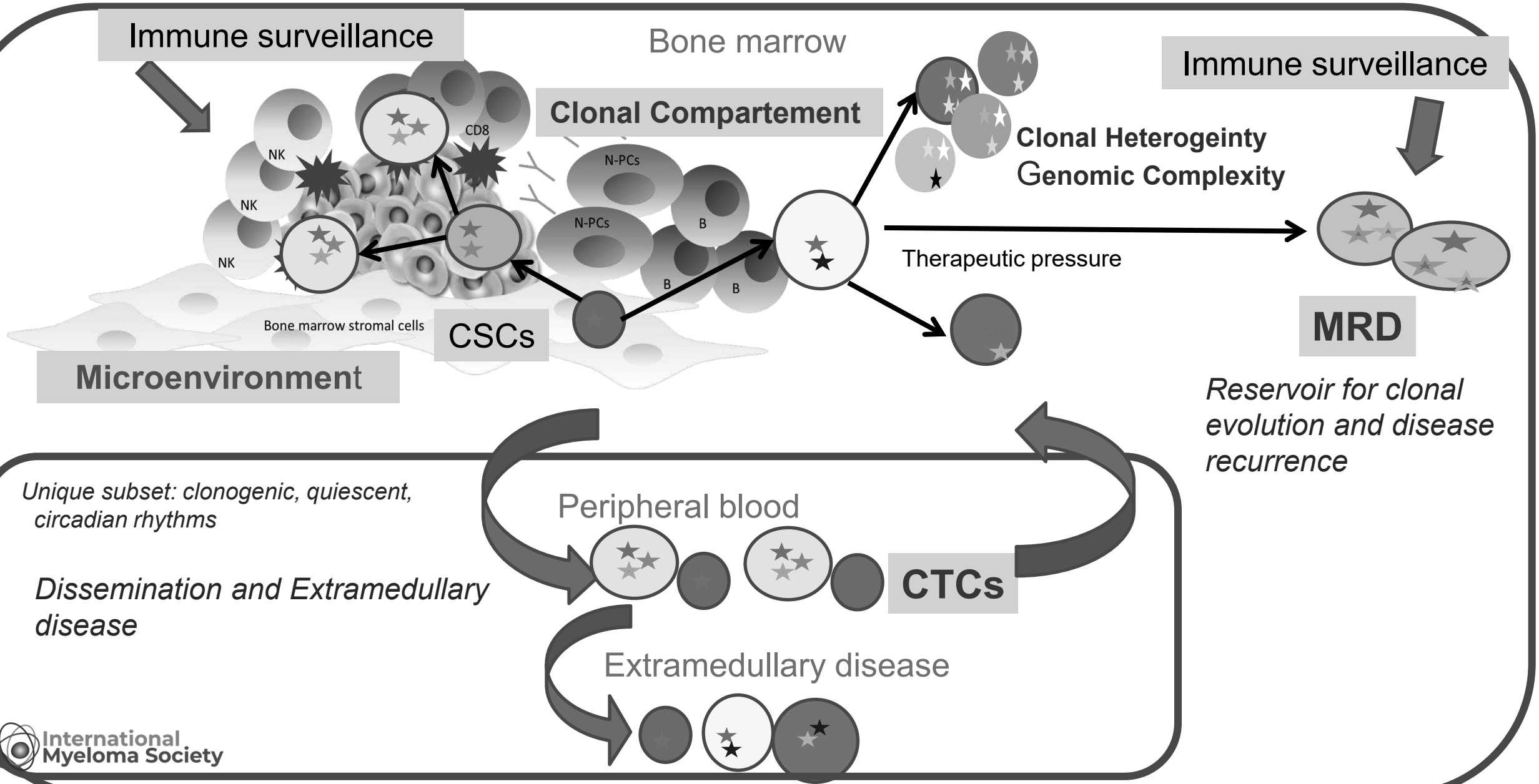
3) *Early detection & early intervention:* **to treat disease causation instead of symptomatology**

4) *To use the most active treatments in standard risk patients.*

5) *To investigate experimental therapies upfront in High risk patients.*

Myeloma Pathogeneis

To identify signatures of High Risk clones: **as tools for understanding disease dissemination & resistance " Achilees´heel"**



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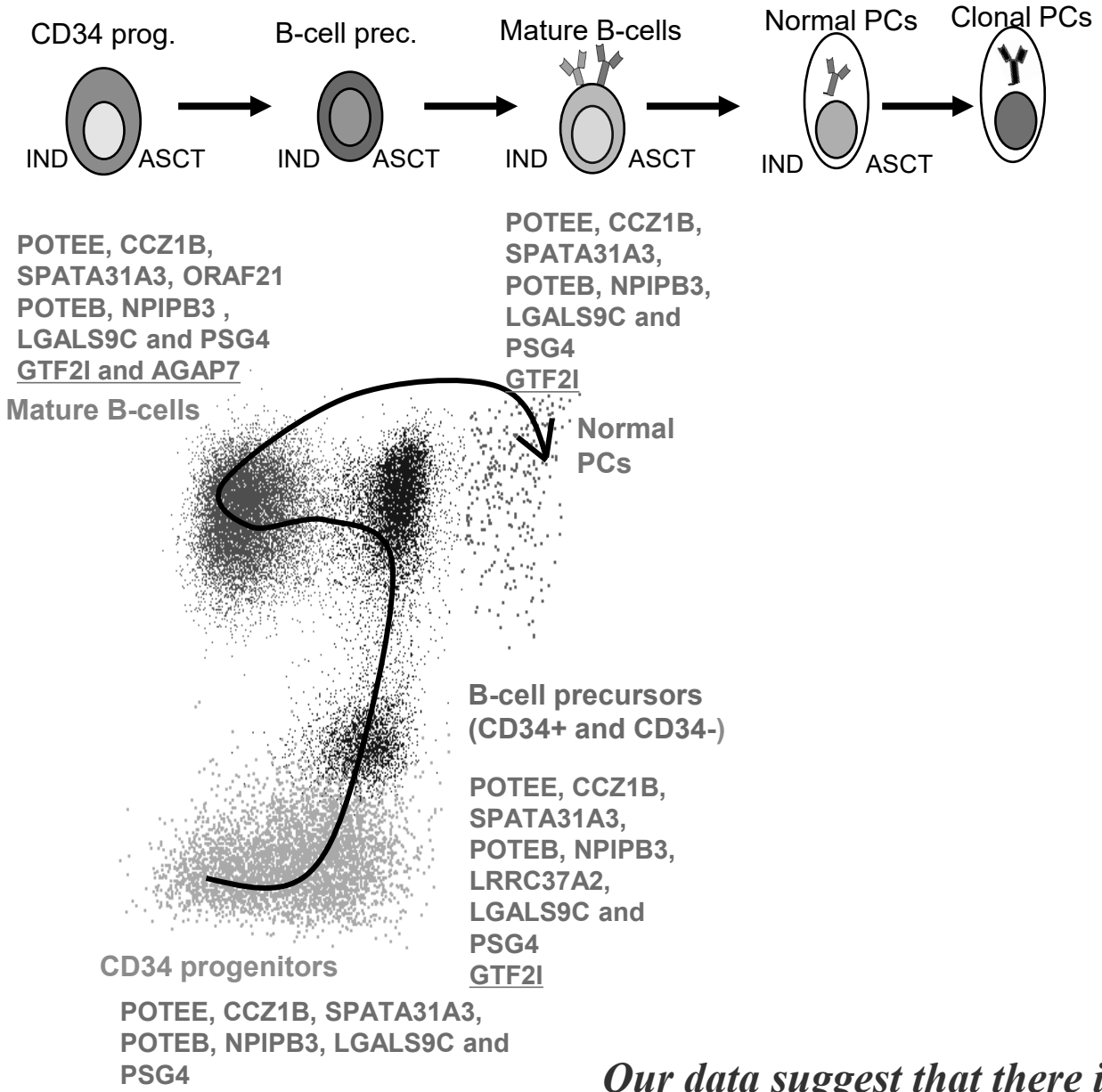
Clonal Compartment: *the pathogenesis of MM is preceded by mutated lymphopoiesis*



Normal cells isolated from double negative MRD patients to avoid contamination

- *Mature B Lymphocytes & normal PC display* **the same clonal IgG rearrangement** *observed in clonal PC (at diagnosis) (5/6)*
- Whole exome sequencing *revealed that not only normal PC and mature B cells,* ***but also*** *B cell precursors and CD34 progenitors shared with clonal PC some* **somatic mutations (but not recurrent mutations)**. ***However critical MM driver mutations or copy number alterations were not detected****……MM patients have somatic mutations in the B cell lineage, likely before the disease onset*

- *Mutated lymphopoiesis may increase risk of developing B cell and PC oligoclonality, which precedes secondary driver mutations or CNV leading to the expansion of MM PCs*

- *Can these cells secrete the same immunoglobulin as MM cells?*

Our data suggest that there is a clonal B lymphopoiesis that preceded MM

Rodriguez S, et al. Blood 2020; 136 (Supplement 1): 5–6
Rodriguez S, et al. Blood 2019;134: abstract 509

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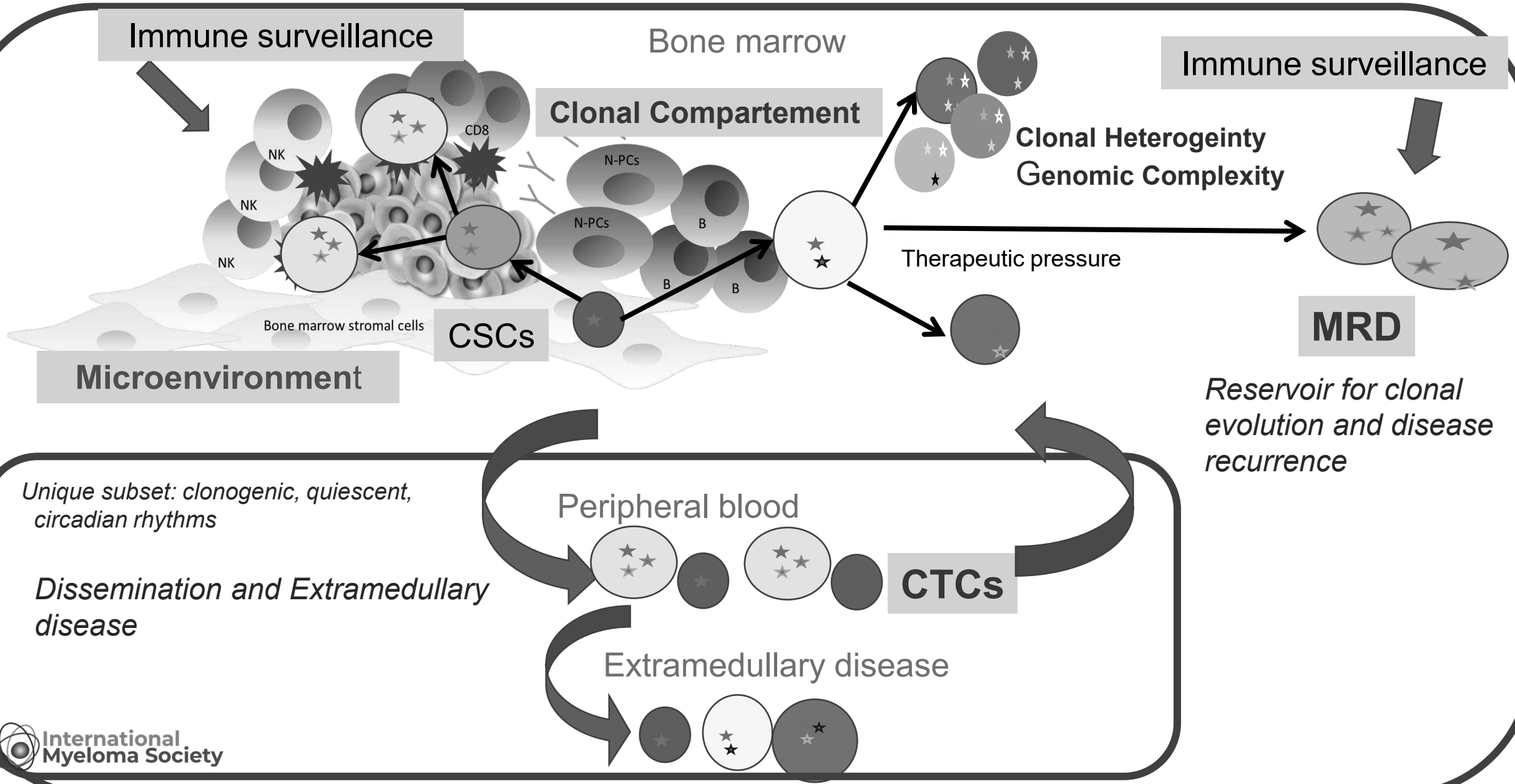

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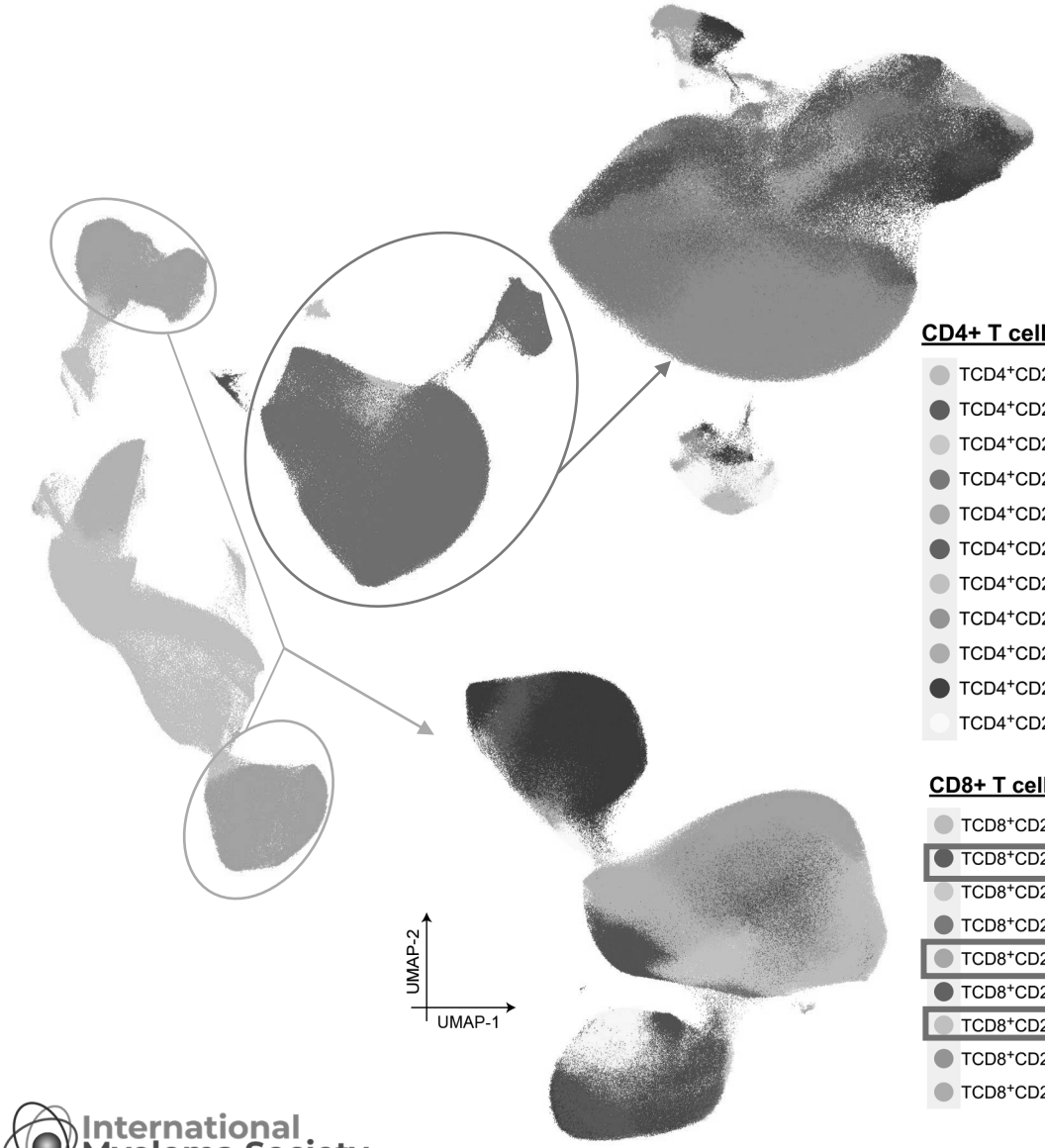
T cell subsets in blood associated with the progression of SMM

Expansion of 6 subsets with exhausted phenotype associated with inferior TTP

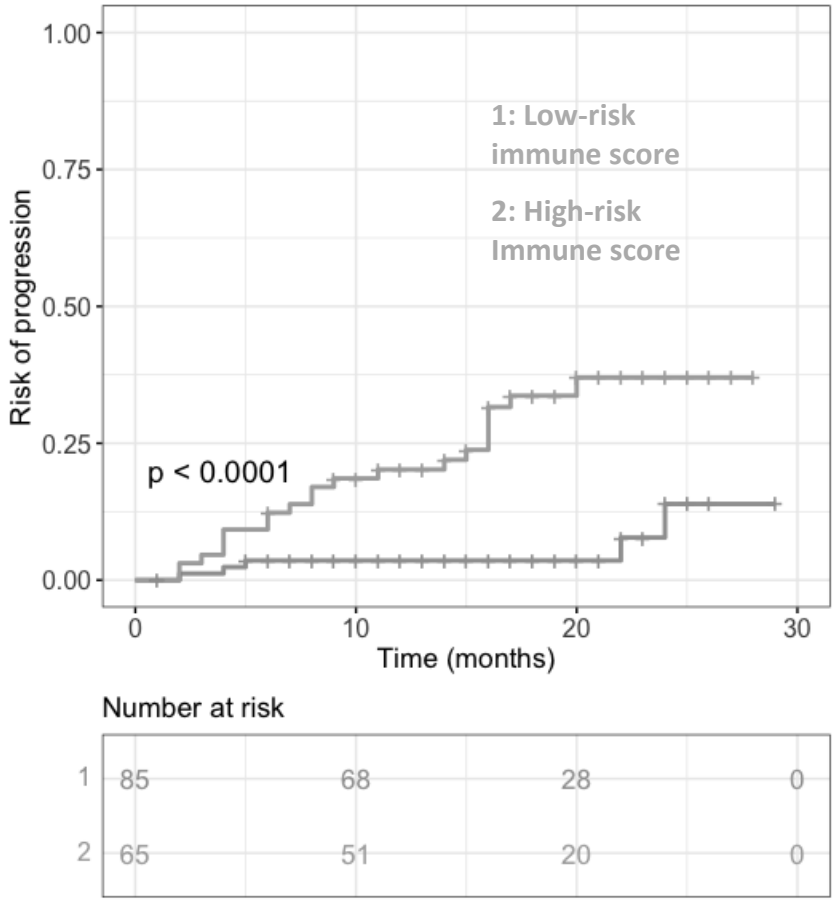


CD4+ T cell clusters

- $TCD4^+CD28^{dim}CD127^{low}$
- $TCD4^+CD28^-CD127^{low}$
- $TCD4^+CD28^-CD127^+$
- $TCD4^+CD28^-PD1^+CD127^{low}$
- $TCD4^+CD28^-PD1^+CD127^+$
- $TCD4^+CD28^-TIGIT^+PD1^+CD127^+$
- $TCD4^+CD28^+CD127^{low}$
- $TCD4^+CD28^+CD127^+$
- $TCD4^+CD28^+PD1^+CD127^{low}$
- $TCD4^+CD28^+PD1^+CD127^+$
- $TCD4^+CD28^+PD1^+CD127^+CD25^+$
- $TCD4^+CD28^+TIGIT^+CD127^{low}$
- $TCD4^+CD28^+TIGIT^+CD127^+$
- $TCD4^+CD28^+TIGIT^+CD127^+CD25^+$
- $TCD4^+CD28^+TIGIT^+PD1^+CD127^{low}$
- $TCD4^+CD28^+TIGIT^+PD1^+CD127^+$
- $TCD4^+CD28^+TIGIT^+PD1^+CD39^+CD127^{low}$
- $TCD4^+CD8^{dim}CD28^+PD1^+CD127^+$
- Treg $CD28^+TIGIT^+PD1^-CD39^{low}$
- Treg $CD28^+TIGIT^+PD1^-CD39^-$
- Treg $CD28^+TIGIT^+PD1^-CD39^+$
- Treg $CD28^+TIGIT^+PD1^+CD39^{low}$

CD8+ T cell clusters

- $TCD8^+CD28^-$
- $TCD8^+CD28^-CD127^+$
- $TCD8^+CD28^-PD1^+$
- $TCD8^+CD28^-PD1^+CD127^+$
- $TCD8^+CD28^-TIGIT^+$
- $TCD8^+CD28^-TIGIT^+CD127^+$
- $TCD8^+CD28^-TIGIT^+PD1^+$
- $TCD8^+CD28^-TIGIT^+PD1^+CD127^+$
- $TCD8^+CD28^+$
- $TCD8^+CD28^+CD127^+$
- $TCD8^+CD28^+PD1^+$
- $TCD8^+CD28^+PD1^+CD127^+$
- $TCD8^+CD28^+TIGIT^+$
- $TCD8^+CD28^+TIGIT^+CD127^+$
- $TCD8^+CD28^+TIGIT^+CD39^+CD127^+CD25^{het}$
- $TCD8^+CD28^+TIGIT^+PD1^+$
- $TCD8^+CD28^+TIGIT^+PD1^+CD127^+$
- $TCD8^+CD28^+TIGIT^+PD1^+CD39^+CD127^+$



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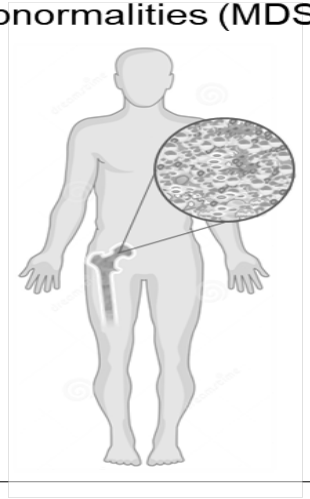
Termini R, et al. IMW 2021: abstract 1087023

Biological and clinical significance of dysplastic hematopoiesis

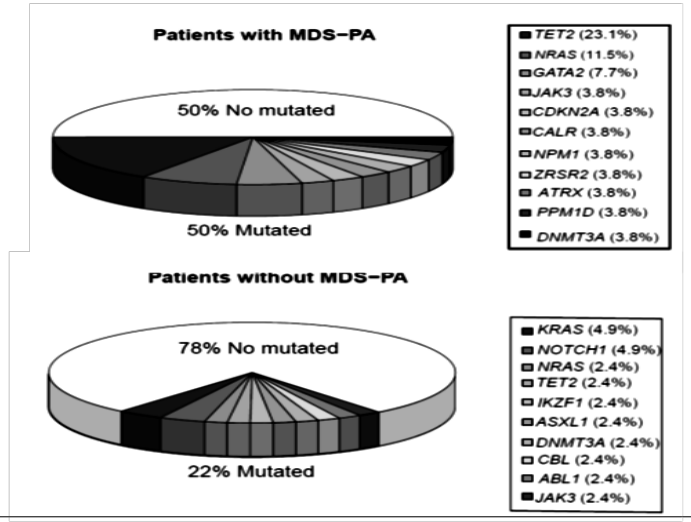
MDS-PA modify the tumor microenvironment and induce greater risk of hematological toxicity from treatment

Approximately 1 out of 10 patients with myeloma displays MDS-associated phenotypic abnormalities (MDS-PA) at diagnosis, which…

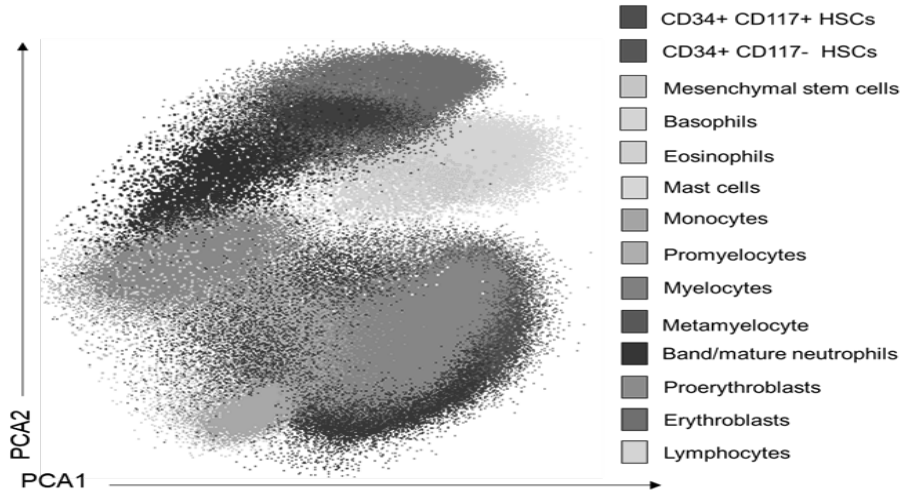


…induce greater risk of hematological toxicity from treatment.

MDS-PA and clonal hematopoiesis

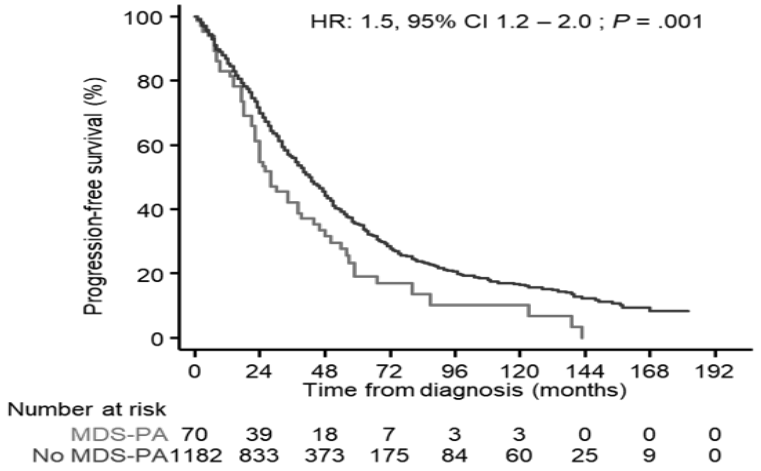


MDS-PA modify the tumor microenvironment



Higher frequency of T-regulatory cells & matuaration blockage in neutrophils

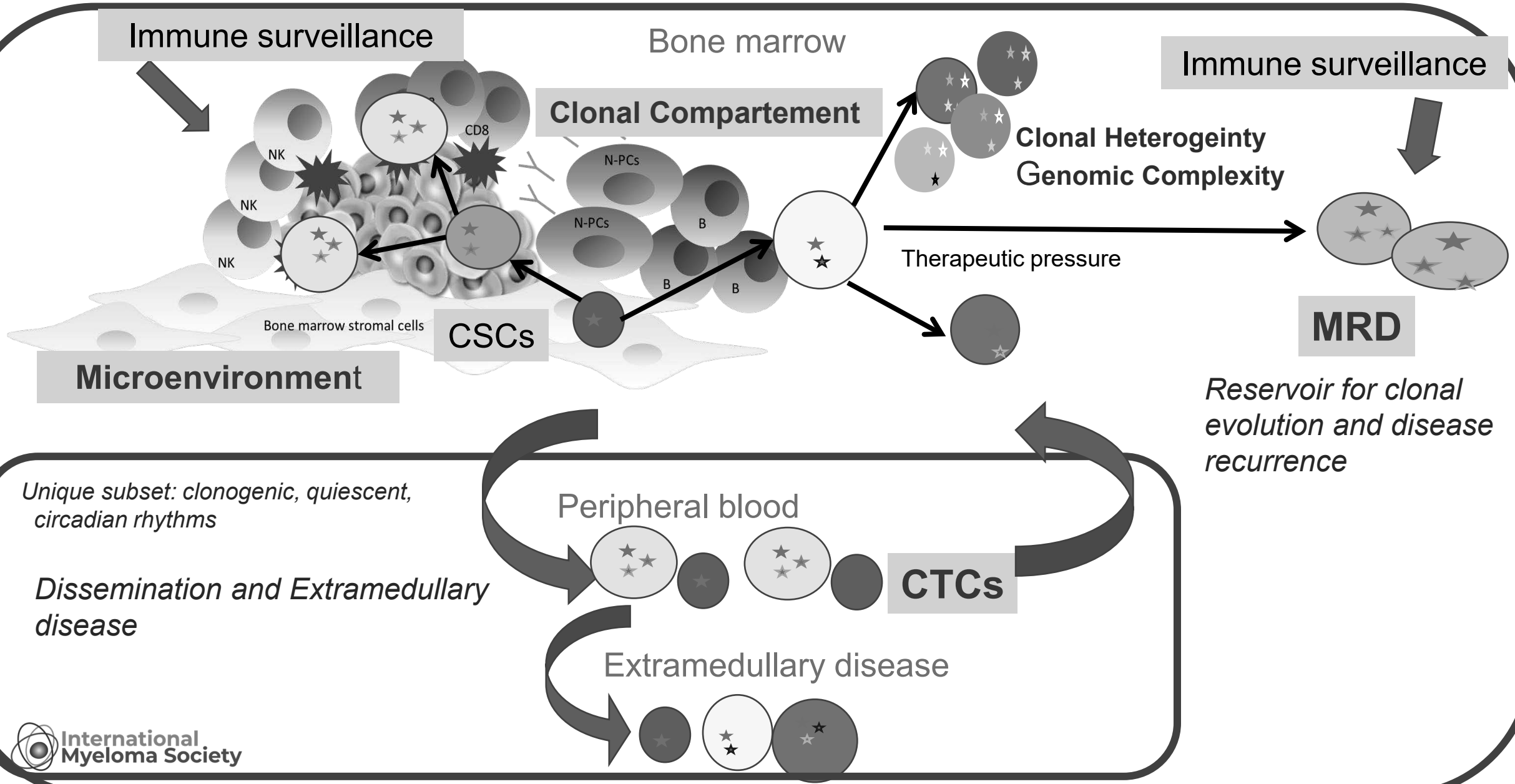
MDS-PA at diagnosis was independently associated with inferior progression-free survival



Maia C, et al. Blood. 2020;135(26):2375-2387.

Myeloma Pathogeneis

To identify signatures of High Risk clones: **as tools for understanding disease dissemination & resistance " Achilees´heel"**



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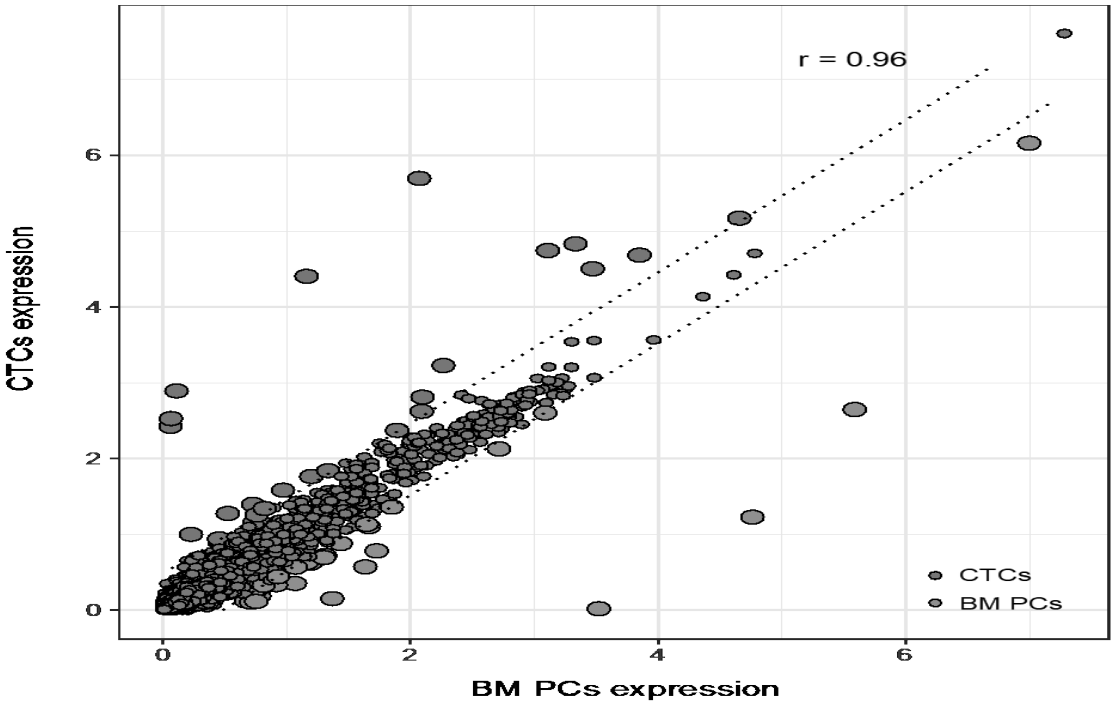
Biologic characterization of paired CTCs vs BM clonal PCs
A new model to understand disease dissemination

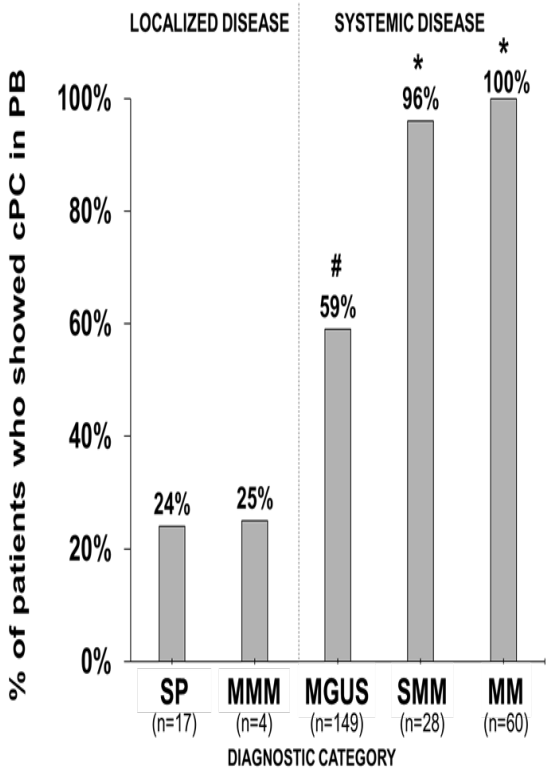
Transcriptional profile at single cell level & GEP of CTCs and BM clonal PCs highly overlapping

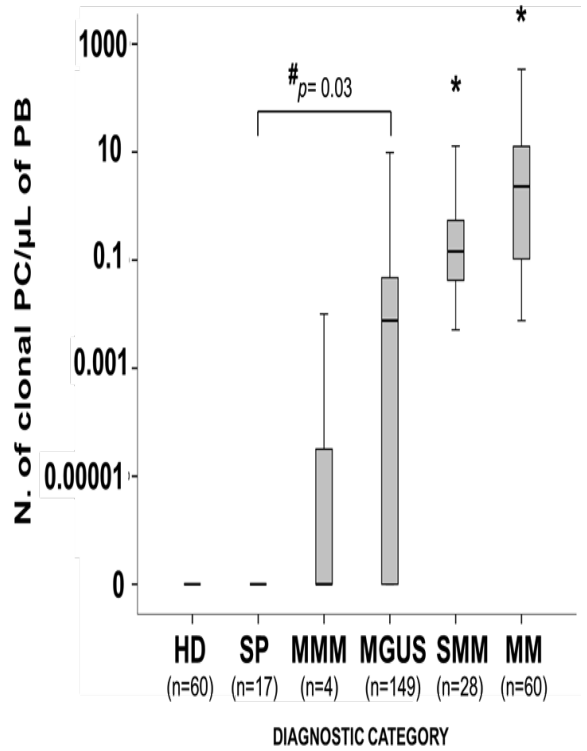
Only **58 genes significantly deregulated** in CTCs (7 infra- and 51 over-expressed) : some of them: Filanin, WEE1, LAMP3 and SAMD9 prognostic value .



The transcriptional profile of CTCs vs patient-matched BM clonal PCs identify ***gene regulatory networks related to MM dissemination.***

CTCs detected in half MGUS and virtually all MM patients
Highly significant differences between MGUS vs SMM and active MM



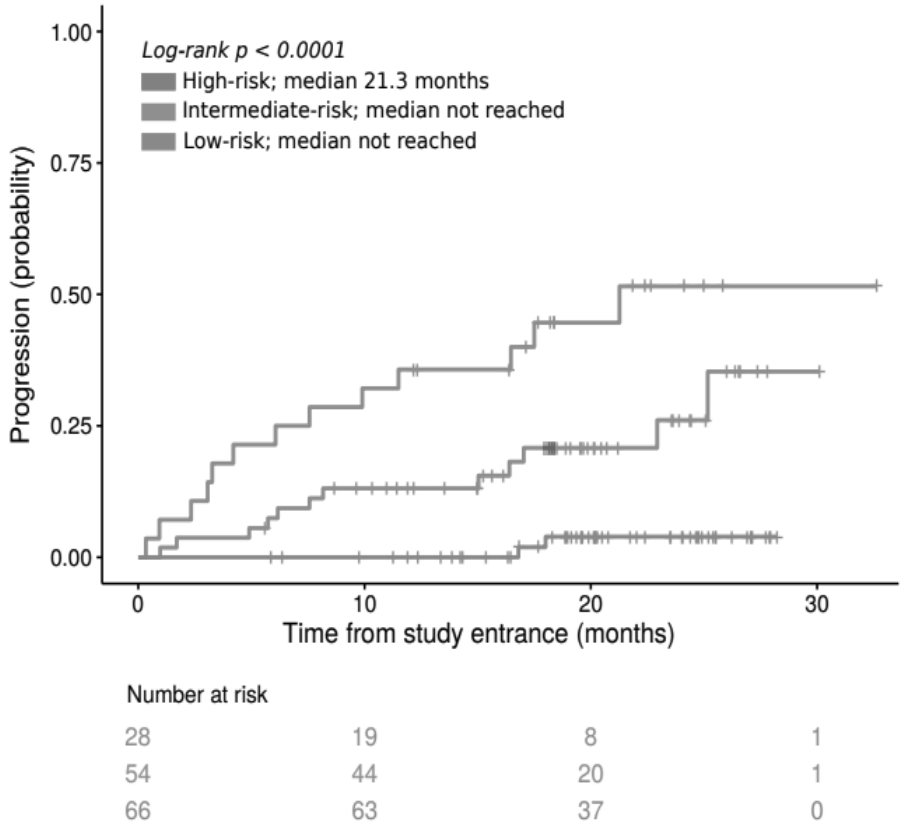


Garces JJ, et al. Blood 2018;132: abstract 245

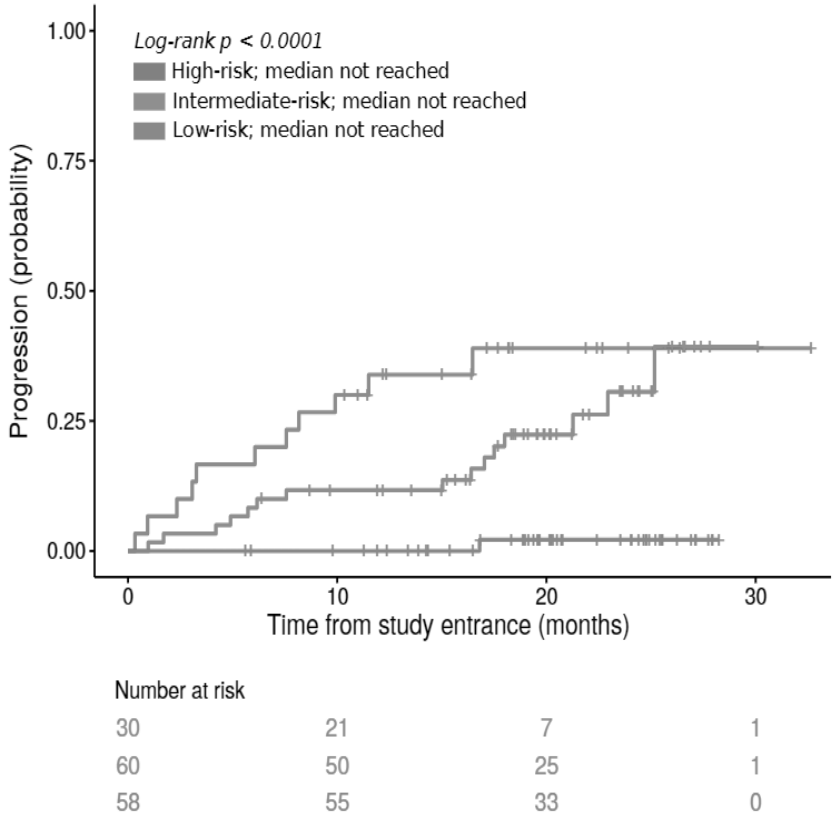
CTC predicts risk of progression in SMM: *Risk stratification using CTCs vs BM PCs*

Minimally invasive vs partially invasive models

2/20/0.7 Model (CTC/µL >0.7)



2/20/20 Model (BMPC >20%)



Sequential monitoring of CTCs: new and easy to obtain evolving profile in SMM

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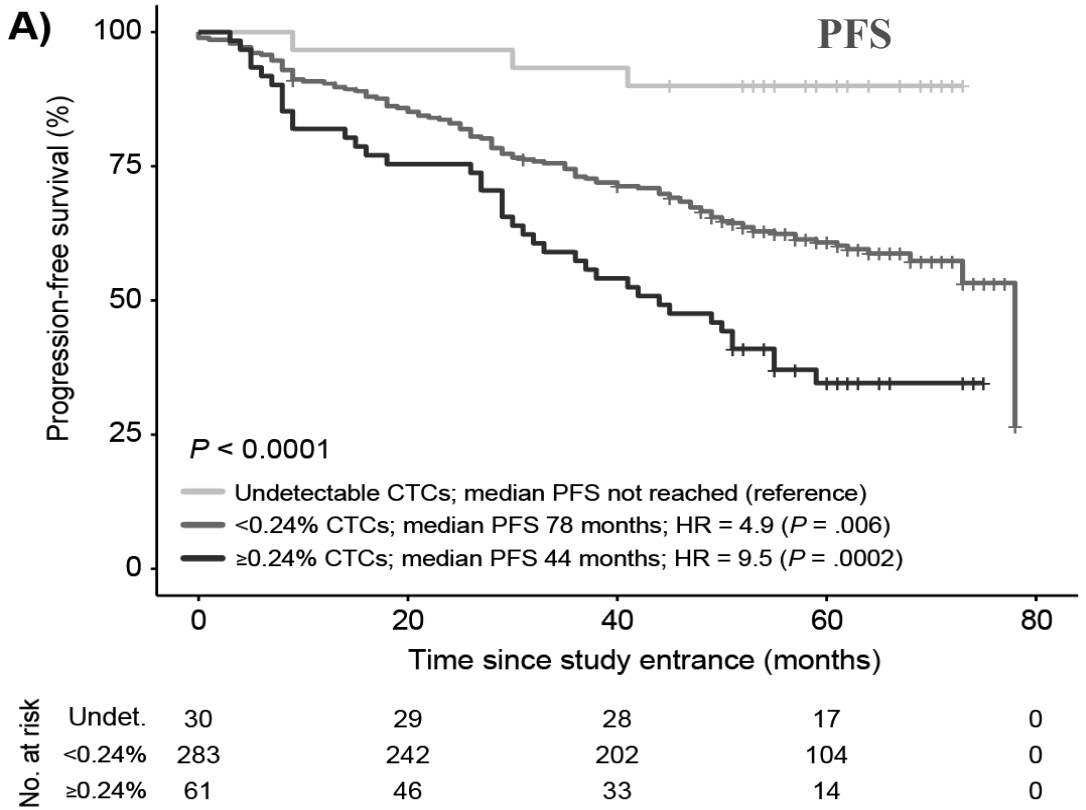
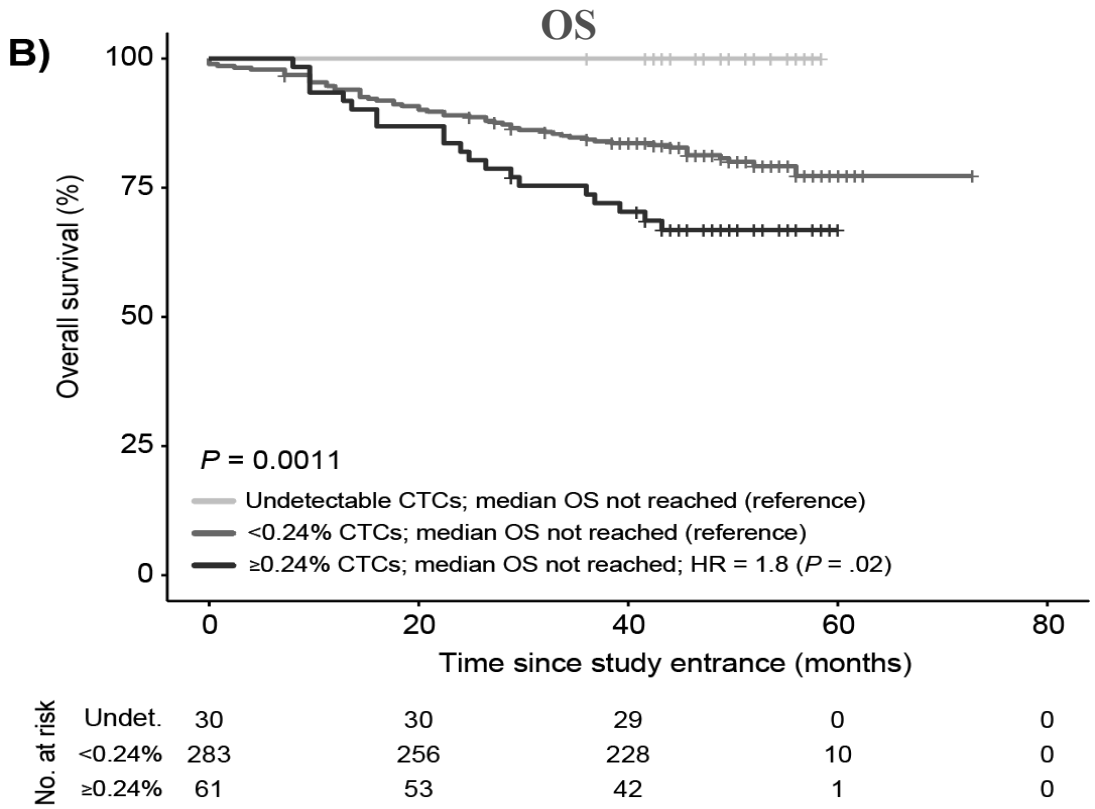
Termini R, et al. IMW 2021: abstract 1087023

CTCs are the most relevant diagnostic biomarker in MM (GEM12)

- ***Detected by NGF in 92% of patients.***
- ***Higher number of CTCs were observed in patients with advanced ISS, elevated LDH and high-risk genetics***





CTC levels are the most powerful independent prognostic factor at diagnosis

Model for MM dissemination: a high occupancy of hypoxic BM niches + pro-inflammatory microenvironment: force cancer cells to stop proliferating, recirculate in PB and seek other BM niches to continue growing

Garces JJ, et al. EHA 2021, Manuscript in preparation

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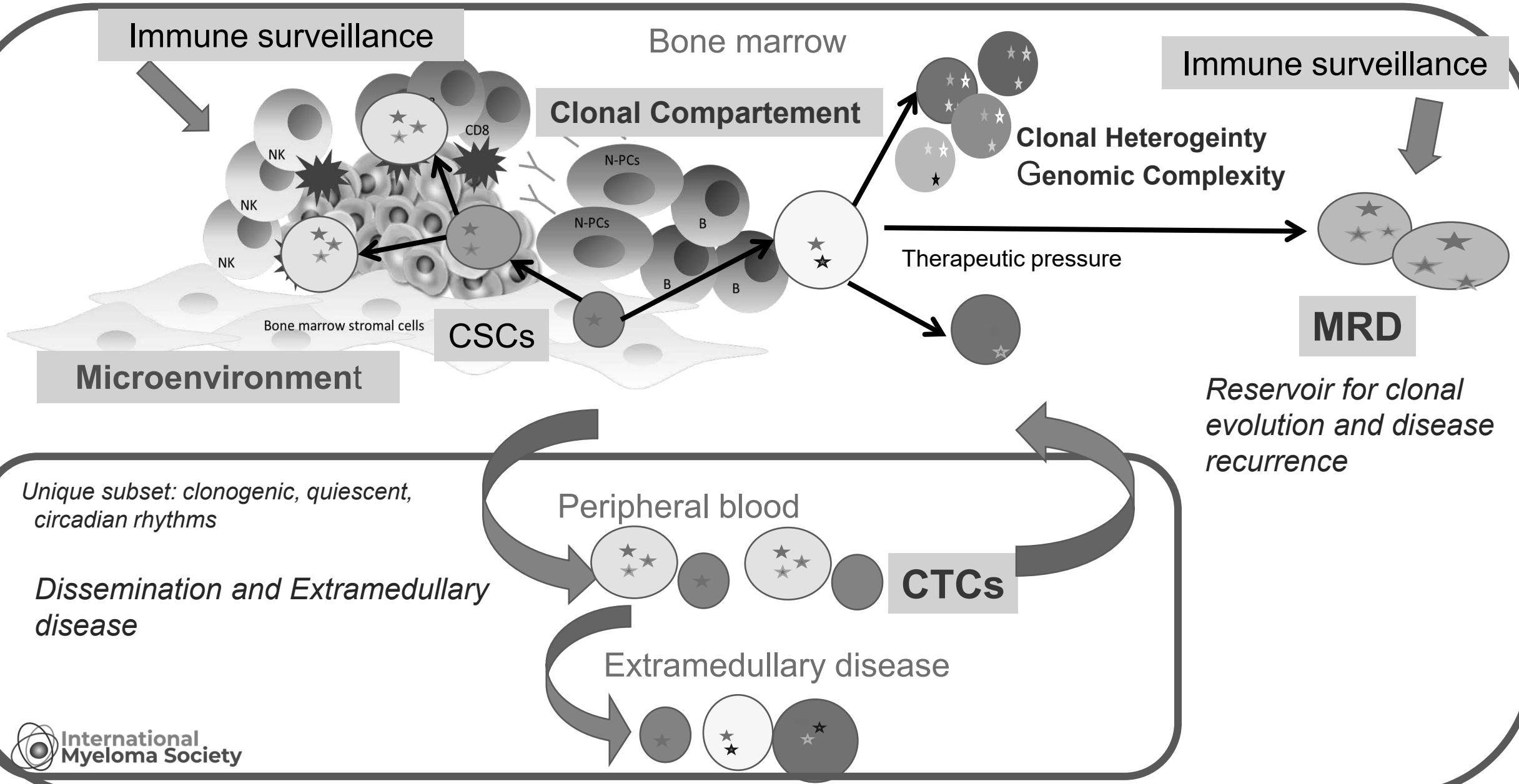

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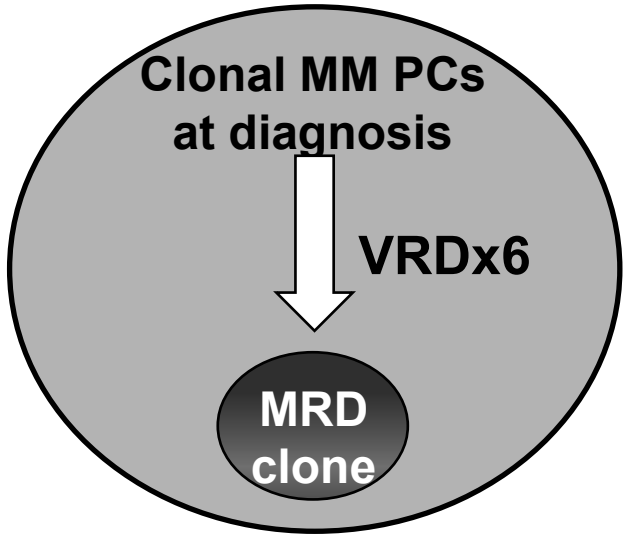
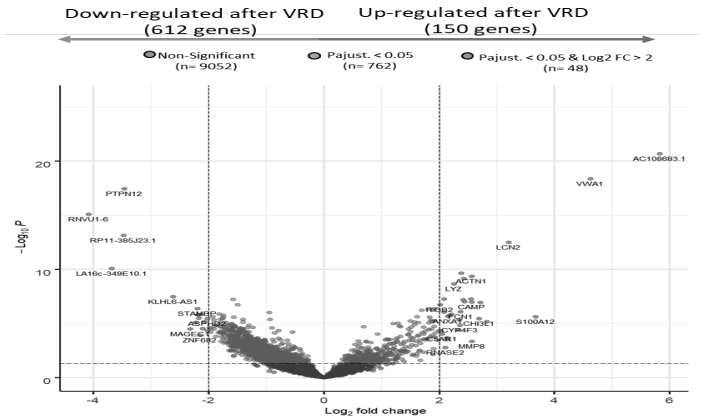
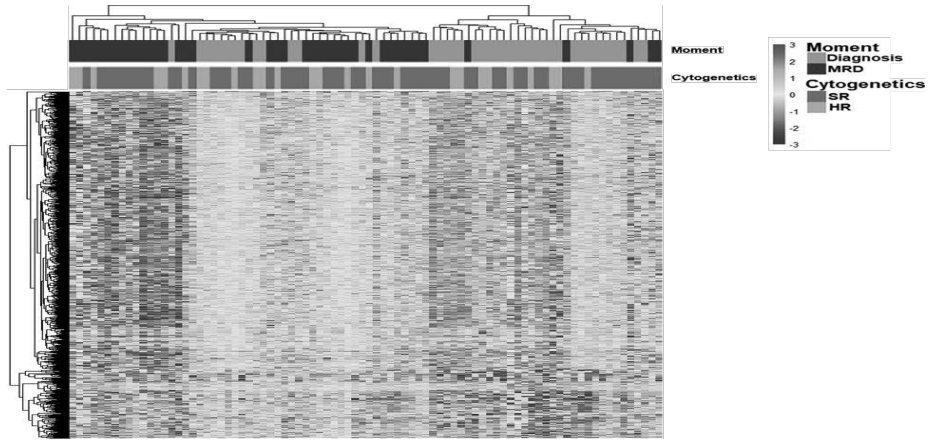
Transcriptomic comparison: paired diagnostic vs MRD cells *following VRD*

FACs sorted cells & Massively parallel single-cell RNA-seq (MARSeq)



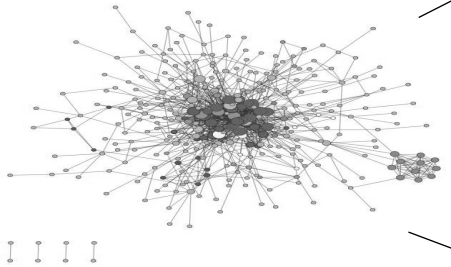
N=40 (28 SR + 12 HR FISH)

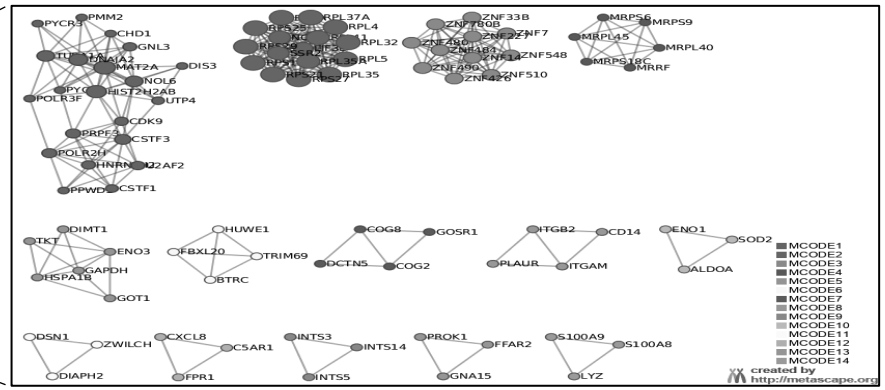




MRD cells showed 762 genes significantly deregulated

Derregulated functional networks





- RNA splicing
- Nonsense Mediated Decay
- DNA binding
- Mitochondrial translation
- **Metabolism**
- **Proteasome**

9-fold higher deregulated genes in MRD cells of SR patients compared to HR patients

In SR, there is a clonal selection or transcriptomic adaptation in order to resist treatment, but in HR, the cytogenetic abnormality may predispose cells to resist treatment

Goicoechea I, et al. Blood. 2021;137(1):49-60.

The roadmap to cure patients with multiple myeloma

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2) *To eradicate all tumour cells: high sensitive techniques to evaluate treatment efficacy.*

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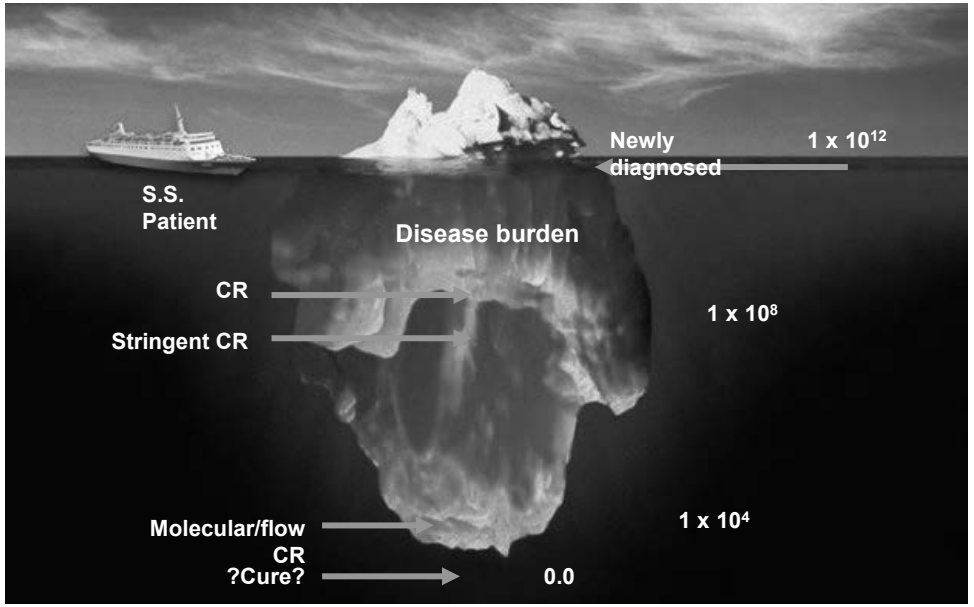
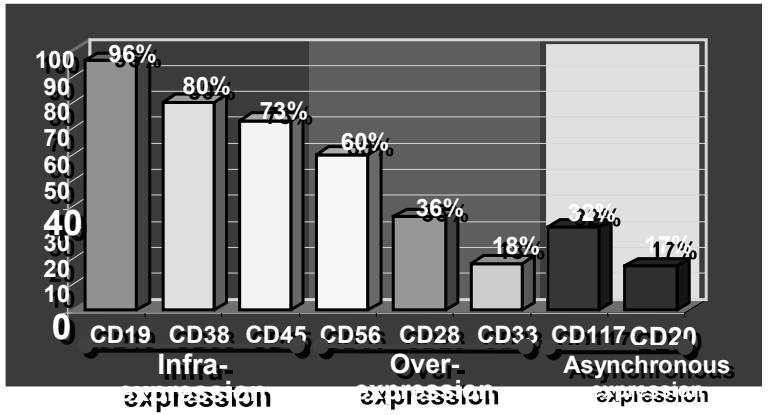
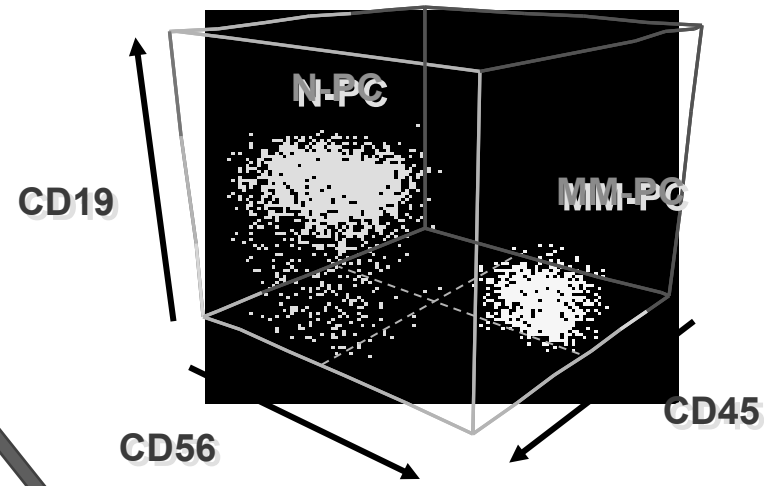
4) *To use the most active treatments in standard risk patients.*

5) *To investigate experimental therapies upfront in High risk patients.*

Response to therapy is the key element to evaluate treatment efficacy and critical for survival …*But definition of CR in MM is suboptimal*



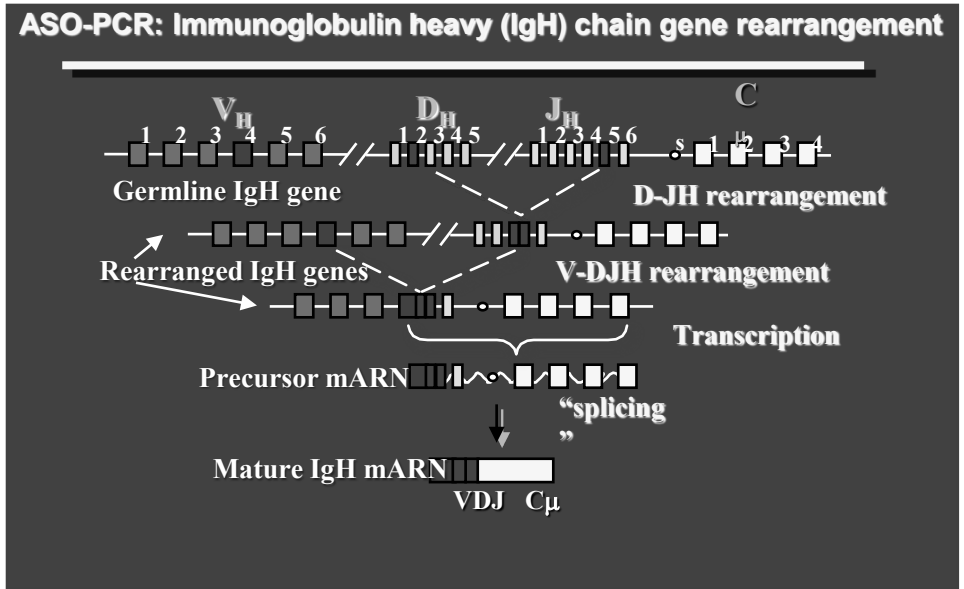


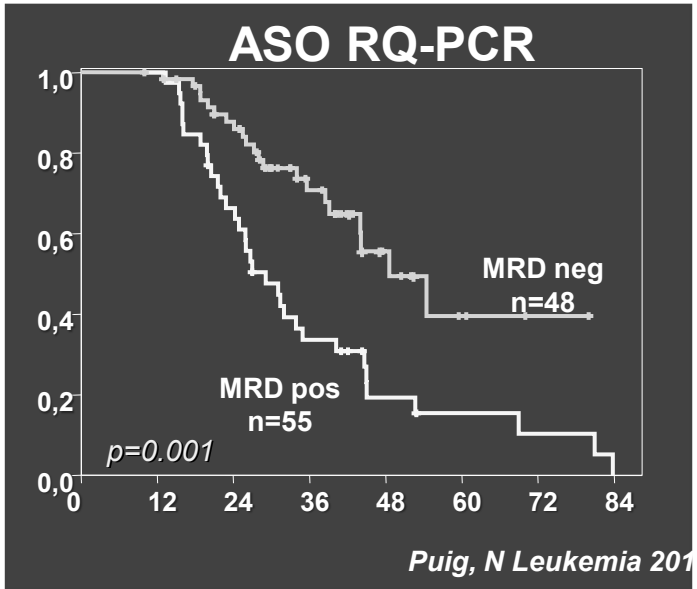


FCM

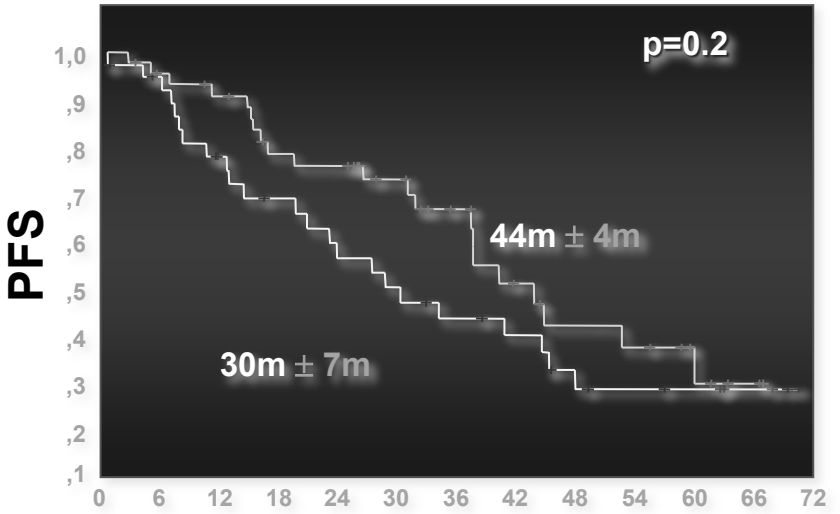
Gate CD38

Level of MM-PC





Puig, N Leukemia 201

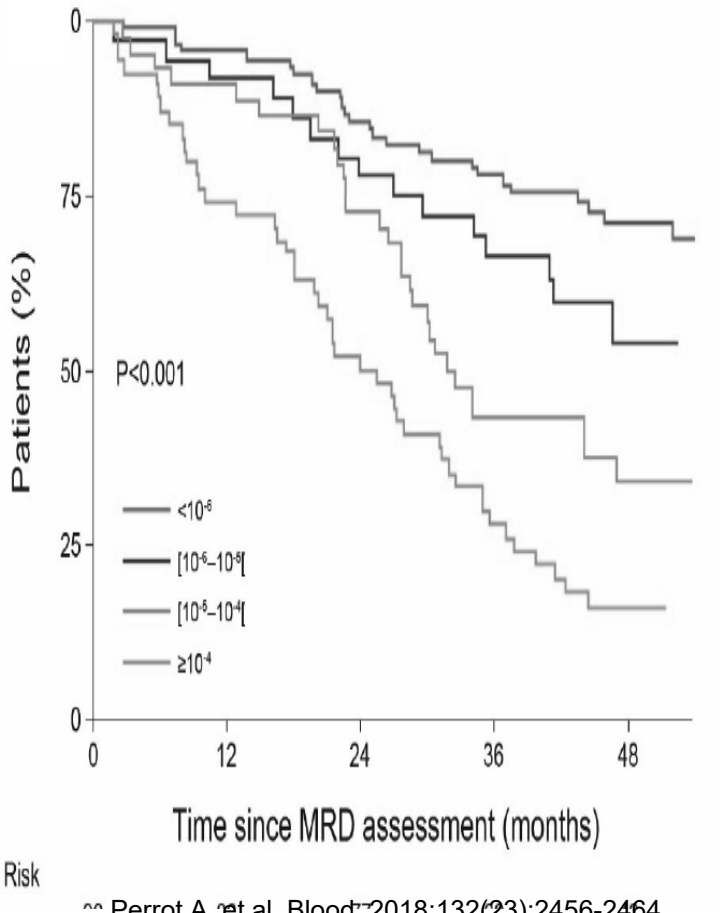


San Miguel et al Blood 2002:99, p1853-56

Response to therapy is the key element to evaluate treatment efficacy and critical for survival *Why we do not use to change treatment except in cases of refractory disease?*

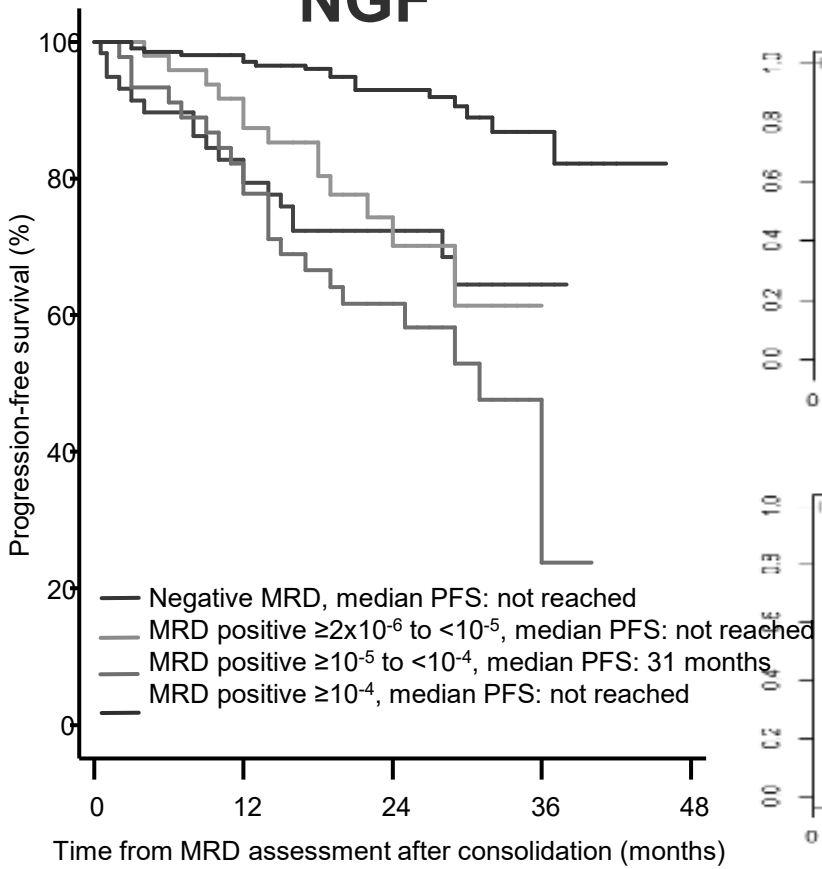
MRD assessment *(endpoint)*

NGS



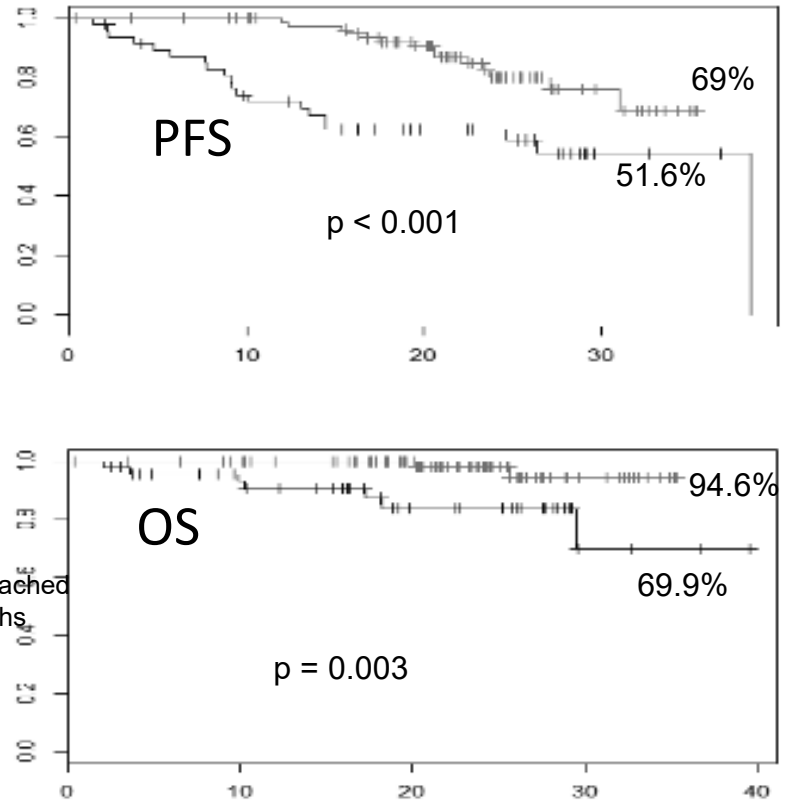
Perrot A, et al. Blood. 2018;132(23):2456-2464.

NGF



Paiva B, et al. JCO Manuscript in review

PET



Zamagni E, et al. Clin Cancer Res 2015;21(19):4384-90
Moreau P, et al. Blood 2015 126:395

The lowest the level of MRD the longer the survival
MRD in the logarithmic range of 10^{-6} is clinically relevant

The concept of PET CR……Methionine?

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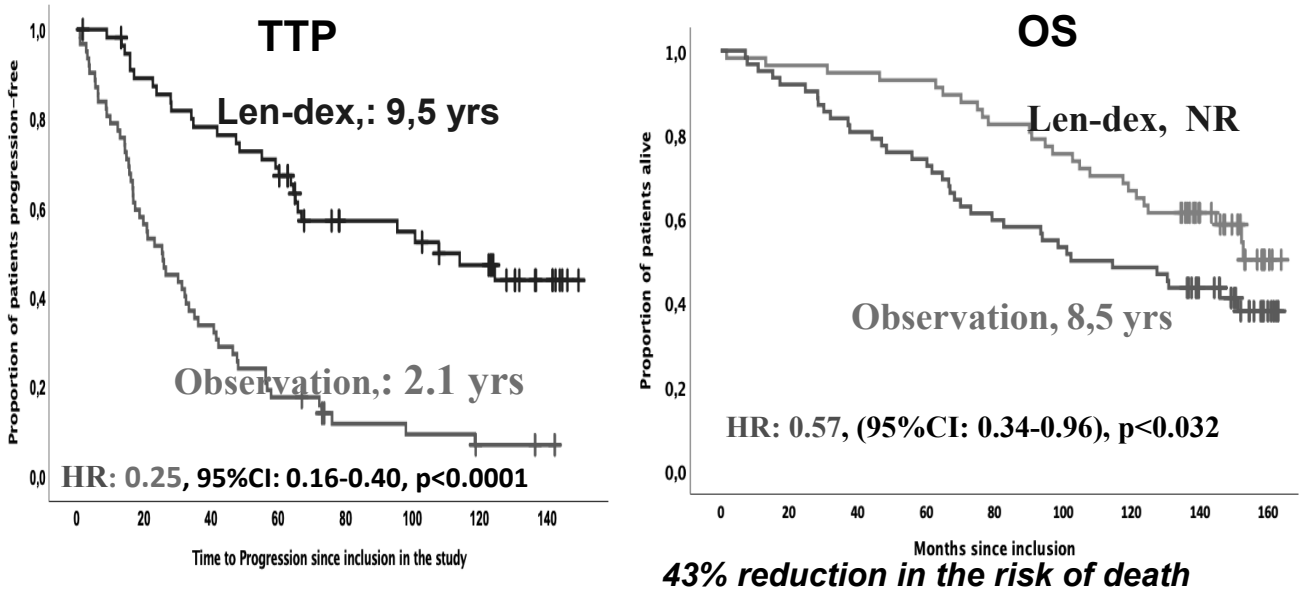
Rationale for Early Intervention in High Risk SMM

➢ To treat the disease early: to achieve cure

- ➢ *Early detection and intervention is a pre-requisite for cure in most malignancies*
- ➢ *Why is the standard of care in MM no treatment until CRAB?* Risk of harm: *clonal selection, toxicities.*

Numerous clinical trials in SMM (~ 75 in clinicaltrials.gov)
TO DELAY THE DISEASE PROGRESSION **TO CURE THE DISEASE**

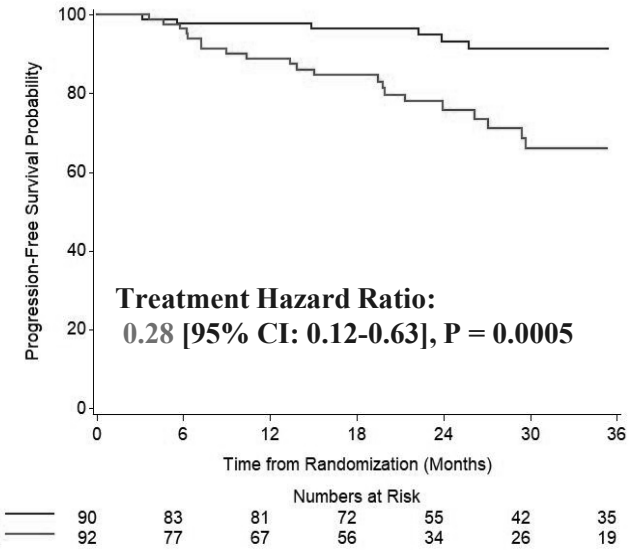
Len-Dex vs Observation (n = 119) *Median f/u: 12,8y*



43% reduction in the risk of death

Mateos MV, et al. NEJM. 2013. Mateos MV, et al. Lancet Oncology 2016; EHA2020

Len vs Observation (n = 182)



Lonial S et al. J Clin Oncol. 2020 Apr 10;38(11):1126-1137.

Curative Strategy for High Risk Smoldering (CESAR trial) (n = 90)

High risk definition based on Pethema and/or Mayo models

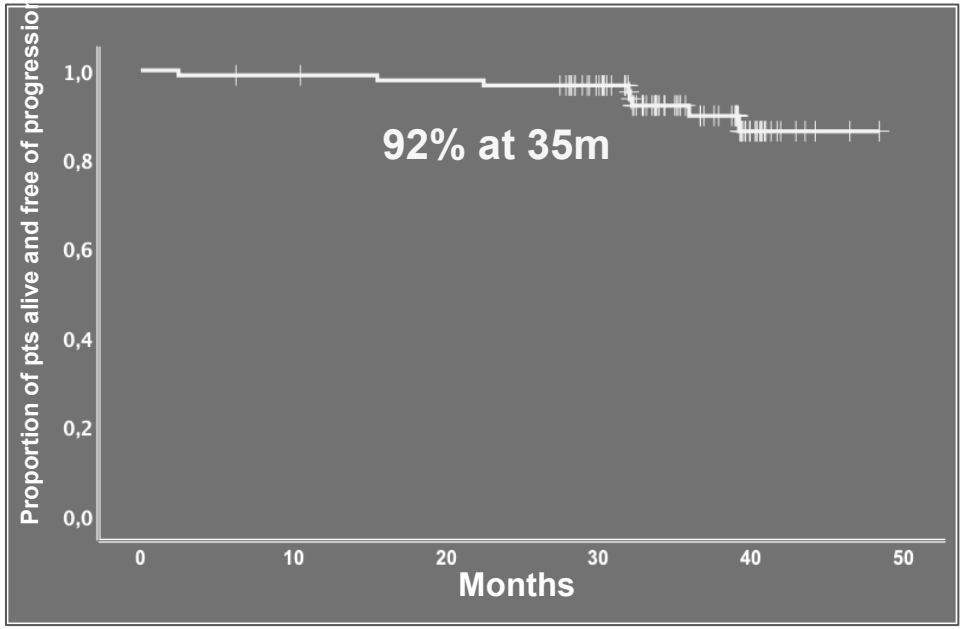
CR and MRD status

Response, %	Induction (KRd x 6) (n = 77)	HDT-ASCT (n = 77)	Consolida (KRd x 2) (n = 77)	Maintenan (Rd x 1 Yr) (n = 77)
≥ CR	43	63	75	81
MRD negative	33	49	65	62

- 6 pts did progress (In 5 it was biological & 4 were ultra-HR):
2 during induction; one after ASCT and 4 during maintenance

- Three deaths: Only 1 treatment related death(Ischemic stroke)

PFS



Mateos et al. ASH 2019. Abstract 781;.

ASCENT : KRD-Dara

Results to date:

- 54 patients accrued
- Median patient age 63 years
- 6% have completed maintenance, 56% consolidation, 80% induction and 17% in induction phase

- ≥1 patient needed a dose modification
- ≥ grade 3 AE seen in 43% of patients

Quadruplet regimen KRd-D is well tolerated in high-risk SMM

AE, adverse event; CR, complete response; KRd-D, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response.

Kumar et al., ASH 2020: Abstract 2285 (poster presentation)

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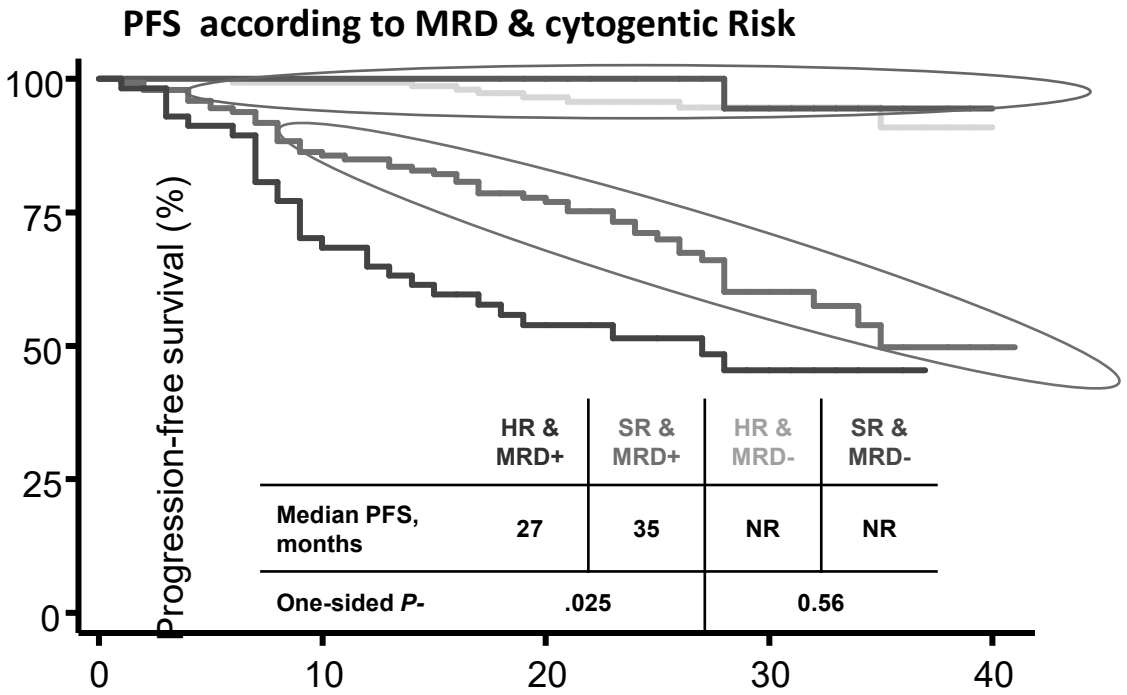
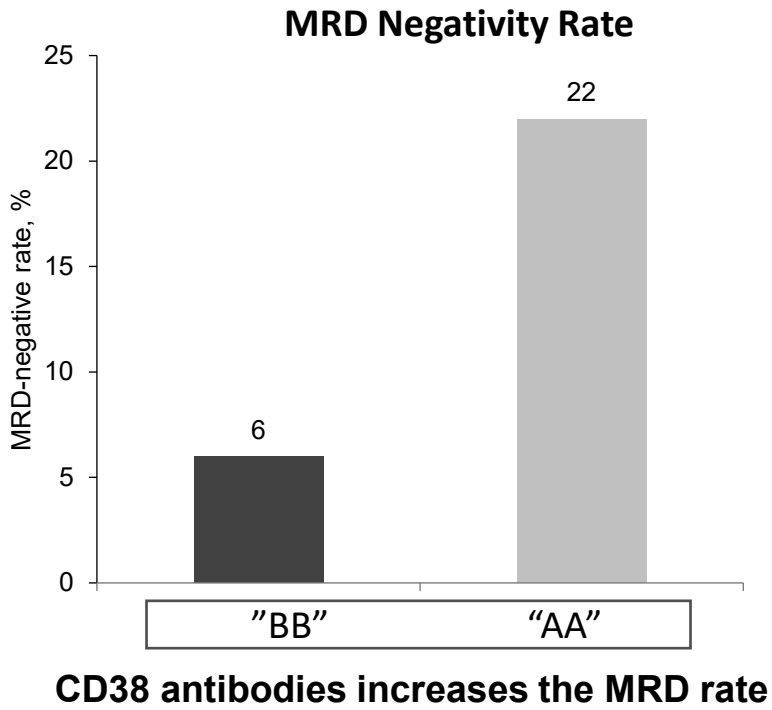
Influence of depth of Response in Standard Risk patients

Evidences that support MRD directed therapy





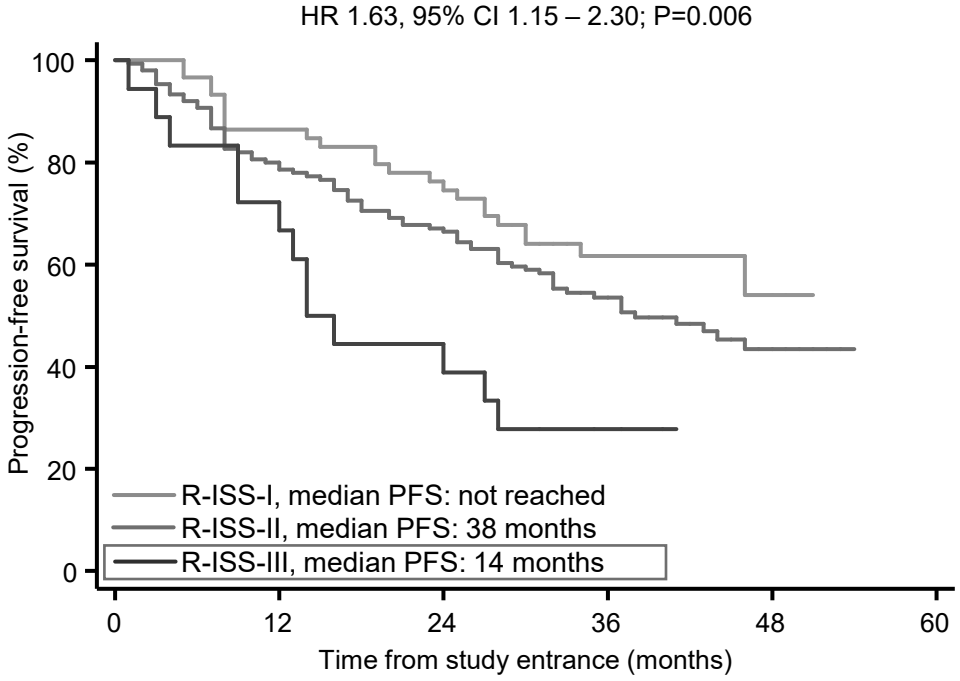
CD38 antibodies increases the MRD rate

If cure is the goal : To offer intensive therapies to high-risk patients &
a gentle one to standard risk patients.....Wrong philosophical approach?

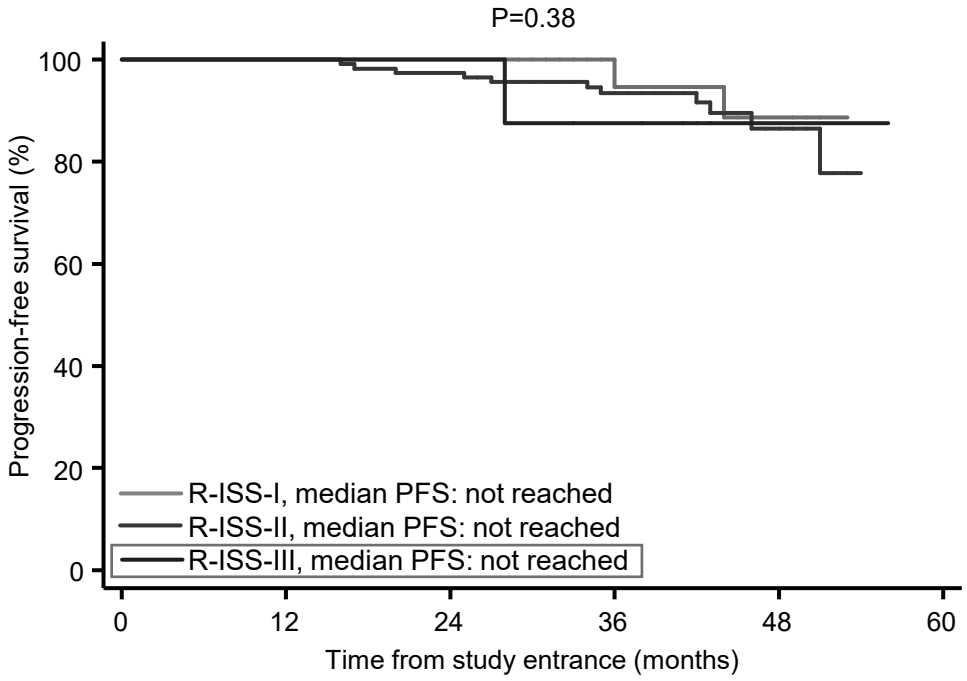
Goicoechea I Blood. 2021, 137(1):49-60.
Paiva B J Clin Oncol 2020; 38(8):784-792

The best pathway to overcome the poor prognosis of high-risk cytogenetics is through the achievement of MRD-negativity: *overcomes poor prognosis of high-risk*

MRD-positive



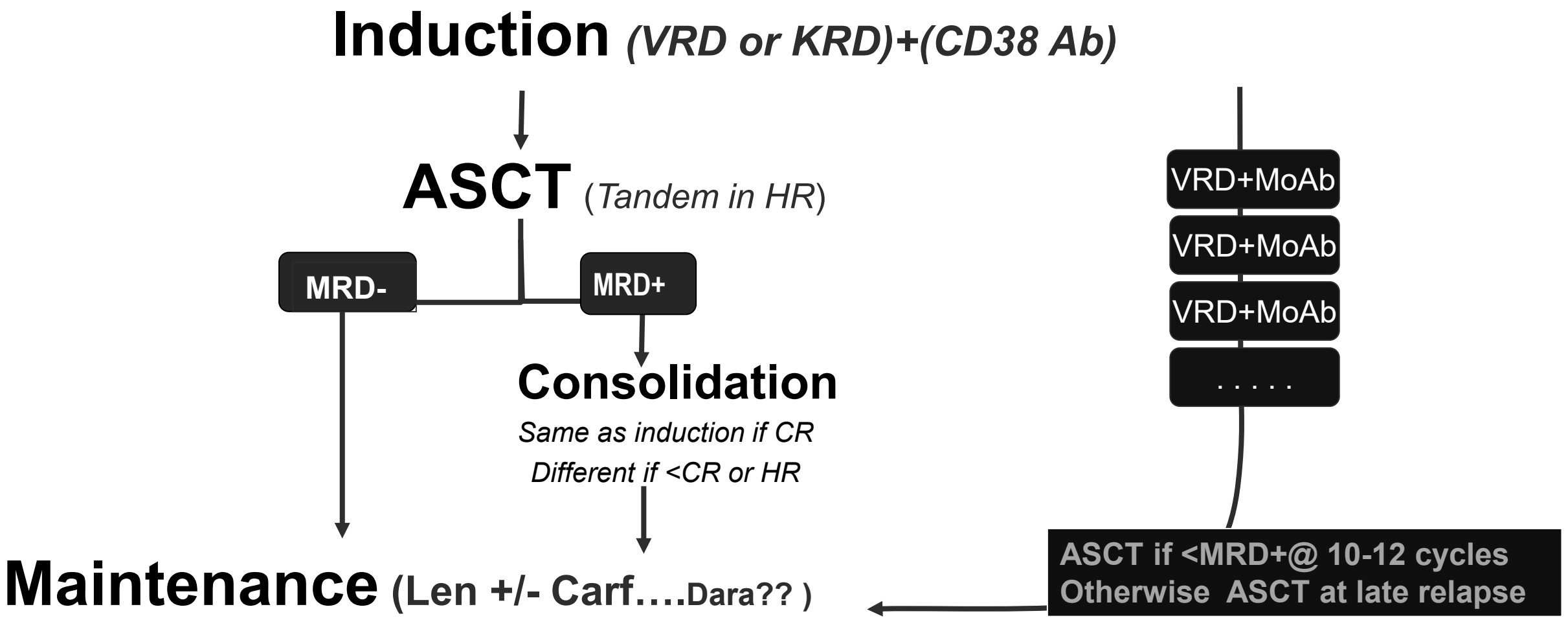
MRD-negative (Undetectable)



Paiva B, et al. Blood 2017;130: abstract 905

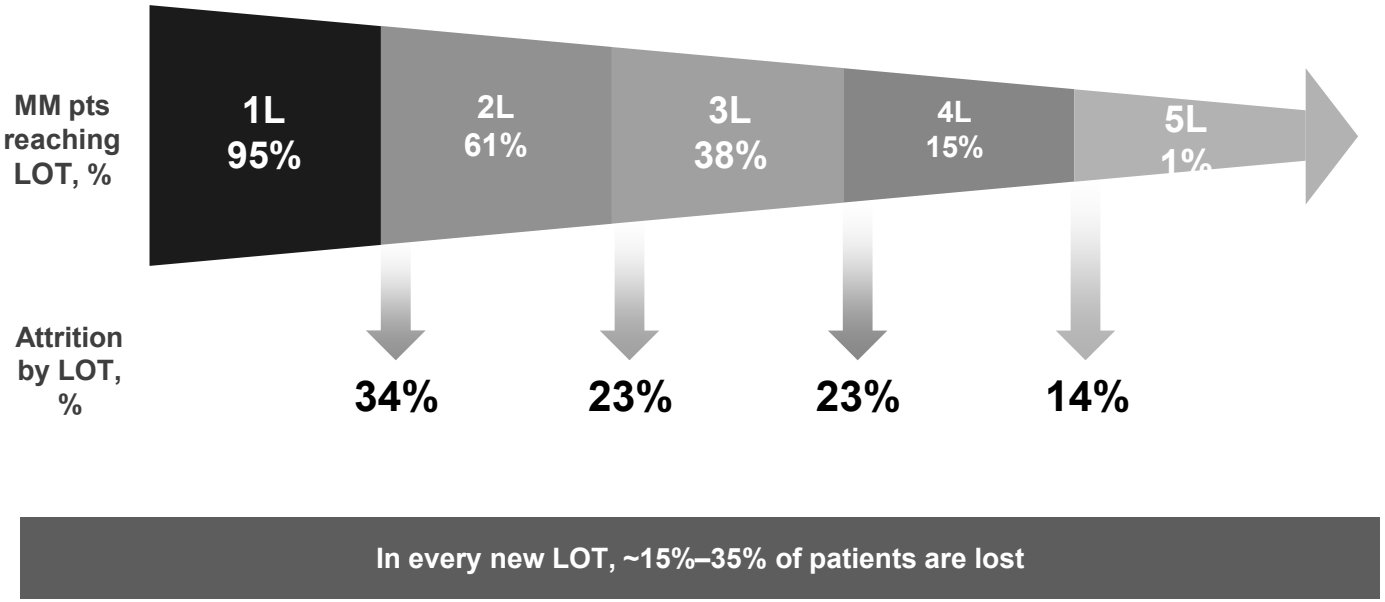
- ***Treatment should be adapted in High risk patients in order to eradicate MRD inside and outside BM***
- *MoAb improve outcome…but does not overcome the adverse prognosis*
- *Effective treatment may not be a matter of dose intensity…… but of dose density*
- *Investigate experimental therapies: sequential courses including immunotherapy to avoid early tumour regrowth?.*

Transplant candidate Patient: *Proposal for today*



PFS >80% @4y in SR

In Myeloma treatment there is a high attrition rate, particularly in the elderly population….
therefore front line is critical



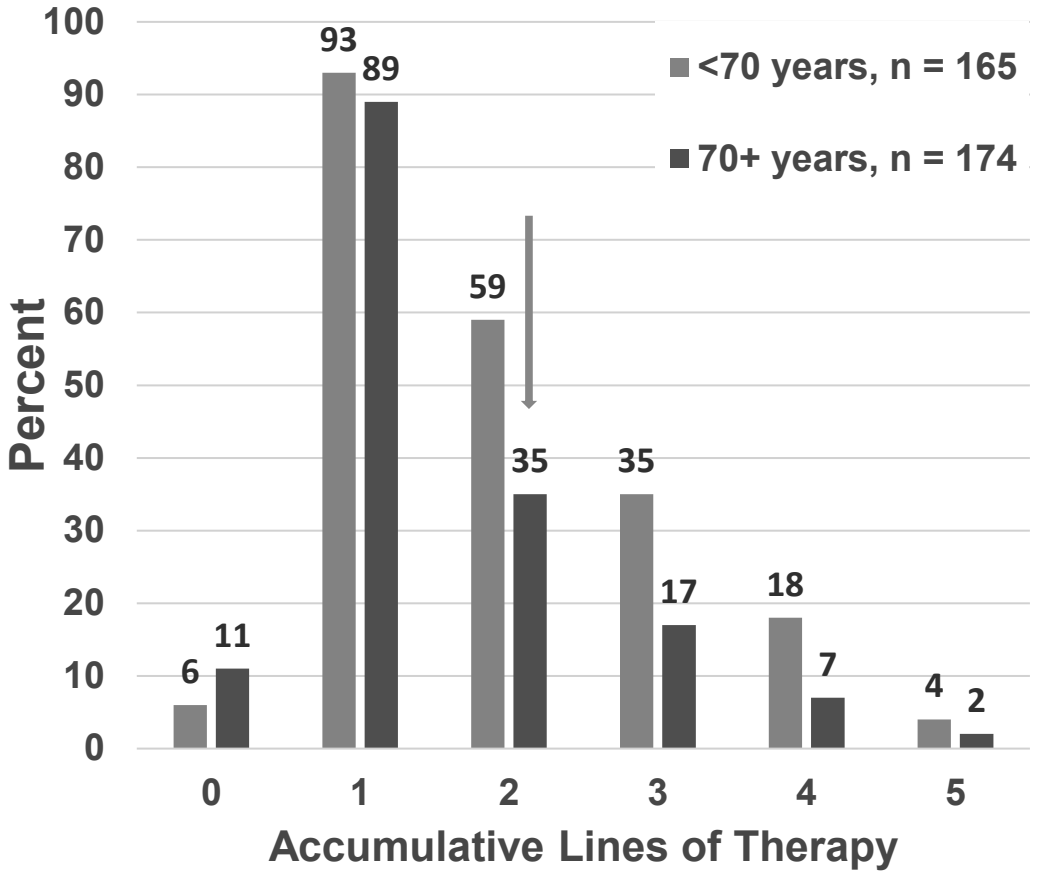


Figure adapted from: Yong K et al. *Br J Haematol* 2016;175(2):252-264.

LOT, line of therapy.

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Courtesy of A Spencer

What are the Optimal Regimens In non- transplant candidates?

1. San Miguel J, *et al.* N Engl J Med 2008;359:906–17; 2. Benboubker L, *et al.* N Engl J Med 2014;371:906–17 3. Durie. Lancet. 2017;389:519. 4. Kumar. ASCO 2020 Abstr LBA3; 5.Facon T et al. ASH 2020. Abstract 551 6. Mateos. ASH 2019. Abstr 859. 7. Facon. NEJM. 2019;380:2104

If cure is the goal……..We need to improve……*Future Perspectives*

Many unsolved questions…. *Absence of robust data to guide treatment decision*

- ✓ High Risk Cytogenetics (particularly R-ISS3 & Double Hit)
- ✓ Early Relapses or Primary Refractory disease
- ✓ Extramedullary disease: efficacy of novel agents remains controversial

Therefore…….

- ❖ ***New strategies ……since conventional approaches are suboptimal***

- ➢ **Adapted treatment approach upfront to erradicate MRD**
- ➢ **Early Rescue Interventions (ERI): based on early detection of resistance**
- ➢ **Immunotherapy (Biespecific T-cell engagers and CAR-Ts) may be the way to improve the outcome in this high risk patient population.**

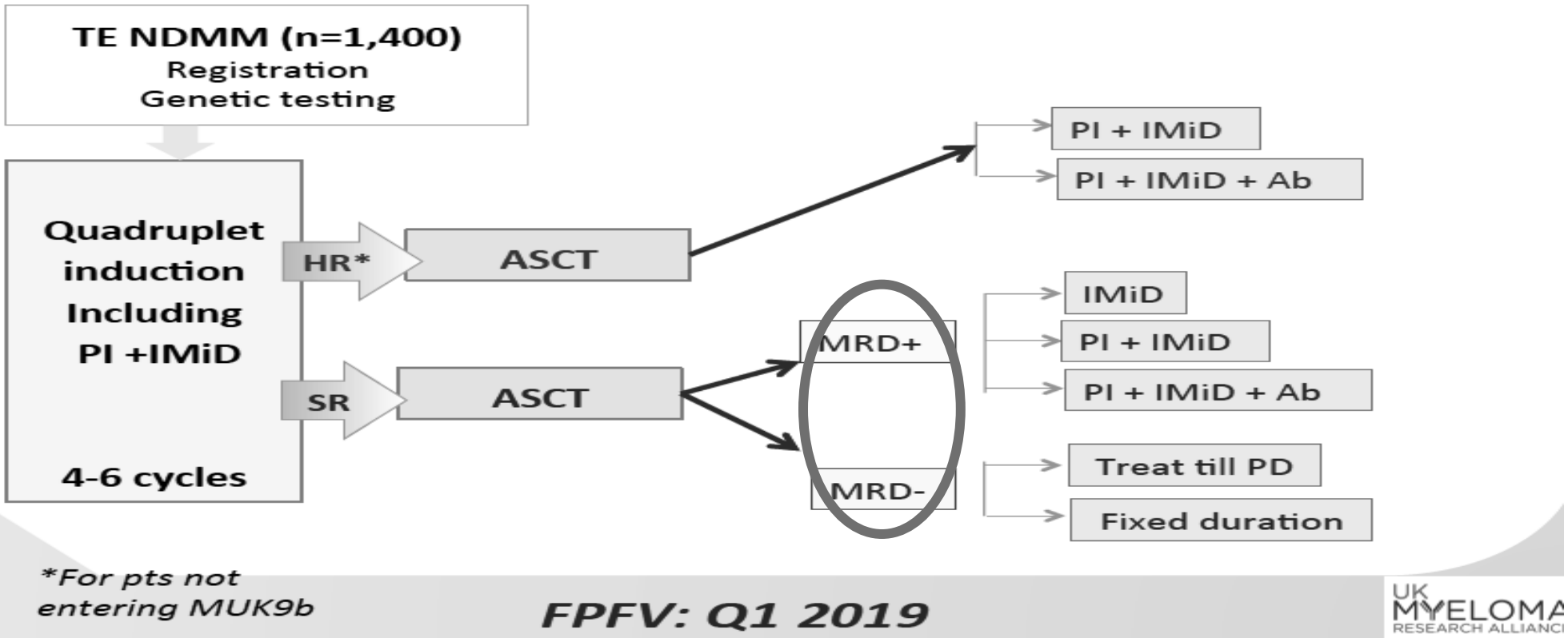
- ✓ **Early relapses:** OS for R-ISS 3 in early relapses post-ASCT **is 1.5 years** (Gopalakrishnan S et al. BBMT 2018).
- ✓ In **Primary Refractory** Patients, to move into HDM/ASCT is inadequate (PFS:6m; OS:13m) Rosiñol L et al. Haematologica 2012

IFM 2021

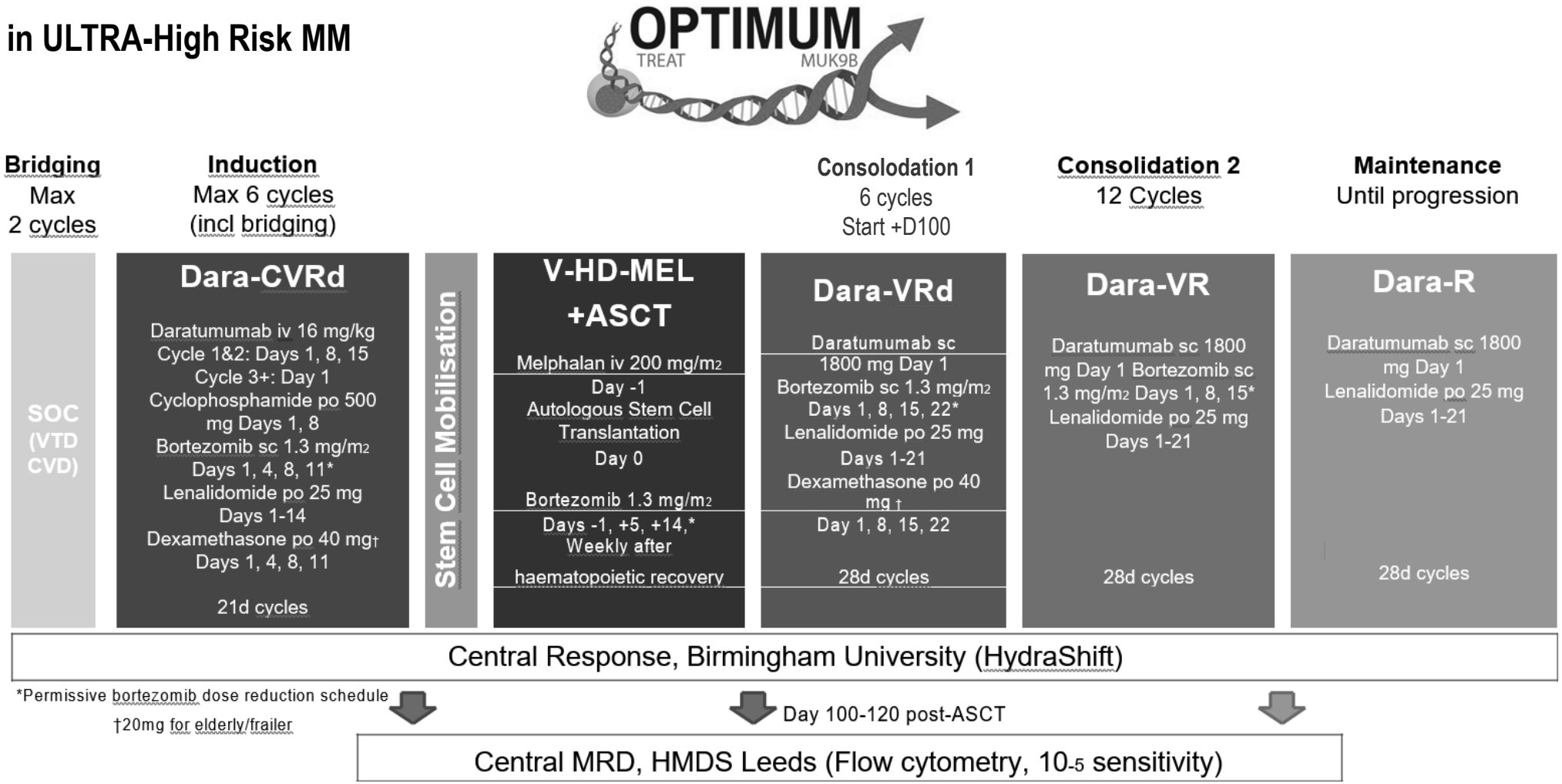
IFM 2019 : HR Trial	IFM 2019: Non-HR Trial (Phase III, n= 1 100)			
	Randomisation			
	Non-Adapted Therapy		Adapted Therapy	
KRD-Dara x 6	IRD-Dara x 6		IRD-Dara x 6	
MRD1	*MRD1*		*MRD1*	
	--	+	--	+
HDM	HDM		HDM	
KRD-Dara x 4	IRD-Dara x 4		IRD-Dara x 4	KPD-Dara x4
MRD2	*MRD2*		*MRD2*	
	--	+	--	+
HDM				HDM
Rev + Dara 2 years	Rev 2 years		Rev 2 years	Rev + Dara 2 years
TEP	TEP		TEP and optional tomotherapy of residual targets	
MRD3 (end of therapy)	*MRD3 (end of therapy)*		*MRD3 (end of therapy)*	
MRD 4, 5, 6 (each year)	*MRD 4, 5, 6 (each year)*		*MRD 4, 5, 6 (each year)*	
Phase II-PO: 30% increase of PFS as compared with HR in the IFM 2009 trial	PO:MRD3 from 45% to 55% with adapted therapy. SO:PFS, OS, Operational cure (ie: MRD3+4+5+6=Neg), Stringent-MRD (ie: MRD3 + TEP = Neg)			

UK group: RADAR study. Risk adapted therapy according to response. NDMM transplant eligible

UKMRA Myeloma XV (*RADAR: Risk Adapted therapy Directed According to Response in newly diagnosed patients with multiple myeloma (NDMM) suitable for stem cell translation (TE)*) ***Kwee Yong, Mark Cook***



UK Trial in ULTRA-High Risk MM



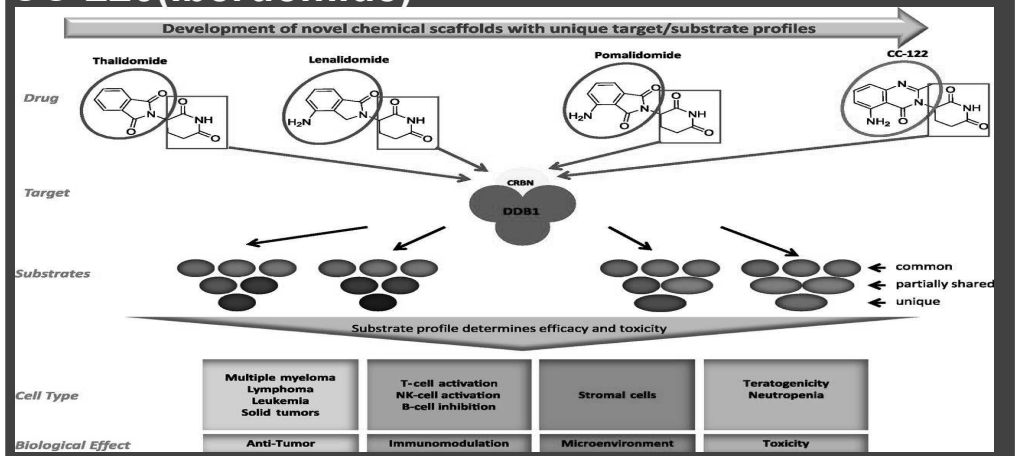
From a total of 462 Pts, 128 were Ultra-High Risk* (107 included in the study….102 evaluable for response)
VGPR post induction and Post ASCT**:** **84% and 87%**
MRD-ve post induction and Post ASCT**:** **50% and 88%**

* 27% : 11% GEP+ Double hit & 16% GEP or Double hit

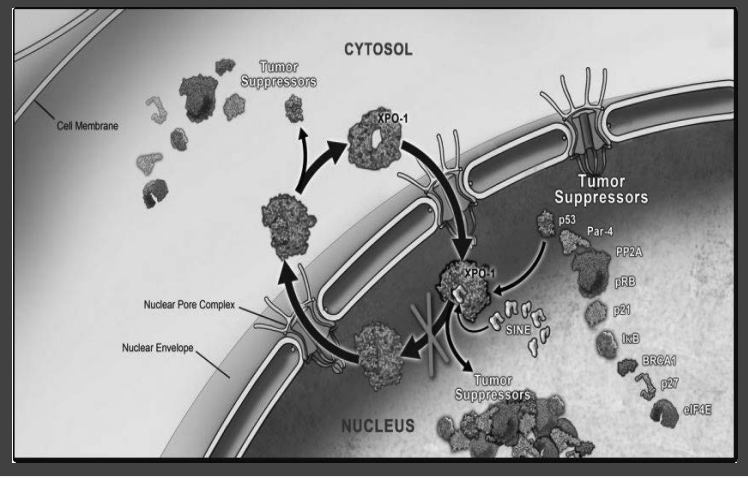
Kaiser EHA 2021

New agents

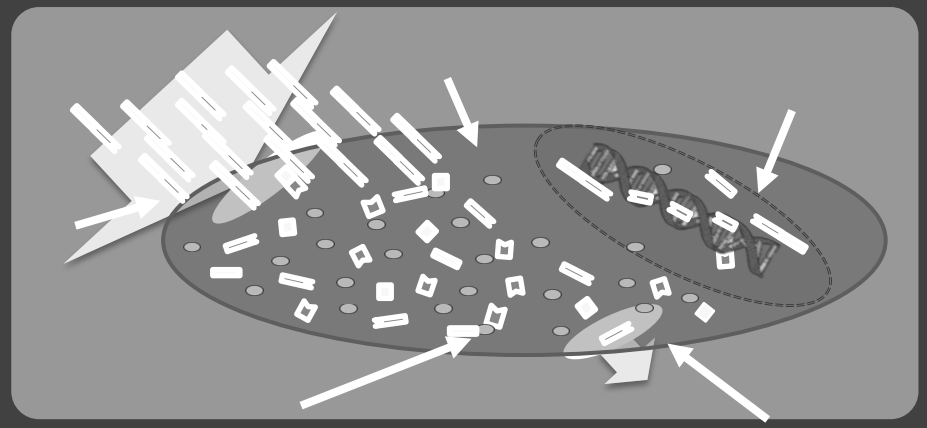
CC-220(Iberdomide) New IMiDs CC-92480



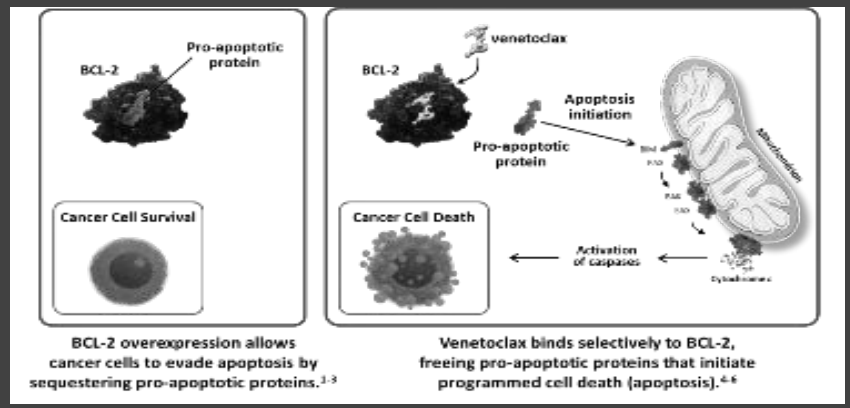
Selinexor: XPO-1 inhibitor



Melflufen is a new alkylator



Venetoclax



Monoclonal antibodies: New perspectives

To overcome the limitations of an immunosuppressive tumour microenvironment by linking CTLs with the tumour cell.

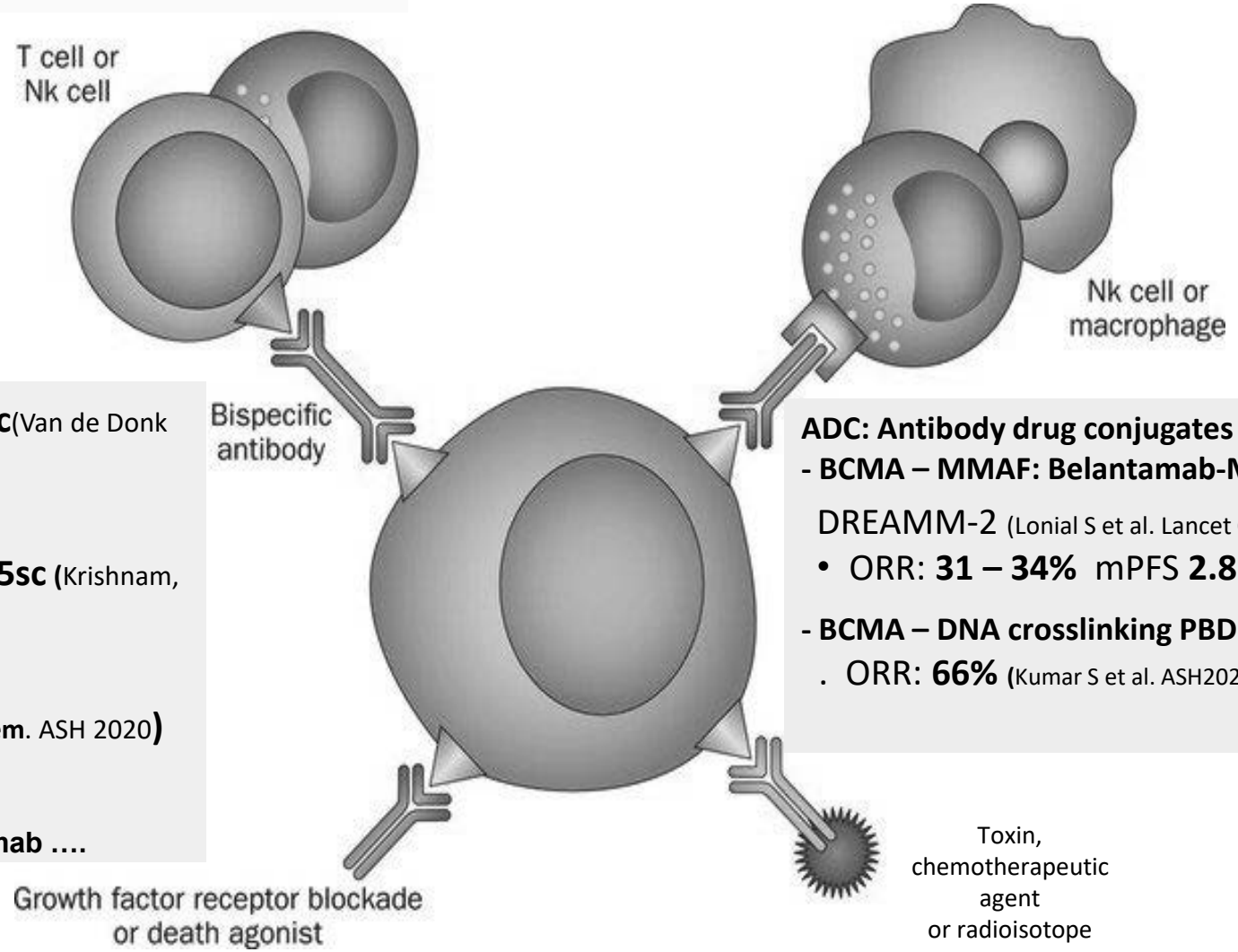
Bispecific T cell engagers:
BCMA & Others –CD3 Phase I trials

-Teclistamab (BCMA) Pts: 157, 75sc(Van de Donk EHA 2021**)** ORR **65% (58%VGPR)**

- Talquetamb (GPRC5D).Pts: 184, 75sc (Krishnam, EHA2021 ORR **70.9% (60%VGPR)**

-Cevostamab (FcRH5). Pts: 80 (Cohem. ASH 2020**)** ORR **61% (17%VGPR)**

CC-93269; REG 5458, TNB3838, Elranatamab ….



ADC: Antibody drug conjugates
- BCMA – MMAF: Belantamab-Mafodotin

DREAMM-2 (Lonial S et al. Lancet Oncol 2019)

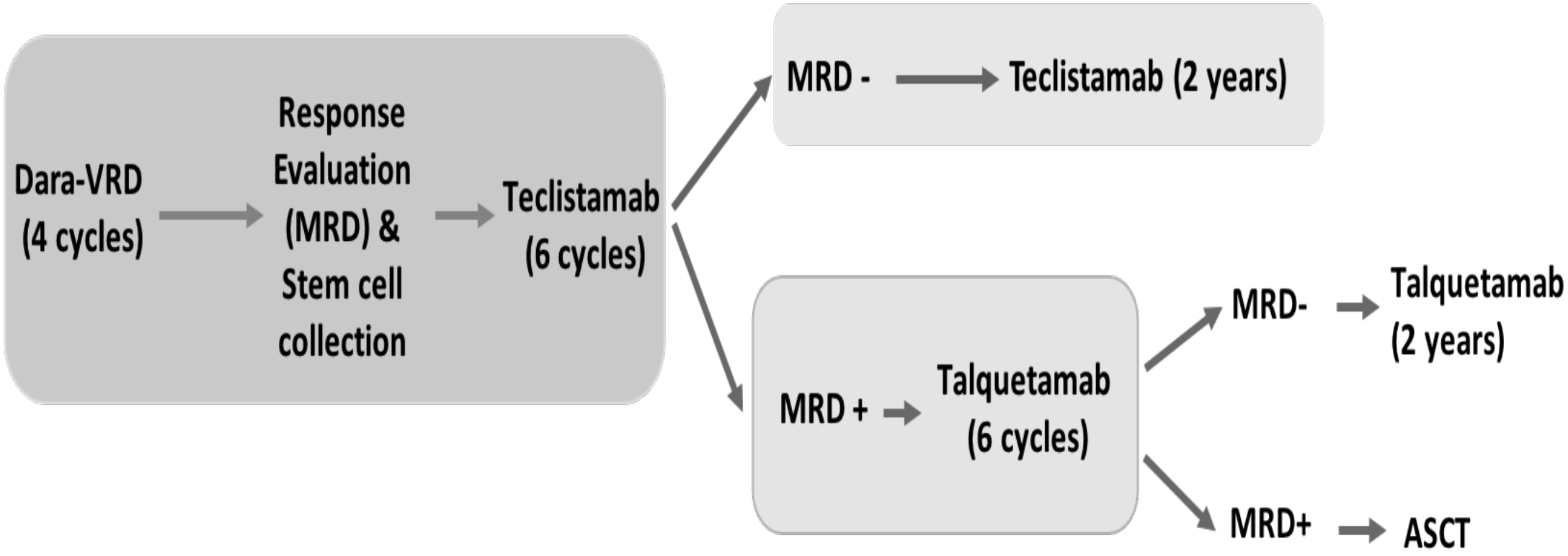
- ORR: **31 – 34%** mPFS **2.8 m – 4.9 m**

- BCMA – DNA crosslinking PBD : MEDI2228

. ORR: **66%** (Kumar S et al. ASH2020 Abst #179)

MMAF, monomethyl auristatin F; DM1, maytasanoid N(2')- deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine. BCMA-targeted ADC with **a DNA cross-linking pyrrolobenzodiazepine (PBD)**

PETHEMA/GEM: High Risk MM Patients 2021



Patient population: High-risk transplant & Fit non-Trx candidates

-FISH: del(17p), t(4;14), t(14;16) and 1q amplifications .

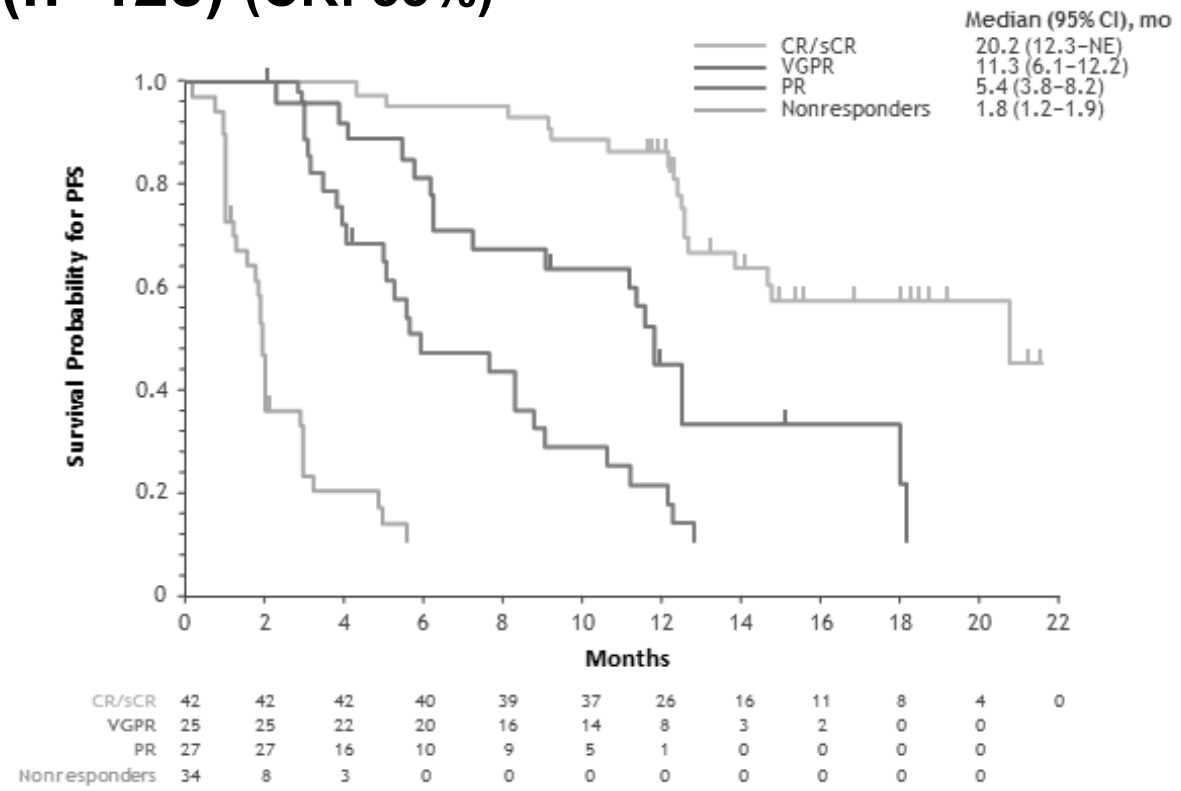
-R-ISS 3

-Presence of extramedullary disease

Outcomes with current BCMA-directed CAR T cells in CR patients

The importance of depth of response with CAR T cell treatment

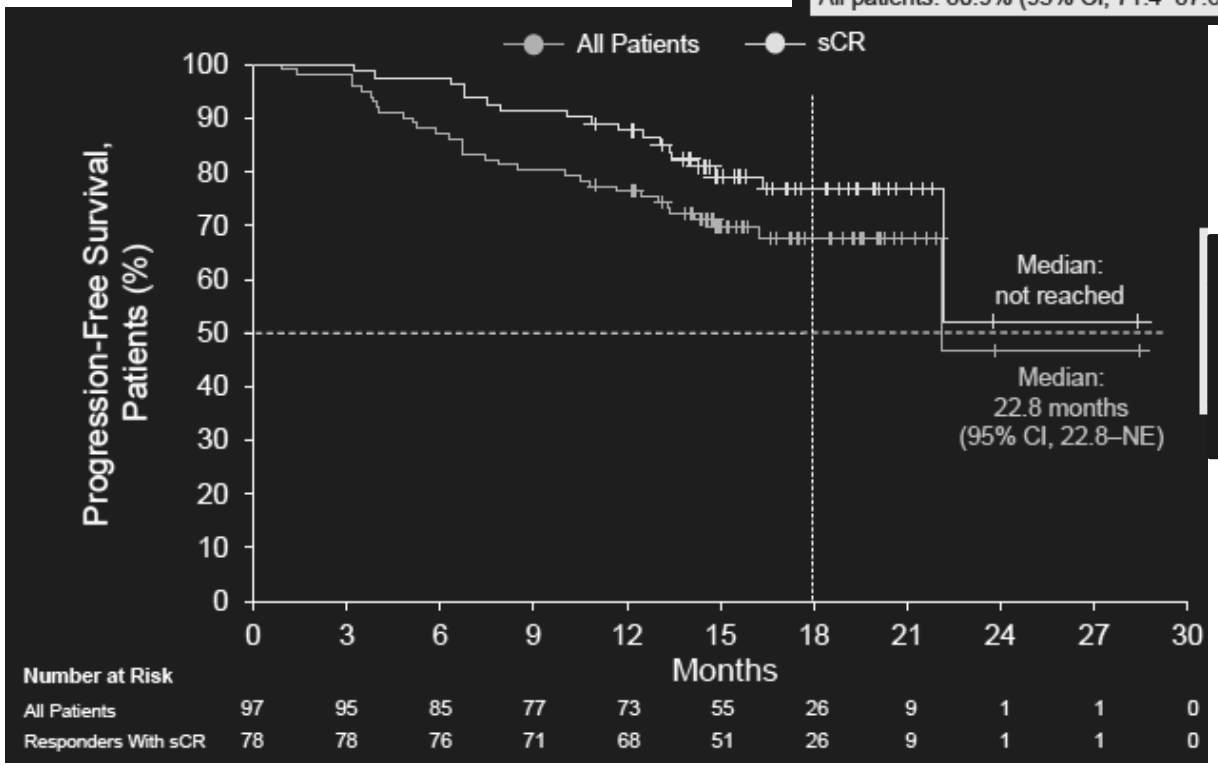
Ide-cel KarMMa (n=128) (CR: 33%)



Cilta-Cel CARTITUDE-1 (n=97) (CR: 80%)

18-month PFS
All Patients: 66.0% (95% CI, 54.9–75.0)
sCR: 75.9% (95% CI, 63.6–84.5)

18-month OS
All patients: 80.9% (95% CI, 71.4–87.6)



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Munshi et al. ASCO meeting, 2020; May 29-31, 2020. Abs. 8503. Munshi et al. NEJM 2021.
Usmani S et al. ASCO 2021. Oral presentation. Abstract #8005

Future of CAR-T cell therapy

- **Early relapse**
  - CARTITUDE 4 (1-3 PL Len-ref)…….*cilta-cel vs SoC*
  - KarMMa-3 (2-4 PL, prior antiCD38)…….*Ide-cel vs SoC*
- **Frontline setting**
  - CARTITUDE-5: NDMM not intended for ASCT (Ph 3 randomized): *VRD+Cilta-cel vs VRD-Rd*
  - KarMMa-4: NDMM R-ISS 3*: induction + ide-cel + Len maintenance*
  - BMT-CTN SOSS 2021 Concept: HR-NDMM
- **Suboptimal response after ASCT& 6m Maint:** BMT-CTN 1902
- **Combinations trying to improve the outcomes**
  - KarMMa-7*: ide-cel + Iberdomide /+ gammasecretase inhibitor /+ DPd or PVd*

- ***Fine-tuning the infusion product: increase % of memory like T-cells, armoured CARs, etc.***
- ***Dual targeting***

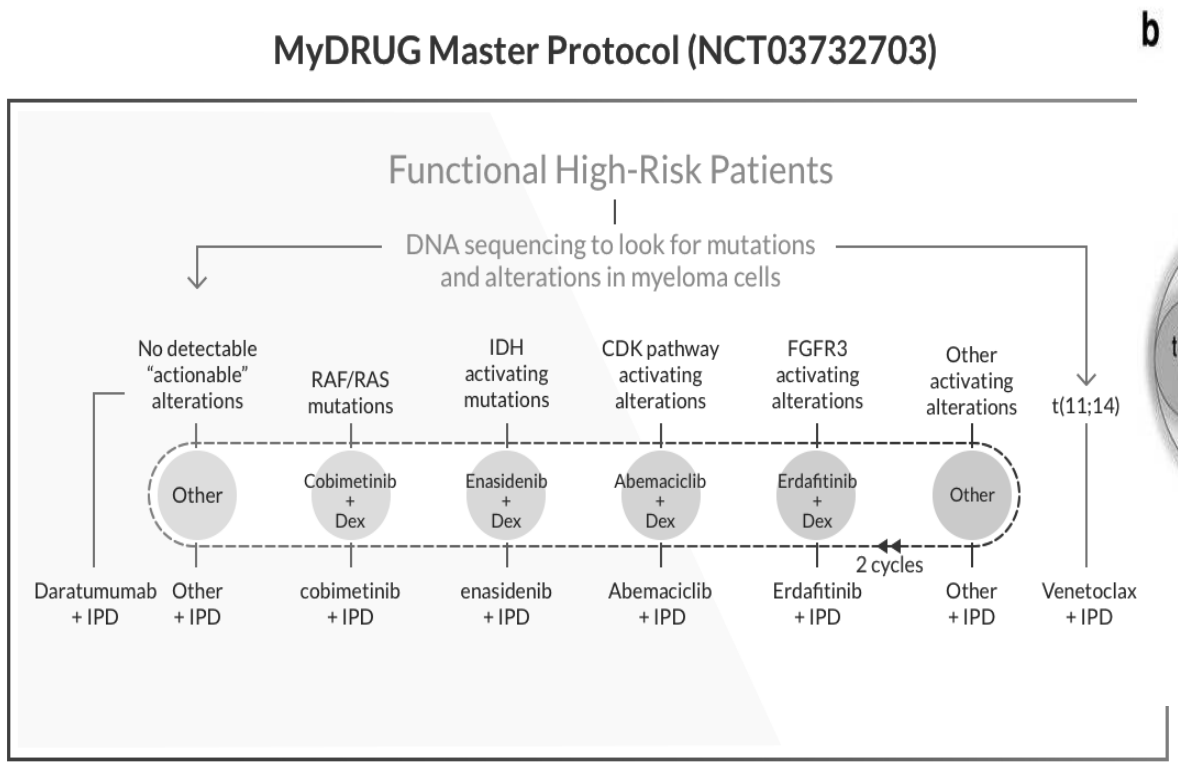
BMT-CTN: Blood and Marrow Transplant Clinical Trials Network.

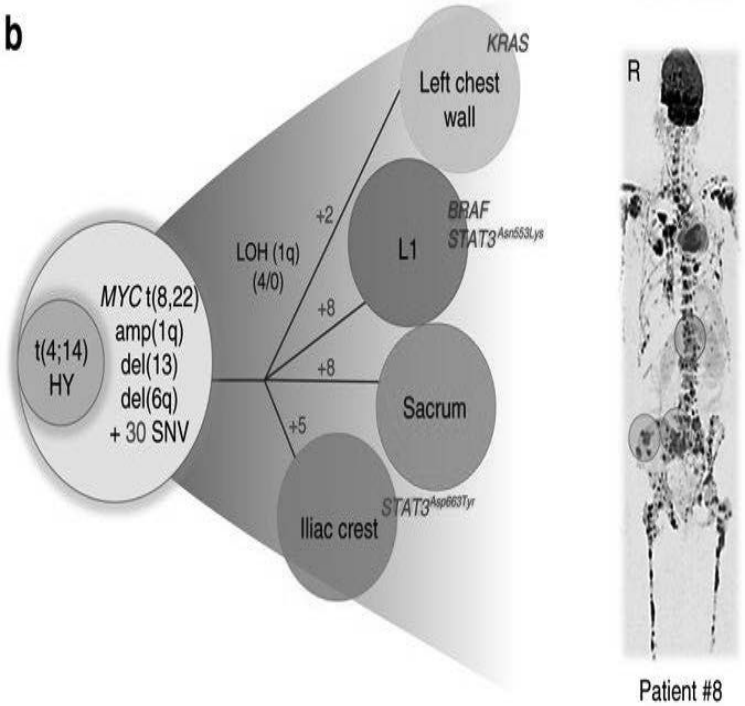
Optimizing Clinical Trials for MM Patients
Individualized therapies

- **Targeted Therapy: Molecular lesions predicting* response**
  - **Venetoclax** : for t(11;14) and high BCL2 patients
  - **Targeted agents**: RAS/MAPK pathway inhibitors, IDH inhibitors...*But*

.....clonal heterogeneity: *KRAS in Chest; STAT3 & BRAF in L1*

** PROGNOSTIC/ PREDICTIVE*



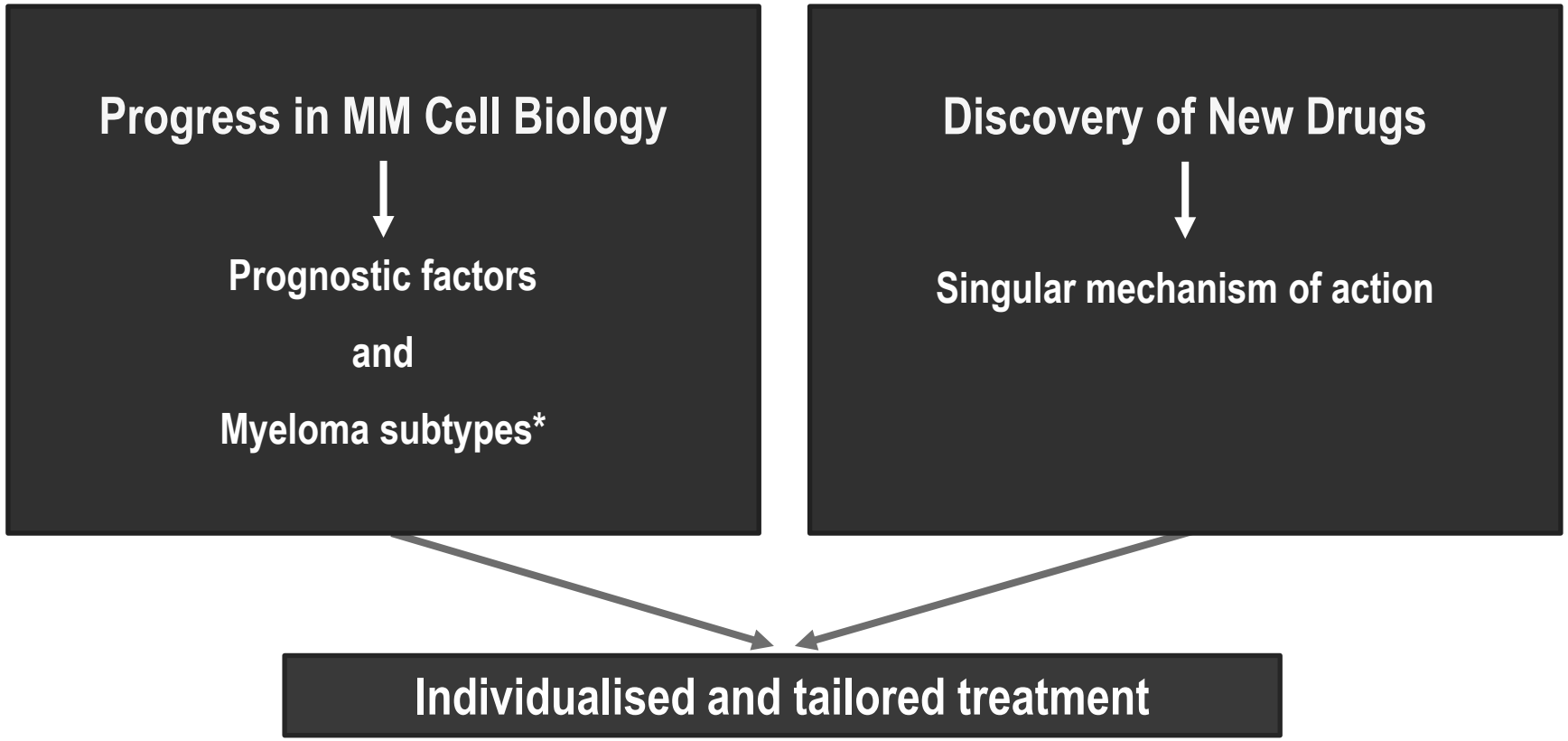


Rasche et al, *Nature Communications* 2017

- Received at least one but no more than three prior therapies
- Relapsed within 12-18 months of starting their second-line treatment or were refractory to their initial treatment

MULTIPLE MYELOMA

A model for scientific and clinical progress from biology to therapeutics



*MM should not be considered a single entity.

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We will beat myeloma!!

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The Real Future