Global Multiple Myeloma Academy

Global Multiple Myeloma Academy

Emerging and Practical Concepts in Multiple Myeloma

23–24 June 2022 – Latin America and Canada

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Global Multiple Myeloma Academy

Welcome and Meeting Overview

Rafael Fonseca, MD

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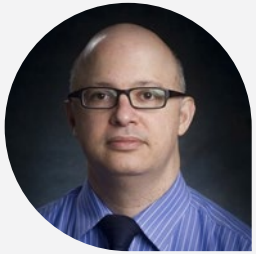
Faculty

Chair

Rafael Fonseca, MD
Mayo Clinic Cancer Center, USA

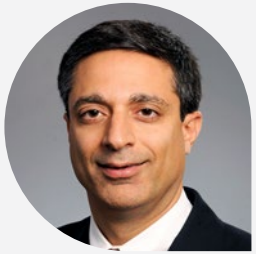
Keith Stewart, MBChB, MBA
Princess Margaret Cancer Centre, Canada

Vania Hungria, MD, PhD
São Germano Clinic, Brazil



Luciano Costa, MD, PhD
University of Alabama at Birmingham, USA

Eloisa Riva, MD
Hospital de Clínicas, Uruguay



Sagar Lonial, MD, FACP
Emory University, USA

Objectives of the Program

Share key data from recent conferences that could lead to improved treatment and management for patients with myeloma

Discuss early treatment strategies for smoldering myeloma and initial therapies for multiple myeloma

Provide insights into the evolving role of minimal residual disease (MRD) monitoring in the management of patients with multiple myeloma

Present the latest research on identifying multiple myeloma patients at high risk for early relapse, and management strategies for early relapse

Discuss the benefits and limitations of current options for treating patients with multiple myeloma refractory to multiple therapeutic modalities

Explore regional challenges in the treatment of multiple myeloma across Latin America

LATAM Agenda Day 2

Time UTC-3	Topic	Time	Speaker
15.30 – 15.40	**Session Open**	10 min	Rafael Fonseca, MD
15.40 – 16.00	**Defining and Understanding High-Risk Multiple Myeloma**	20 min	Eloisa Riva, MD
16.00 – 16.25	**Early Relapse of Multiple Myeloma: Current and Emerging Treatment Options**	25 min	Rafael Fonseca, MD
16.25 – 16.45	**Patient Case Discussion and Q&A: Relapsed/Refractory Multiple Myeloma** Case 1 from the region	20 min	Ana Luiza Silva, MD
16.45 – 16.55	**Break**	10 min	
16.55 – 17.20	**Management of Heavily Pretreated Multiple Myeloma**	25 min	Keith Stewart, MBChB, MBA
17.20 – 17.40	**Patient Case Discussion and Q&A: Relapsed/Refractory Multiple Myeloma** Case 2 from the region	20 min	Lucía Pérez Baliero, MD
17.40 – 18.30	**Beyond the Horizon: New and Future Multiple Myeloma Treatment Approaches** • Optimal use of treatment choices in relapsed/refractory MM – Bispecifics in MM – CAR Ts in MM	 25 min 25 min	 Vania Hungria, MD, PhD (bispecifics), Luciano Costa, MD, PhD (CAR T)
18.30 – 18.55	**Interactive Discussion and Q&A** • Treatment landscape evolution	25 min	All faculty discussion
18.55 – 19.00	**Session Close**	5 min	Rafael Fonseca, MD

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Introduction to the Audience Response System

Rafael Fonseca, MD

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Question 1

What treatment belongs to the T-cell engagers category?

a) Melflufen
b) Belantamab
c) Ide-cel
d) Selinexor
e) Venetoclax

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Question 2

Which of the following combinations has not been tested in phase III clinical trials in RR MM?

a) Dara-Pd
b) Elotuzumab, venetoclax, dexamethasone
c) Bortezomib, pomalidomide, dexamethasone
d) Bortezomib, daratumumab, dexamethasone
e) Carfilzomib, lenalidomide, dexamethasone

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Question 3

Which statements are true for the treatment of myeloma?

a) There is a high rate of attrition (loss)
b) Several drug trials show that 2 drugs can be as good as 3 in terms of efficacy
c) Myeloma is a heterogeneous disease with increased rates of *p53* abnormalities with progression
d) All the above
e) A and C

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Defining and Understanding High-Risk Multiple Myeloma

Eloisa Riva, MD

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Disclosures

- Honoraria: AbbVie, Sanofi, Janssen

Single-Choice Question 1

Which of the following is correct (one option) in the HR MM setting?

a) Daratumumab-based induction and maintenance is the best option
b) ASCT has no role in this context
c) Lenalidomide is the best option for long-term maintenance
d) KRD + ASCT achieves high sustained MRD negativity

Agenda

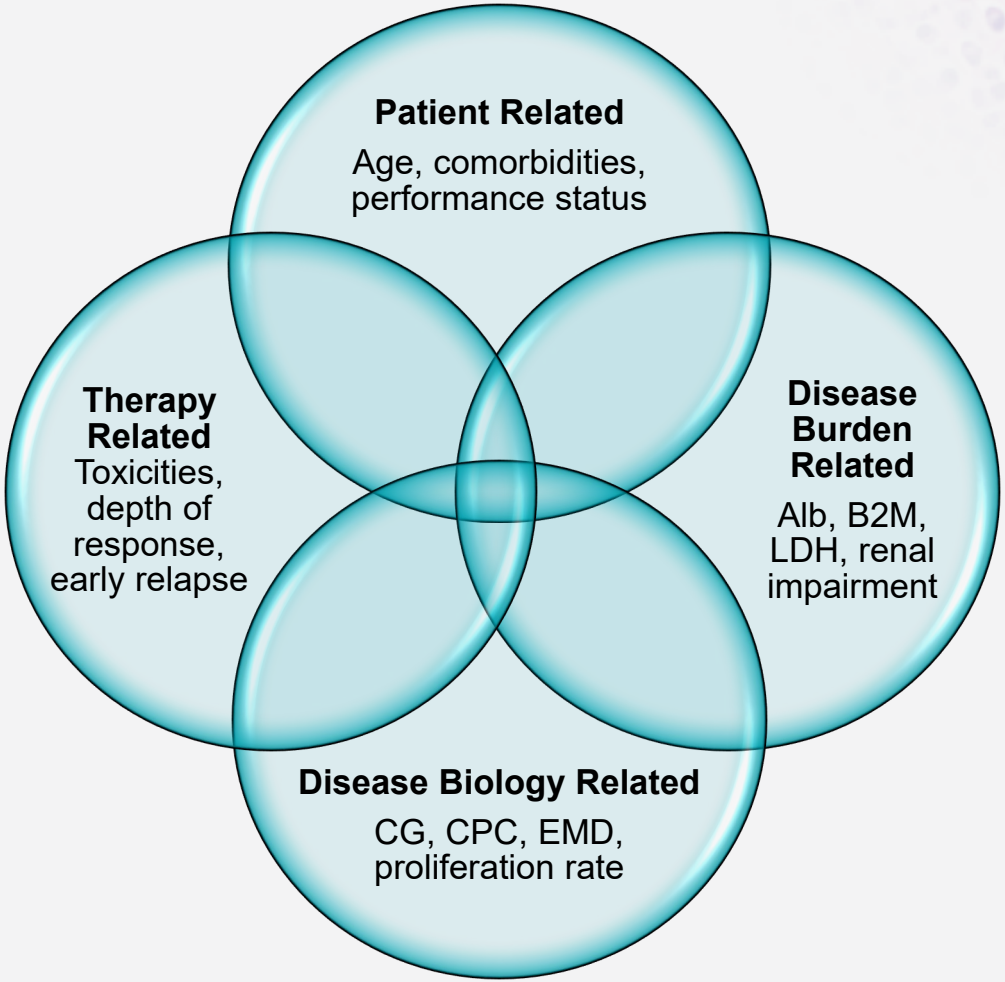
- HR MM definition
- Risk stratification
- Prognosis
- Therapeutic choices

HR MM Definition

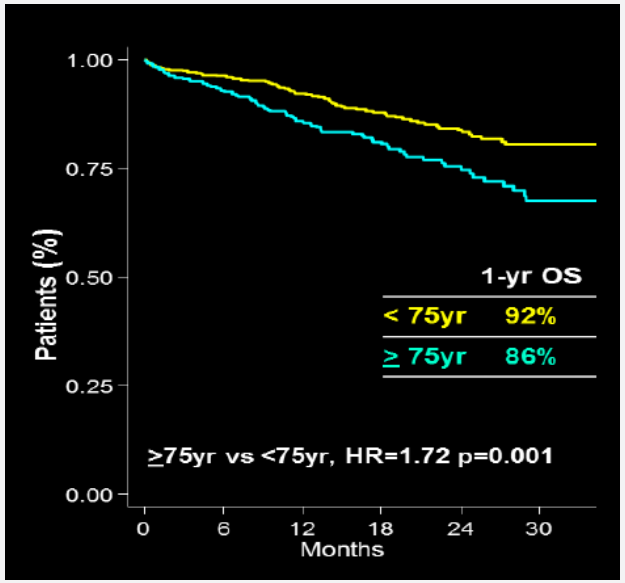
- Improvement in OS in MM has not been uniform
- 15%–20% of patients have a predicted OS <3 years
- Ultra high-risk OS <2 years

Sonneveld P, et al. *Blood*. 2016;127(24):2955-2963; Moreau P, et al. *J Clin Oncol*. 2014;32(20):2173-2180.

Risk Factors



Age



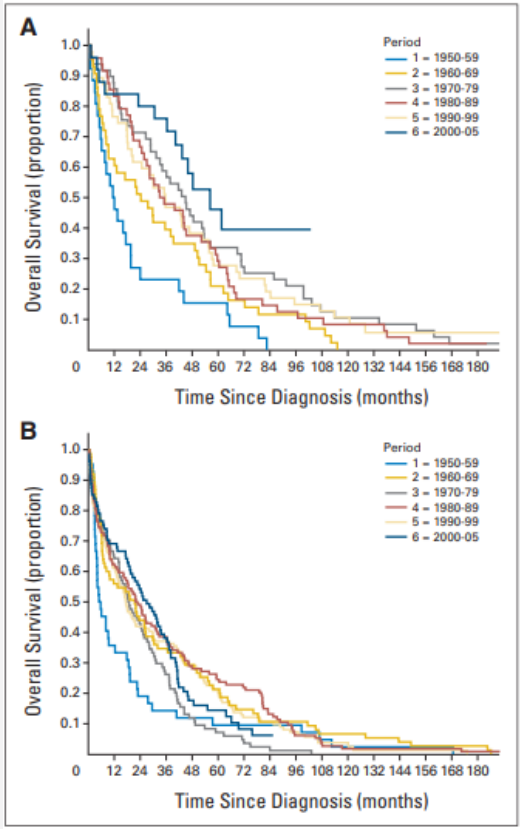


Fig 1. Overall survival in patients with multiple myeloma according to date of diagnosis and age at diagnosis: (A) ≤ 65 years old (n = 242) and (B) > 65 years old (n = 431). Periods of diagnosis were as follows: 1 = 1950 to 1959; 2 = 1960 to 1969; 3 = 1970 to 1979; 4 = 1980 to 1989; 5 = 1990 to 1999; and 6 = 2000 to 2005.


VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Patterns of Improved Survival in Patients With Multiple Myeloma in the Twenty-First Century: A Population-Based Study

Ingemar Turesson, Ramon Velez, Sigurdur Y. Kristinsson, and Ola Landgren

From the Department of Medicine, Section of Hematology, Malmö Univer-

ABSTRACT

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Turesson I, et al. *J Clin Oncol*. 2010;28(5):830-834; Palumbo A, et al. *J Clin Oncol*. 2015;33(26):2863-2869.

Frailty

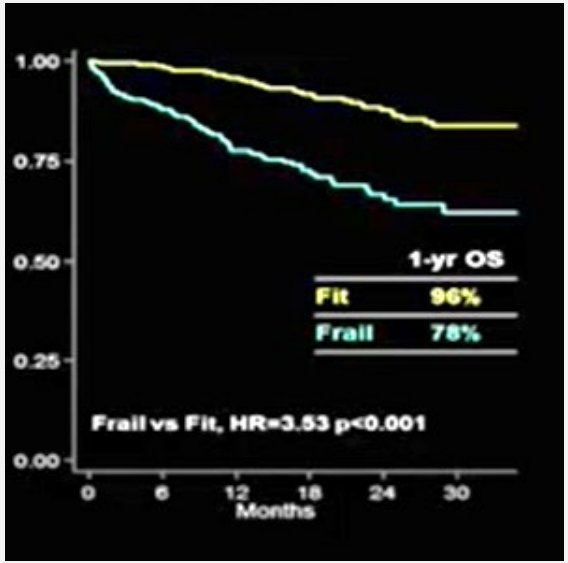


Table 2. The final Cox regression model

	HR (95% CI)	*P*	Score
Age, y			
≤75	1	—	0
76-80	1.13 (0.76-1.69)	.549	1
>80	2.40 (1.56-3.71)	<.001	2
ADL			
>4	1	—	0
≤4	1.67 (1.08-2.56)	.020	1
IADL			
>5	1	—	0
≤5	1.43 (0.96-2.14)	.078	1
CCI			
≤1	1	—	0
≥2	1.37 (0.92-2.05)	.125	1
ISS			
I	1	—	—
II	2.37 (1.38-4.09)	.002	—
III	3.21 (1.85-5.58)	<.001	—
Chromosome abnormalities			
Favorable	1	—	—
Unfavorable	1.79 (1.23-2.60)	.002	—
Missing	1.13 (0.69-1.83)	.036	—
Therapy			
Proteasome inhibitors	1	—	—
Lenalidomide	0.74 (0.50-1.11)	.142	—

HRs and relative risks are for OS in patients with the factors as compared with those without the factors. The model was adjusted for ISS, chromosome abnormalities, and therapy. Unfavorable profile defined as t(4;14) or t(14;16) or del17p13.

AIC = 1748.918; Harrell C index = 0.7069.

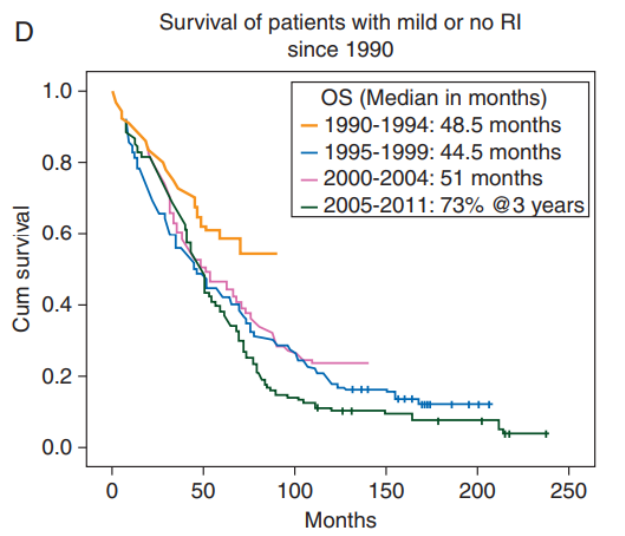
Table 3. Additive total score and related rate of OS and PFS at 3 years

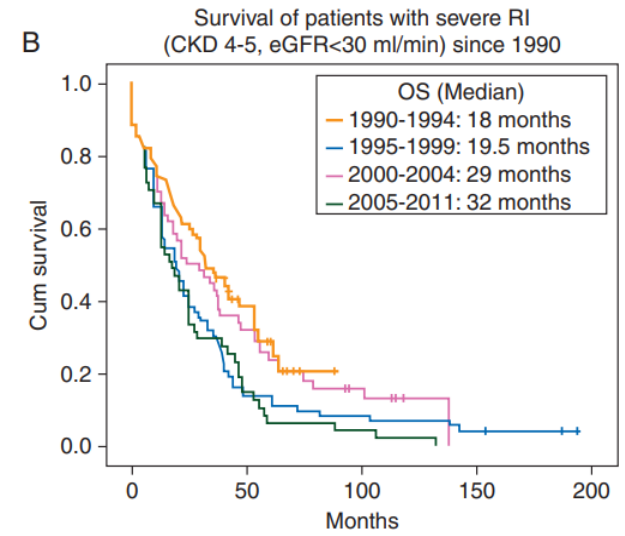
			% (95% CI)		Cumulative incidence at 12 mo, %	
Additive total score	**Patient status**	**No. of patients (%)**	**OS**	**PFS**	**Treatment discontinuation**	**Grade 3-4 nonhematologic AEs**
0	Fit	340 (39)	84 (78-89)	48 (41-56)	16	22
1	Intermediate-fitness	269 (31)	76 (67-82)	41 (32-49)	21	26
≥2	Frail	260 (30)	57 (45-68)	33 (25-41)	31	34

Palumbo A, et al. *Blood*. 2015;125(13):2068-2074.

Renal Impairment

- 50% of MM patients have GF <60 mL/min, 4%–10% dialysis
- Risk for early death





Dimopoulos MA, et al. *Ann Oncol*. 2014;25(1):195-200.

International Scoring System

Table 2. New International Staging System

Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III*	44
III	Serum β_2-microglobulin ≥ 5.5 mg/L	29

*There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

Greipp PR, et al. *J Clin Oncol*. 2005;23(15):3412-3420.

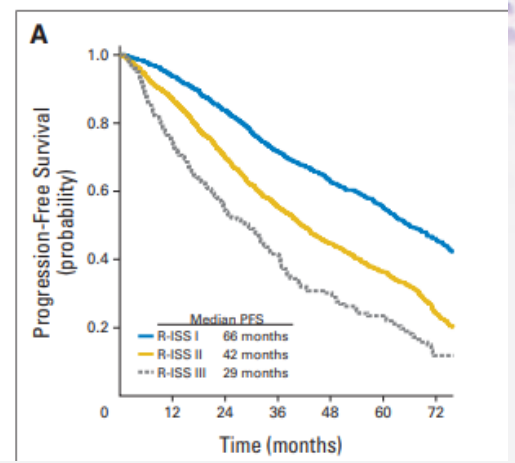
Score	Definition	Percentage of overall population	Outcome
0	Absence of adverse factors (neither high LDH, nor ISS III, nor t[4;14] and/or del[17p])	57%	4-year OS: 84%
1	Presence of only 1 adverse factor (either high LDH, or ISS III, or t[4;14] and/or del[17p])	32%	4-year OS: 73%
2	Presence of high LDH plus ISS III in the absence of t(4;14) and/or del(17p)	6%	4-year OS: 68%
3	Presence of t(4;14) and/or del(17p) in addition to either ISS III or high LDH	5%	Median OS: 19 mo 3-year OS: 24%

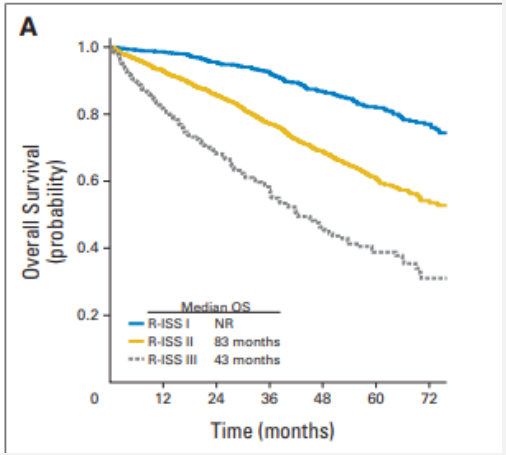
Moreau P, et al. *Blood*. 2012;120(21): abstract 598.

R-ISS

Stage	Criteria
I	Serum β2 microglobulin < 3.5 mg/l Serum albumin ≥ 3.5 g/dl Standard-risk chromosomal abnormalities (CA) Normal LDH
II	Not R-ISS stage I or III
III	Serum β2 microglobulin ≥ 5.5 mg/L and either High-risk CA by FISH OR High LDH

- HR CA: t(4;14), t(14;16) y/o del17p
- 60% RISS 2: heterogeneous group
- 26% ISS1 had HR CG and/or elevated LDH
- 57% ISS 3 had normal CG and LDH





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Palumbo A, et al. *J Clin Oncol*. 2015;33(26):2863-2869.

Cytogenetic abnormalities and relationship with outcomes		
Chromosome/region (frequency)	**Gene involved/effect**	**Prognostic implication**
14q32 (locus IGH) (45-50%)		
t(11;14) (20%)	Cyclin D1 hyperexpression	Neutral
t(4;14) (10% to 15%)	FGFR3 and MMSET deregulated	Unfavorable (worsened by chromosome 1 alterations, improved by trisomy 5)
t(14;16) (<5%)	cMAF	Doubt, mainly unfavorable
t(14;20) (<5%)	UK	Doubt, mainly unfavorable
1q21 acquisition (30%)	CKS1B, MCL1	
Gain (2-3 copies)		Partially unfavorable
Amplification (≥4)		Unfavorable
1p32 deletion (10%)	FAF1/ CDKN2C	Unfavorable
17p deletion (8% to 15% according to PC cutoff)	TP53 and UK	
Single-hit	Deletion	Unfavorable
Double-hit	Biallelic inactivation (deletion + mutation)	Very unfavorable

Zamagni E, et al. *Blood.* 2022;139(19):2889-2903.

R2-ISS

Table 1. Multivariate analysis on OS and PFS of the most impacting prognostic variables in the overall population (n=7077). Score calculation and stratification into 4 risk groups according to the total additive score in pts with complete data (n=2227) is shown as well.

Risk feature	OS Hazard ratio*	PFS Hazard ratio*	Score value**
ISS II	1.55 (1.42-1.69)	1.35 (1.26-1.44)	1
ISS III	2.02 (1.83-2.24)	1.53 (1.42-1.66)	1.5
del(17p)	1.74 (1.56-1.94)	1.41 (1.29-1.55)	1
High LDH	1.65 (1.50-1.83)	1.33 (1.23-1.45)	1
t(4;14)	1.56 (1.40-1.74)	1.49 (1.36-1.63)	1
1q CNAs	1.45 (1.29-1.63)	1.37 (1.25-1.50)	0.5

Group	**Number of patients (%)**	**Total additive score**
Low	429 (19.3%)	0
Low-Intermediate	686 (30.8%)	0.5-1
Intermediate-High	917 (41.2%)	1.5-2.5
High	195 (8.8%)	3-5

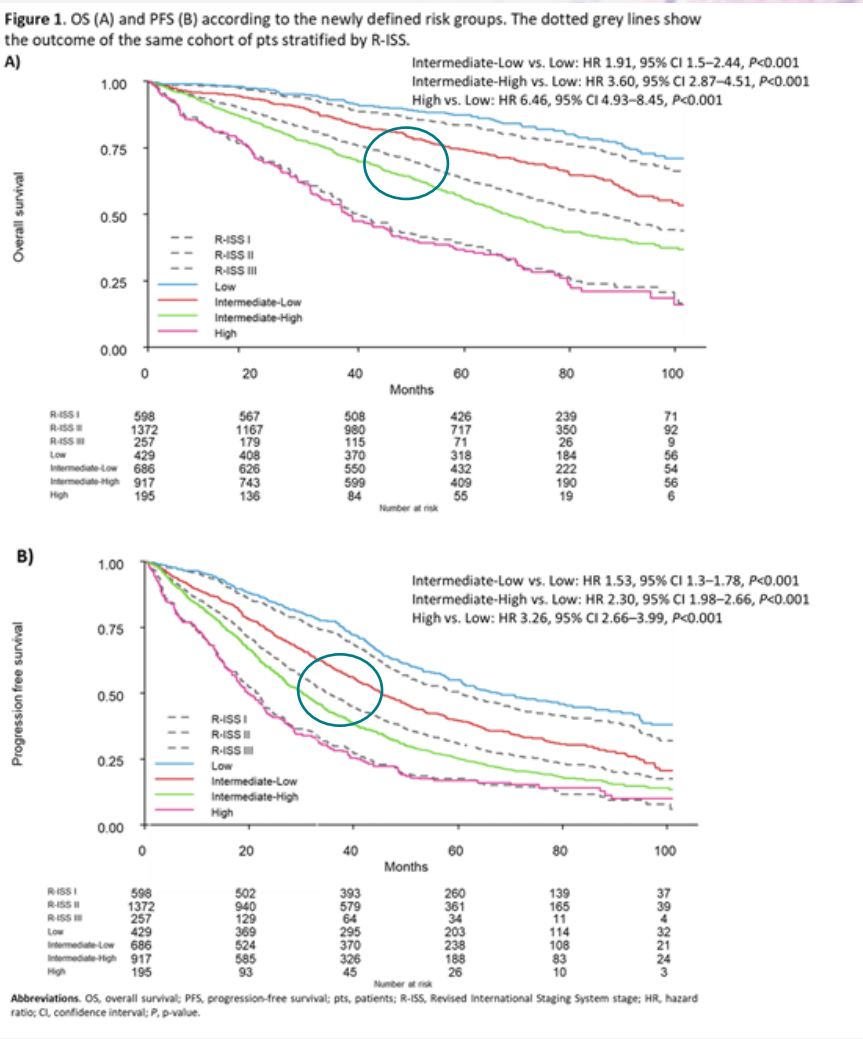

Figure 1. OS (A) and PFS (B) according to the newly defined risk groups. The dotted grey lines show the outcome of the same cohort of pts stratified by R-ISS.

Abbreviations. OS, overall survival; PFS, progression-free survival; pts, patients; R-ISS, Revised International Staging System stage; HR, hazard ratio; CI, confidence interval; *P*, p-value.

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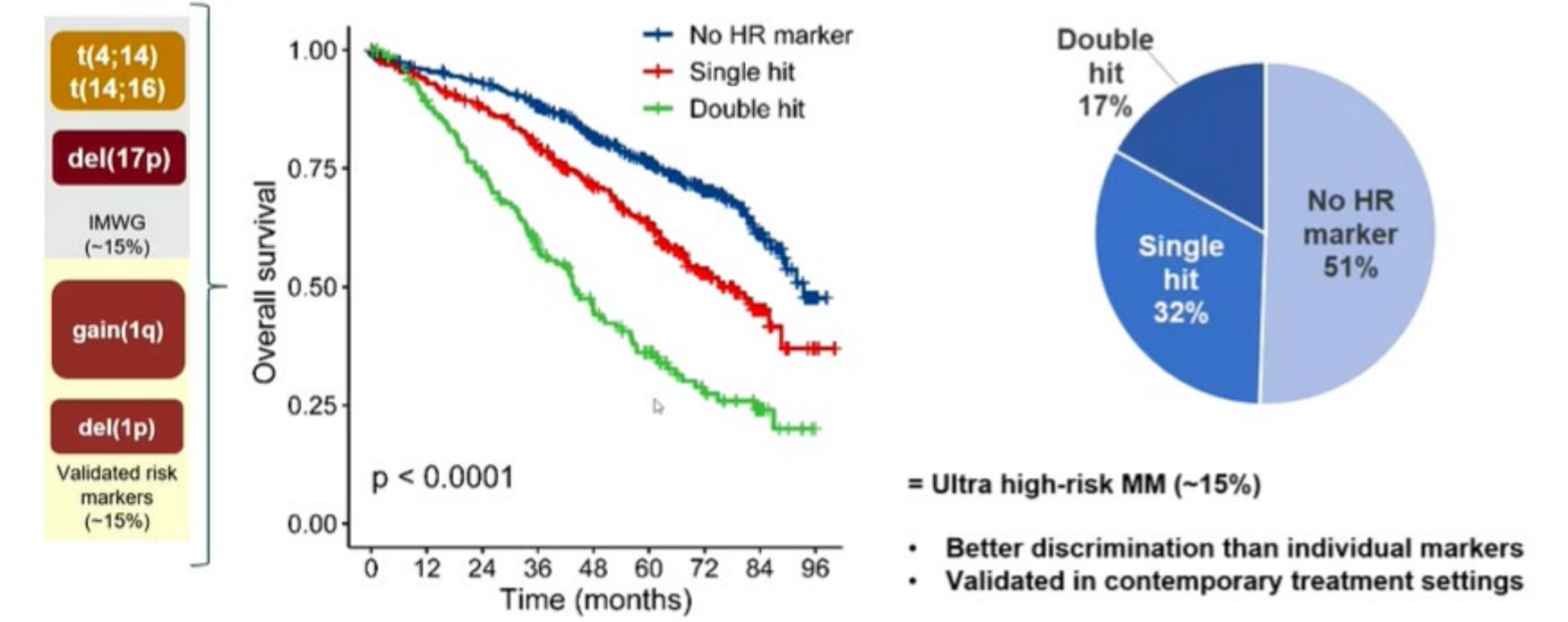
D´Agostino M, et al. *Blood*. 2020;136(suppl 1):34-37.

Co-occurrence of Molecular Risk Markers



Shah V, et al. *Leukemia*, 2017.34:3091-3096.

Double-Hit MM

- 6.1% ND MM
- Biallelic inactivation *TP53*
- Amplification (≥4 copies) 1q21 in ISS 3
- PFS = 15.4 mo
- OS = 20.7 mo

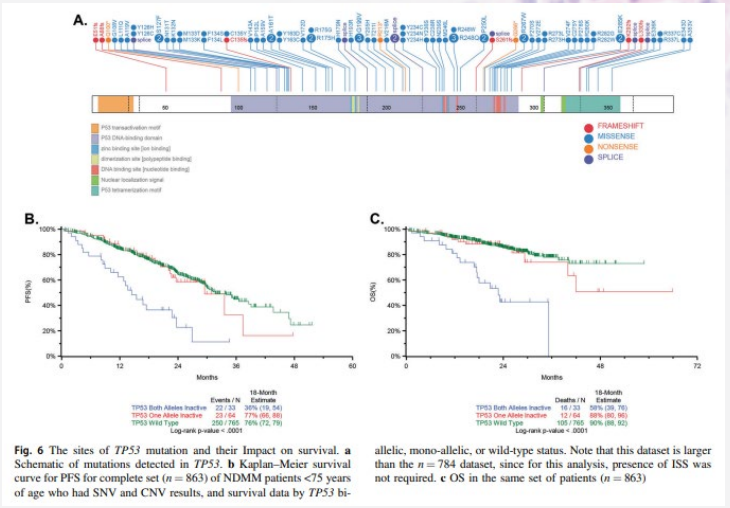


Fig. 6 The sites of *TP53* mutation and their Impact on survival. **a** Schematic of mutations detected in *TP53*. **b** Kaplan–Meier survival curve for PFS for complete set ($n = 863$) of NDMM patients <75 years of age who had SNV and CNV results, and survival data by *TP53* bi-allelic, mono-allelic, or wild-type status. Note that this dataset is larger than the $n = 784$ dataset, since for this analysis, presence of ISS was not required. **c** OS in the same set of patients ($n = 863$)

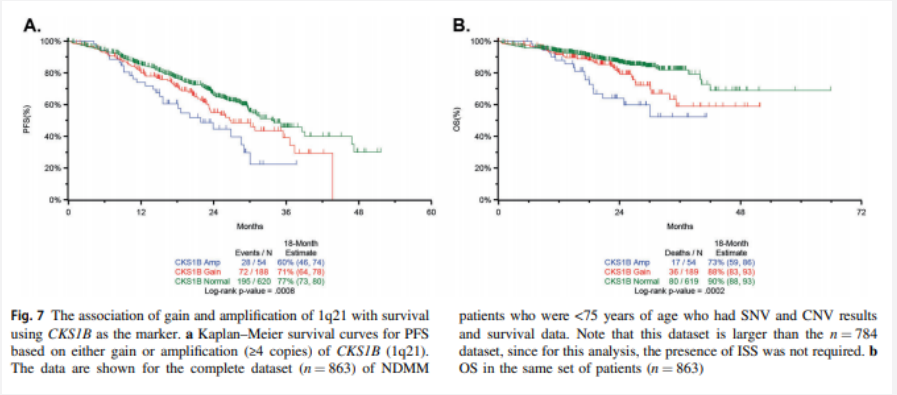
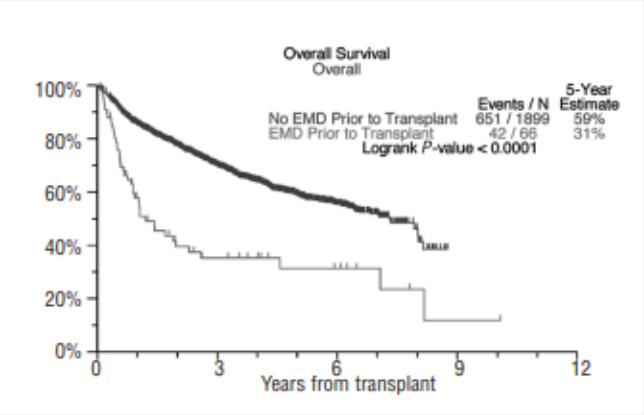


Fig. 7 The association of gain and amplification of 1q21 with survival using *CKS1B* as the marker. **a** Kaplan–Meier survival curves for PFS based on either gain or amplification (≥4 copies) of *CKS1B* (1q21). The data are shown for the complete dataset ($n = 863$) of NDMM patients who were <75 years of age who had SNV and CNV results and survival data. Note that this dataset is larger than the $n = 784$ dataset, since for this analysis, the presence of ISS was not required. **b** OS in the same set of patients ($n = 863$)

Walker BA, et al. *Leukemia*. 2019;33(1):159-170.

EMD

- 1.7%–5% at diagnosis, 20% at relapse
- Skin, soft tissues, liver, pleura, kidneys, CNS, poor prognosis

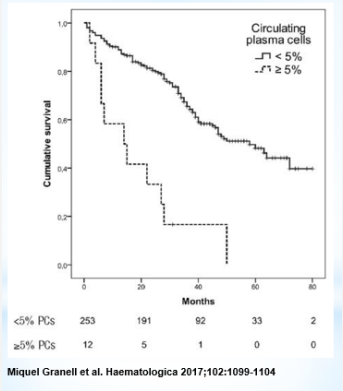


- PCL: ≥5% CPC; OS <1 year

Table 1. Main results of the two clinical studies used for this position paper [16, 17].

	Clinical series	
Variable	Granell et al. [16]	Ravi et al. [17]
Number of patients	482[a]	176[b]
Age (median; years)	69	62
Sex (M/F); %	42/58	56/44
Patients with CPC; *n*	100	176
Distribution according CPC (n; %)[c]		
1–4%	83 (83%)	54 (31%)
5–20%	12 (12%)	63 (36%)
More than 20%	5 (5%)	59 (34%)
Median overall survival according to CPC; months		
0%	47	53
1-4%	50	17
5–20%	6	13
More than 20%	14	13

[a]Totally, 382 patients (included in the number in the table) without circulating plasma cells were used as controls.
[b]Totally, 9724 patients (not included in the number in the table) diagnosed in the same period without circulating plasma cells at diagnosis were used as controls.
[c]Considering only patients with circulating plasma cells.
CPC circulating plasma cells.



Fernández de Larrea C, et al. *Blood Cancer J.* 2021;11(12):192.

Usmani SZ, et al. *Haematologica*. 2012;97(11):1761-1777.

Number and Size of Lytic Lesions

- DWI-MRI
  - 3 or more focal lesions >5 cm^2
  - Independent of R-ISS, GEP70, and EMD

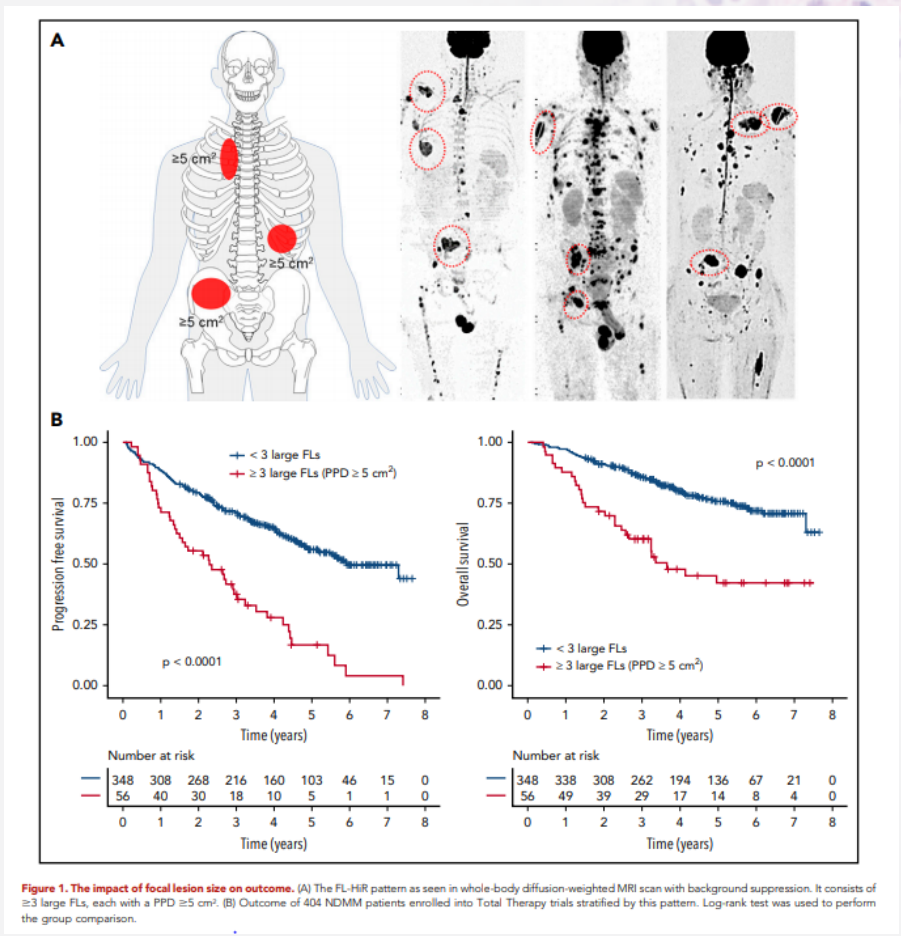


Figure 1. The impact of focal lesion size on outcome. (A) The FL-HiR pattern as seen in whole-body diffusion-weighted MRI scan with background suppression. It consists of ≥3 large FLs, each with a PPD ≥5 cm². (B) Outcome of 404 NDMM patients enrolled into Total Therapy trials stratified by this pattern. Log-rank test was used to perform the group comparison.

Rasche L, et al. *Blood.* 2018;132 (1):59-66.

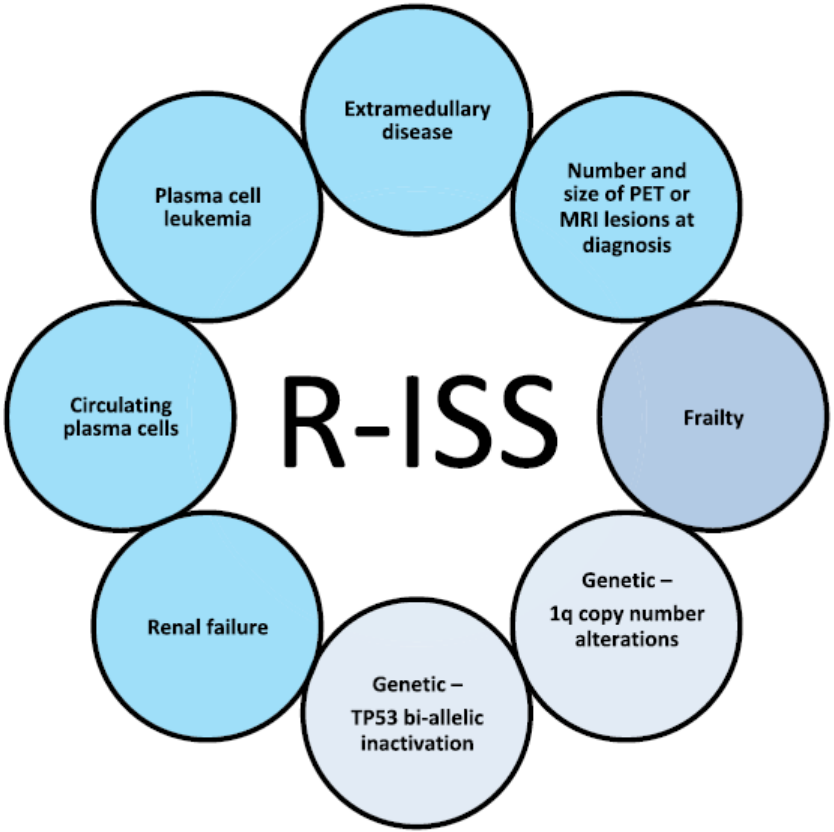


FIGURE 1. Proposed Modifications to Revised International Scoring System to Incorporate Additional High-Risk Features

Dynamic Factors

Depth of Response

- MRD is a dynamic risk factor
- Achieving MRD negativity overcomes high R-ISS impact

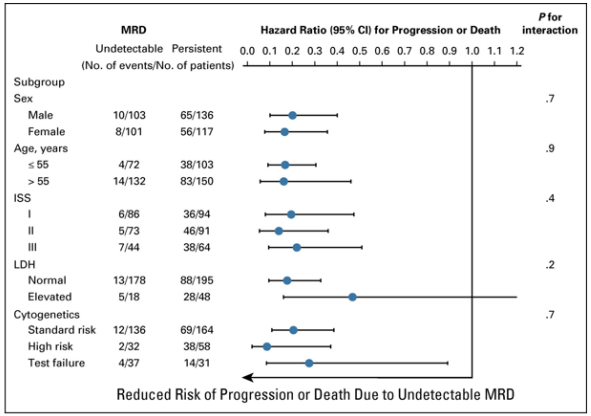


FIG 3. Subgroup analysis of progression-free survival according to patients' time-dependent measurable residual disease status. The intent-to-treat patient population was sub grouped according to sex, age, International Staging System (ISS), lactate dehydrogenase (LDH) levels, and cytogenetic abnormalities.

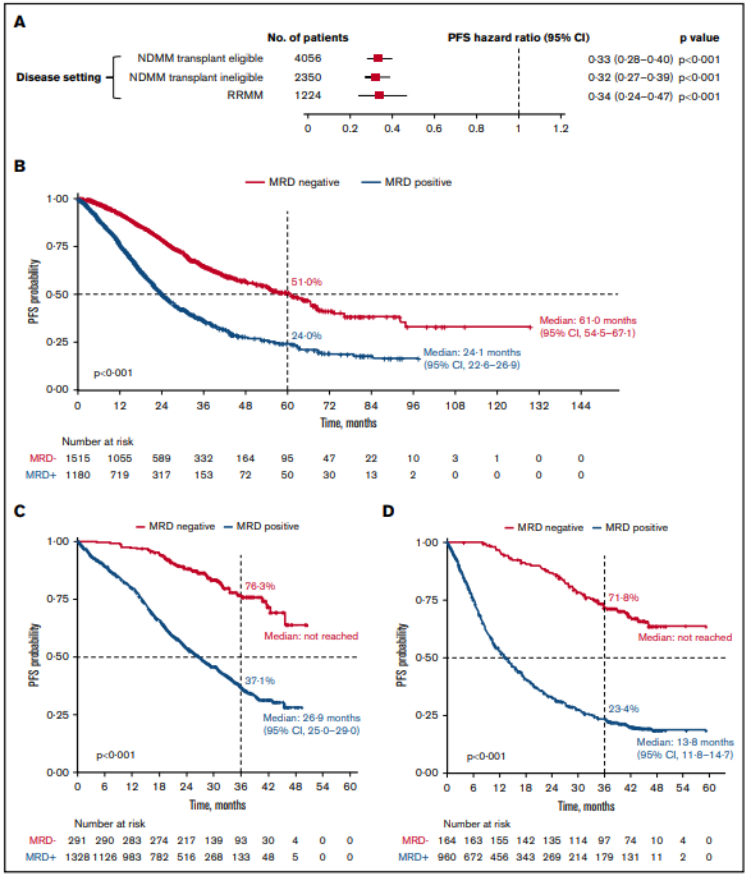


Figure 3. PFS outcomes. (A) Association of MRD negativity with PFS outcomes in patients by disease setting. (B-D) KM estimates of PFS in patients with NDMM who were transplant eligible (B), NDMM who were transplant ineligible (C), and RRMM (D).

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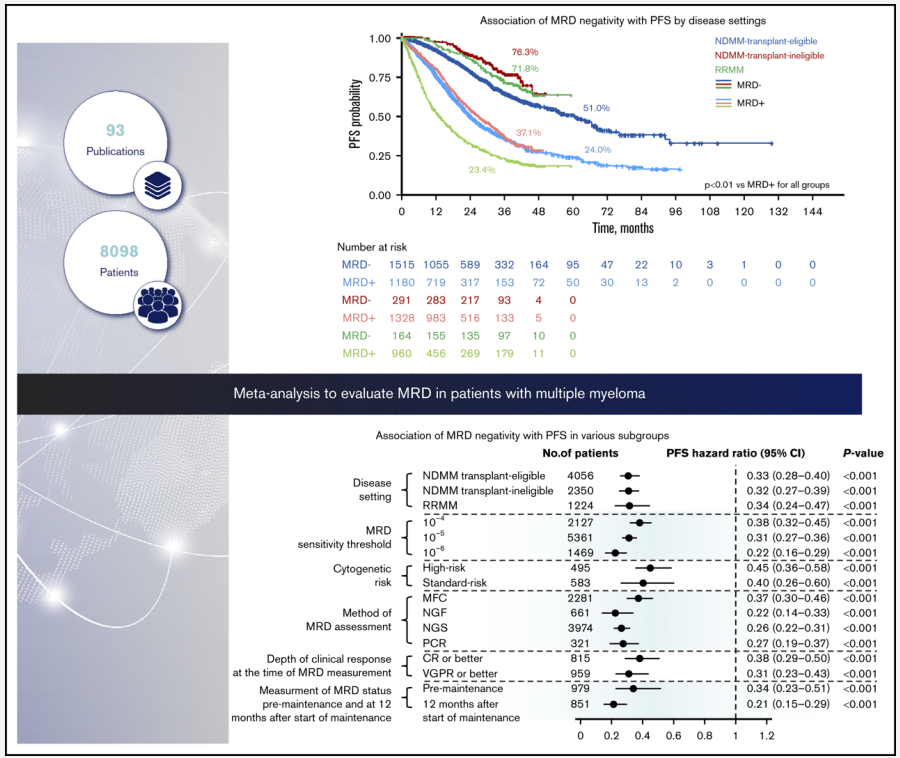
Paiva B, et al. *J Clin Oncol*. 2020;38(8):784-792.

Objective of Therapy: Sustained MRD Negativity



Superior PFS and OS

Overcomes HR CG impact

Independent of disease setting, method, depth of clinical response

When? How often? What to do if MRD+?

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Munshi NC, et al. *Blood Adv.* 2020;4(23):5988-5999.

Early Relapse

- <18 mo from initiation of tx
- <12 mo post-TPH
- Independent of CG features
- Functional high risk

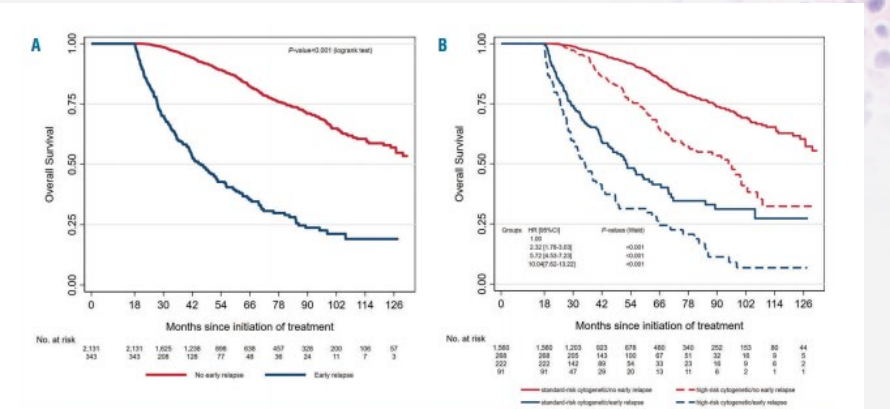
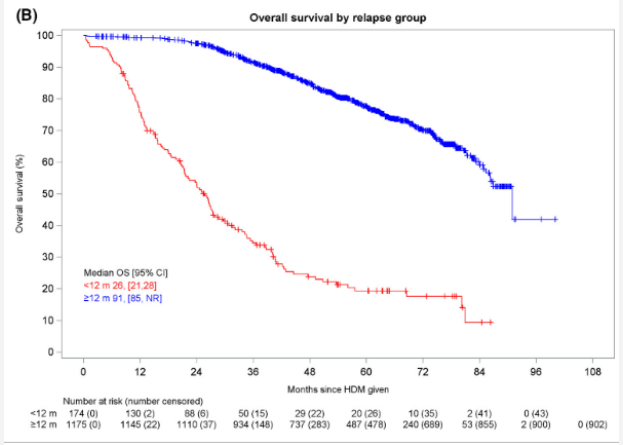


Figure 1. Kaplan-Meier overall survival curves for patients according to early or no early relapse. Landmark analysis at 18 months. (A) Patients with no early relapse (ER) (n=2,131) *versus* patients with ER (n=343). (B) Patients with no ER and standard-risk cytogenetic (n=1,560, red line) *versus* patients with no ER and high-risk cytogenetic (n=268, red dashed line) *versus* patients with ER and standard-risk cytogenetic (n=222, blue line) *versus* patients with ER and high-risk cytogenetic (n=91, blue dashed line). High-risk cytogenetic was defined by the presence of t(4;14) and or del(17p) in more than 55% of plasma cells.



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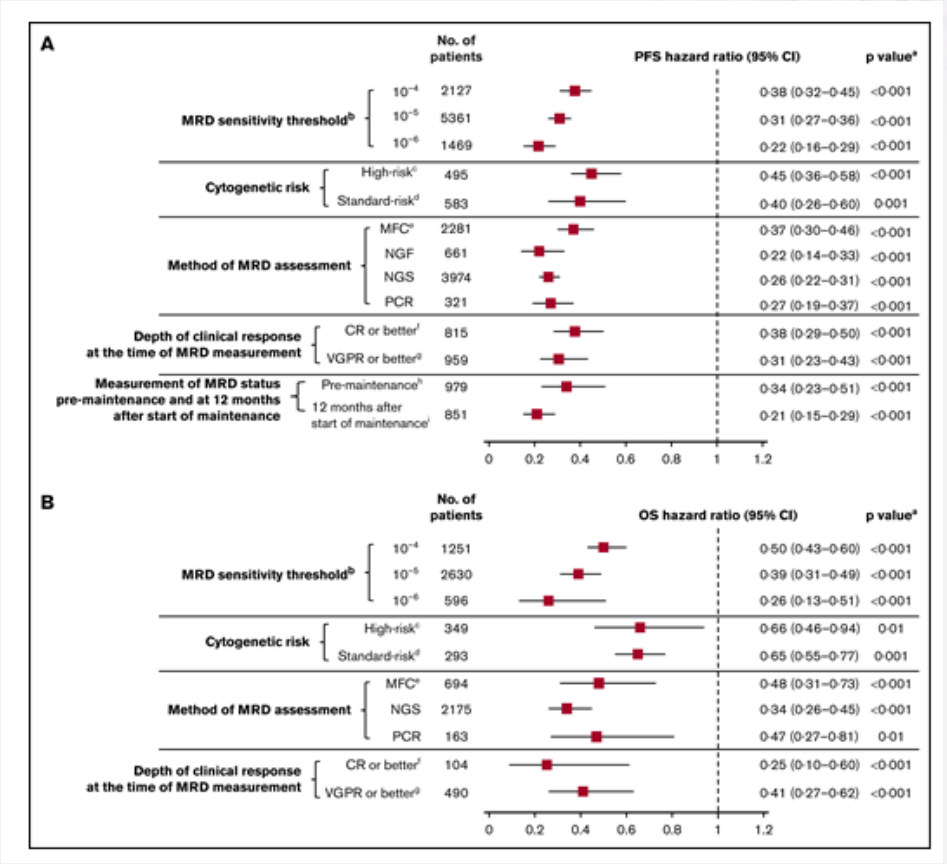
Corre J, et al. *Haematologica*. 2020;105(9):e480-483; Bygrave C, et al. *Br J Haematol*. 2020;193(3):551-555.

Treatment Options

- HR MM represents <20% of patients included in CT
- Heterogeneous definition of HR MM
- There is no standard treatment
  - Use novel-agent combinations
  - Achieving MRD negativity overcomes HR CG



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VRD

VRd + AutoSCT

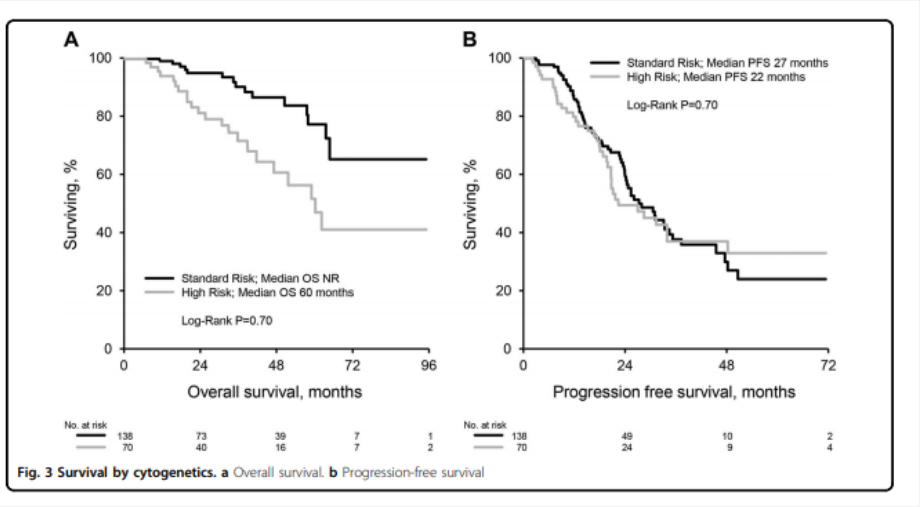


Fig. 3 Survival by cytogenetics. a Overall survival. **b** Progression-free survival

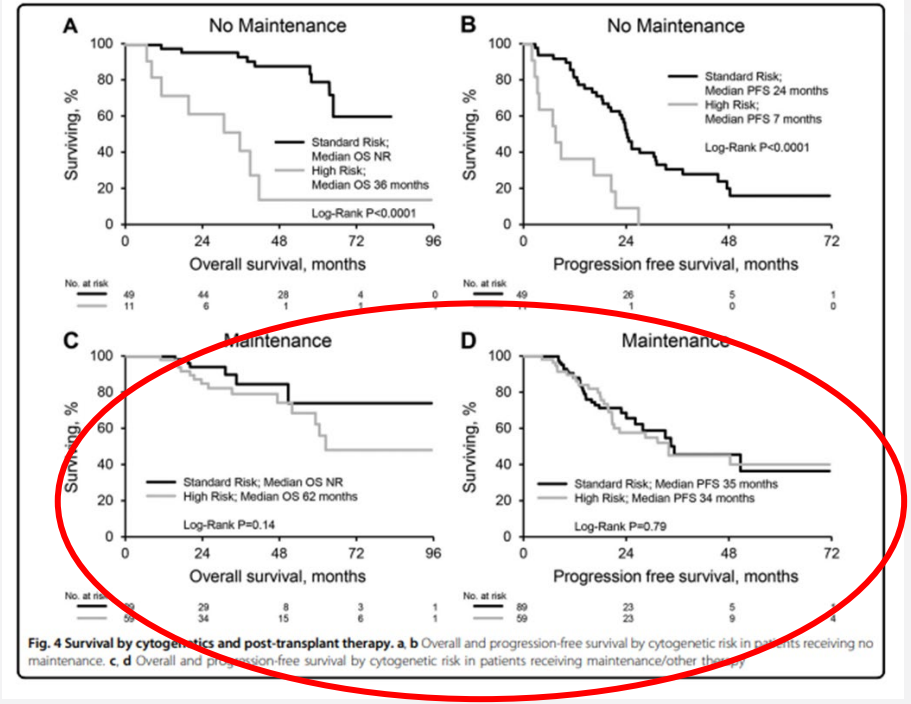


Fig. 4 Survival by cytogenetics and post-transplant therapy. a, **b** Overall and progression-free survival by cytogenetic risk in patients receiving no maintenance. **c**, **d** Overall and progression-free survival by cytogenetic risk in patients receiving maintenance/other therapy

Global Multiple Myeloma Academy

Sidiqi MH, et al. *Blood Cancer J*. 2018;8(11):106.

Table 4. Results of selected prospective clinical trials for newly diagnosed non-transplant-eligible patients carrying high-risk features

Trial	Regimen	Study design (primary endpoint)	Study definition of HR	No. HR patients (%)	Outcomes in HR vs SR	PFS rates	MRD⁻ (%)
SWOG-1211[8]	elo-VRd vs VRd	Phase 2, only HR patients, transplant ineligible (PSF)	HR-GEP, t(14;16), t(14;20), del (17p), amp(1q21), primary PCL, or elevated serum LDH (≥2 × ULN)	100 (100)	Median FU 53 mo: no difference in median PFS	Median PFS: 31.47 mo (elo-VRd) vs 33.64 mo (VRd) $P = .45$	—
SWOG S0777[86]	VRd vs Rd	Phase 3, transplant ineligible (PSF)	t(4;14), t(14;16), or del (17p)	104 (33)	Median PFS in HR pts: 38 (VRd) vs 16 (Rd) mo* $P = .19$ 34 (VRd) vs 17 (Rd) mo† $P = .96$ (median overall FU 55 mo)	Unstratified median PFS: 43 mo (VRd) vs 30 mo (Rd)	—
ALCYONE[88,94]	D-VMp vs VMp	Phase 3, transplant ineligible (PSF)	t(4;14), t(14;16), or del(17p)	98 (14)	PFS in HR pts NR HzR (95% CI) 0.78 (0.4-1.43) CR rate (HR) and MRD (HR) NR	HR pts: NR vs NR ITT: 36.4 mo (D-VMp) vs 19.3 mo (VMp)	HR pts: NR vs NR ITT: 28% (D-VMp) vs 7% (VMp)
MAIA[87,92]	D-Rd vs Rd	Phase 3, transplant ineligible (PSF)	t(4;14), t(14;16), or del(17p)	92 (12)	PFS in HR pts: NR (D-Rd) vs 29.6 mo (Rd) HzR: (95% CI) 0.57 (0.32-1.04) CR rate (HR) and MRD (HR) NR	HR pts: 45.3 (D-Rd) vs 29.6 mo (Rd) ITT: NR (D-Rd) vs 38.8 mo (Rd)	HR pts: NR vs NR ITT: 29% (D-Rd) vs 9% (Rd)

CI, confidence interval; CR, complete response; D-, daratumumab; elo, elotuzumab; GEP, gene expressing profiling; HR, high-risk; HzR, hazard ratio; ITT, intention-to-treat; LDH, lactate dehydrogenase; NE, not estimable; NR, not reported; NS, not significant; Rd, lenalidomide, dexamethasone; PCL, plasma cell leukemia; PFS, progression-free survival; pts, points; SR, standard risk; ULN, upper limit of normal; VMp, bortezomib, melphalan, prednisone; VRd, bortezomib, lenalidomide, dexamethasone.

*In the 44 pts HR by FISH.

†In the 17 pts with t(4;14) by FISH.

VRd: PFS 33 m (100% HR)

VRd: PFS 43 m (1/3 HR). Better than Rd

Usmani SZ, et al. *Lancet Haematol*. 2021;8(1):e45-e54.

Addition of Anti-CD38

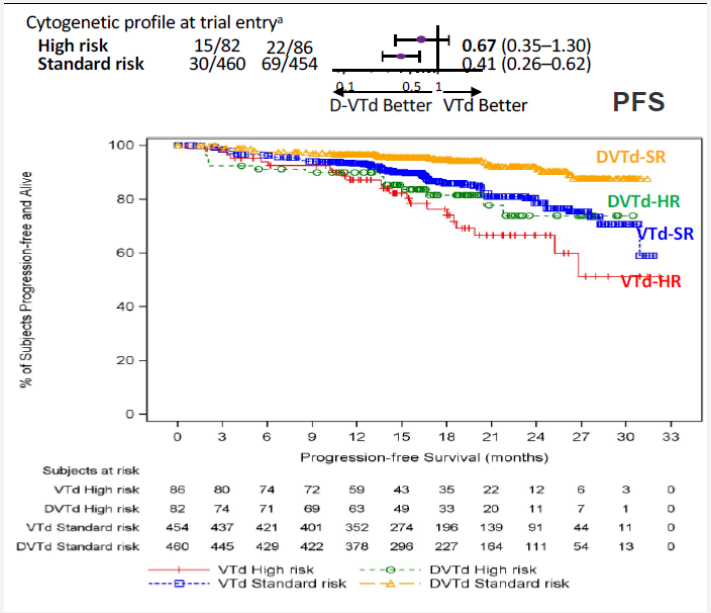
Table 3. Results of selected prospective clinical trials for newly diagnosed-transplant eligible patients carrying high-risk features

Trial	Regimen	Study design (primary endpoint)	Study definition of HR	No. HR patients (%)	Outcomes in HR vs SR	PFS rates	MRD^{-} (%)
CASSIOPEA[53,115]	Dara-VTd vs VTd	Phase 3, transplant eligible (sCR at 100 d post-ASCT)	del(17p) ≥50% or t(4;14) ≥30%	168 (15.5)	Prespecified subgroup analysis (sCR) showed consistent treatment benefit of D-VTd over VTd except for HR pts. However, ≥CR rates in HR pts favored D-VTd vs VTd (36.6% vs 32.6%; OR, 1.11; 95% CI, 0.58- 2.10).	D-VTd vs VTd reduced risk of progression/death (-53%) (median FU 18.8 mo): HzR 0.67; 95% CI, 0.35-1.30 (HR group) HzR 0.47; 95% CI, 0.33-0.67 (SR group)	10^{-5} MRD post-cons (D-VTd vs VTd): 59.8% vs 44.2% (HR pts; OR, 1.88; 95% CI, 1.02-3.46) 63.7% vs 43.5% (all pts; OR, 2.27; 95% CI, 1.78-2.90; P< .0001)
GRIFFIN[54]	Dara-VRd vs VRd	Phase 2, transplant eligible (sCR at the end of post-ASCT cons)	t(4;14), t(14;16), or del(17p)	30 (15.4)	Subgroup analysis of sCR (end of post-ASCT at 13.5 mo): 18.8% (D-RVd) vs 30.8% (RVd), (OR, 0.52 95% CI, 0.09-2.90)	Median PFS not reached in either group. Insufficient power to analyze HR subgroup of pts	10^{-5} MRD^{-} at 22.1 mo FU (D-RVd vs RVd): 37.5 vs 28.6 (HR) 54.9 vs 20.5 (SR) 51.0 vs 20.4 (ITT) 47.1 vs 18.4 (ITT ≥CR)
STAMINA[64,116]	ASCT + len maintenance (auto/len) vs ASCT + VRd consolidation + len maintenance (auto/VRd) vs tandem ASCT + len maintenance (auto/auto)	Phase 3, transplant eligible (38 mo PFS)	β2M > 5.5 mg/L, t(4;14), t(14;20), t(14;16), del (17p), del(13) detected by SC only, or aneuploidy	223 (29)	38-mo estimates PFS (95% CI): 57.6% (auto/len) vs 61.6% (auto/VRd) vs 62.9% (auto/ auto) P value unavailable 6-y PFS in HR pts as treated analysis were 43.6% and 26% for auto/auto and auto/len, respectively (P = 0.03).	38-mo estimates (95% CI): 57.6% (HR) vs 53.9% (SR) (auto/len) 61.6% (HR) vs 57.8% (SR) (auto/ VRd) 62.9% (HR) vs 58.5% (SR) (auto/ auto) PFS at 6 y (ITT population, P = 0.6): 40.9% (auto/len), 39.7% (auto/VRD), 43.9 (auto/auto), PFS at 6 y (as treated population, P = 0.03): 26% (HR) vs 38.6% (SR) (auto/len) NR (HR) vs 39.7% (SR) (auto/VRd) 43.6% (HR) vs 49.4% (SR) (auto/ auto)	—
EMN02/HO95[62]	VCD, followed by VMp or ASCT (single or tandem)	Phase 3, transplant eligible (PFS)	t(4;14) ≥10%, t(14;16) ≥10%, or del(17p) ≥20%	225 (19)	Median PFS: 20.3 mo (VCD/VMp) vs 37.3 mo (VCD/ASCT), HzR 0.63 (95% CI, 0.46-0.88)	Median PFS: 20.3 mo (HR) vs 46.7 mo (SR) (VMp) 37.3 mo (HR) vs NR (SR) (ASCT)	—
GMMG-HD6 (NCT02495922)	VRD ± elo in induction and consolidation, followed by len-dex ± elo maintenance	Phase 3, transplant eligible (PFS)	—	—	Ongoing study	—	—

β2M, β$_2$ microglobulin; cons, consolidation; CI, confidence interval; CR, complete response; FU, follow-up; HR, high-risk; HzR, hazard ratio; ITT, intention-to-treat population; Ixa, ixazomib; len, lenalidomide; NR, not reported; ns, not significant; OR, odds ratio; PFS, progression-free survival; pts, patients; SC, standard cytogenetics; sCR, stringent complete response; SR, standard risk; VCd, bortezomib, cyclophosphamide and dexamethasone; VMp, bortezomib, melphalan, prednisone; VRd, bortezomib, lenalidomide, dexamethasone; VTd, bortezomib, thalidomide, dexamethasone.

Usmani SZ, et al. *Lancet Haematol*. 2021;8(1):e45-e54.

CASSIOPEIA: D-VTd Reduced Risk of Progression or Death in HR and ISS III

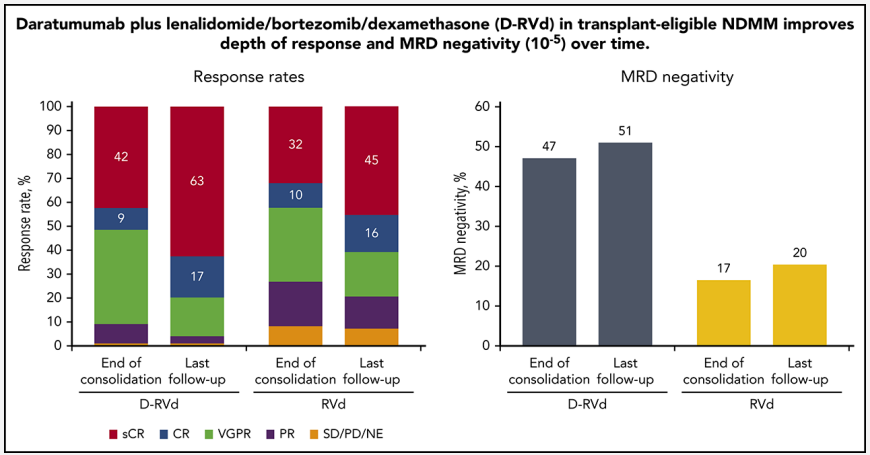


Probability of MRD negativity

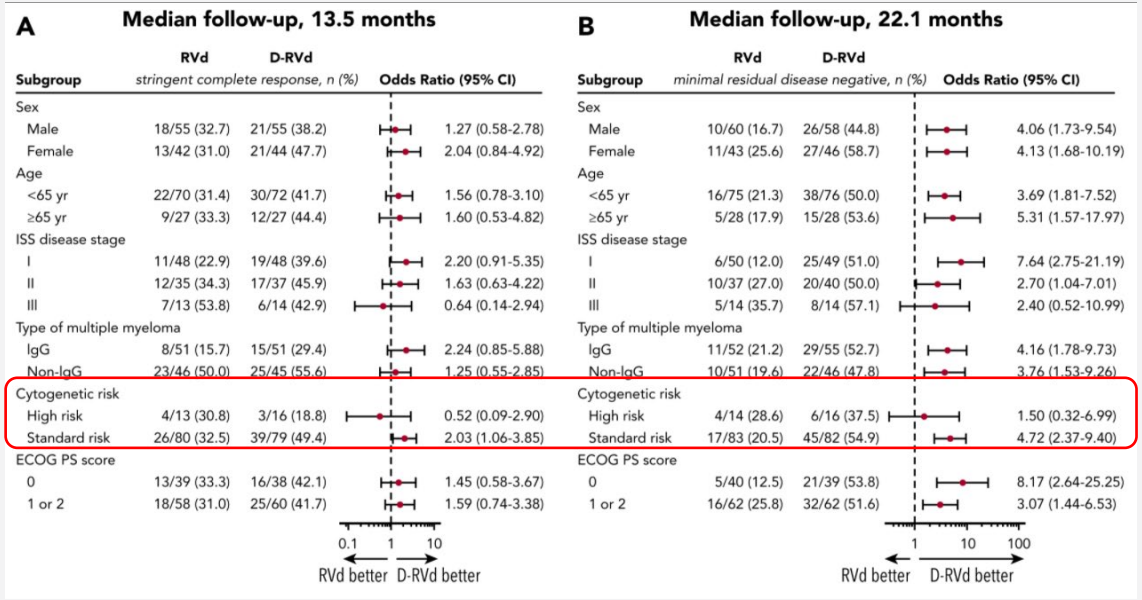
Subgroup	VTd minimal residual disease negative, n (%)	D-VTd minimal residual disease negative, n (%)	Odds Ratio (95% CI)
Sex			
Male	131 (41)	192 (61)	2.22 (1.62–3.05)
Female	105 (47)	154 (68)	2.37 (1.62–3.48)
Age			
<50 years	38 (42)	56 (68)	2.84 (1.53–5.28)
≥50 years	198 (44)	290 (63)	2.19 (1.68–2.85)
Site			
IFM	204 (45)	287 (64)	2.16 (1.65–2.81)
HOVON	32 (38)	59 (65)	3.05 (1.65–5.65)
ISS disease stage			
I	103 (45)	137 (67)	2.48 (1.68–3.67)
II	96 (41)	155 (61)	2.21 (1.54–3.18)
III	37 (46)	54 (64)	2.14 (1.15–4.00)
Cytogenetic profile at trial entry[b]			
High risk	38 (44)	49 (60)	1.88 (1.02–3.46)
Standard risk	197 (43)	296 (64)	2.35 (1.80–3.07)

1 5 10
VTd Better D-VTd Better

Sonneveld P, et al. 17th International Myeloma Workshop (IMW) 2019. Oral presentation.



- GRIFFIN study (15% HR each arm)
- D-VRd vs VRd
- MRD negative: 80%



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Voorhees P, et al. *Blood.* 2020;136(8):936-945.

Table 4. Results of selected prospective clinical trials for newly diagnosed non-transplant-eligible patients carrying high-risk features

Trial	Regimen	Study design (primary endpoint)	Study definition of HR	No. HR patients (%)	Outcomes in HR vs SR	PFS rates	MRD⁻ (%)
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SWOG S0777[86]	VRd vs Rd	Phase 3, transplant ineligible (PSF)	t(4;14), t(14;16), or del (17p)	104 (33)	Median PFS in HR pts: 38 (VRd) vs 16 (Rd) mo* $P = .19$ 34 (VRd) vs 17 (Rd) mo† $P = .96$ (median overall FU 55 mo)	Unstratified median PFS: 43 mo (VRd) vs 30 mo (Rd)	—
ALCYONE[88,94]	D-VMp vs VMp	Phase 3, transplant ineligible (PSF)	t(4;14), t(14;16), or del(17p)	98 (14)	PFS in HR pts NR HzR (95% CI) 0.78 (0.4-1.43) CR rate (HR) and MRD (HR) NR	HR pts: NR vs NR ITT: 36.4 mo (D-VMp) vs 19.3 mo (VMp)	HR pts: NR vs NR ITT: 28% (D-VMp) vs 7% (VMp)
MAIA[87,92]	D-Rd vs Rd	Phase 3, transplant ineligible (PSF)	t(4;14), t(14;16), or del(17p)	92 (12)	PFS in HR pts: NR (D-Rd) vs 29.6 mo (Rd) HzR: (95% CI) 0.57 (0.32-1.04) CR rate (HR) and MRD (HR) NR	HR pts: 45.3 (D-Rd) vs 29.6 mo (Rd) ITT: NR (D-Rd) vs 38.8 mo (Rd)	HR pts: NR vs NR ITT: 29% (D-Rd) vs 9% (Rd)

CI, confidence interval; CR, complete response; D-, daratumumab; elo, elotuzumab; GEP, gene expressing profiling; HR, high-risk; HzR, hazard ratio; ITT, intention-to-treat; LDH, lactate dehydrogenase; NE, not estimable; NR, not reported; NS, not significant; Rd, lenalidomide, dexamethasone; PCL, plasma cell leukemia; PFS, progression-free survival; pts, points; SR, standard risk; ULN, upper limit of normal; VMp, bortezomib, melphalan, prednisone; VRd, bortezomib, lenalidomide, dexamethasone.

*In the 44 pts HR by FISH.

†In the 17 pts with t(4;14) by FISH.

Addition of daratumumab improved outcomes in non-TE patients

Usmani SZ, et al. *Lancet Haematol*. 2021;8(1):e45-e54.

Table 5. Outcomes of the current approved triplet combinations for relapsed/refractory MM in genomic high-risk patients

Trial	Regimen	Study design (primary endpoint)	Study definition of HR	No. HR patients (%)	PFS rates	MRD^{-} (%)
CANDOR[110]	D-Kd vs Kd	Randomized, open-label, controlled, phase 3, RRMM (PFS)	t(4;14), t(14;16), or del(17p)	74 (16)	Median PFS: NE (D-Kd) vs 15.8 mo (Kd)	—
ELOQUENT-3[117]	Elo-Pd vs Pd	Randomized, open-label, controlled, phase 3, RRMM (PFS)	ISS stage II or III and del(17p), t(4;14), t(14;16)	27 (23)	Median PFS: 6.2 mo (HR) vs 10.3 mo (SR) (Elo-Pd) 2.2 mo (HR) vs 5.2 mo (SR) (Pd)	—
CASTOR[100,105]	D-Vd vs Vd	Randomized, open-label, controlled phase 3, RRMM (PFS)	del(17p), t(4;14), t(14;16)	91 (18)	Median PFS: 12.6 mo (HR) vs 16.6 mo (SR) (D-Vd) 6.2 mo (HR) vs 6.6 mo (SR) (Vd)	15% (HR) vs 13% (SR) (D-Vd) 0 (HR) vs 3% (SR) (Vd)
OPTIMISMM[109]	PVd vs Vd	Randomized, open-label, controlled, phase 3, RRMM (PFS)	del(17p), t(4;14), t(14;16)	110 (20)	Median PFS: 8.44 mo (HR) vs 11.2 mo (ITT) (PVd) 5.32 mo (HR) vs 7.1 (ITT) (Vd)	—
POLLUX[101,105]	D-Rd vs Rd	Randomized, open-label, controlled, phase 3, RRMM (PFS)	del(17p), t(4;14), t(14;16)	65 (11)	Median PFS: 26.8 mo (HR) vs 52.0 mo (SR) (D-Rd) 8.3 mo (HR) vs 18.6 mo (SR) (Rd)	29% (HR) vs 35% (SR) (D-Rd) 3% (HR) vs 9% (SR) (Rd)
ASPIRE[102]	KRd vs Rd	Randomized, open-label, controlled, phase 3, RRMM (PFS)	del(17p), t(4;14), t(14;16)	100 (13)	Median PFS: 23.1 mos (HR) vs 29.6 mo (SR) (KRd) 13.9 mo (HR) vs 19.5 mo (SR) (Rd)	—
ENDEAVOR[118]	Kd vs Vd	Randomized, open-label, controlled, phase 3, RRMM (PFS)	del(17p), t(4;14), t(14;16)	210 (23)	Median PFS: 8.8 mo (HR) vs NE (SR) (Kd) 6.0 mo (HR) vs 10.2 mo (SR) (Vd)	—

D, daratumumab; Elo, elotuzumab; HR, high-risk; ITT, intention-to-treat; Kd, carfilzomib, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; NE, not estimable; NR, not reached; Pd, pomalidomide, dexamethasone; PVd, pomalidomide, bortezomib, dexamethasone; Rd, lenalidomide, dexamethasone; SR, standard risk; Vd, bortezomib, dexamethasone.

Usmani SZ, et al. *Lancet Haematol*. 2021;8(1):e45-e54.

Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients With High-risk Cytogenetic Factors

A Systematic Review and Meta-analysis

Smith Giri, MD, MHS[1,2]; Alyssa Grimshaw, MSLIS[3]; Susan Bal, MD[2]; et al

Author Affiliations

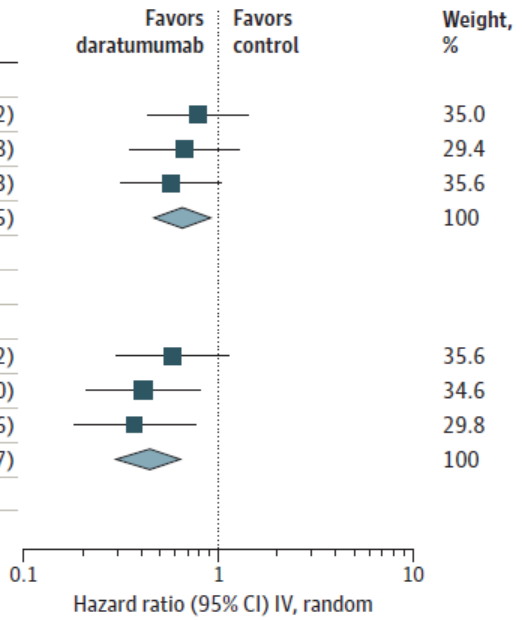
JAMA Oncol. 2020;6(11):1759-1765. doi:10.1001/jamaoncol.2020.4338

- Six phase III trials: 3 ND MM (n = 358) and 3 RR MM (n = 222)
- 4061 patients, 580 HR MM
- **The addition of daratumumab was associated with increased PFS** (pooled HR, 0.67; 95% CI, 0.47-0.95; P = .02)**, and OS** (pooled HR, 0.45; 95% CI, 0.30-0.67; *P* <.001)

Giri S, et al. *JAMA Oncol*. 2020;6(11):1759-1765.

Figure 2. Outcomes Associated With the Addition of Daratumumab to Backbone Multiple Myeloma Regimens for Patients With High-risk Multiple Myeloma

Source	Log (hazard ratio)	SE	Daratumumab total	Control total	Hazard ratio (95% CI) IV, random	Weight, %
Newly diagnosed high-risk multiple myeloma						
ALCYONE,[11] 2018	-0.2485	0.3038	53	45	0.78 (0.43-1.42)	35.0
CASSIOPEIA,[12] 2019	-0.4005	0.3313	82	86	0.67 (0.35-1.28)	29.4
MAIA,[13] 2019	-0.5621	0.301	48	44	0.57 (0.32-1.03)	35.6
Subtotal			183	175	0.67 (0.47-0.95)	100
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.54$; $P = .76$; $I^2 = 0\%$						
Overall effect: $z = 2.25$; $P = .02$						
Relapsed or refractory high-risk multiple myeloma						
CANDOR,[16] 2019	-0.5447	0.3364	48	26	0.58 (0.30-1.12)	35.6
CASTOR,[19] 2019	-0.8916	0.3414	41	37	0.41 (0.21-0.80)	34.6
POLLUX,[18] 2019	-0.9943	0.3676	35	35	0.37 (0.18-0.76)	29.8
Subtotal			124	98	0.45 (0.30-0.67)	100
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.93$; $P = .63$; $I^2 = 0\%$						
Overall effect: $z = 3.98$; $P < .001$						



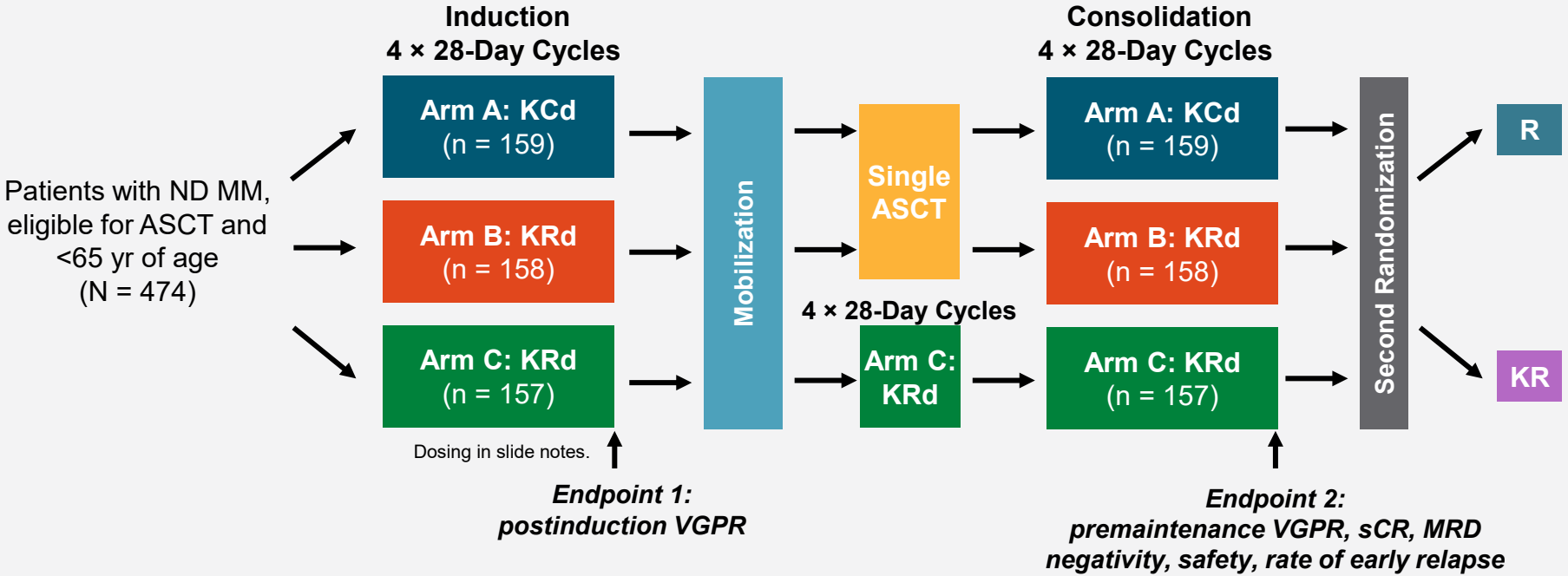
Significant improvement in progression-free survival was seen among patients with first-line and relapsed or refractory disease. Squares represent mean values, with the size of the squares representing the weight, and horizonal lines represent 95% CIs. Diamonds are pooled means with the points representing 95% CIs. IV indicates inverse variance.

Giri S, et al. *JAMA Oncol*. 2020;6(11):1759-1765.

Carfilzomib

FORTE Efficacy by Cytogenetic Risk: Study Design

> Multicenter, randomized, open-label phase II study



Gay F, et al. ASCO 2021. Abstract 8002.

FORTE Efficacy by Cytogenetic Risk: Investigator Conclusions

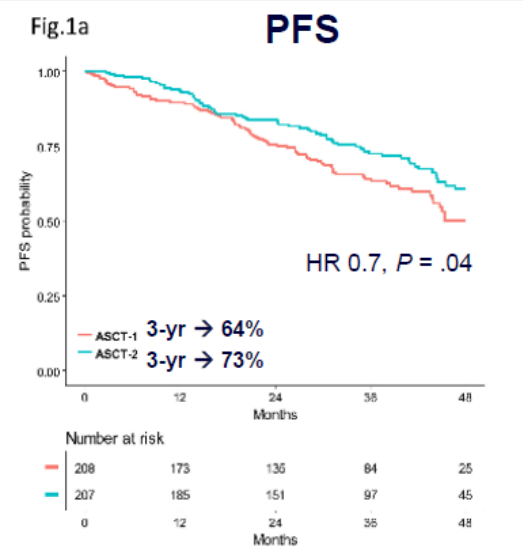
- KRd-ASCT significantly prolonged 4-yr PFS vs KRd12 across cytogenetic risk groups
  - Standard-risk MM (82% vs 67%), high-risk MM (62% vs 45%), double-hit MM (55% vs 33%)
- KRd-ASCT increased rate of 1-yr sustained MRD negativity vs KRd12 in patients with high-risk MM (50% vs 39%) and double-hit MM (47% vs 25%)
- Maintenance therapy with KR significantly prolonged 3-yr PFS vs R alone across cytogenetic risk groups when assessed from start of maintenance
  - Standard-risk MM (90% vs 73%), high-risk MM (69% vs 59%), double-hit MM (67% vs 42%)
- The benefit of KRd-ASCT vs KRd12 and KR vs R was observed in all cytogenetic subgroups except patients with amp(1q)

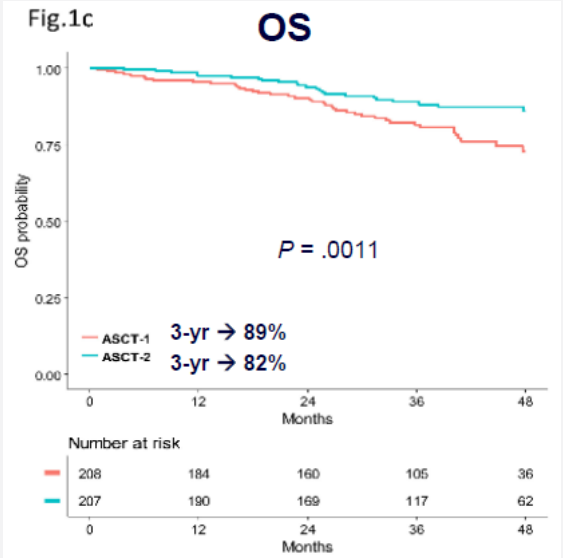
Gay F, et al. ASCO 2021. Abstract 8002.

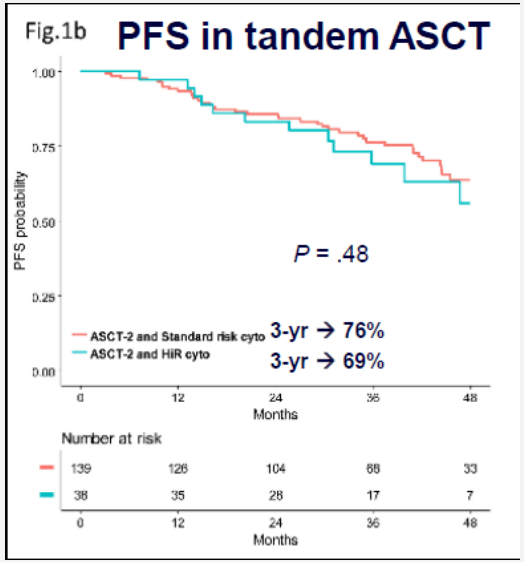
Tandem ASCT

VCD × 4c → VMP × 4 → 1R → RVD × 2 → Len maintenance

VCD × 4c → VMP × 4 → 1R → HDM 1-2 → 2R → Observ → Len maintenance







Global Multiple Myeloma Academy

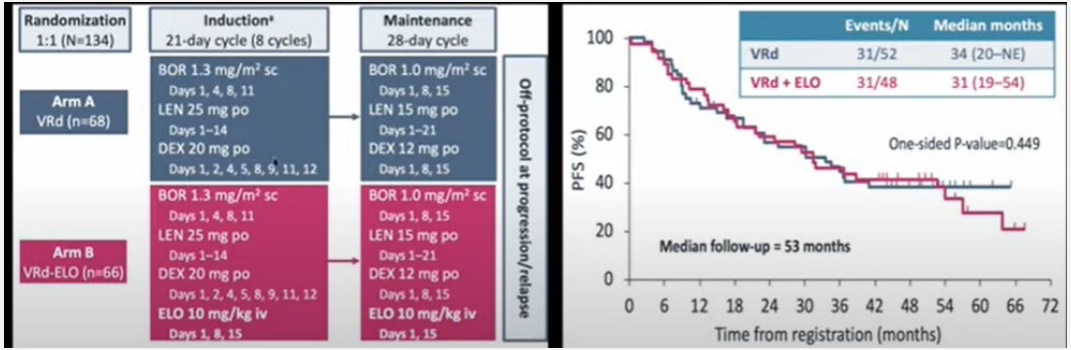
Cavo M, et al. ASH 2017.

Maintenance

- Lenalidomide suboptimal
- GRIFFIN: MRD negativity higher with Dara-R as maintenance in HR MM (77% vs 42%)
- FORTE: KR improves PFS in HR MM (Gay et al)

SWOG 1211

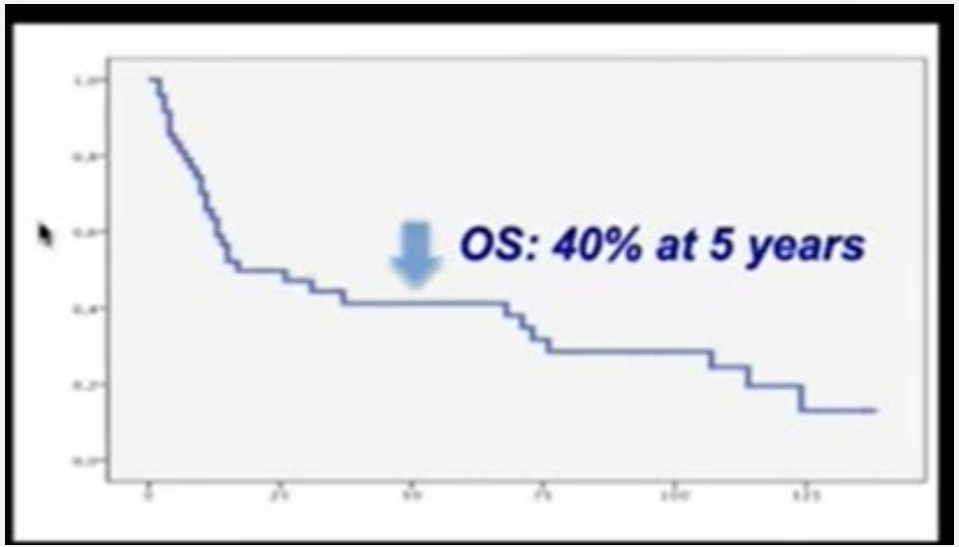
- HR MM
- VRd-Elo vs VRd
- Benefit in continuous maintenance PI + IMiD



Usmani SZ, et al. *Lancet Haematol*. 2021;8(1):e45-e54.

Role of Allogeneic TPH

- Not a curative strategy
- MRT: 14%
- PFS: 1 yr
- OS 40%: 5 yr



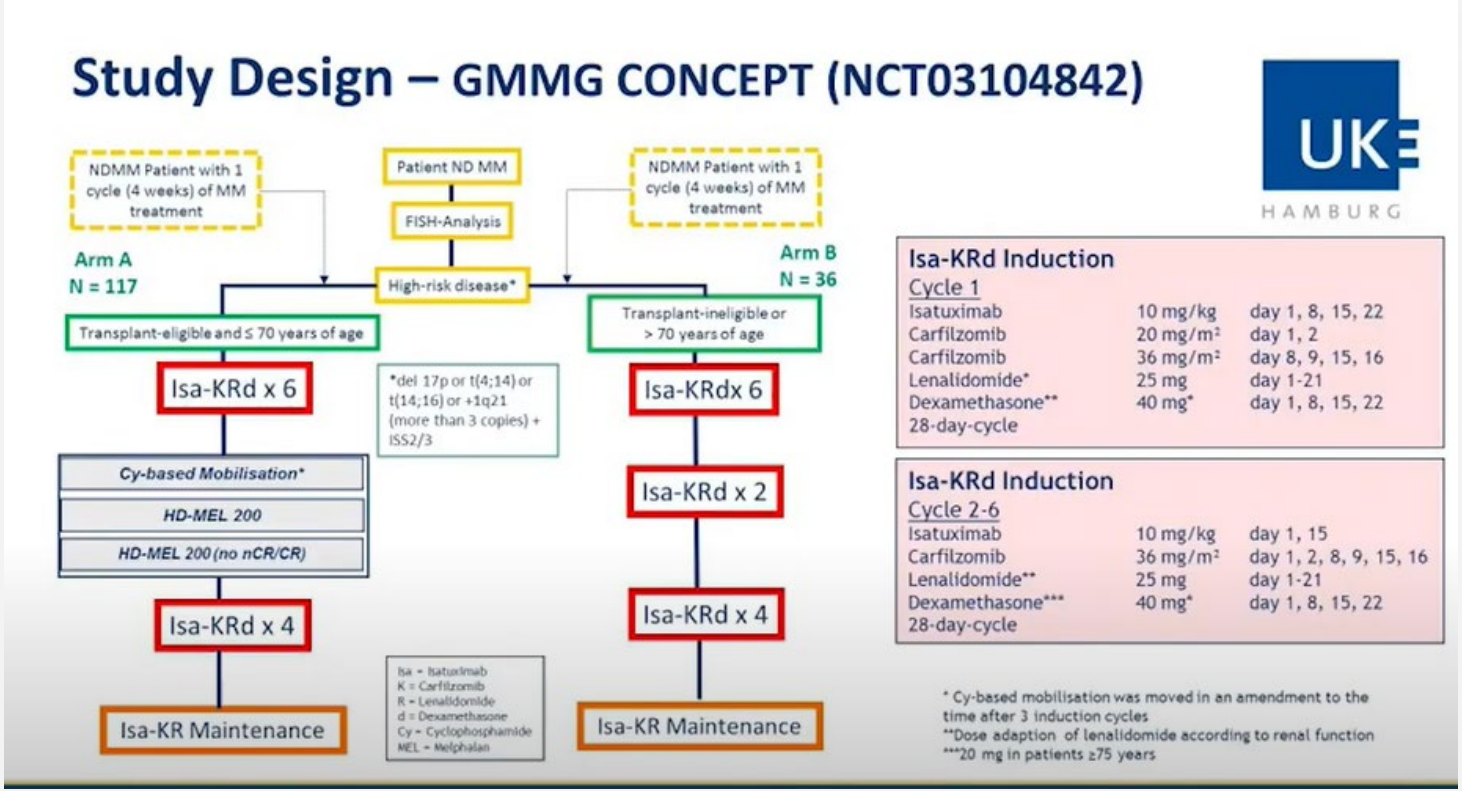
Lopez-Godino O, et al. EBMT 2014. Abstract PH534.

HR MM Clinical Trials

Table 6. Selected published/ongoing/planned clinical trials specifically dedicated to patients with high-risk ND MM according to prespecified different definitions

Trial	Regimen	Study design (primary endpoint)	Study definition of HR	Results
OPTIMUM[57,119]	Dara-CVRd vs VRd	Phase 2b, first-line TE and TNE NDMM (MRD 100 d post-ASCT and PFS)	Two or more of: t(4;14), or t(14;16), t(14;20), del(1p32) gain(1q) or del(17p), HR-GEP, PCL (>20% cPCs)	93% ORR, 52% CRs, 35% VGPRs, 5% PR MRD 50%
UK-MRA Myeloma XV (RADAR) (EudraCT: 2019- 001258-25)	Cy-PI-RD + ASCT followed by len ± PI ± Isa/12-mo Isa*	Phase 2, first-line TE and TNE NDMM (MRD and response)	t(4;14), t(14;16), t(14;20), del(17p), gain(1q)	Ongoing study
GMMG-CONCEPT[90]	Isa-KRd in induction, consolidation, and maintenance ± ASCT	Phase 2, TE (arm A) and TNE (arm B) NDMM (MRD^{-} 10^{-5} postconsolidation)	del17p or t(4;14) or t(14;16) or >3 copies 1q21 and ISS 2 or 3 stage disease	Interim analysis on 50 pts: 46 (A), 4 (B) ORR, ≥PR: 100%, ≥VGPR: 90%, CR/sCR: 46% MRD^{+}: 20/33 (61%), MRD^{-}: 11/33 (33%)
IRD Study (Nordic Myeloma Study Group) (HR-Maintenance Arm)[120]	IRd induction and consolidation followed by IR maintenance (HR arm)	Phase 2, TE NDMM (MRD <0.01%)	t(4;14), del(17p) (60%), t(14;16), t(14;20), gain(1q)	Ongoing study
ANTARES EMN19 (NCT04166565)	CyBorD ± ASCT	Phase 2, NDMM or first relapse MM with EMD (≥CR)	EMD associated with high LDH level, del(17p) and HR-GEP	Ongoing study
SWOG 1211[9]	VRd vs VRd-Elo	Phase 2, TNE NDMM (PSF)	HR-GEP, t(14;16), t(14;20), del (17p), amp(1q21), primary PCL, or elevated serum LDH (≥2 × ULN)	Median FU 53 mo PFS 33.6 vs 31.5 mo (P = .449) OS NR vs 68 mo (P = .239) ORR 88% (44) vs 83% (39) ≥CR 6 vs 2.1%
EMN12[121]	KRd ± ASCT followed by KR maintenance	Phase 2, no-randomized, TE and TNE pPCL patients (PFS)	(del(17p), t(4;14), t(14;16), del(1p), ampl(1q), ISS stage 3; elevated LDH	14/15 pts ≤65 y received the planned 4 cycled of induction (1/15 off protocol for PD) ORR ≥ PR 93% ORR ≥ VGPR 80% (≥ CR 33%) (13% PR,

GMMG-CONCEPT



Leypoldt I, et al. *Leukemia.* 2022;36:885-888.

GMMG-CONCEPT: Isa-KRD in High-Risk Patients

> TE (N = 117) and TNE (n = 36). Median age 58 (42–82) and at 24.9 mos

Characteristic	N=50
Median age (range), years	58 (42-82)
Arm A	58 (42-69)
Arm B	77 (72-82)
male/female	21/29
ECOG performance status	
0	21 (42%)
1	23 (46%)
2	6 (12%)
Characteristic	**N=50**
ISS	
Stage II	28 (56%)
Stage III	22 (44%)
High-risk cytogenetics**	
Del 17p*	26 (52%)
t(4;14)	19 (38%)
t(14;16)	5 (12%)
> 3 copies +1q21	21 (42%)

All evaluable patients: n = 50

- Overall response rate (ORR, ≥ PR): 100%
- ≥ VGPR : 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable

PFS 12 mo: 79.6%, PFS 24 mo: 75.5%

Leypoldt I, et al. *Leukemia.* 2022;36:885-888.

Novel Strategies: CAR T, BiTEs

- Ide-cel (KarMMa)
- Cilta-cel (CARTITUDE)
- Bispecific antibodies: teclistamab, talquetamab: ORR 60%–80%

Final Comments

HR MM definition is complex and dynamic

Use the most potent novel agent combination upfront:

Anti-CD38 Ab + PI (second?) + IMiD + Dex

(ASCT ×2) ± consolidation

+

Continuous maintenance (V, Dara?, KR)

Sustained MRD negativity is the goal of therapy

Clinical trials are needed in HR MM

Multiple-Choice Question 2

Which of the following is correct (one option) in the HRMM setting?

a) Daratumumab-based induction and maintenance is the best option
b) ASCT has no role in this context
c) Lenalidomide is the best option for long term maintenance
d) KRD + ASCT achieves high sustained MRD negativity

THANK YOU!!!

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Discussion

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Early Relapse of Multiple Myeloma: Current and Emerging Treatment Options

Rafael Fonseca, MD

APTITUDE HEALTH®

MAYO CLINIC

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Multiple Myeloma – Treatment of Early Relapse

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Disclosures – Industry Relationships

- **Consulting:** ***AMGEN***, BMS, Celgene, Takeda, Bayer, Janssen, AbbVie, Pharmacyclics, Merck, Sanofi, Kite
- **SAB:** Adaptive Biotechnologies, Caris Life Sciences (stock options)
- **Patent for FISH in MM: ~$2000/year**
- **Registered independent**
- **Believes in stem cell transplant**

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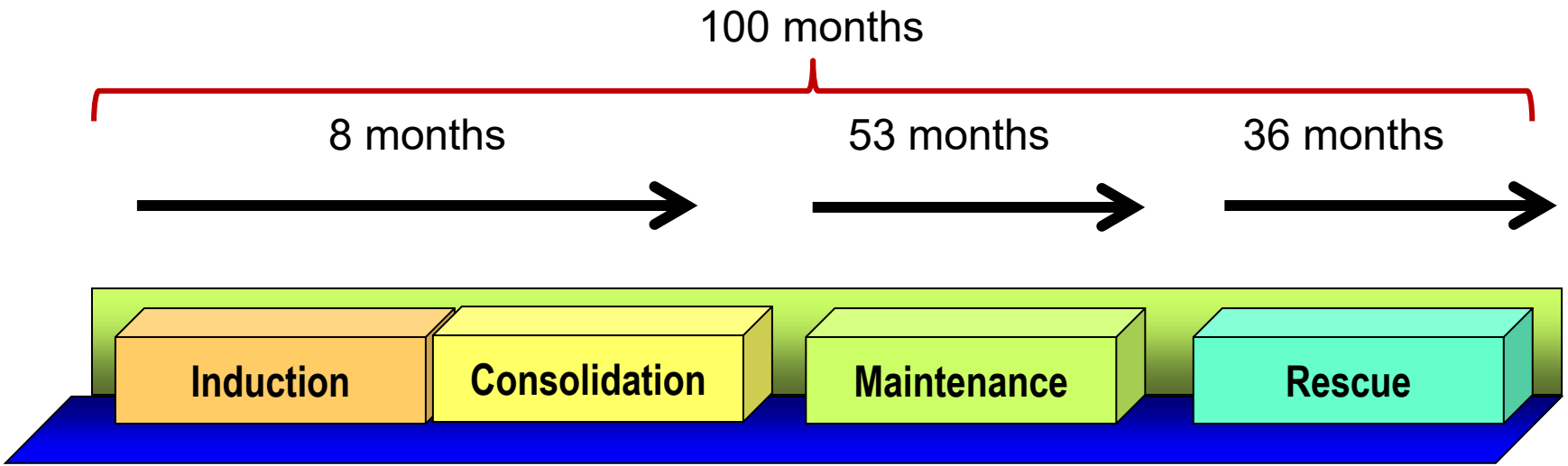
Multiple Myeloma Treatment Lines 2021



@rfonsi1, fonseca.rafael@mayo.edu

Fonseca, unpublished.

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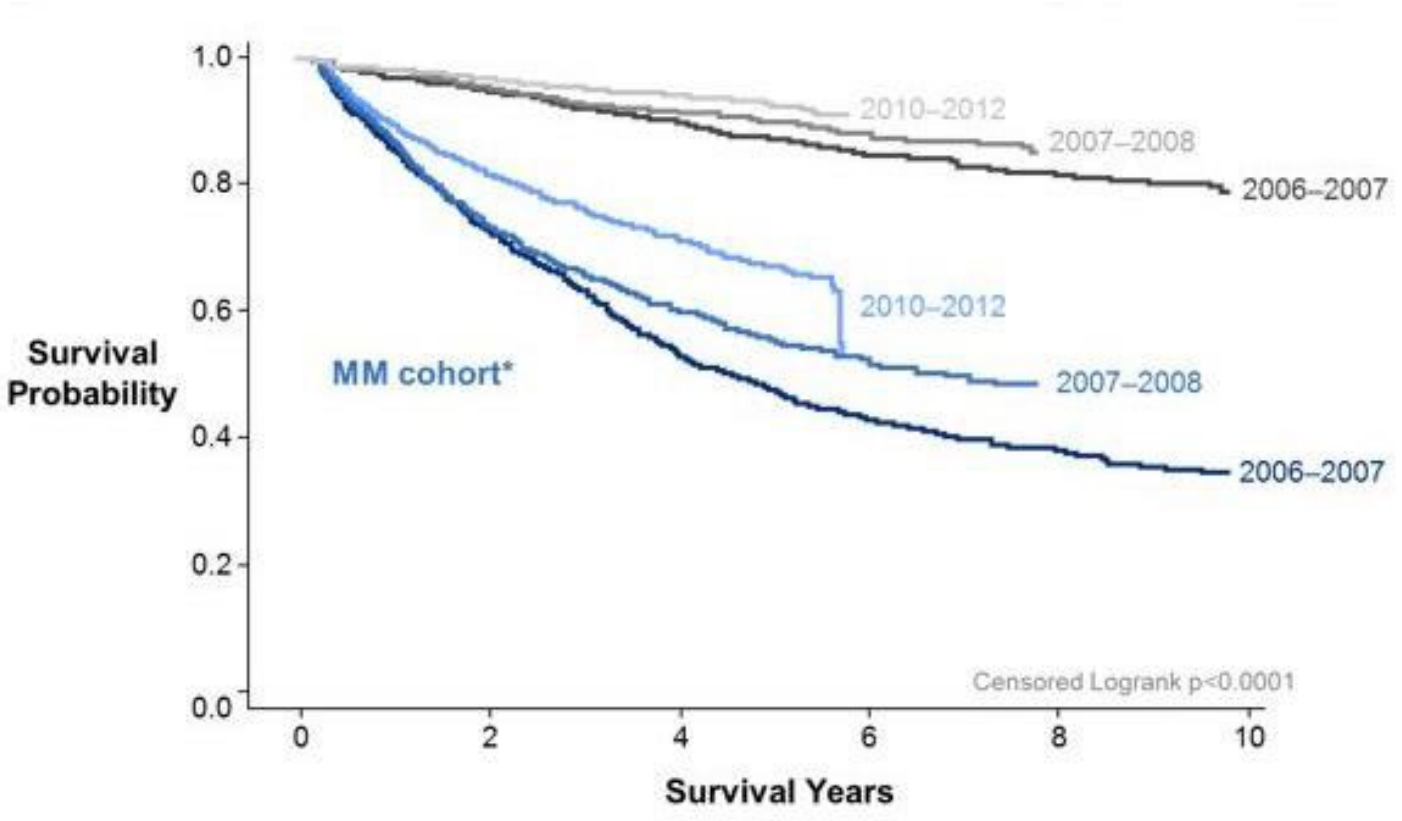
Improvements in Survival



@rfonsi1, fonseca.rafael@mayo.edu

Fonseca R, et al. *Leukemia.* 2017;31:1915-1921.

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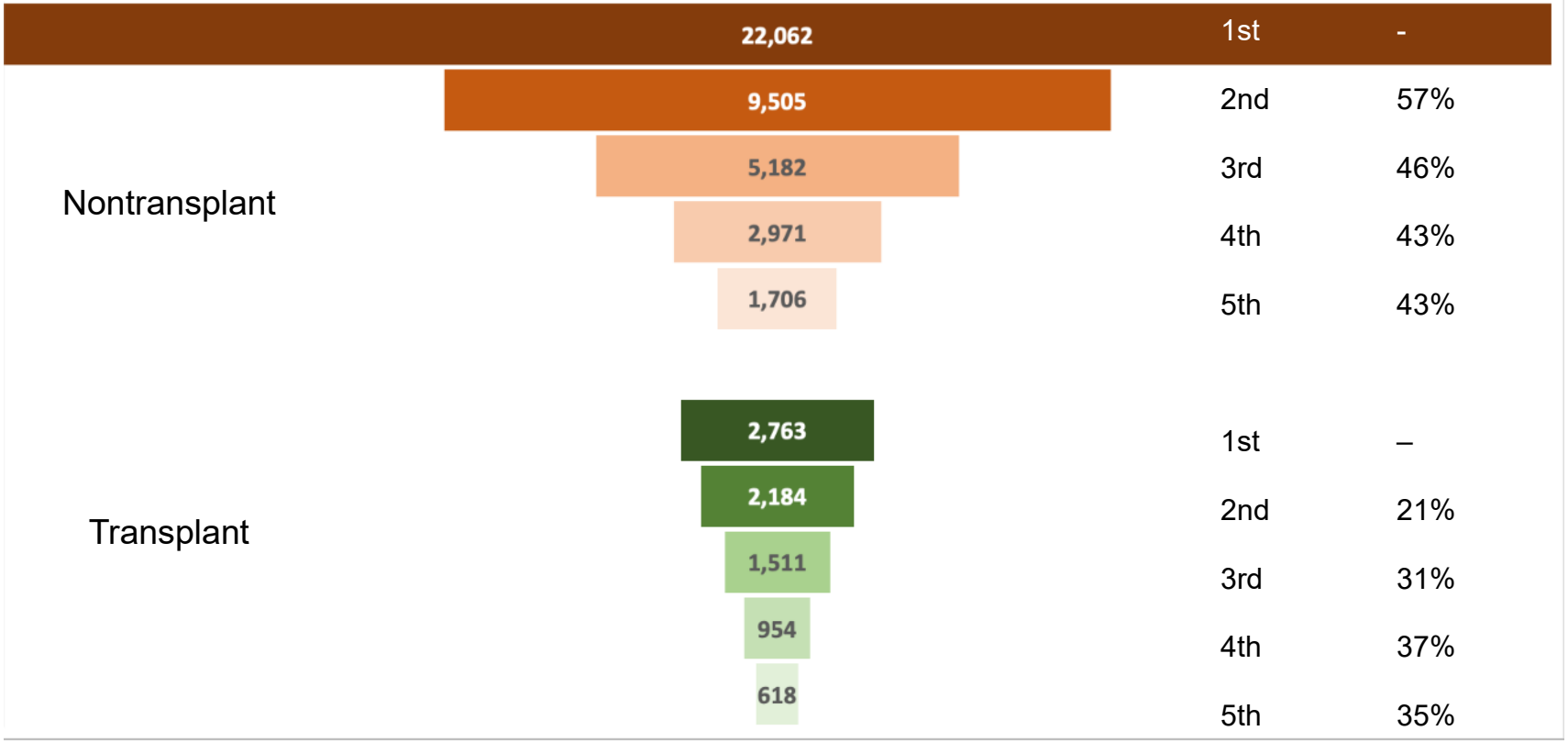
Attrition With Subsequent Treatment



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Fonseca R, et al. *BMC Cancer*. 2020;20:1087.

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High Rate of Attrition

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POLLUX Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

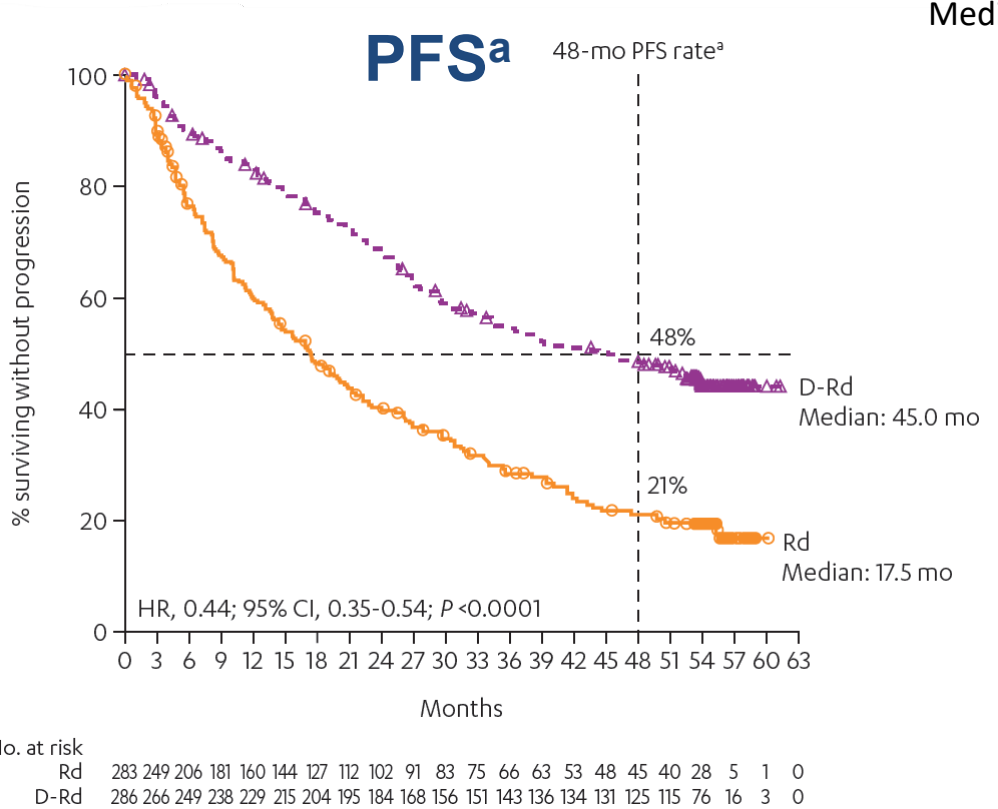
Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.

MAYO CLINIC

Median follow-up: 54.8 months



DRd continued to demonstrate a significant PFS benefit with extended follow-up

[a]Kaplan-Meier estimate, intention-to-treat population.
DRd, daratumumab plus lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; PFS, progression-free survival; HR, hazard ratio.

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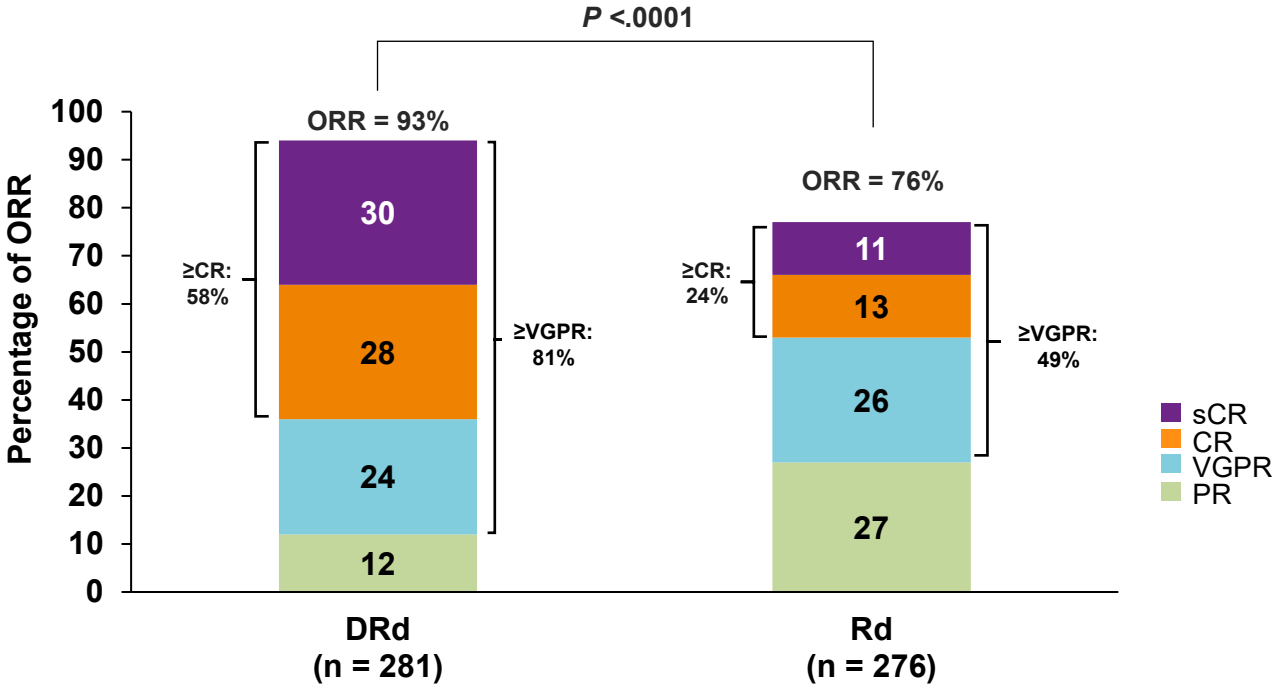
Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.

Median follow-up: 54.8 months

ORR



Deeper responses were observed with DRd

DVd, daratumumab plus bortezomib-dexamethasone; Vd, bortezomib-dexamethasone; ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.

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Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.

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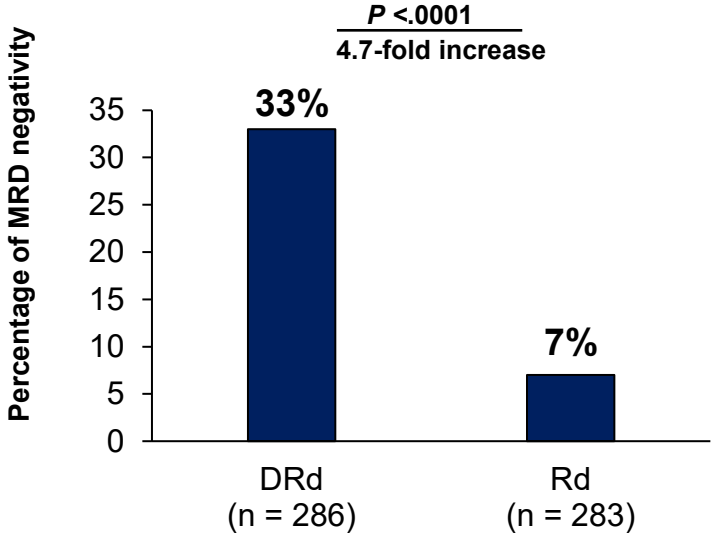
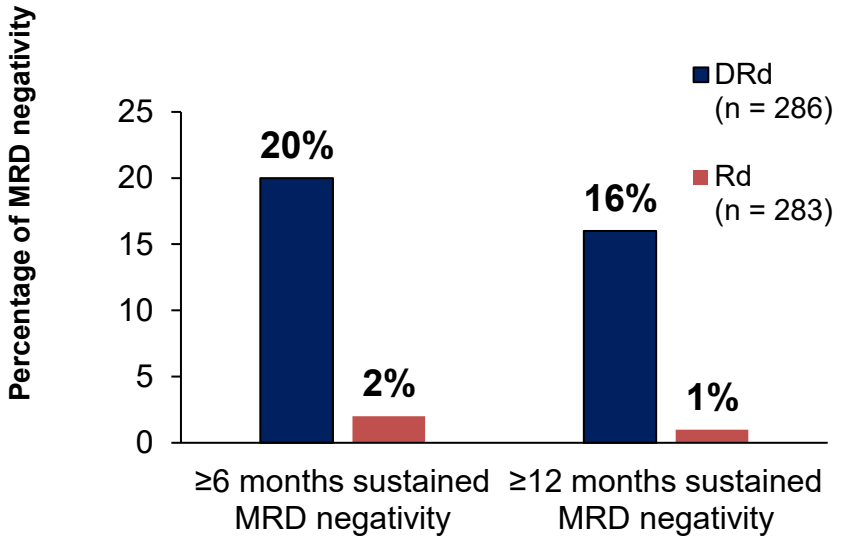
Median follow-up: 54.8 months

MRD Negativity (10-5, NGS)

MRD negativity rate



Sustained MRD negativity rate



Improved and sustained MRD negativity rates with DRd vs Rd

DRd, daratumumab plus lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; MRD, minimal residual disease; NGS, next-generation sequencing.

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Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.

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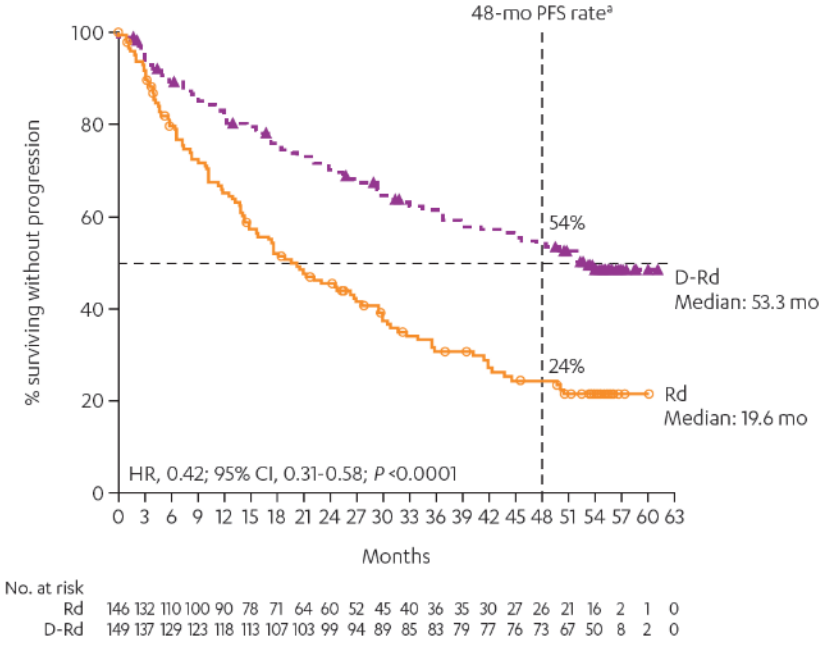
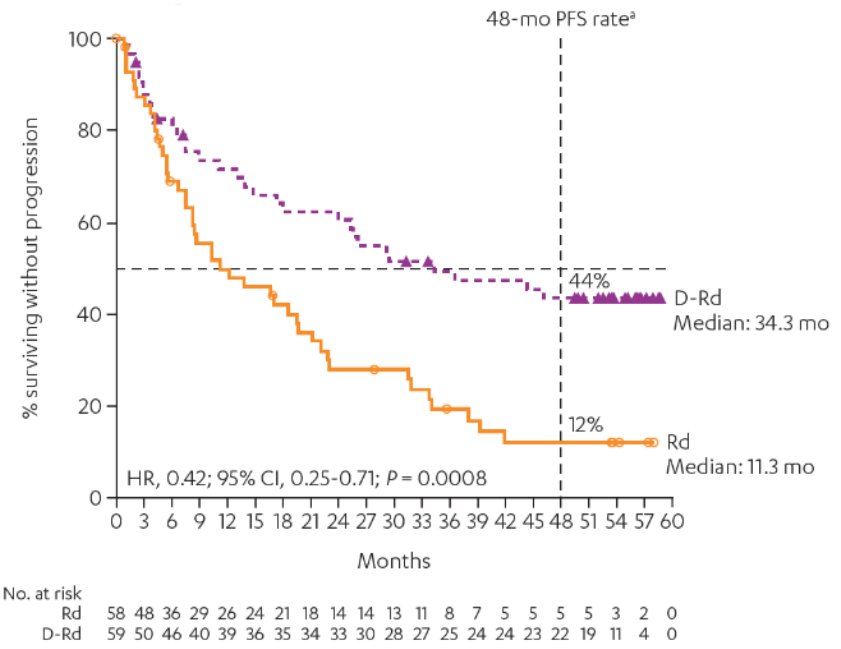
Median follow-up: 54.8 months

PFS in Subgroups

1 prior line of therapy



Refractory to bortezomib



Greatest benefit of DRd was seen in patients with 1 prior line of therapy

DRd, daratumumab plus lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; PFS, progression-free survival; HR, hazard ratio.

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Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.

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Demographic and Baseline Disease Characteristics

	DRd (n = 286)	Rd (n = 283)
Age, years		
Median (range)	65 (34–89)	65 (42–87)
≥75, n (%)	29 (10)	35 (12)
ISS staging, n (%)[a]		
I	137 (48)	140 (50)
II	93 (33)	86 (30)
III	56 (20)	57 (20)
Time from diagnosis, years		
Median (range)	3.5 (0.4–27.0)	4.0 (0.4–21.7)
Cytogenetic profile,[b] n (%)		
N	228	211
Standard risk	193 (85)	176 (83)
High risk	35 (15)	35 (17)

	DRd (n = 286)	Rd (n = 283)
Prior lines of therapy		
Median (range)	1 (1–11)	1 (1–8)
1, n (%)	149 (52)	146 (52)
2, n (%)	85 (30)	80 (28)
3, n (%)	38 (13)	38 (13)
>3, n (%)	14 (5)	19 (7)
Prior ASCT, n (%)	180 (63)	180 (64)
Prior PI, n (%)	245 (86)	242 (86)
Bortezomib	241 (84)	238 (84)
Prior IMiD, n (%)	158 (55)	156 (55)
Lenalidomide	50 (18)	50 (18)
Prior PI + IMiD, n (%)	125 (44)	125 (44)
Refractory to bortezomib, n (%)	59 (21)	58 (21)
Refractory to last line of therapy, n (%)	80 (28)	76 (27)

[a]ISS staging was based on the combination of serum B2-microglobulin and albumin; [b]Cytogenetic risk status was established by FISH/karyotyping. Patients with high cytogenetic risk had a t(4;14), t(14;16). and/or del(17p) abnormality. Patients with standard cytogenetic risk had an absence of high cytogenetic risk abnormalities.
ITT, intent-to-treat; DRd, daratumumab plus lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; ISS, International Staging System; ASCT, autologous stem cell transplant; PI, proteasome inhibitor, IMiD, immunomodulatory drug; FISH, fluorescence in situ hybridization.

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Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.

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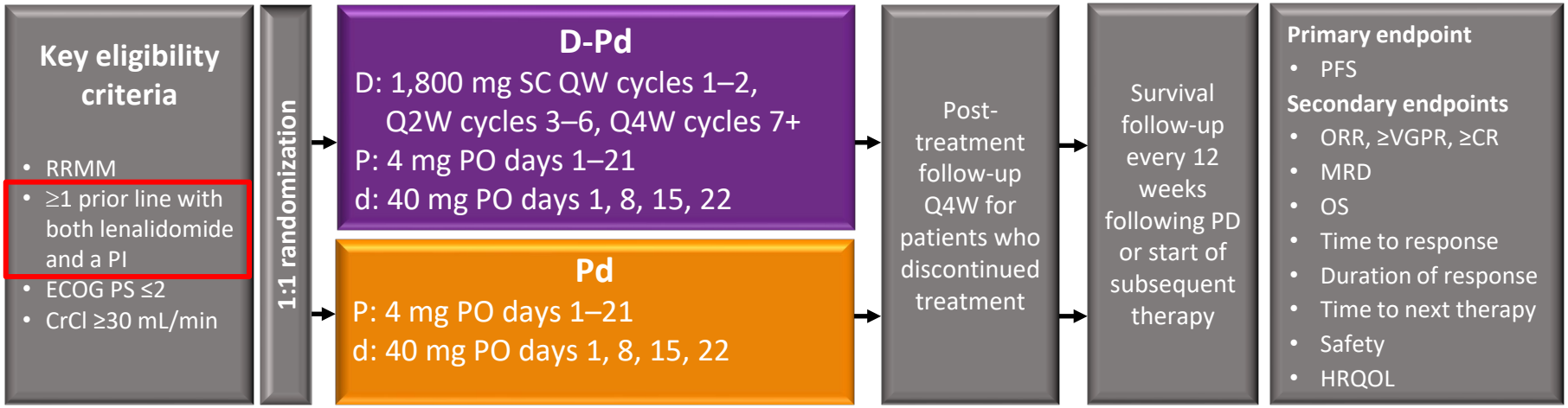
APOLLO: Dara-Pd



Stratification factors
- Number of lines of prior therapy (1 vs 2–3 vs ≥4)
- ISS disease stage (I vs II vs III)

Cycle duration: 28 days
Treatment until PD or unacceptable toxicity

D-Pd, daratumumab, pomalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; HRQOL, health-related quality of life; ISS, International Staging System; MRD, minimal residual disease OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor;PO, per oral; Pd, pomalidomide and dexamethasone; PD, progressive disease; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RRMM, relapsed or refractory multiple myeloma.

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Dimopoulos MA, et al. ASH 2020. Abstract 412.

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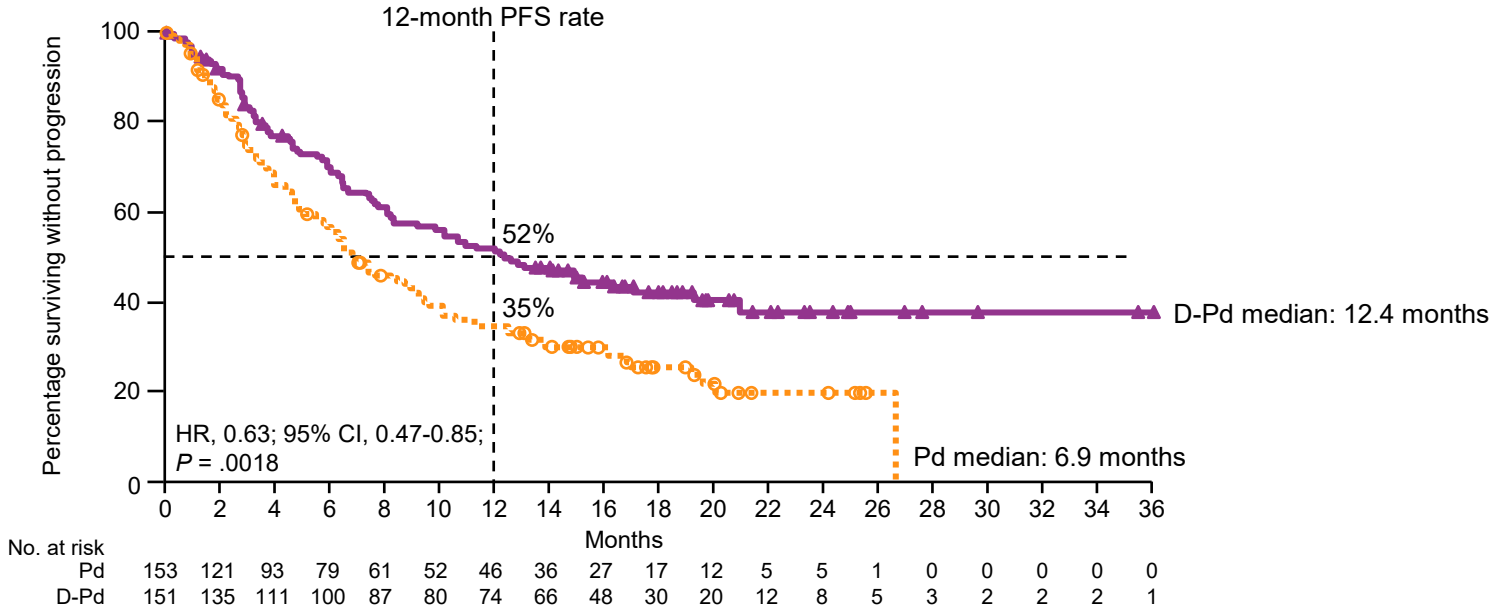
APOLLO: Dara-Pd

Median follow-up 17 mo



Median PFS among patients who are refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

D-Pd, daratumumab, pomalidomide, and dexamethasone; HR, hazard ratio; PFS, progression-free survival; Pd, pomalidomide and dexamethasone.

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Dimopoulos MA, et al. ASH 2020. Abstract 412.

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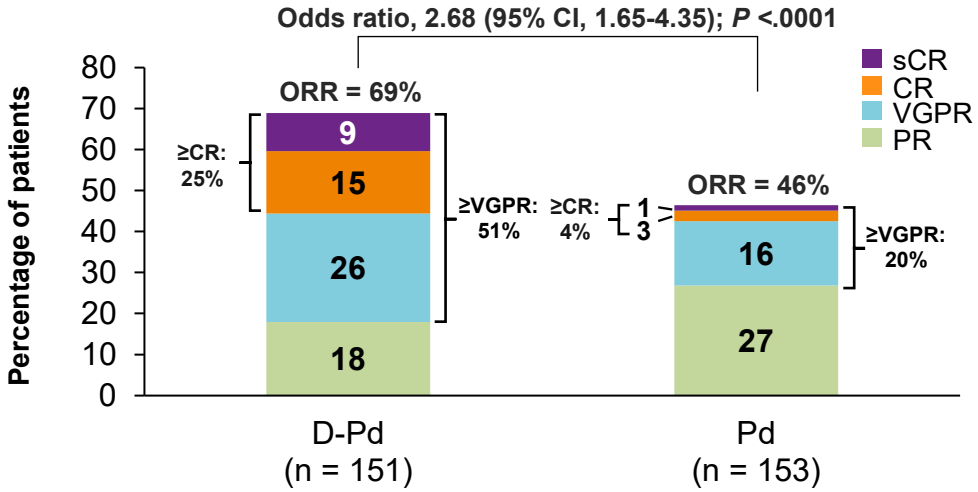
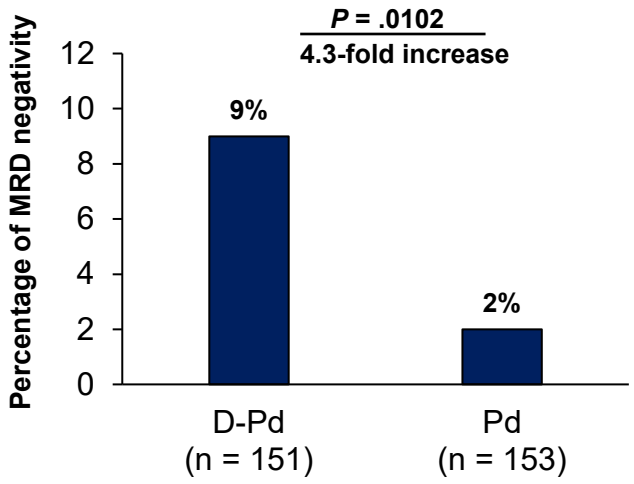
APOLLO: Dara-Pd

Hematologic response



MRD negativity



CI, confidence interval; CR, complete response; D-Pd, daratumumab, pomalidomide, and dexamethasone; MRD, minimal residual disease ORR, overall response rate; Pd, pomalidomide and dexamethasone; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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Dimopoulos MA, et al. ASH 2020. Abstract 412.

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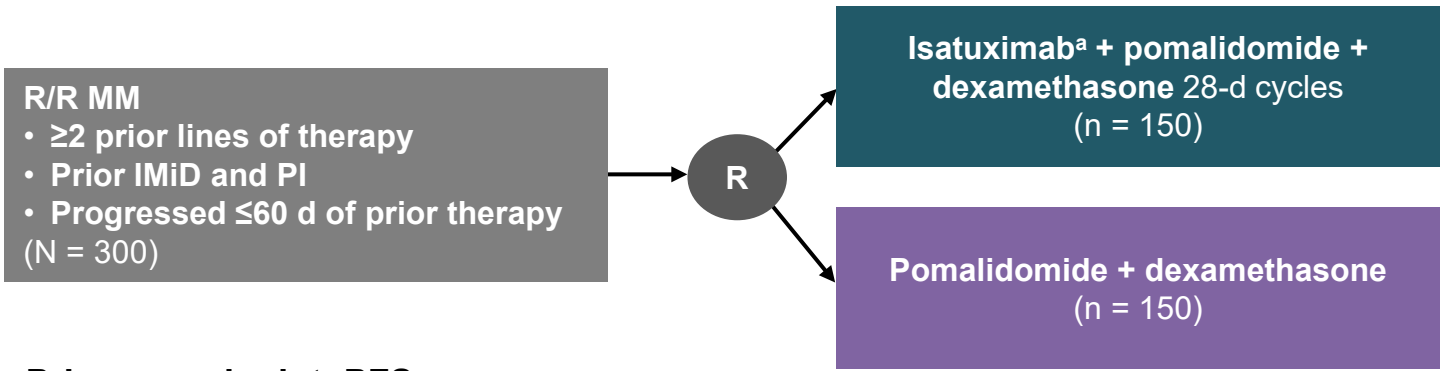
ICARIA: Isatuximab + Pd



Until disease progression, occurrence of unacceptable AEs, or patient's decision to discontinue the study

- **Primary endpoint: PFS**
- **Key secondary endpoints: ORR, OS, safety**

[a]Isatuximab 10 mg/kg IV on d 1, 8, 15, and 22 in the first cycle; d 1 and 15 in subsequent cycles.
Pomalidomide 4 mg on d 1–21.
Dexamethasone 40 mg for patients aged <75 yr and 20 mg for patients aged ≥75 yr on d 1, 8, 15, and 22.

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Richardson PG, et al. ASCO 2019. Abstract 8004;
https://clinicaltrials.gov/ct2/show/NCT02990338. Accessed September 6, 2019.

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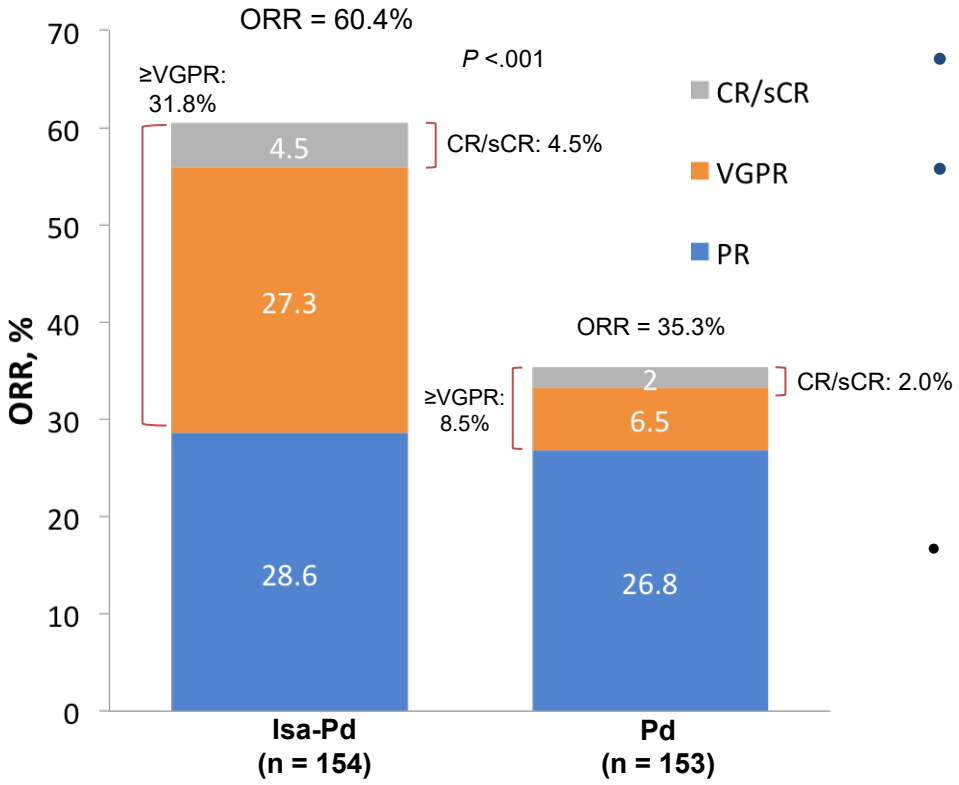
ICARIA-MM: Response



- **Median time to first response: Isa-Pd = 35 days vs Pd = 58 days**
- **True CR rate in Isa-Pd underestimated because of isatuximab interference with M-protein measurement**

	Isa-Pd (n = 154)	Pd (n = 153)
nCR, %	15.6	3.3

- MRD negativity at 10^{-5} (ITT): 5.2% for Isa-Pd vs 0% for Pd

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Richardson PG, et al. ASCO 2019. Abstract 8004..

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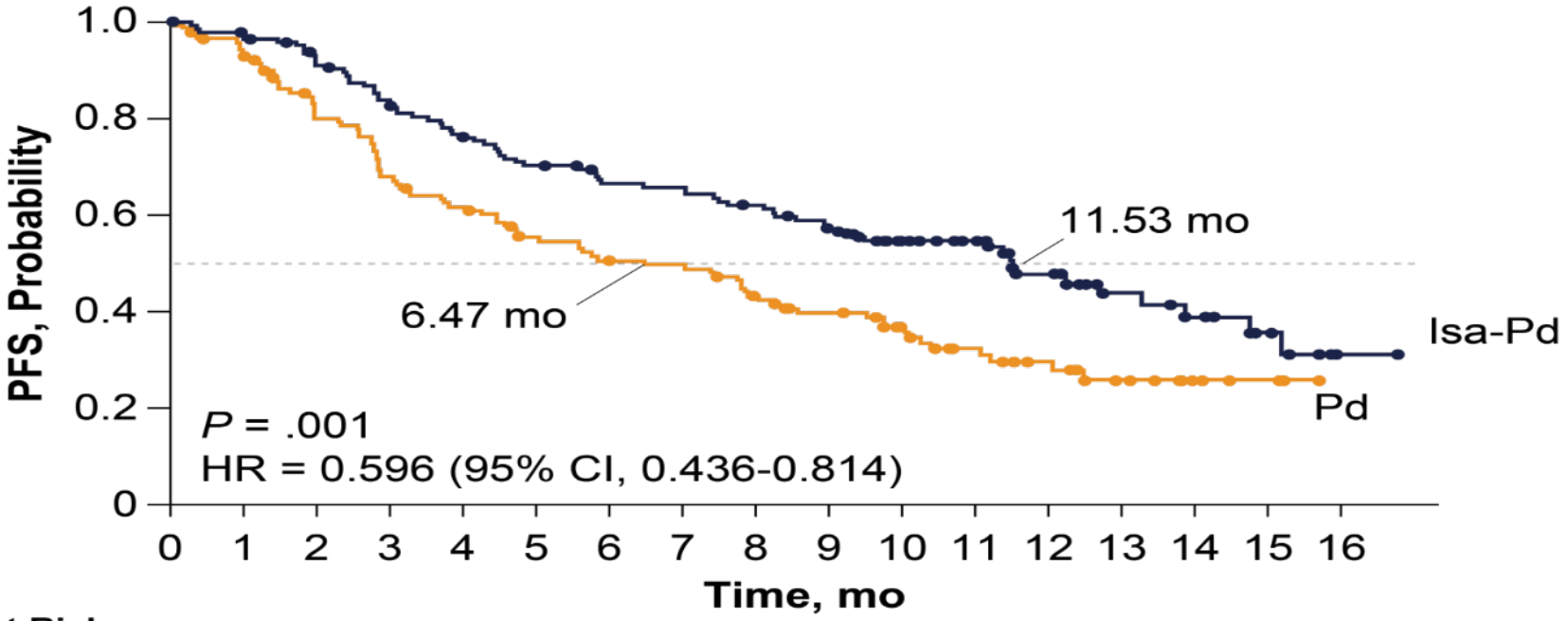
ICARIA-MM: PFS



No. at Risk

Isa-Pd	154	129	106	89	81	52	30	14	1
Pd	153	105	80	63	51	33	17	5	0

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Richardson PG, et al. ASCO 2019. Abstract 8004..

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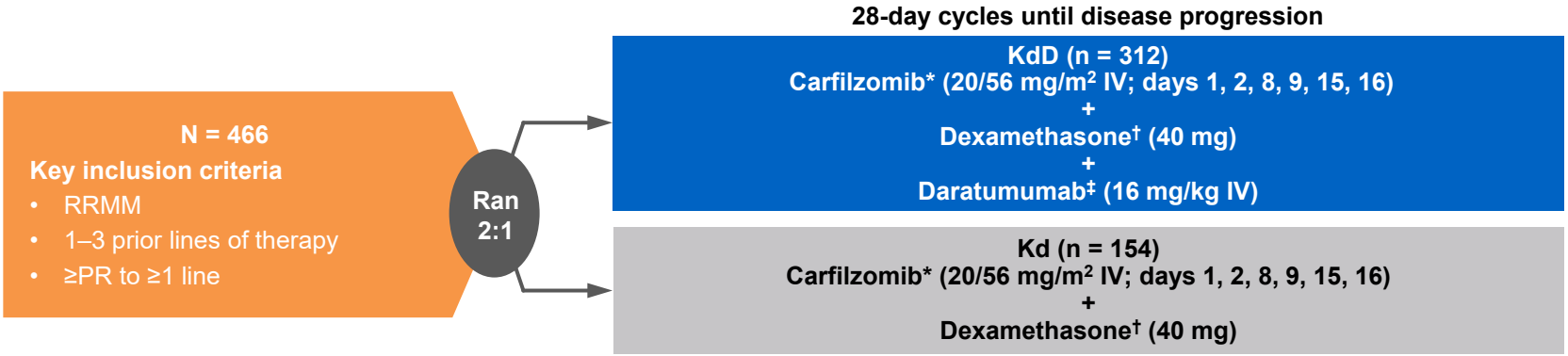
CANDOR (KdD vs Kd in RRMM)

- The CANDOR study previously demonstrated that KdD improved progression-free survival (PFS) vs Kd (HR, 0.63; 95% CI, 0.46–0.85) in patients with RRMM[1]
- This abstract reports updated efficacy and safety outcomes from CANDOR up to the data cutoff of ~36 months after enrollment of the first patient[2]



Primary endpoint: PFS§

Select secondary endpoints: ORR, MRD-negative CR at 12 months, OS, safety

*Carfilzomib dose was 20 mg/m^2 on days 1 and 2 of cycle 1. †PO or IV weekly; 20 mg for patients >75 years. ‡8 mg/kg on days 1 and 2 of cycle 1; 16 mg/kg weekly thereafter for cycles 1–2; Q2W for cycles 3–6; and Q4W thereafter. §Disease progression was determined locally by investigators in an unblinded manner and centrally by the sponsor using a validated computer algorithm (ORCA) in a blinded manner.
CR, complete response; HR, hazard ratio; IV, intravenous; Kd, carfilzomib, dexamethasone; KdD, carfilzomib, dexamethasone, daratumumab; MRD, minimal residual disease; ORCA, Onyx Response Computer Algorithm; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, per oral; PR, partial response; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Ran, randomized; RRMM, relapsed or refractory multiple myeloma.

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1. Dimopoulos M, et al. *Lancet.* 2020;396:186-197; 2. Dimopoulos M, et al. ASH 2020. Abstract 2325.

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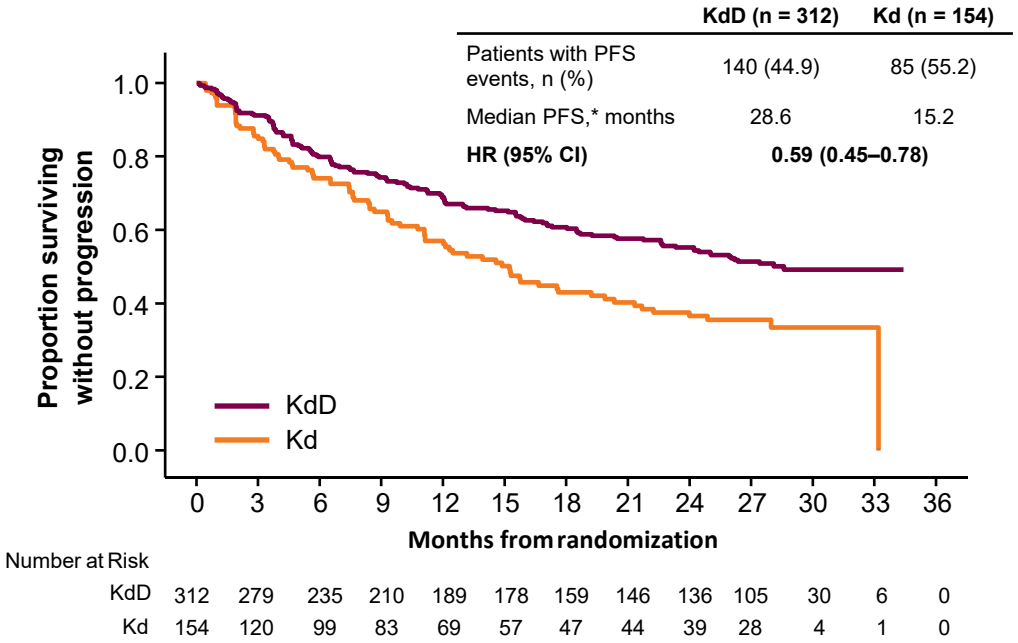
CANDOR (KdD vs Kd in RRMM)



Safety	KdD (n = 312)	Kd (n = 154)
Grade ≥3 AEs, %	87.0	75.8
Fatal AEs,† %	8.8	4.6
Carfilzomib discontinuation due to AEs, %	26.0	22.2
Exposure-adjusted AE rates, per 100 patient-years:		
Grade ≥3 AEs	171.2	151.9
Fatal AEs	6.9	5.6

- Safety was consistent with previously reported results
- KdD continues to show a favorable benefit-risk profile

With ~11 months of additional follow-up, median PFS was improved in patients treated with KdD (28.6 months) vs Kd (15.2 months)

*By ORCA. †One fatal AE in the KdD arm (due to arrhythmia) and 1 fatal AE in the Kd arm (due to COVID-19 pneumonia) had occurred since the primary analysis.
AE, adverse event; HR, hazard ratio; Kd, carfilzomib, dexamethasone; KdD, carfilzomib, dexamethasone, daratumumab; ORCA, Onyx Response Computer Algorithm; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma.

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Dimopoulos M, et al. ASH 2020. Abstract 2325.

MAYO CLINIC

CANDOR (KdD vs Kd in RRMM)

- This posthoc analysis evaluated MRD in patients participating in CANDOR
- MRD was evaluated by next-generation sequencing (threshold <10^{-5} unless otherwise specified)

	Kd	KdD	OR	*P* Value
Best overall MRD-negative CR rate at any time	3.2%	13.8%	4.95	<.0001
MRD negative regardless of overall response status	5.8%	22.8%	5.15	<.0001
MRD-negative CR rate at 12 months	1.3%	12.5%	11.3	<.0001

- MRD-negative CR rates at the 12-month landmark for KdD vs Kd were consistent across clinically relevant subgroups

Subgroup Analyses of MRD-Negative Rates at 12 Months for Patients Who Achieved CR

	Kd		KdD		Odds Ratio
Group	n/N	MRD[-]CR	n/N	MRD[-]CR	**(95% CI)**
Prior lines of therapy per IXRS					
1	1/67	1.5%	22/133	16.5%	13.1 (1.7, 99.3)
≥2	1/87	1.1%	17/179	9.5%	9.0 (1.2, 69.0)
Age at baseline, years					
≤75	1/136	0.7%	37/287	12.9%	20.0 (2.7, 147.2)
>75	1/18	5.6%	2/25	8.0%	1.5 (0.1, 17.7)
Baseline CrCl, mL/min					
≥15 to 49	0/27	0.0%	4/38	10.5%	NE
≥50 to 79	1/50	2.0%	14/97	14.4%	8.3 (1.0, 64.8)
≥80	1/77	1.3%	21/176	11.9%	10.3 (1.4, 78.0)
Prior lenalidomide					
Yes	0/74	0.0%	14/123	11.4%	NE
No	2/80	2.5%	25/189	13.2%	5.9 (1.4, 25.7)
Refractory to lenalidomide					
Yes	0/55	0.0%	13/99	13.1%	NE
No	2/99	2.0%	26/213	12.2%	6.7 (1.6, 29.0)
Prior bortezomib or ixazomib exposure					
Yes	2/137	1.5%	34/289	11.8%	9.0 (2.1, 38.0)
No	0/17	0.0%	5/23	21.7%	NE
Refractory to bortezomib or ixazomib					
Yes	1/55	1.8%	7/100	7.0%	4.1 (0.5, 33.9)
No	1/99	1.0%	32/212	15.1%	17.4 (2.3, 129.4)
Prior IMiD exposure					
Yes	0/110	0.0%	24/206	11.7%	NE
No	2/44	4.5%	15/106	14.2%	3.5 (0.8, 15.8)
Refractory to IMiD					
Yes	0/65	0.0%	16/130	12.3%	NE
No	2/89	2.2%	23/182	12.6%	6.3 (1.4, 27.3)

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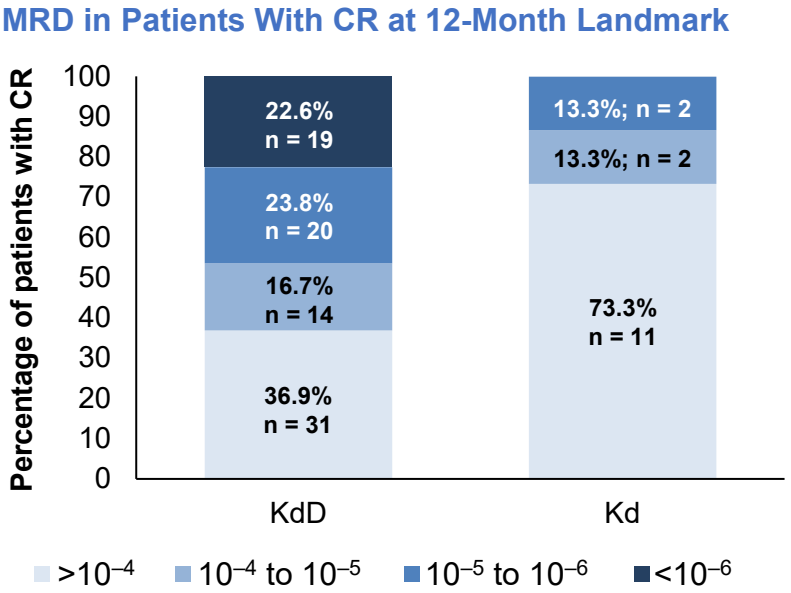
Landgren O, et al. ASH 2020. Abstract 2282.

MAYO CLINIC

CANDOR (KdD vs Kd in RRMM)



- At the 12-month landmark, patients treated with KdD had a greater proportion of CR rates (26.9% vs 9.7%) and deeper MRD responses than patients treated with Kd
- Among patients with CR, depth of response was deeper for KdD relative to Kd regardless of MRD sensitivity
- Within the KdD arm, prior lenalidomide exposure or refractoriness did not diminish the MRD-negative CR rate
- With a median of 6 months follow-up, no patients with MRD-negative CR progressed

Patients treated with KdD achieved significantly higher MRD-negative CR rates vs Kd at 12 months, which supports the efficacy of the KdD regimen as an effective treatment for RRMM including patients who have become refractory to lenalidomide

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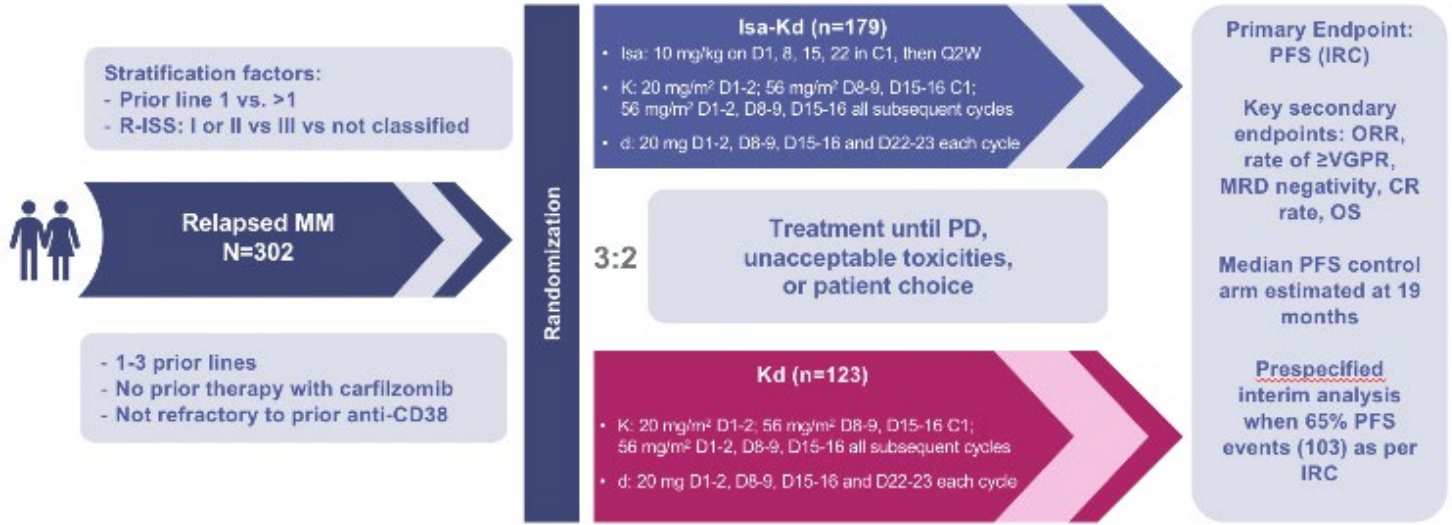
Landgren O, et al. ASH 2020. Abstract 2282.

MAYO CLINIC

IKEMA



Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

Patients refractory to, n (%)		
IMiD	78 (43.6)	58 (47.2)
Lenalidomide	57 (31.8)	42 (34.1)
PI	56 (31.3)	44 (35.8)

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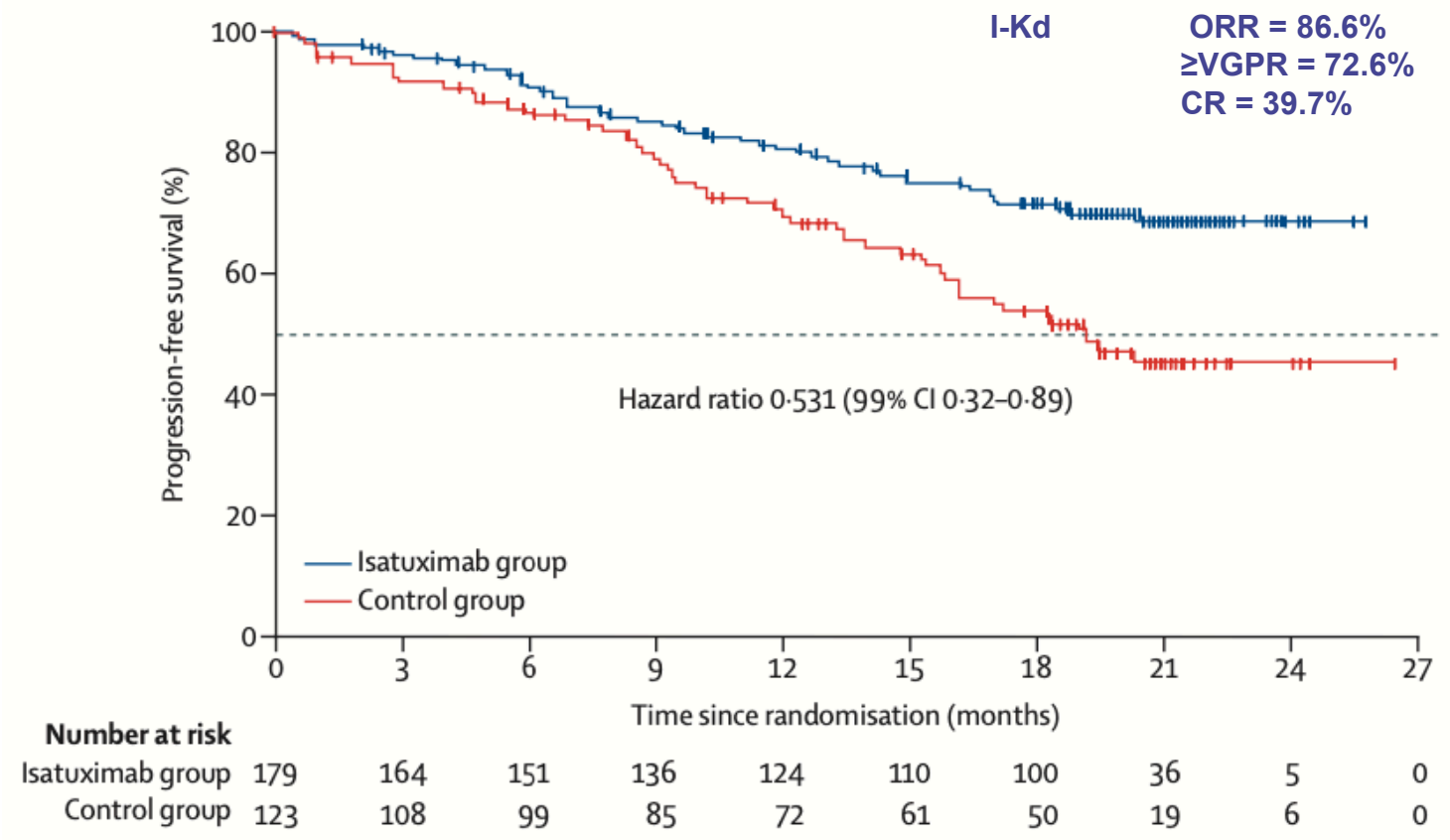
Moreau P, et al. *Lancet*. 2021;397:P2361-P2371.

MAYO CLINIC

IKEMA



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Moreau P, et al. *Lancet*. 2021;397:P2361-P2371.

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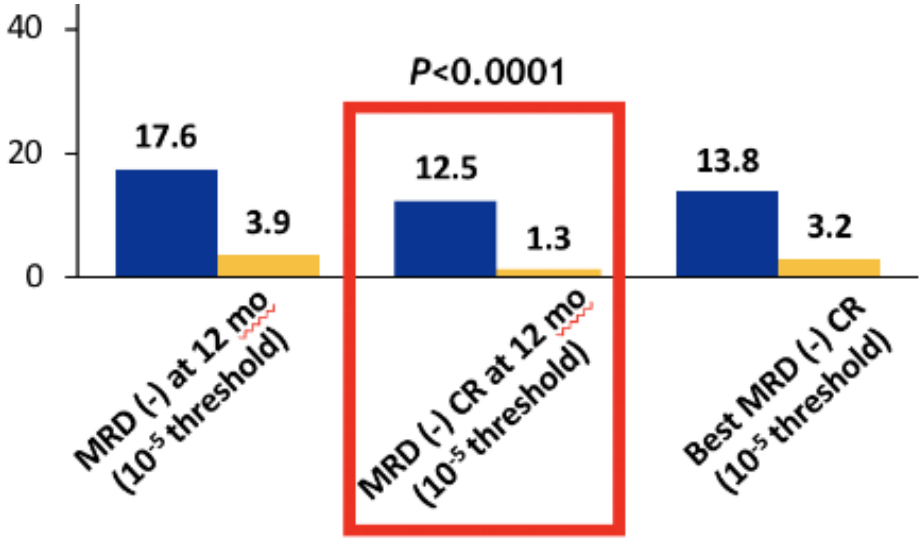
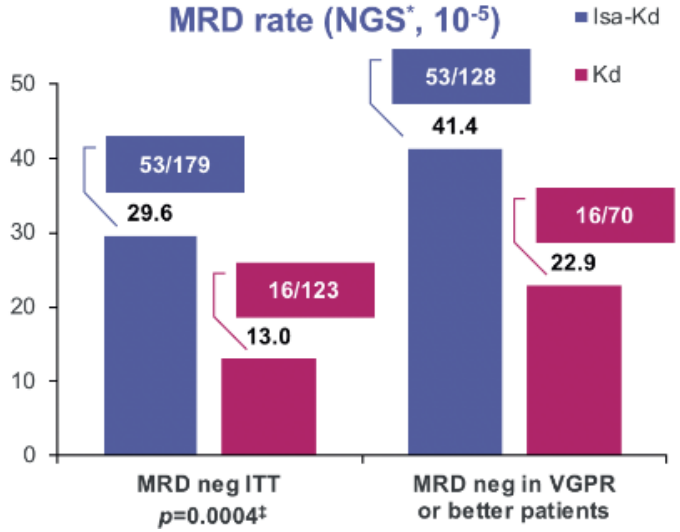
MRD Results

CANDOR



IKEMA



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Moreau P, et al. *Lancet*. 2021;397:P2361-P2371.

MAYO CLINIC

Anti-CD38 at Relapse

Studies	POLLUX[1] DRd vs Rd	APOLLO[1] DPd vs Pd	CANDOR[1] DKd vs Kd	MAIA[2] DRd vs Rd	CASTOR[3,4] DVd vs Vd	ICARIA[1] IPd vs Pd	IKEMA[1] IKd vs Kd
	2 publications		*Lancet*	*NEJM* 2019	2 publications	ASCO 2019	ASCO 2021
	Daratumumab					Isatuximab	
Eligibility (prior lines of Rx)	1	1–3	1–3	NDMM	1	2+	1–3
n	569	304	466	737	498	307	302
mPFS Exp (mo)	44.5	12.4	28.6	44.5	16.7	11.5	NR
mPFS Control (mo)	17.5	6.9	15.2	17.5	7.1	6.5	19.2
Median no. prior lines	1	2	2	0	2	3	NA
1 prior line	53%	11%	46%	NA	49%	NA	NA
2 prior lines	30%	89% (combined)	54% (combined)	NA	28%	NA	NA
3 or more	19%	89% (combined)	54% (combined)	NA	24%	NA	NA
High risk	15%	38%	15%	14%	8%	20%	24%
Deletion 17p13	11%	NA	NA	Not defined	5%	NA	NA
ORR experimental	93%	69%	84%	93%	85%	60%	87%
MRD experimental	22%	9%	14%	81%	63%	5% (-5)	30%

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1. https://twitter.com/Rfonsi1/status/1397594631148384257; 2. Facon T, et al. *Lancet.* 2021;11:P1582-P1596; 3. Weisel, et al. *Am J Hematol*. 2020;95:548-567; 4. Mateos MV, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:509-518.

MAYO CLINIC

Thank you!

They say you cannot compare trials?

FALSE – we always do.

You just cannot conclude!

But you can postulate hypotheses.

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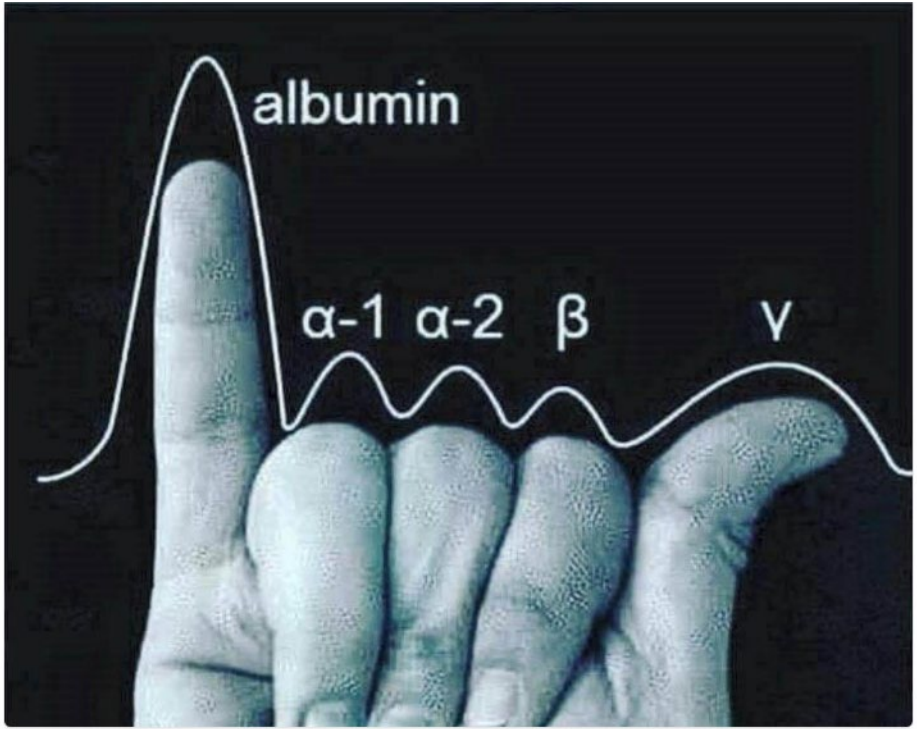
MAYO CLINIC

Thank you!



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Global Multiple Myeloma Academy

Discussion

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Relapsed/Refractory Multiple Myeloma: Patient Case 1

Ana Luiza Miranda Silva Dias

São Germano Clinic, São Paulo, Brazil

APTITUDE HEALTH®

Relapsed Multiple Myeloma Patient Case

Ana Luiza Miranda Silva Dias

São Germano Clinic, São Paulo, Brazil

Clinical Case Study

56-year-old woman with back pain for 1 month (August 2019)

Lab test	Bone marrow	FISH	Image
Hb: 8.3 g/dL **Creatinine:1.6 mg/dL** Creatinine: 41 mL/min Calcium: 1.39 mg/dL **M-spike: 6.23 g/dL** **IgA lambda** B2m: 7.8 mg/dL Albumin: 2.93 g/dL LDH: 210 IU/L (nl) **sFLC (k/L): 0.004**	64% of clonal plasma cells with lambda restricted	No abnormalities	Whole-body low-dose CT showed **multiple lytic lesions** and **vertebral fractures** (T5, T10, L1, L3) and in third, fourth, and fifth right ribs

Clinical Case Study

- 56-year-old woman
- Comorbidities: hypothyroidism
- Multiple myeloma IgA lambda
- ISS 3
- R-ISS 2
- Fit

Multiple-Choice Question 1

Which treatment do you propose?

a) VRd + ASCT
b) Dara-VTd + ASCT
c) VCd + ASCT
d) VTd + ASCT
e) CTd + ASCT

Clinical Case Treatment Proposal

- 4 cycles of VRd since Oct 2019
- After induction: VGPR
- ASCT in Feb 2020
- After ASCT: VGPR (Apr 2020)

Consolidation

- Consolidation with 4 cycles VRd from 13 May 2020 to 05 Aug 2020
- After consolidation: sCR
- Adverse event during the treatment: peripheral neuropathy, grade 1

Clinical Case Outcome

- After induction → VGPR
- After transplant → VGPR
- After consolidation → sCR + MRD by flow cytometry 10^{-5}

Personal data: Dra Ana Luiza Miranda.

Maintenance

- Lenalidomide 10 mg (21/28d) started in Aug 2020

Follow-up

- After 16 months, in Nov 2021, reappearance of M component
- Doubled in 30 days

Clinical Case Study

Lab test	Bone marrow	FISH	Image
Hb: 13.3 g/dL Creatinine: 0.70 mg/dL Calcium: 1.20 mg/dL M-spike: 0.24 g/dL **IgA: 1179** B2m: 2.3 mg/dL Albumin: 3.90 g/dL LDH: 233 IU/L (increased) Lambda: 187 mg/L Kappa: 15.1 sFLC (k/l): 0.008	Bone marrow biopsy: **12%** lambda-restricted clonal CD138 plasma cells and CD56 positive	No abnormalities	Whole-body low-dose CT does not show any new lesions

Multiple-Choice Question 2

Which treatment do you propose for second-line therapy?

a) Anti-CD38–Kd
b) Anti-CD38–Pd
c) PVd
d) KCd
e) Others including clinical trials

Treatment Proposed for Second Line

- Dara-Kd since Jan 2022
- After 1 cycle: 83% of reduction of M-spike – PR
- Adverse event: thrombocytopenia, grade 3
- Carfilzomib reduced due to thrombocytopenia
- After third cycle, suspected CR

THANK YOU!!!

GBRAM
GRUPO BRASILEIRO DE MIELOMA

São Germano
Oncologia

Global Multiple Myeloma Academy

Discussion

All faculty and case presenters

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Break

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Management of Heavily Pretreated Multiple Myeloma

Keith Stewart, MBChB, MBA

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Management of Heavily Pretreated Multiple Myeloma

Keith Stewart, MBChB, MBA
Professor of Medicine
Director, Princess Margaret Cancer Centre
Toronto

What approximate percentage of MM patients are estimated to survive long enough to receive third-line therapy?

a) 90%

b) 80%

c) 65%

d) 50%

e) 40%

Which of the following is a true statement about belantamab mafodotin?

a) Ocular toxicity can be reduced by starting with graduated dosing

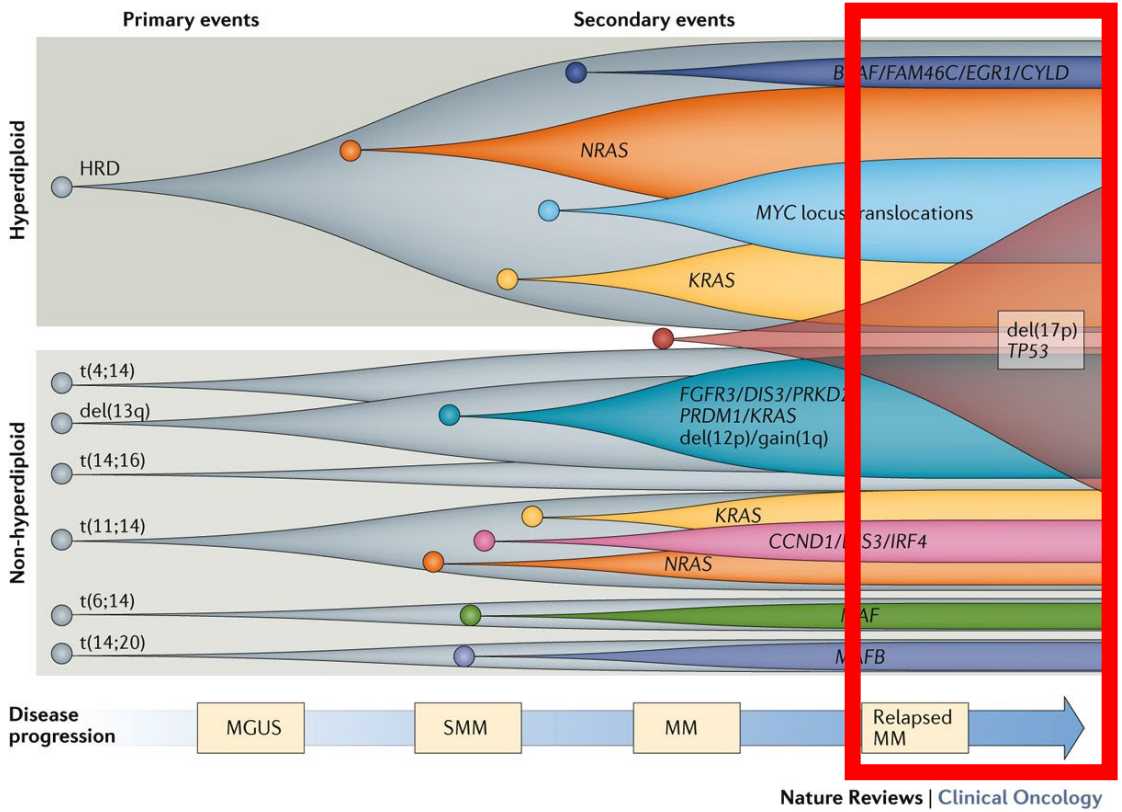
b) A less common but significant toxicity is early onset cytokine release syndrome

c) The response rate is 30%–35% partial response or better

d) The response rate in first relapse is 72%

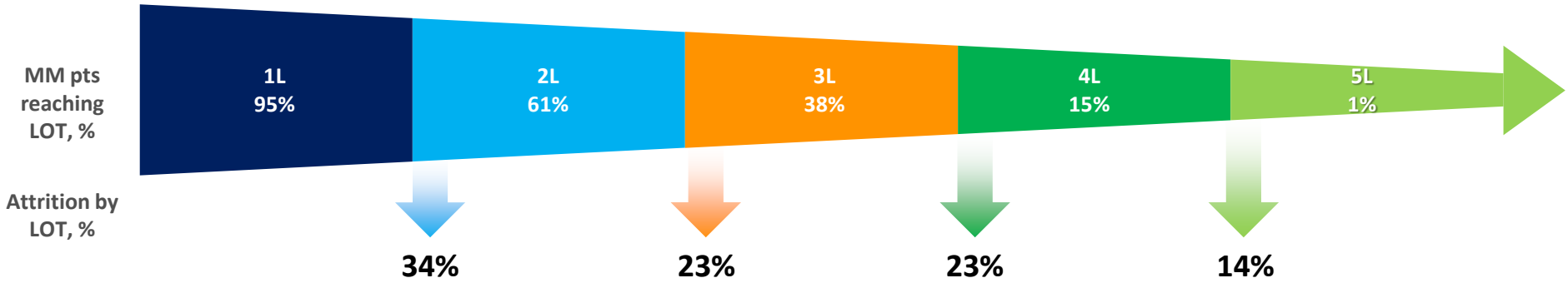
e) Ocular toxicity is manageable with steroid eye drops

Relapsed MM Is a Biologically and Genetically Heterogeneous Disease



Manier S, et al. *Nat Rev Clin Oncol.* 2017;14(2):100-113.

Only a Few MM Patients Reach Later Lines of Therapy



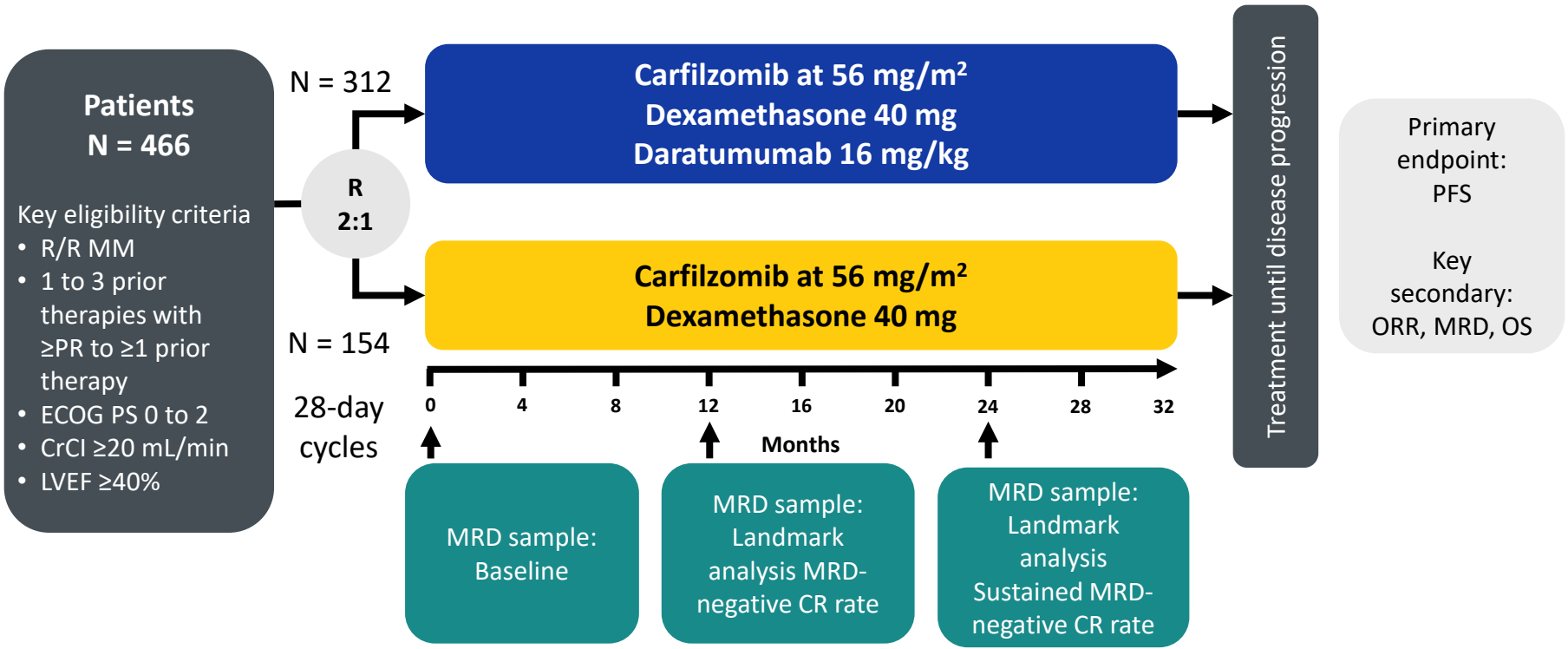
In every new LOT, ~15%–35% of patients are lost

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

What to Do After Lenalidomide and Bortezomib Fail

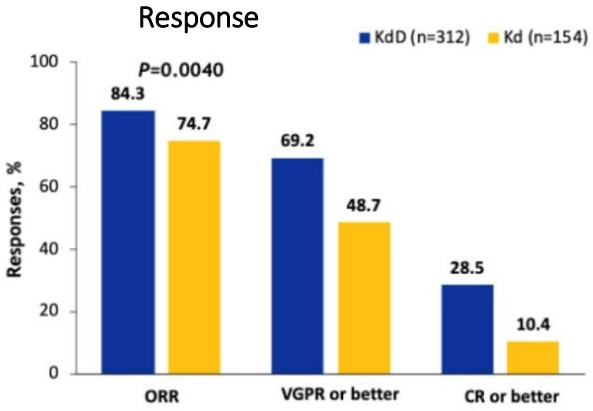
NOVEL COMBINATIONS?

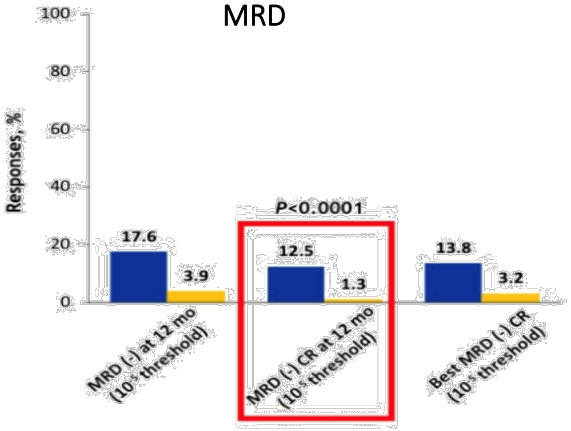
CANDOR: CAR-DARA-DEX vs CAR-DEX

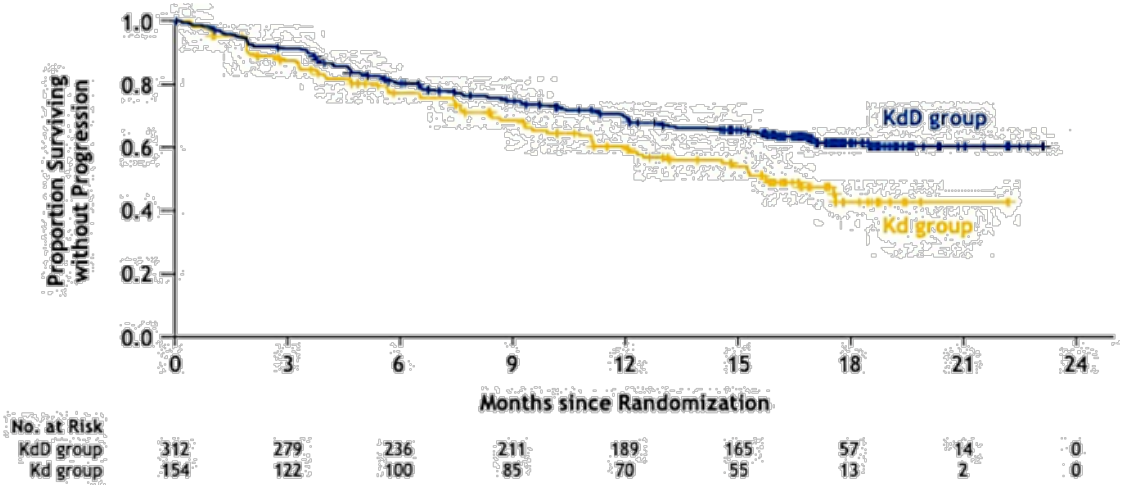


Usmani SZ, et al. ASH 2019. Abstract LBA6.

CANDOR: Response and PFS



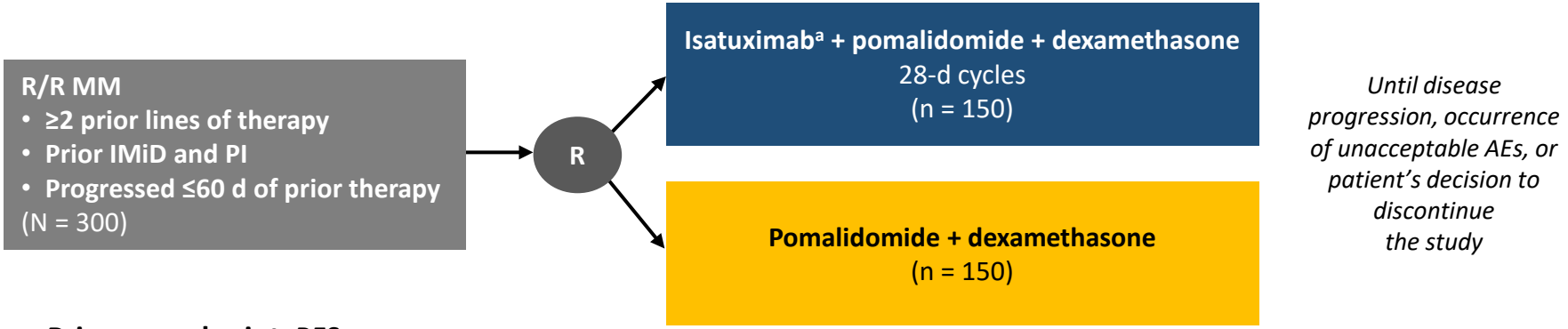




	KdD (n = 312)	Kd (n = 154)
Median follow-up time, months	16.9	16.3
Progression/death, n (%)	110 (35%)	68 (44%)
Median PFS, months	NE	15.8
HR (KdD/Kd) (95% CI)	0.63 (0.46–0.85)	
P value (1-sided)	.0014	

Usmani SZ, et al. ASH 2019. Abstract LBA6.

Phase III ICARIA-MM Study: Isatuximab + Pomalidomide-Dexamethasone in R/R MM[1,2]

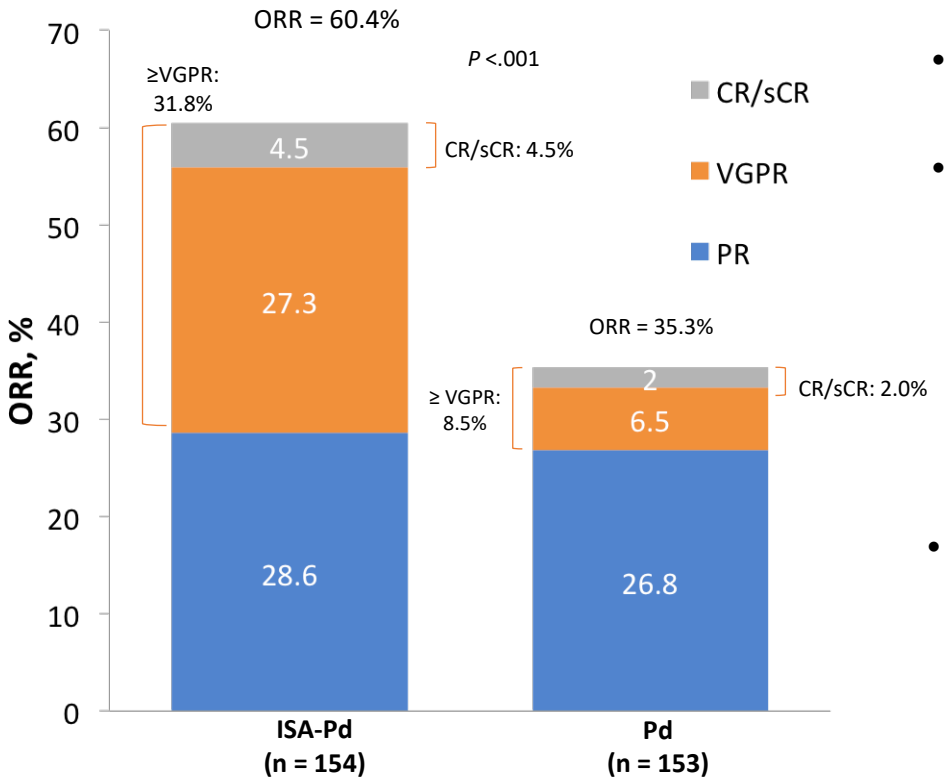


- **Primary endpoint:** PFS
- **Key secondary endpoints:** ORR, OS, safety

[a]Isatuximab 10 mg/kg IV on d 1, 8, 15, and 22 in the first cycle; d 1 and 15 in subsequent cycles. Pomalidomide 4 mg on d 1-21. Dexamethasone 40 mg for patients aged <75 yr and 20 mg for patients aged ≥75 yr on d 1, 8, 15, and 22.

1. Richardson PG, et al. ASCO 2019. Abstract 8004; 2. https://clinicaltrials.gov/ct2/show/NCT02990338. Accessed September 6, 2019.

ICARIA-MM: Response



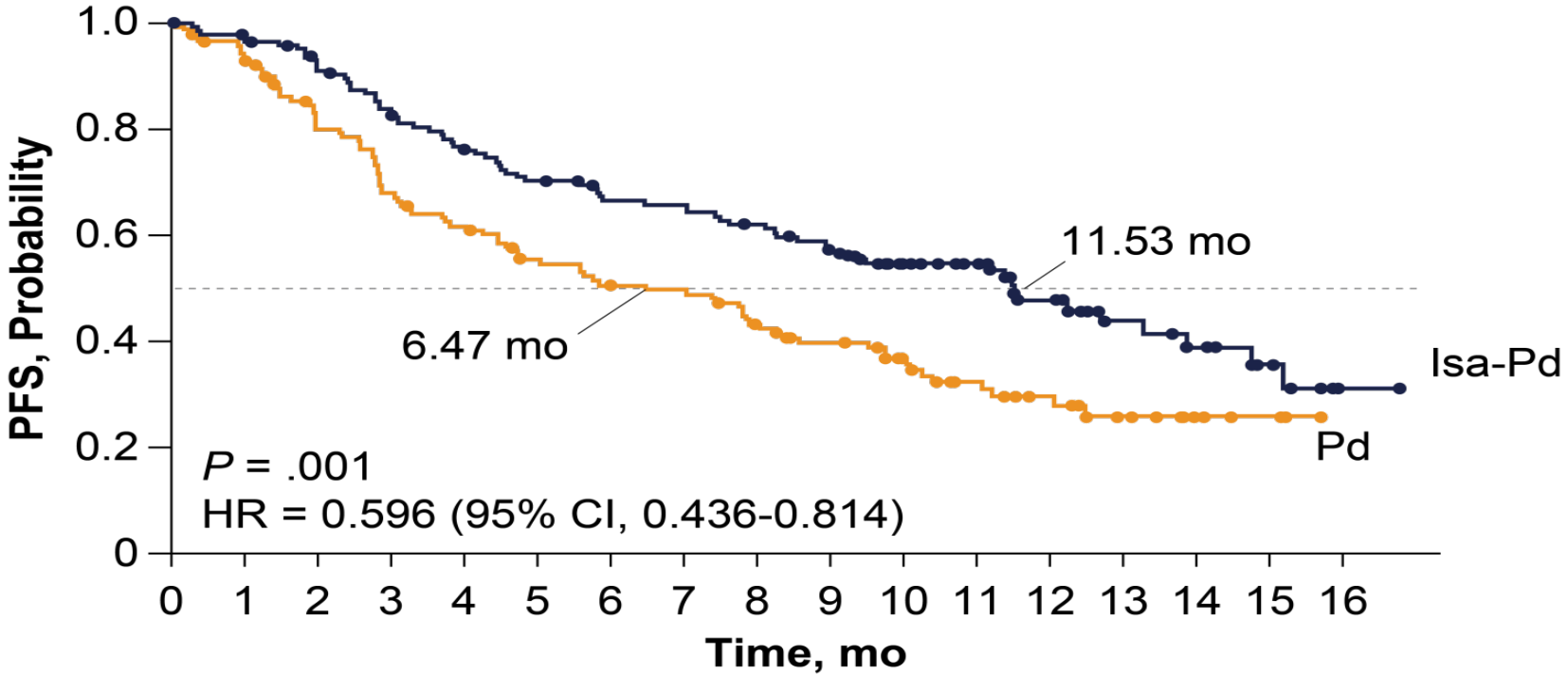
- Median time to first response: ISA-Pd = 35 days vs Pd = 58 days
- True CR rate in ISA-Pd underestimated because of ISA interference with M-protein measurement

	ISA-Pd (n = 154)	Pd (n = 153)
nCR, %	15.6	3.3

- MRD negativity at 10^{-5} (ITT): 5.2% for ISA-Pd vs 0% for Pd

Richardson PG, et al. ASCO 2019. Abstract 8004.

ICARIA-MM: PFS (by IRC)



No. at Risk

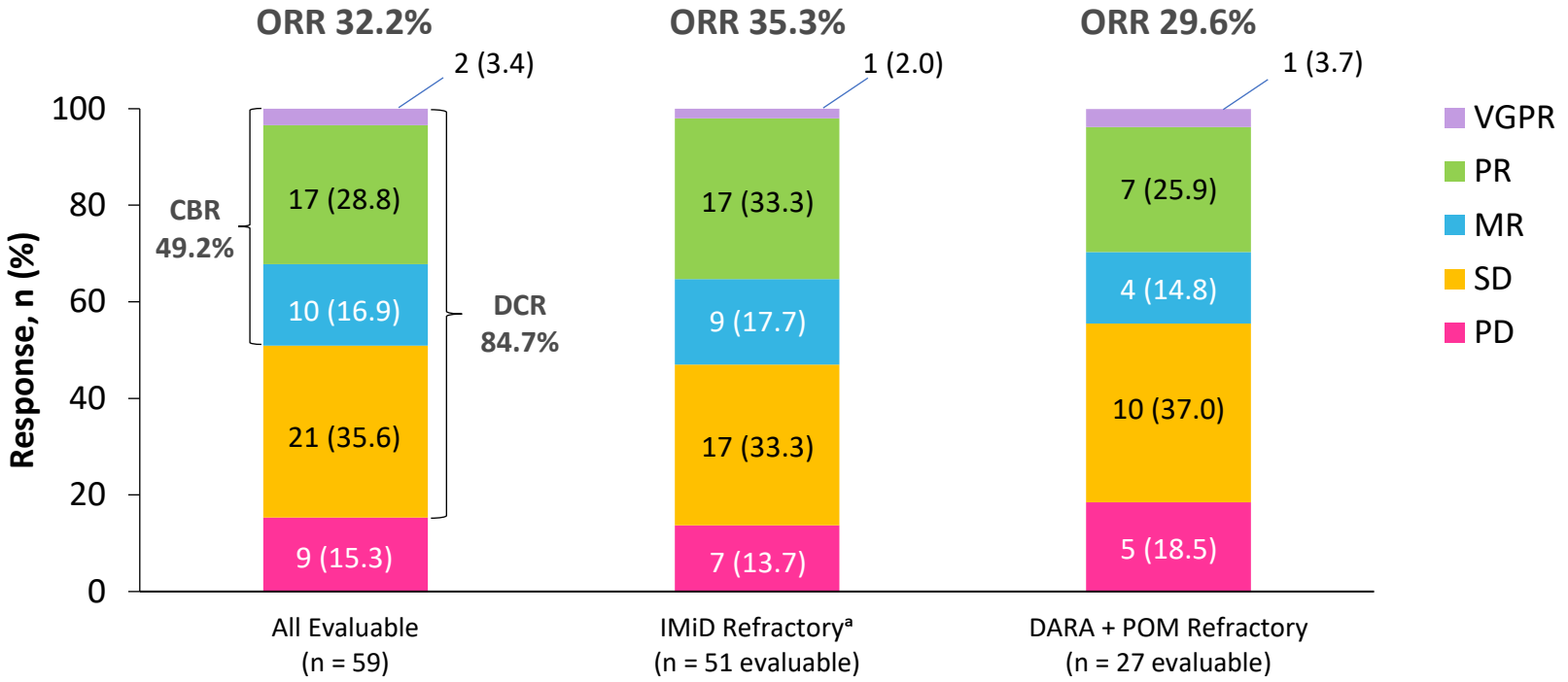
Isa-Pd	154	129	106	89	81	52	30	14	1
Pd	153	105	80	63	51	33	17	5	0

Richardson PG, et al. ASCO 2019. Abstract 8004.

What to Do After Lenalidomide and Pomalidomide?

NOVEL IMiDs

Iberdomide Responses in R/R MM



Evaluable patients include those who have received ≥1 dose of IBER, had measurable disease at baseline, and ≥1 postbaseline response assessment.

[a]Includes LEN and POM.

CBR, clinical benefit rate; DCR, disease control rate; MR, minimal response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.

Lonial S, et al. ASCO 2019. Abstract 8006.

CC-92480, the Next Son of Lenalidomide

Responses in patients with EMP

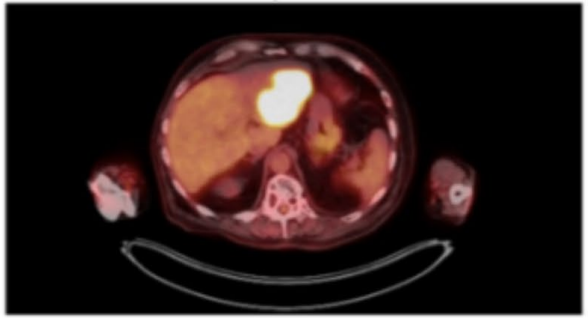
- Only patients on continuous schedules are shown

Dosing schedule[a]	Dose level	C2	C3	C4	C5	C6	C7	C8	C9	C10
10/14 days × 2	0.1 mg QD	SD	PD							
	0.2 mg QD	PD								
	0.3 mg QD	SD	PD							
		PD								
	0.6 mg QD	PD								
		SD	PD							
21/28 days	0.8 mg QD	SD								
		SD								
		SD	PD							
		PR								
		SD								
10/14 days × 2	1.0 mg QD	MR	PR	VGPR						
		SD								
		SD	PR							
21/28 days	1.0 mg QD	PR	PD							
		SD	PR	VGPR						
		PR	VGPR	CR						
		PR (case study)								
		SD								

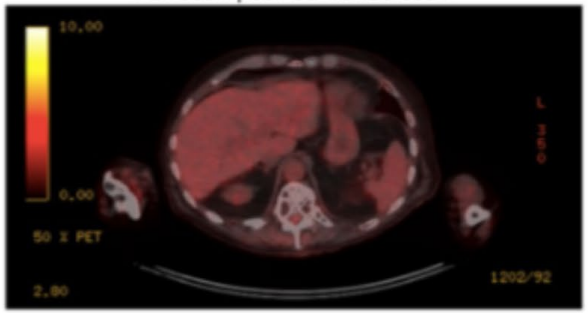
CR
VGPR[a]
PR[b]
MR
SD
PD[c]
On treatment at time of data cut

1.0 mg dose active in EMP

PET scan pretreatment



PET scan post-CC-92480 C3D1



[a]1 patient in the 21/28-day 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date;
[b]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date;
[c]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PD as of the data cutoff date.

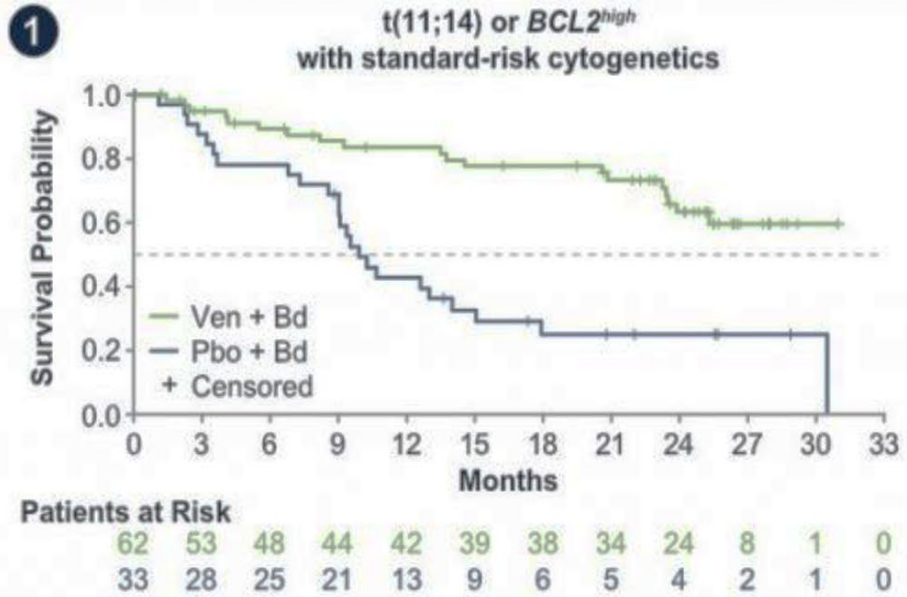
C, Cycle; CR, complete response; D, Day; EMP, extramedullary plasmacytoma; MR, minimal response; PD, progressive disease; PET, positron emission tomography; PR, partial response; QD, once daily; SD, stable disease; VGPR, very good partial response.

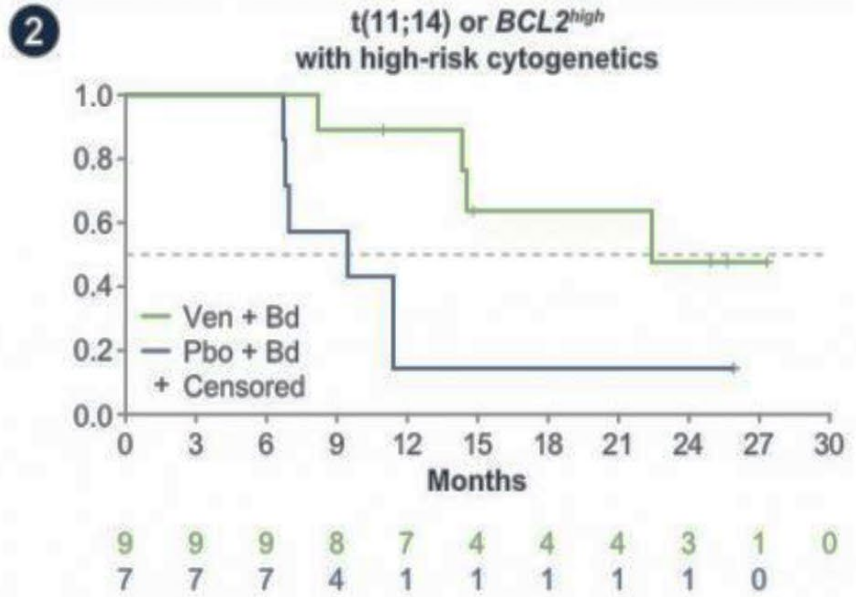
Richardson PG, et al. ASH 2020. Abstract 2295.

NEW SMALL MOLECULES

Venetoclax Is Highly Active in t(11;14) or High BCL2

Figure 4. Investigator-Assessed PFS by *BCL2* Gene Expression and Cytogenetic Risk Status





Harrison S, et al. ASH 2019. Abstract 142.

Selinexor

Oral selinexor 80 mg + dexamethasone 20 mg

Selinexor-dexamethasone twice weekly, days 1, 3, until disease progression

- Patient population
  - MM, prior treatment with PI, IMiD, CD38 mAb, alkylator, steroids
  - Refractory to ≥1 PI, ≥1 IMiD, daratumumab, steroid
- Primary endpoint
  - Overall response rate
- Secondary endpoints
  - Duration of response
  - Clinical benefit rate
  - Overall survival
  - PFS
- **Key eligibility criteria**
  - Creat clearance ≥20 mL/min
  - ANC ≥1,000/mm^3
  - Plt ≥75,000
  - Hemoglobin ≥8.5 g/dL

Chari A, et al. *N Engl J Med.* 2019;381(8):727-738.

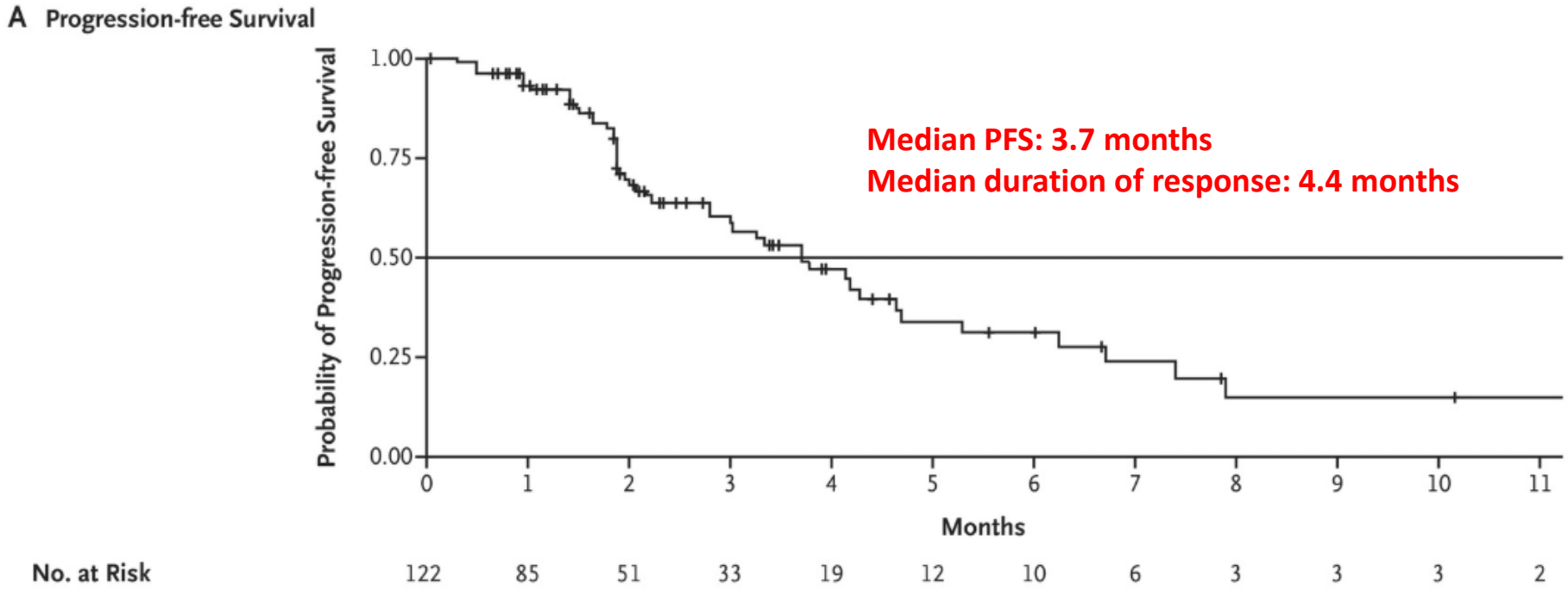
Phase II Selinexor Trial: Response Assessment

Variable	N	ORR (CR + VGPR + PR)	CBR (CR + VGPR + PR + MR)
Total	122	32 (26%)	48 (39%)
Penta-refractory	83	21 (25%)	31 (37%)
Quad-refractory	101	26 (26%)	37 (37%)
High-risk cytogenetic feature[a]	65	12 (18%)	24 (37%)

[a]This category included any of del(17p)/p53, t(14;16), t(4;14), or 1q21 (1q gain >2).

Chari A, et al. *N Engl J Med.* 2019;381(8):727-738.

STORM Trial: Kaplan-Meier Analysis for PFS



Median PFS: 3.7 months
Median duration of response: 4.4 months

Chari A, et al. *N Engl J Med.* 2019;381(8):727-738.

STORM: Selinexor Toxicity

Most commonly occurring grade ≥3 AEs

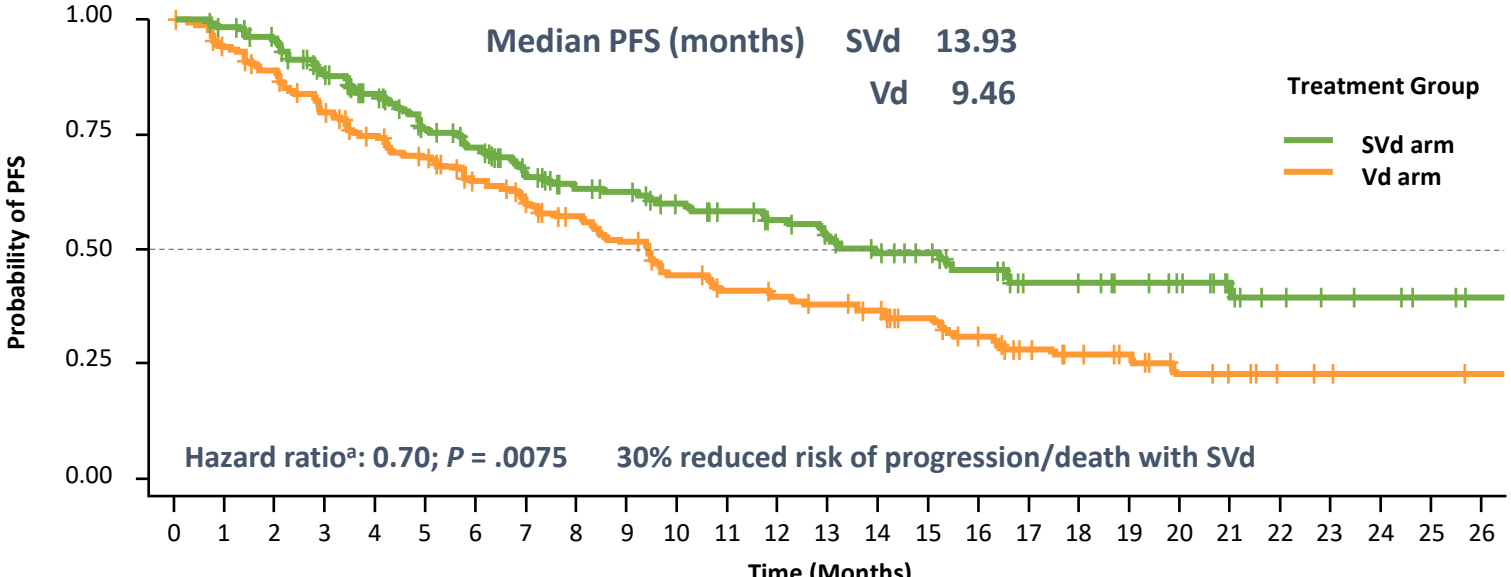
- Hematologic, GI related, constitutional symptoms, and hyponatremia
- Typically responsive to dose modification and standard supportive care agents

Early identification of AEs, frequent assessment, and use of supportive care measures deemed crucial to toxicity management, including

- **Fatigue:** methylphenidate
- **GI:** ondansetron, olanzapine, or substance P/neurokinin antagonists
- **Hyponatremia:** hydration (oral or IV), salt replacement
- **Thrombocytopenia:** romiplostim or eltrombopag if selinexor dose held

Chari A, et al. ASH 2018. Abstract 598.

BOSTON Trial: Selinexor-Vd Compared With Vd



Median follow-up: 13.2 and 16.5 months in SVd and Vd arms, respectively.

Intention-to-treat (ITT) population N = 402; data cutoff February 18, 2020.
[a]Hazard ratio 95% CI = 0.53–0.93 one-sided *P* value.
Dimopoulos MA, et al. ASCO 2020. Abstract 8501.

BOSTON Trial: Safety – Selected Nonhematologic TEAEs*

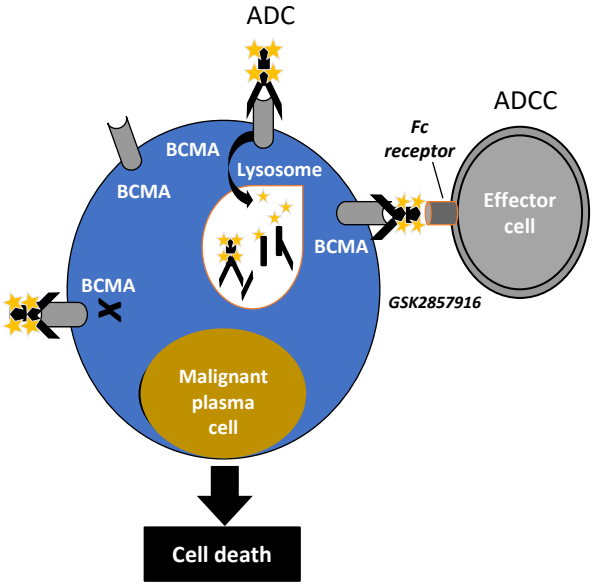
	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-hematological (%)				
Nausea	50.3	7.7	9.8	0
Fatigue	42.1	13.3	18.1	1.0
Decreased Appetite	35.4	3.6	5.4	0
Diarrhea	32.3	6.2	25.0	0.5
Peripheral Neuropathy†	32.3	4.6	47.1	8.8
Upper Respiratory Tract Infection‡	29.2	3.6	21.6	1.5
Weight decreased	26.2	2.1	12.3	1.0
Asthenia	24.6	8.2	13.2	4.4
Cataract§	21.5	8.7	6.4	1.5
Vomiting	20.5	4.1	4.4	0

*Shown are events that occurred in at least 15% of patients and had a >5% difference between treatment arms. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. For patients who crossed over, adverse events that occurred after the crossover are not included. †Includes high-level term Peripheral Neuropathies NEC. ‡Includes upper respiratory infection, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, and viral upper respiratory tract infection. § Per ophthalmology exam after 24% of patients on SVd arm vs 8.5% of patients on the Vd arm had new-onset cataracts, and worsening of cataracts on study was noted in 20.5% of patients on the SVd arm vs 7.9% on the Vd arm. Data cutoff February 18, 2020.

Dimopoulos MA, et al. ASCO 2020. Abstract 8501.

Belantamab Mafodotin: BCMA-Targeted ADC

- Belantamab mafodotin
  - Humanized, afucosylated IgG1 anti-BCMA antibody
  - Conjugated to microtubule-disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker
- Preclinical studies demonstrate its selective and potent activity



Mechanisms of action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death

Fc region of the antibody	• Target specific • Enhanced ADCC
Linker	• Stable in circulation
Drug	• MMAF (non-cell permeable, highly potent auristatin)

Tai YT, et al. *Blood*. 2014;123: abstract 3128.

Belantamab Mafodotin: DREAMM-2 – Response

ORR

- 30/97 patients (31%) in the 2.5-mg/kg cohort
- 34/99 patients (34%) in the 3.4-mg/kg cohort

Adverse events

- Most common grade 3/4 AE
  - Keratopathy (27% in the 2.5-mg/kg cohort; 21% in the 3.4-mg/kg cohort)
  - Thrombocytopenia (20% and 33%)
  - Anemia (20% and 25%)
- Serious AE in 40% in 2.5-mg/kg cohort and 47% in the 3.4-mg/kg cohort

Lonial S, et al. *Lancet Oncol*. 2019;21(2):207-221.

Algonquin Study (Bela + Pd): ORR* and PFS by Dosing

- ORR/VGPR across all cohorts: 89%/72%
  - LEN/PI refractory: 87%/87% (n = 15)
  - LEN/PI/anti-CD38 refractory: 92%/69% (n = 27)
- PFS: 17 months

Response by Cohort	1.92 Q4W N=12	2.5 Q4W N=20	2.5 Q8W N=12	2.5 Q12W N=12
ORR	9/11 (81.8%)	19/20 (95.0%)	10/12 (83.3%)	10/11 (90.9%)
sCR/CR	3/11 (27.3%)	8/20 (40.0%)	2/12 (16.7%)	1/11 (9.1%)
VGPR	4/11 (36.4%)	9/20 (45.0%)	7/12 (58.3%)	5/11 (45.5%)
PR	2/11 (18.2%)	2/20 (10.0%)	1/12 (8.3%)	4/11 (36.4%)
mPFS (95% CI), months	16.2 (8.7-NYR)	25.3 (24.9-NYR)	NYR (11.3-NYR)	NYR (7.6-NYR)
Follow-up, median, months	15.3 (1.8-24.4)	14.5 (2.4-30.9)	9.3 (2.6-12.0)	6.2 (0.5-11.0)

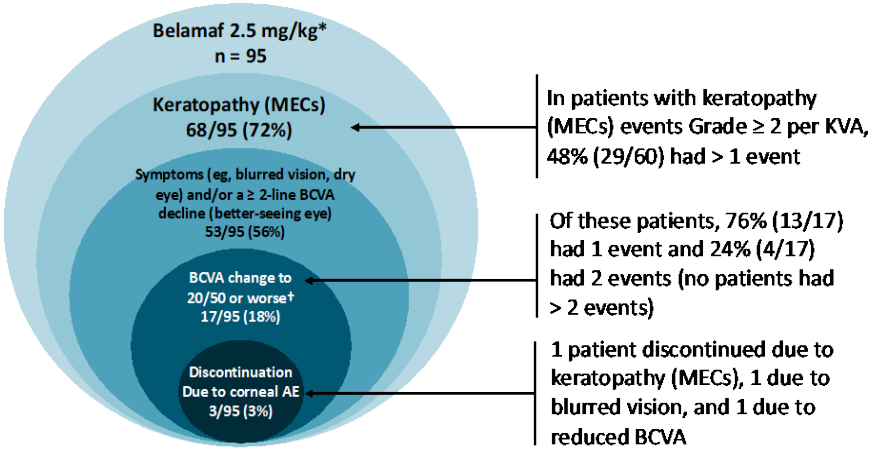
Trudel et al. ASH 2021. Abstract 1653.

Corneal Toxicities and Management

The corneal events reported in the DREAMM studies are common for immunoconjugates, which use MMAF or other microtubule-targeting cytotoxins.

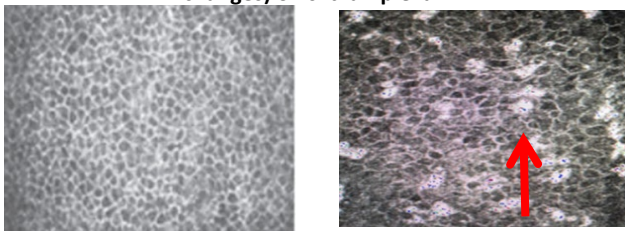
Most commonly reported symptoms are blurred vision and dry eyes

Increased drug exposure is associated with higher and earlier occurrence of keratopathy



One patient developed a grade 4 corneal ulcer.
84% pts with G3/4 AEs recovered or were recovering at last follow-up.

Keratopathy MECs (microcyst-like epithelial changes) on slit lamp exam



Normal corneal epithelial cells

Deposits in epithelium

<u>Mitigating ocular toxicity</u>

Eye exam at baseline and prior to each dose

Preservative-free artificial tears for the duration of treatment

Dose reductions and delays if corneal AEs emerge

Avoid use of contacts

Lonial S, et al. Blood Cancer J. 2021;11:103; Lonial S, et al. 7th World Congress on Controversies In Multiple Myeloma (COMy) 2021.

*Only data from the approved dose of 2.5 mg/kg are presented;
†Visual acuity change = 20/50 or worse in better seeing eye.

Summary

- No “one-size-fits-all”
- Daratumumab (or isatuximab) as a backbone logical
- Carfilzomib > bortezomib > ixazomib
- It’s not either-or – DARA and carfilzomib is a powerful combination
- 92480 > Iberdomide > pomalidomide > lenalidomide
- Selinexor active but GI toxicity problematic
- Belamaf active, but eye toxicity limiting
- Venetoclax if you can get it in t(11;14)

What approximate percentage of MM patients are estimated to survive long enough to receive third-line therapy?

a) 90%

b) 80%

c) 65%

d) 50%

e) 40%

Which of the following is a true statement about belantamab mafodotin?

a) Ocular toxicity can be reduced by starting with graduated dosing

b) A less common but significant toxicity is early onset cytokine release syndrome

c) The response rate is 30%–35% partial response or better

d) The response rate in first relapse is 72%

e) Ocular toxicity is manageable with steroid eye drops

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Discussion

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Relapsed/Refractory Multiple Myeloma Patient Case 2

Lucia Perez Baliero, MD

Hospital de Clínicas, Montevideo, Uruguay.

APTITUDE HEALTH®

Clinical Case

66-year-old male

- Past medical history: nephrectomy due to kidney tumor in 2005. Metastasectomy of solitary lung metastasis in 2019. Currently in complete remission

- 2011: MM IgG lambda, DS IIIB, ISS 2, R-ISS 2
- Initial presentation: anemia, renal failure, bone lytic lesions

Treatment History

Treatment	Best Response	Duration of Response	AEs
Diagnosis (2011): VTd + BMT	VGPR	33 months	None
First relapse (2014): VCd + BMT + V maintenance	PR	24 months	Mild cytopenia
Second relapse (2017): Rd + R maintenance	VGPR	12 months	Asthenia
Third relapse (2019): Dara-Pom-Dex	CR	24 months	Skin infection (*S. aureus*); CTCAE grade 3

BMT, autologous blood and marrow transplant; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Dara-Pom-Dex, daratumumab-pomalidomide-dexamethasone; PR, partial response; VCd, cyclophosphamide-bortezomib-dexamethasone; VTd, bortezomib-thalidomide-dexamethasone; Rd, lenalidomide-dexamethasone.

Fourth Relapse

Renal failure, λLC elevation, and U peak increase

Lab Tests May 2022		Patient Status
• Hb: 13.4 g/dL; no CPC • Creatinine: 12 mg/dL • Calcium: 9.2 mg/dL • λLC: 6832 mg/L • Albumin: 3.4 g/dL • LDH 220 IU/L • M-spike: 3.2 g/dL • BM: 20% plasma cells • CG/FISH: no HR features	Fourth relapse PI exposed, IMiD and anti-CD38 refractory	ECOG = 0

λLC, lambda free light chain; Hb; hemoglobin; HR, high-risk; IMiD, immunomodulatory drugs; LDH, lactate dehydrogenase; PS, performance status; PI, proteasome inhibitors, U peak, serum monoclonal protein.

Question 1

What would be the best therapeutic option for this patient?
(Assume all treatments are available in your region.)

a) PI-based regimen
b) CAR T cells in clinical trial
c) Bispecifics in clinical trial
d) Anti-BCMA conjugated antibody
e) Selinexor-based regimen

Question 2

What would be the best therapeutic option for this patient?
(On the basis of availability in Uruguay.)

a) Bortezomib-dexamethasone
b) Carfilzomib-dexamethasone
c) Bortezomib-chemotherapy
d) Chemotherapy alone

Fourth Relapse

Renal failure, λLC elevation, and U peak increase

Lab Tests May 2022		Patient Status
• Hb: 13.4 g/dL; no CPC • Creatinine: 12 mg/dL • Calcium: 9.2 mg/dL • λLC: 6832 mg/L • Albumin: 3.4 g/dL • LDH 220 IU/L • M-spike: 3.2 g/dL • BM: 20% plasma cells • CG/FISH: no HR features	Fourth relapse PI exposed, IMiD and anti-CD38 refractory	ECOG = 0

λLC, lambda free light chain; Hb; hemoglobin; HR, high-risk; IMiD, immunomodulatory drugs; LDH, lactate dehydrogenase; PS, performance status; PI, proteasome inhibitors, U peak, serum monoclonal protein.

Panel Discussion Questions

Considering options in our country, a PI-based regimen would be our choice.

A. Would you prefer bortezomib or carfilzomib?

B. Which carfilzomib-based regimen would you recommend?

C. What anti-infectious prophylaxis is recommended?

THANK YOU!!!

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Discussion

All faculty and case presenters

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Beyond the Horizon: New and Future Multiple Myeloma Treatment Approaches – Bispecifics in MM

Vania Hungria, MD, PhD

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New and Future Multiple Myeloma Treatment Approaches:

Bispecifics

Vania Tietsche de Moraes Hungria, MD, PhD

Associate Professor of Hematology at Santa Casa Medical School
Clinical Director at Clínica São Germano
São Paulo, Brazil

GBRAM
GRUPO BRASILEIRO DE MIELOMA

São Germano
Oncologia

Global Multiple Myeloma Academy

Disclosures

Honoraria: Amgen, BMS, Celgene, GSK, Janssen, Pfizer, Sanofi, Takeda

Introduction

- ✓ Multiple myeloma treatment has achieved remarkable progress in the past decade
- ✓ Several classes of drugs and combinations have been incorporated into the therapeutic strategies
- ✓ New immunotherapies and targeted agents are emerging to improve the treatment
- ✓ Median patient survival has been extended 3- to 4-fold, from 3 to at least 8–10 years. There is an ever-increasing number of patients living over 10 years
- ✓ But multiple myeloma it is still an incurable disease that relapses

Question for the Audience

What is the overall survival for a triple-class-refractory MM patient?

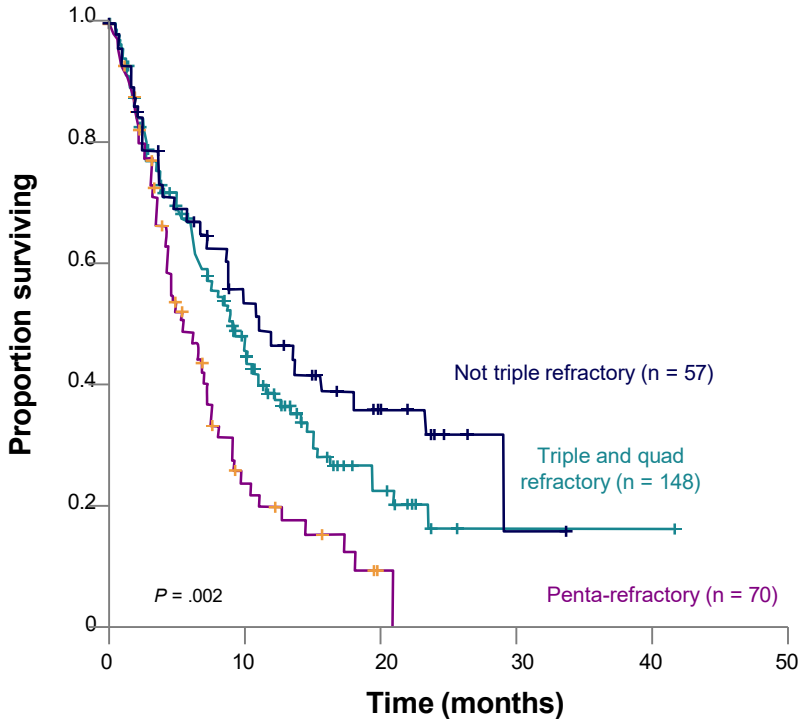
a) 9–12 months
b) 15–18 months
c) 21–24 months
d) I don’t know

Outcomes in Triple-Class-Refractory Patients

MAMMOTH study

- 275 MM patients refractory to anti-CD38 mAbs
  - mOS from refractoriness to CD38
    - All patients: 8.6 months
    - “Non-triple refractory”: 11.2 months
    - “Triple and quad refractory”: 9.2 months
    - “Penta-refractory”: 5.6 months
- 249 patients received further treatment
  - mPFS: 3.4 months
  - mOS: 9.3 months

OS according to refractoriness



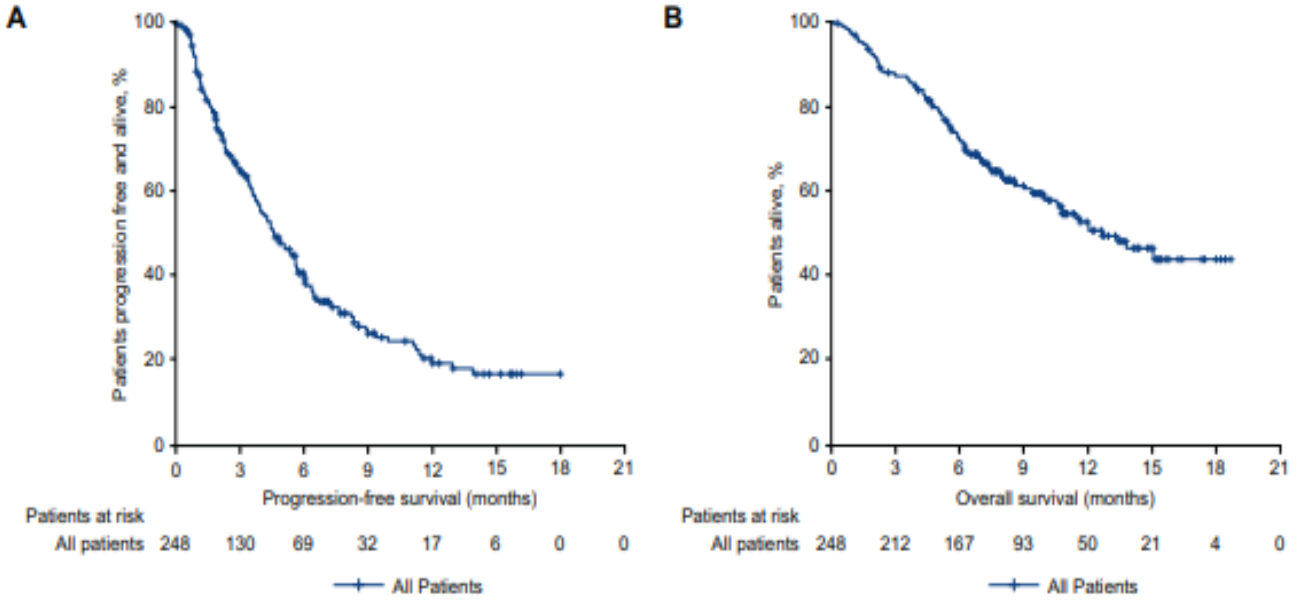
Non-triple refractory: refractory to 1 CD38 mAb, and not both PI and IMiD compound.
Triple and quad refractory: refractory to 1 CD38 mAb + 1 IMiD compound + 1 PI; or 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds; or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD compound.
Penta-refractory: refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds.

mOS, median overall survival; mPFS, median progression-free survival.

Gandhi UH, et al. *Leukemia*..2019;33:2266-2275.

Outcomes in Triple-Class-Refractory Patients

LocoMMotion: a prospective, non-interventional study conducted in the USA and 9 European countries to evaluate the efficacy of rescue therapies in patients with RRMM exposed to PIs, IMiDs, and anti-CD38 mAbs

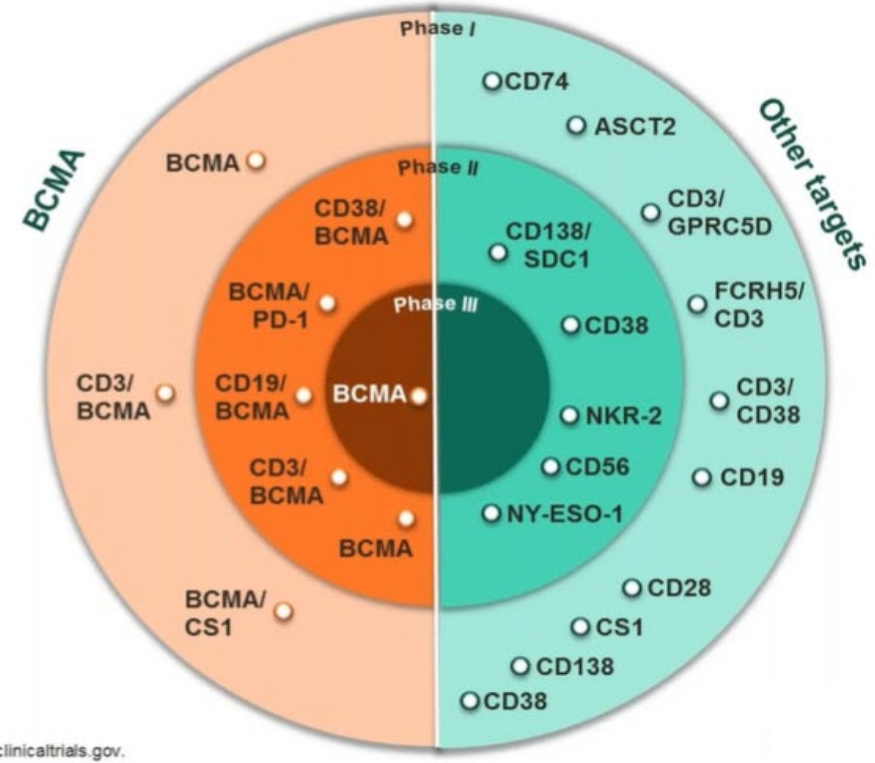


Triple class refractory median PFS 3.9 months; median OS 11.1 months

Triple class exposed median PFS 8.2 months; median OS NE

Mateos MV, et al. *Leukemia*. 2022.

Numerous myeloma immunotherapy modalities are currently under investigation



For more information on antigen targets currently in clinical trials, please go to www.clinicaltrials.gov.

This information is intended for healthcare providers only.

Compounds are investigational. Inclusion in this presentation does not imply regulatory approval for these compounds or indications.

Immunotherapies in multiple myeloma

There are currently **three main immunotherapeutic strategies** in multiple myeloma[1,2]:

- IMiDs and immune checkpoint inhibitors: **reverse tumour-mediated immune paralysis.**
- Monoclonal antibodies: **selectively target malignant clones**.
- CAR-Ts and T cell engagers: **activate immune cells to target the tumour.**

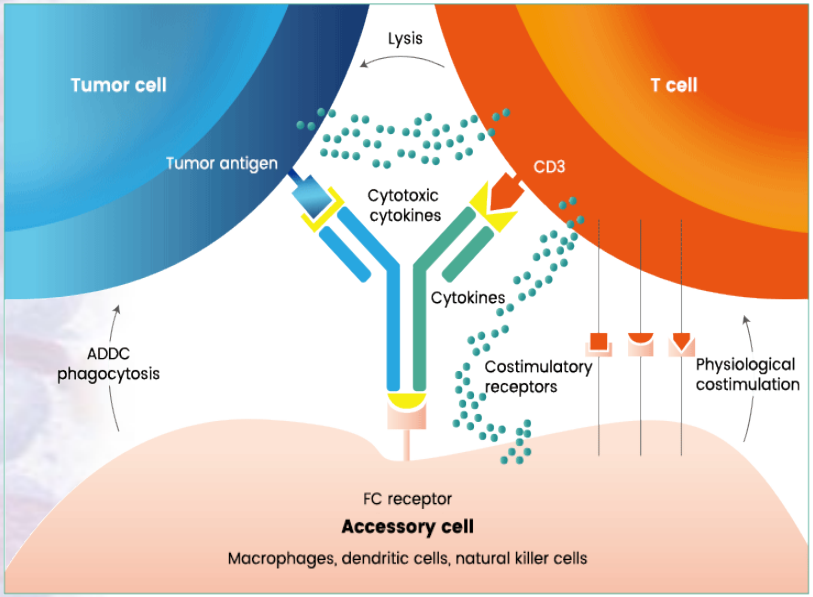
BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; IMiD, immunomodulatory drug; mAb, monoclonal antibody.

1. Neri P, et al. *Clin Cancer Res.* 2016; 22:5959-65; 2. Shah N, et al. *Leukemia.* 2020; 34:985-1005.

Bispecific T-Cell Engagers

What are bi/trispecific mAbs?

There are more than 100 different bispecific antibody formats produced due to the modular architecture of antibodies.



Bispecific antibodies (bsAbs) are antibodies containing 2 antigen-binding sites for different epitopes

- One binding specificity will be directed against a specific cell-surface antigen of the target cell
- The other will be directed against a “triggering” molecule on the surface of the effector cell, eg, one of the FcyR or the CD3/T-cell receptor complex

The bispecific antibody can override the specificity of an effector cell for its natural target and redirect it to kill a target that it would otherwise ignore that is relevant in MM.

1. Ross SL, et al. PLoS One. 2017;12(8):e0183390; 2. Labrijn AF, et al. Nat Rev Drug Discov. 2019;18(8):585-608.

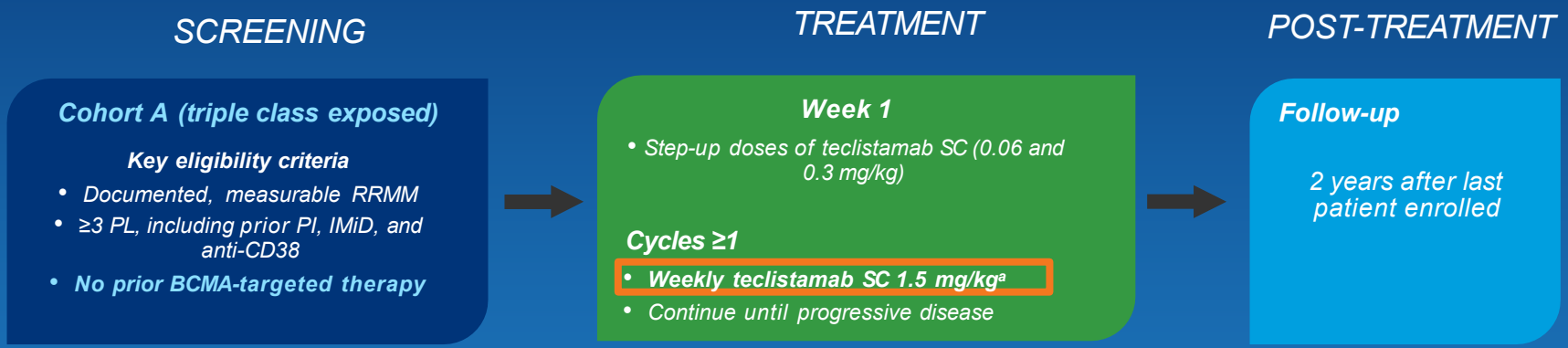
Question for the Audience

In general, what is the adverse event that is more frequent with bispecifics?

a) Nausea
b) Alopecia
c) Fatigue
d) Cytokine release syndrome

Teclistamab: A BCMA×CD3 Bispecific Antibody MajesTEC-1: Study Design

First-in-human, phase I/II, open-label, multicohort, multicenter, dose-escalation study evaluating teclistamab in patients with RRMM who previously received ≥3 lines of therapy (triple-class exposed)



Primary endpoint: *ORR*

Key secondary endpoints: *DOR, ≥VGPR, ≥CR, sCR, TTR, MRD status, PFS, OS, safety, PK, immunogenicity, PROs*

[a]*Schedule change to biweekly (every other week) dosing was permitted based on response.*

BCMA, B-cell maturation antigen; CR, complete response; DOR, duration of response; IMiD, immunomodulatory drug; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PL, prior line; PRO, patient-reported outcome; RRMM, relapsed/refractory multiple myeloma; sCR, stringent CR; SC, subcutaneous; TTR, time to response; VGPR, very good partial response.

Nooka AK, et al. ASCO 2022. Abstract 8007.

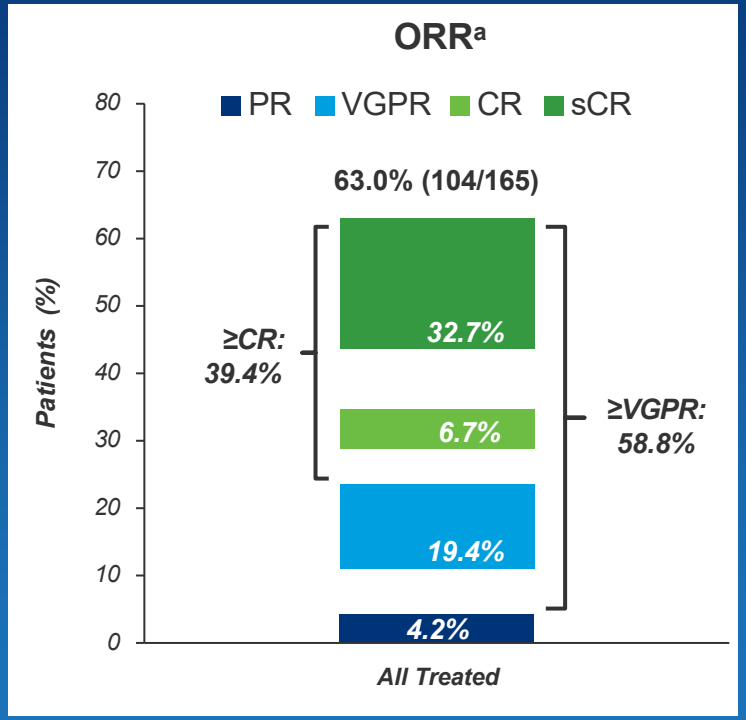
MajesTEC-1: Patient Demographics and Baseline Characteristics

Characteristic	N = 165
Age, years, median (range)	64.0 (33–84)
Age ≥75 years, n (%)	24 (14.5)
Male, n (%)	96 (58.2)
Race, n (%)	
White	134 (81.2)
Black/African American	21 (12.7)
Other[a]	10 (6.1)
Bone marrow plasma cells ≥60%[b], n (%)	18 (11.3)
Extramedullary plasmacytomas ≥1[c], n (%)	28 (17.0)
High-risk cytogenetics[d], n (%)	38 (25.7)
ISS stage[e], n (%)	
I	85 (52.5)
II	57 (35.2)
III	20 (12.3)

Characteristic	N = 165
Baseline renal function, n (%)	
<60 mL/min/1.73m^2	44 (26.7)
≥60 mL/min/1.73m^2	121 (73.3)
Time since diagnosis (years), median (range)	6.0 (0.8–22.7)
Prior lines of therapy, median (range)	5.0 (2–14)
≥4 prior lines, n (%)	122 (73.9)
Autologous transplantation, n (%)	135 (81.8)
Allogeneic transplantation, n (%)	8 (4.8)
Exposure status, n (%)	
Triple class[f]	165 (100)
Penta-drug exposed	116 (70.3)
Refractory status, n (%)	
Triple class[f]	128 (77.6)
Penta-drug[g]	50 (30.3)
To last line of therapy	148 (89.7)

Analysis cutoff date: March 16, 2022. [a]Reported as Asian, other, multiple, or not reported. [b]Percentages calculated from n = 160, includes bone marrow biopsy and aspirate. [c]Soft-tissue plasmacytomas not associated with the bone were included. [d]Del(17p), t(4:14), and/or t(14;16) (n=148). [e]At baseline, percentages calculated from n = 162. [f]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [g]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. IMiD, immunomodulatory drug; ISS, international Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor.

MajesTEC-1: Overall Response to Teclistamab

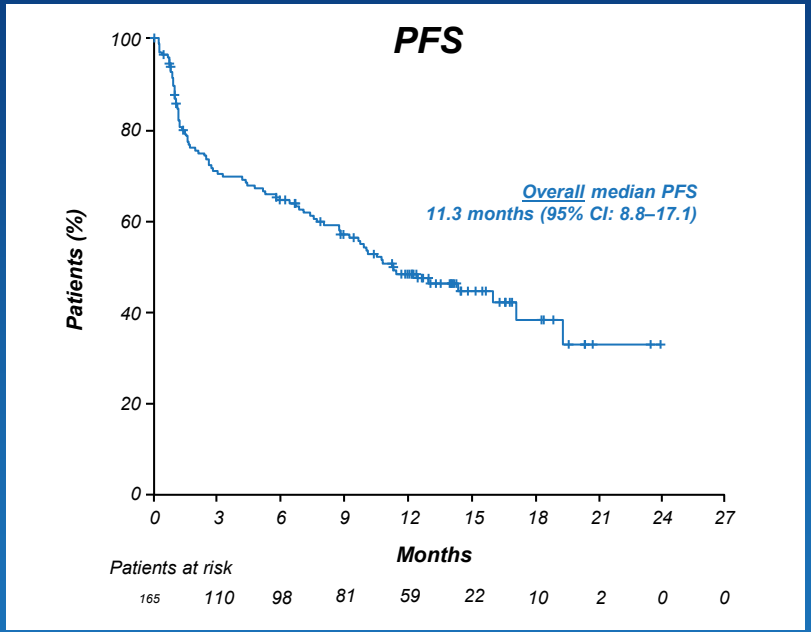


ORR of 63.0% (95% CI: 55.2–70.4) represents a substantial benefit for patients with triple-class-exposed disease

- Median time to response (n = 104)
  - First response: 1.2 months (range: 0.2–5.5)
  - Best response: 3.8 months (range: 1.1–16.8)
- MRD negativity rate at 10^{-5}[b]
  - 26.7% in the all-treated (N = 165) patient population
    - 81.5% of MRD-evaluable patients (44 of 54) were MRD negative
  - Almost half (46.2%) of patients with ≥CR were MRD negative

Analysis cutoff date: March 16, 2022. [a]PR or better, IRC assessed, per IMWG 2016 criteria. [b]All MRD assessments were done by next-generation sequencing.
CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

MajesTEC-1: Progression-Free Survival



With a median follow-up of 14.1 months, median PFS was 11.3 months (95% CI: 8.8–17.1)

- Median OS was 18.3 months (95% CI: 15.1–NE) and was not yet mature, with data from 97 patients (58.8%) censored

Analysis cutoff date: March 16, 2022.
NE, not estimable; OS, overall survival; PFS, progression-free survival.

MajesTEC-1: Overall Safety Profile

AEs ≥20%, n (%)	Any grade	Grade 3/4
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Nonhematologic		
CRS	119 (72.1)	1 (0.6)
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Pyrexia	45 (27.3)	1 (0.6)
Injection site erythema	43 (26.1)	0 (0)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0 (0)
Cough	33 (20.0)	0 (0)

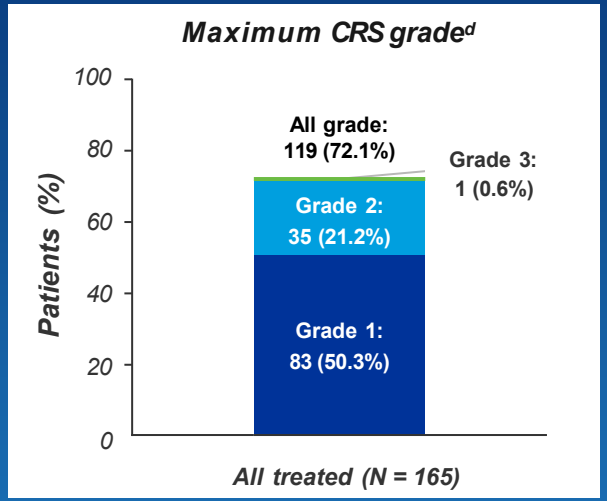
Teclistamab was well tolerated; discontinuations and dose reductions were infrequent

- 2 patients (1.2%) discontinued due to AEs (grade 3 adenoviral pneumonia; grade 4 PML)
- 1 patient had dose reduction at cycle 21
- The most common AEs were CRS and cytopenias
- Infections occurred in 126 (76.4%) patients (grade 3/4: 44.8%)
- 123 patients (74.5%) had evidence of hypogammaglobulinemia[a]
- There were 19 deaths due to AEs, including 12 COVID-19 deaths
  - 5 deaths due to teclistamab-related AEs
    - COVID-19 (n = 2)
    - Pneumonia (n = 1)
    - Hepatic failure (n = 1)
    - PML (n = 1)

Analysis cutoff date: March 16, 2022. [a]Assessed by AE or lab values (postbaseline IgG level below 500 mg/dL).
AE, adverse event; CRS, cytokine release syndrome; IgG, immunoglobulin G; PML, progressive multifocal leukoencephalopathy.

MajesTEC-1: Cytokine Release Syndrome

Parameter	N = 165
Patients with CRS, n (%)	119 (72.1)
Patients with ≥2 CRS events	55 (33.3)
Time to onset[a], days, median (range)	2 (1–6)
Duration, days, median (range)	2 (1–9)
Received supportive measures[a] for CRS, n (%)	110 (66.7)
Tocilizumab[b]	60 (36.4)
Low-flow oxygen by nasal cannula[c]	21 (12.7)
Corticosteroids	14 (8.5)
Single vasopressor	1 (0.6)



- *Most CRS events were confined to step-up and first full treatment doses*
- *All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that occurred in the context of concurrent pneumonia (resolved in 2 days)*
- *All CRS events fully resolved without treatment discontinuation or dose reduction*

Analysis cutoff date: March 16, 2022.
[a]A patient could receive >1 supportive therapy. [b]Tocilizumab was administered at physician discretion. [c]≤6 L/min. [d]CRS was graded using Lee et al Blood 2014 in the phase I portion of the study and ASTCT in phase II; in this combined analysis, Lee et al Blood 2014 criteria were mapped to ASTCT criteria for patients in the phase I portion.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome.

MajesTEC-1: Neurotoxic Events

Parameter	N = 165
Neurotoxic event[a], n (%)	24 (14.5)
Headache	14 (8.5)
ICANS[b]	5 (3.0)
Dysgeusia	2 (1.2)
Lethargy	2 (1.2)
Tremor	2 (1.2)
Grade ≥3 events, n (%)	1 (0.6)
Time to onset, median (range) days	3.0 (1–13)
Duration, median (range) days	7.0 (1–291)
Received supportive measures for neurotoxic events[c], n (%)	14 (8.5)
Tocilizumab	3 (1.8)
Dexamethasone	3 (1.8)
Levetiracetam	2 (1.2)
Gabapentin	1 (0.6)

- The overall incidence of neurotoxic events was low
- All neurotoxic events were grade 1/2, except for
  - One grade 4 seizure (in the context of bacterial meningitis during cycle 7)
- 5 patients (3.0%) had a total of 9 ICANS events
  - 7 events were concurrent with CRS
  - All ICANS events were grade 1/2 and fully resolved
- There were no treatment discontinuations or dose reductions due to neurotoxic events, including ICANS

Analysis cutoff date: March 16, 2022. [a]Neurotoxic events defined as AEs under the nervous system disorder" or "psychiatric disorder" SOC that were judged by the investigator to be related to study drug, including ICANS events. [b]ICANS was graded per ASTCT guidelines in phase II; in phase I, one patient had an event of confusional state considered by the sponsor to be consistent with ICANS and is presented as such in summaries of ICANS events. [c]Patients could receive >1 supportive measure; tocilizumab, dexamethasone, and levetiracetam were used to treat ICANS.

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; SOC, system organ class.

MajesTEC-1: Conclusions

After a median follow-up of 14.1 months, teclistamab yields deep and durable responses in patients with highly refractory MM

- Response rate remained high (63.0%) with CR or better achieved in 39.4% of patients
- Median DOR of 18.4 months and in those achieving a CR or better event-free rate was 80.1% at 12 months
- Median PFS of 11.3 months

Teclistamab toxicities were manageable

- CRS was predominantly grade 1/2 and incidence of neurotoxic events was low
- Cytopenias and infections were common but consistent with heavily pretreated RRMM

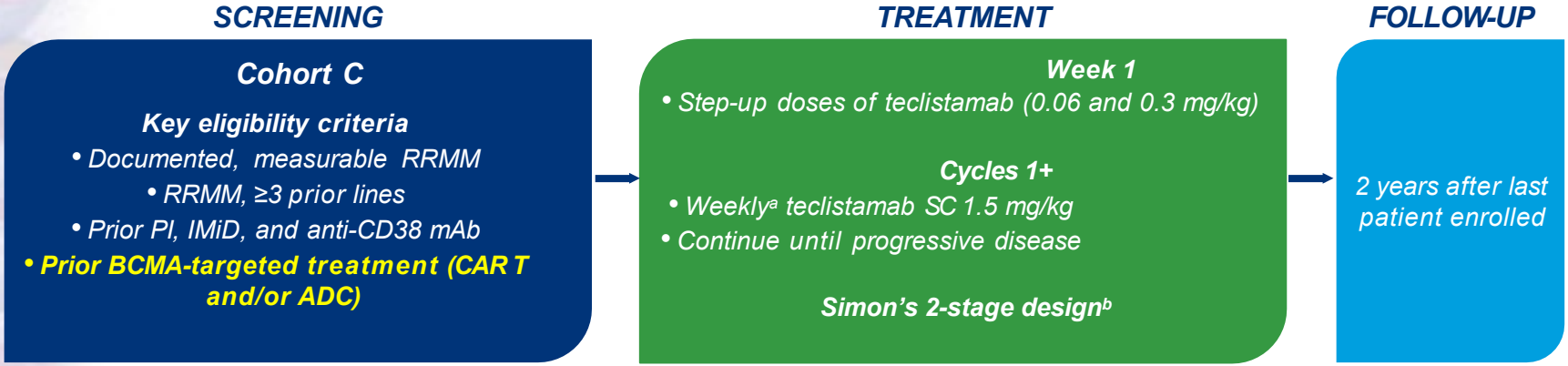
These data support teclistamab as a promising new, off-the-shelf, T-cell–redirecting therapy targeting BCMA for patients with RRMM

BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; MM, multiple myeloma; PFS, progression-free survival; RRMM, relapsed/refractory MM.

MajesTEC-1 Cohort C: Study Design

First-in-human, phase I/II (NCT03145181; NCT04557098), open-label, multicohort, multicenter study in patients with RRMM who were triple class exposed

Cohort C enrolled patients with prior exposure to BCMA-targeted treatment



Primary endpoint: *ORR*

Key secondary endpoints: *DOR, ≥VGPR, ≥CR, sCR, TTR, MRD[c] status, PFS, OS, safety, PK, immunogenicity, PROs*

[a]Patients could transition to Q2W dosing after maintaining CR/sCR for ≥6 months. [b]In cohort C, Simon's 2-stage design was used to test the null hypothesis that the ORR was ≤15% vs ≥35%. [c]Baseline clones were obtained for all patients. All MRD assessments were done by NGS. ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T cell; CR, complete response; DOR, duration of response; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; Q2W, every other week; RRMM, relapsed/refractory multiple myeloma; sCR, stringent CR; SC, subcutaneous; TTR, time to response; VGPR, very good partial response.

Touzeau C, et al. EHA 2022. Abstract S184.

MajesTEC-1 Cohort C: Patients

Characteristic	N = 40
Age (years), median (range)	63.5 (32–82)
Male, n (%)	25 (62.5)
Race, n (%) White African American/Black Asian Not reported	 35 (87.5) 3 (7.5) 1 (2.5) 1 (2.5)
Bone marrow plasma cells ≥60%[a], n (%)	4 (10.0)
Extramedullary plasmacytomas ≥1[b], n (%)	12 (30.0)
High-risk cytogenetics[c], n (%)	12 (33.3)
ISS stage, n (%) I II III	 21 (52.5) 9 (22.5) 10 (25.0)
Time since diagnosis (years), median (range)	6.5 (1.1–24.1)

Characteristic	N = 40
Prior lines of therapy, median (range)	6 (3–14)
Prior stem cell transplantation, n (%)	36 (90.0)
Exposure status, n (%)	
Triple class[d]	40 (100)
Penta-drug[e]	32 (80.0)
BCMA-targeted treatment	40 (100)[f]
ADC	29 (72.5)
CAR T	15 (37.5)
Refractory status, n (%)	
Triple class[d]	34 (85.0)
Penta-drug[e]	14 (35.0)
To last line of therapy	34 (85.0)

- ***Median follow-up*** *was 12.5 months (range: 0.7–14.4); 17 of 40 patients (42.5%) remain on treatment*
- *Median duration of treatment was 5.2 months (range: 0.2–13.6)*
- *Baseline BCMA expression and soluble BCMA levels were comparable in patients with and without prior BCMA-targeted treatment*

Data analysis cutoff date: March 16, 2022.

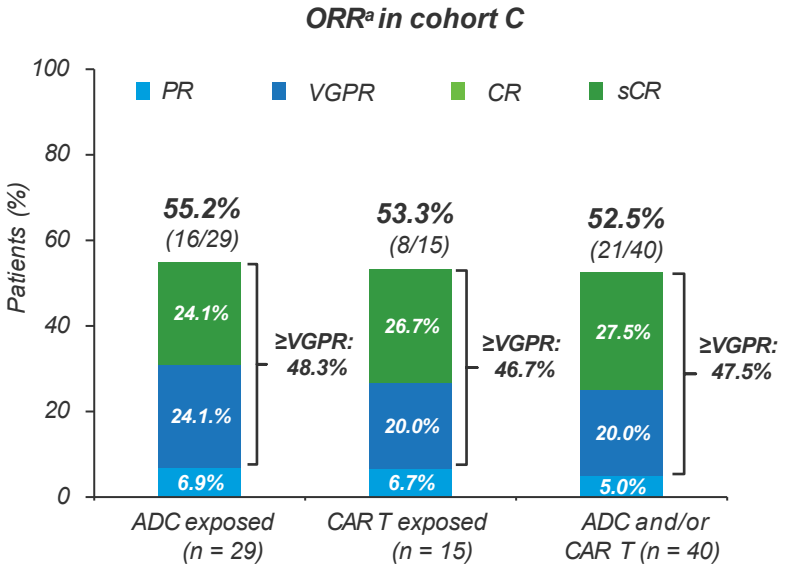
[a]Includes bone marrow biopsy and aspirate. [b]Soft-tissue plasmacytomas not associated with bone were included. [c]Del(17p), t(4:14), and/or t(14;16) (n = 36). [d]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 antibody. [e]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. [f]4 patients had received both ADC and CAR-T.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor.

Touzeau C, et al. EHA 2022. Abstract S184.

MajesTEC-1 Cohort C: Overall Response Rate

- The ORR was **52.5%** (21/40; 95% CI: 36.1–68.5) in patients with prior exposure to either class of BCMA-targeted treatment
  - ADC-exposed patients: **55.2%**
  - CAR T-exposed patients: **53.3%**
  - Both ADC and CAR T: 3 of 4 patients responded
- MRD negativity (10^{-5}) rate was 17.5%
  - Among ≥CR patients: **63.6%** (7/11)



Data analysis cutoff date: March 16, 2022.

[a]PR or better, IRC assessed, per IMWG 2016 criteria.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T cell; CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Touzeau C, et al. EHA 2022. Abstract S184.

MajesTEC-1 Cohort C: Conclusions

Serial targeting of BCMA with teclistamab following treatment with an ADC or CAR T resulted in a promising response rate and was well tolerated in patients with heavily pretreated RRMM

- Responses to teclistamab occurred early and deepened over time, with comparable response rates in patients previously treated with an ADC and/or CAR T
- Teclistamab was well tolerated in patients with prior exposure to BCMA-targeted agents, with a safety profile similar to that observed in BCMA treatment-naive patients
- These data support teclistamab as a promising new, off-the-shelf, T-cell–redirecting therapy for patients with RRMM and prior exposure to BCMA-targeted agents

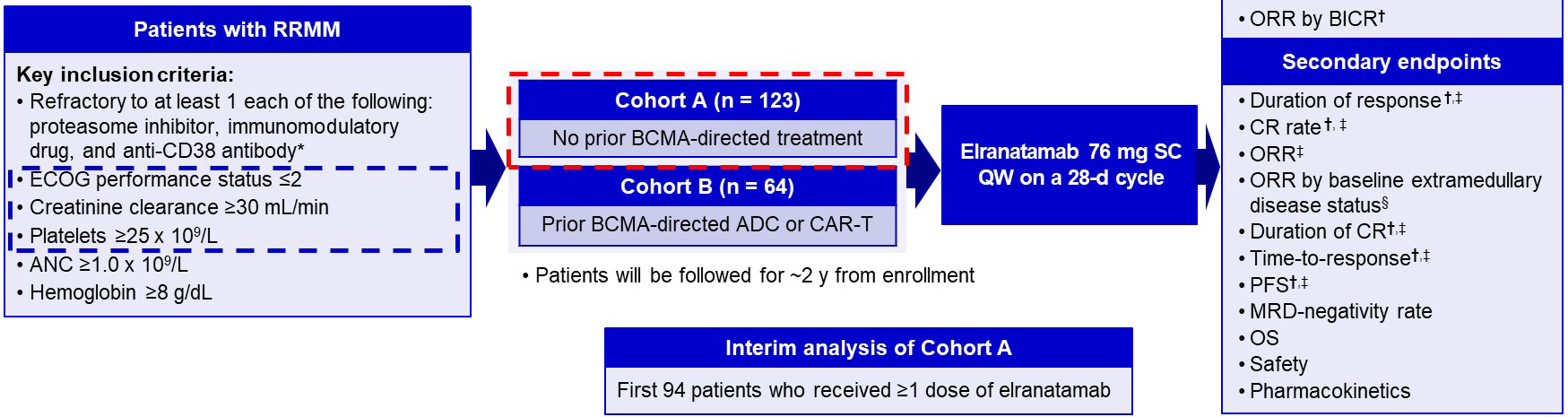
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T cell; RRMM, relapsed/refractory multiple myeloma.

Touzeau C, et al. EHA 2022. Abstract S184.

Elranatamab: a BCMA x CD3 Bispecific Antibody

MagnetisMM-3 Study

- MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study
  - Interim analysis data-cut off: March 23, 2022



*Refractory was defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response. †By BICR assessment per IMWG response criteria (Kumar S, et al. Lancet Oncol 2016;17(8):e328-e346). ‡By investigator assessment per IMWG response criteria. §Includes patients in Cohort A initially dosed at least 4 months prior to the March 23, 2022, data cutoff date.
ADC=antibody drug conjugate; ANC=absolute neutrophil count; BICR=blinded independent central review; CAR-T=chimeric antigen receptor T-cell; CR=complete remission; ECOG=Eastern Cooperative Oncology Group; IMWG=International Myeloma Working Group; MRD=minimal residual disease; OS=overall survival; PFS=progression-free survival; QW=once weekly; SC=subcutaneous

Prior Treatments

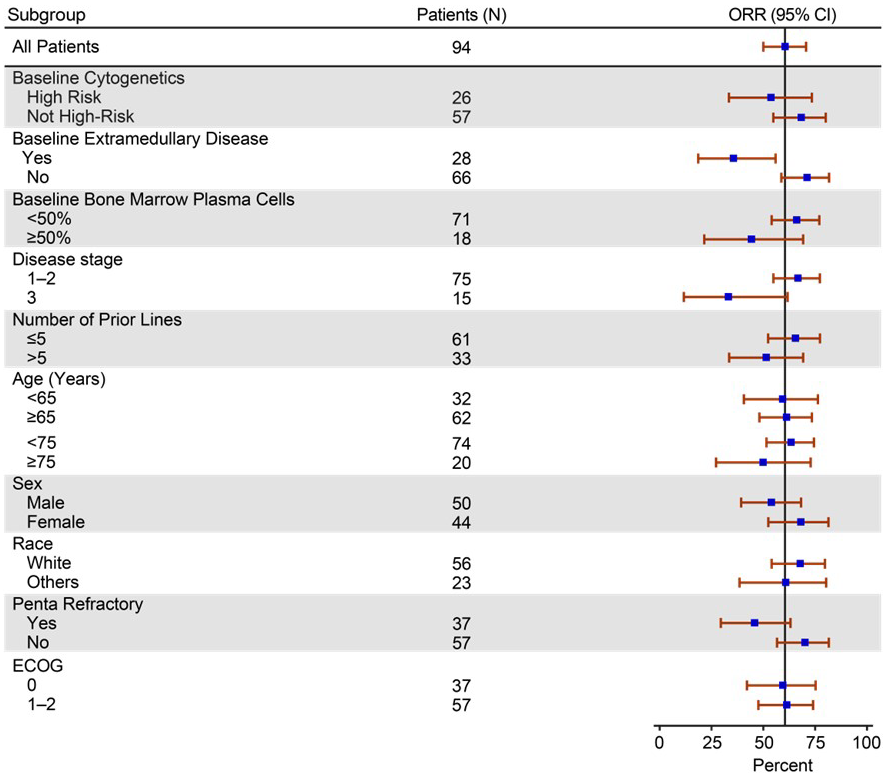
	Cohort A n = 94
Prior anti-myeloma therapies, median (range)	5.0 (2–12)
Prior stem cell transplant, n (%)	70 (74.5)
Prior immunomodulatory drugs, n (%)	94 (100)
Lenalidomide	92 (97.9)
Pomalidomide	75 (79.8)
Thalidomide	24 (25.5)
Other	1 (1.1)
Prior proteasome inhibitor, n (%)	94 (100)
Bortezomib	93 (98.9)
Carfilzomib	70 (74.5)
Ixazomib	23 (24.5)
Other	1 (1.1)
Prior anti-CD38 antibody, n (%)	94 (100)
Daratumumab	85 (90.4)
Isatuximab	15 (16.0)

	Cohort A n = 94
Exposure status, n (%)	
Triple-class*	94 (100)
Penta-drug†	64 (68.1)
Refractory status, n (%)	
Triple-class*	90 (95.7)
Penta-drug†	37 (39.4)
Refractory to last line of therapy	89 (94.7)

*Triple-class refers to at least 1 proteosome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody. †Penta-drug refers to at least 2 proteosome inhibitors, 2 immunomodulatory drugs, and 1 anti-CD38 antibody. Refractory was defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response.

Overall Response

- After a median follow-up of 3.71 (range, 0.03−12.91) months, the ORR was 60.6% (95% CI, 50.0−70.6)
- As of the data cut-off, 89.5% of objective responders were ongoing without confirmed progression or death



ORR was defined as confirmed stringent complete response, complete response, very good partial response, or partial response.

Talquetamab: A GPRC5D×CD3 Bispecific Antibody – MonumenTAL-1 Phase I Study Design

Ongoing phase I (NCT03399799) study of talquetamab in patients with RRMM

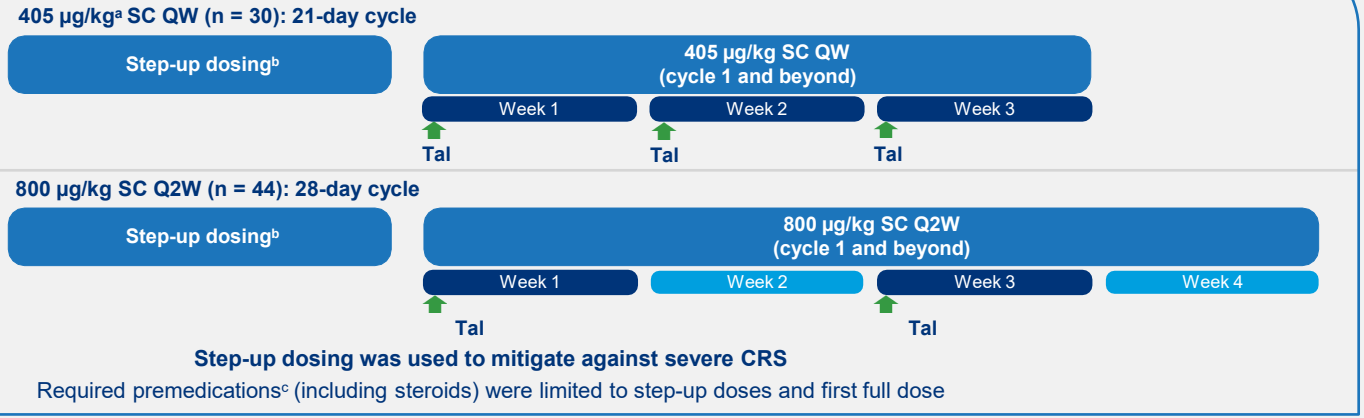
Key eligibility criteria

- Adults with measurable MM
- RR or intolerant to established MM therapies
- Prior BCMA-targeted therapy was permitted

Key study objectives

- **Part 1**: Identify RP2D(s)
- **Part 2**: Safety and tolerability at selected RP2D(s)
- Antitumor activity, PK/PD

RP2D dosing schedules



Step-up dosing was used to mitigate against severe CRS

Required premedications[c] (including steroids) were limited to step-up doses and first full dose

[a]In phase I, 405 µg/kg SC QW was the RP2D; 400 µg/kg SC QW was selected as final dosing concentration in phase II for operational convenience. [b]Two to 3 step-up doses given prior to first full dose. [c]Glucocorticoid, antihistamine, and antipyretic. BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; MM, multiple myeloma; PD, pharmacodynamic; PK, pharmacokinetic; Q2W, every other week; QW, weekly; RP2D, recommended phase II dose; RRMM, relapsed/refractory MM; SC, subcutaneous; Tal, talquetamab.

Minnema MC, et al. ASCO 2022. Abstract 8015; Minnema MC, et al. EHA 2022. Abstract S182.

MonumenTAL-1: Patients

Characteristic		405 µg/kg SC QW[a] n = 30	800 µg/kg SC Q2W[a] n = 44
Age, years, median (range)		61.5 (46–80)	64.0 (47–84)
Male, n (%)		19 (63.3)	21 (47.7)
Race, n (%)	White	25 (83.3)	35 (79.5)
	Black or African	4 (13.3)	4 (9.1)
	American Asian	0	3 (6.8)
	Not reported	1 (3.3)	2 (4.5)
Bone marrow plasma cells ≥60%[b], n (%)		6 (20.7)	5 (12.2)
Extramedullary plasmacytomas ≥1[c], n (%)		11 (36.7)	15 (34.1)
High-risk cytogenetics[d], n (%)		3 (11.1)	9 (22.5)
ISS stage[e], n (%)			
	I	12 (41.4)	16 (37.2)
	II	13 (44.8)	18 (41.9)
	III	4 (13.8)	9 (20.9)
Time since diagnosis (years), median (range)		5.6 (1.7–19.6)	6.4 (0.8–21.3)
Prior lines of therapy, median (range)		6 (2–14)	5 (2–17)
Prior stem cell transplantation, n (%)		27 (90.0)	33 (75.0)

Characteristic	405 µg/kg SC QW[a] n = 30	800 µg/kg SC Q2W[a] n = 44
Exposure status, n (%)		
Triple class[f]	30 (100)	43 (97.7)
Penta-drug[g]	24 (80.0)	30 (68.2)
BCMA-targeted therapy[h]	9 (30.0)	12 (27.3)
ADC or bispecific antibody	5 (16.7)	8 (18.2)
CAR T	4 (13.3)	4 (9.1)
Refractory status, n (%)		
PI[i]	25 (83.3)	37 (84.1)
IMiD[j]	28 (93.3)	42 (95.5)
Anti-CD38 mAb[k]	30 (100)	42 (95.5)
Triple class[f]	23 (76.7)	34 (77.3)
Penta-drug[g]	6 (20.0)	12 (27.3)
BCMA-targeted ADC or bispecific antibody	5 (16.7)	7 (15.9)
To last line of therapy	26 (86.7)	39 (88.6)

Data cutoff date: April 6, 2022.

[a]With 2–3 step-up doses. [b]Percentages calculated from n=29 for 405 µg/kg QW and n = 41 for 800 µg/kg Q2W. [c]Soft tissue plasmacytomas not associated with the bone were included. [d]del(17p), t(4:14), and/or t(14;16); calculated from n = 27 for 405 µg/kg SC QW and n = 40 for 800 µg/kg SC Q2W. [e]At baseline, percentages calculated from n = 29 for 405 µg/kg SC QW and n = 43 for 800 µg/kg Q2W. [f]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [g]≥2 PIs, ≥2 IMiDs, and ≥1 anti–CD38 mAb. [h]Includes ADCs, bispecific antibodies, and CAR T. [i]Bortezomib, carfilzomib, and/or ixazomib. [j]Thalidomide, lenalidomide, and/or pomalidomide. [k]Daratumumab, isatuximab, and/or an investigational anti-CD38 mAb. ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; Q2W, every other week; QW, weekly; SC, subcutaneous.

MonumenTAL-1: Safety

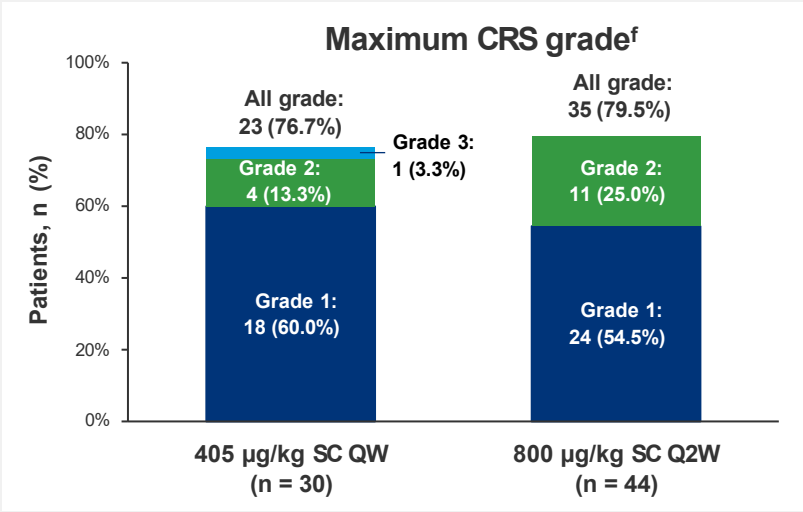
AEs [≥20% of total SC population], n (%)	405 µg/kg SC QW n = 30		800 µg/kg SC Q2W[a] n = 44	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	20 (66.7)	18 (60.0)	18 (40.9)	15 (34.1)
Anemia	17 (56.7)	9 (30.0)	21 (47.7)	12 (27.3)
Lymphopenia	12 (40.0)	12 (40.0)	18 (40.9)	18 (40.9)
Leukopenia	12 (40.0)	9 (30.0)	10 (22.7)	8 (18.2)
Thrombocytopenia	11 (36.7)	7 (23.3)	10 (22.7)	5 (11.4)
Nonhematologic				
CRS	23 (76.7)	1 (3.3)	35 (79.5)	0
Skin-related AEs[b]	20 (66.7)	0	32 (72.7)	1 (2.3)
Dysgeusia	19 (63.3)	N/A	25 (56.8)	N/A
Nail-related AEs[c]	18 (60.0)	0	15 (34.1)	0
Rash-related AEs[d]	14 (46.7)	1 (3.3)	13 (29.5)	7 (15.9)
Dysphagia	12 (40.0)	0	12 (27.3)	0
Pyrexia	11 (36.7)	0	10 (22.7)	0
Fatigue	10 (33.3)	1 (3.3)	12 (27.3)	0
Dry mouth	9 (30.0)	0	25 (56.8)	0
Weight decreased	9 (30.0)	0	19 (43.2)	1 (2.3)
Nausea	9 (30.0)	0	9 (20.5)	0
Diarrhea	9 (30.0)	0	8 (18.2)	0
ALT increased	6 (20.0)	1 (3.3)	14 (31.8)	3 (6.8)
Decreased appetite	7 (23.3)	1 (3.3)	11 (25.0)	1 (2.3)
Headache	7 (23.3)	0	11 (25.0)	0
AST increased	3 (10.0)	0	14 (31.8)	3 (6.8)

- Overall, the most common AEs were CRS, skin-related events, and dysgeusia
- Dysgeusia was managed with supportive care, and at times with dose adjustments
- Cytopenias were mostly confined to step-up and cycle 1–2 doses and generally resolved within 1 week
- Infections occurred in 46.7% of patients at 405 µg/kg QW and 38.6% at 800 µg/kg Q2W (grade 3/4: 6.7%/9.1%)
- No patients died due to drug-related AEs

Data cutoff date: April 6, 2022. AEs were graded by CTCAE v4.03 with CRS events graded per Lee et al 2014 criteria. [a]With 2–3 step-up doses. [b]Includes skin exfoliation, pruritus, dry skin, skin ulcer, eczema, skin hyperpigmentation, skin lesion, asteatotic eczema, skin fissures, skin irritation, and skin toxicity. [c]Includes nail disorder, onychomadesis, nail discoloration, nail dystrophy, onychoclasis, nail ridging, nail bed disorder, and nail hypertrophy. [d]Includes rash, maculopapular rash, dermatitis acneiform, erythematous rash, vesicular rash, dermatitis, contact dermatitis, and exfoliative generalized dermatitis. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; Q2W, every other week; QW, weekly; SC, subcutaneous.

MonumenTAL-1: Cytokine Release Syndrome

Parameter	405 µg/kg SC QW[a] n = 30	800 µg/kg SC Q2W[a] n = 44
Patients with CRS, n (%)	23 (76.7)	35 (79.5)
Time to onset, days,[b] median (range)	2 (1–22)	2 (1–5)
Duration, days, median (range)	2 (1–3)	2 (1–5)
Patients who received supportive measures,[c] n (%)	23 (76.7)	35 (79.5)
Tocilizumab[d]	19 (63.3)	24 (54.5)
Steroids	1 (3.3)	3 (6.8)
Oxygen	1 (3.3)[e]	2 (4.5)
Single vasopressor	1 (3.3)[e]	0

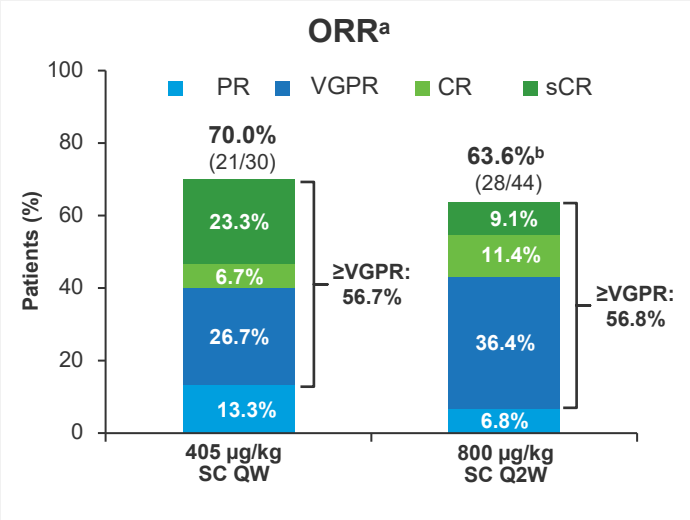


- All CRS events were grade 1/2, except for one grade 3 event
- CRS was largely confined to the step-up doses and first full dose

Data cutoff date: April 6, 2022.
[a]With 2–3 step-up doses. [b]Relative to the most recent dose. [c]Patients could receive >1 supportive therapy. [d]Tocilizumab was allowed for all CRS events. [e]One patient in the 405-µg/kg SC QW cohort received a single vasopressor and high-flow oxygen by face mask as supportive measures for CRS. [f]Graded according to Lee, et al. *Blood.* 2014;124:188.
CRS, cytokine release syndrome; Q2W, every other week; QW, weekly; SC, subcutaneous.

MonumenTAL-1: Overall Response Rate

- The ORR appears to be comparable across both RP2Ds



Response	405 µg/kg SC QW n = 30	800 µg/kg SC Q2W n = 44
Median follow-up, months, median (range)	13.2 (1.1–24.0)	7.7 (0.7–16.0)
ORR[a], n (%)	21 (70.0)	28 (63.6)
Triple-class-refractory patients, n/N (%)	15/23 (65.2)	23/34 (67.6)
Penta-drug-refractory patients, n/N (%)	5/6 (83.3)	9/12 (75.0)
Median time to first confirmed response, months, median (range)	0.9 (0.2–3.8)	1.2 (0.3–6.8)

[a]Investigator assessment of evaluable patients per 2011 IMWG response criteria; includes unconfirmed responses. [b]Due to rounding, individual response rates do not sum to the ORR.
CR, complete response; IMWG, International Myeloma Working Group; PR, partial response; ORR, overall response rate; Q2W, every other week; QW, weekly; RP2D, recommended phase II dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

Bispecific Combination

Teclistamab Plus Daratumumab
TRIMM-2 Study Design: Tec + Dara Cohorts

Ongoing phase Ib, open-label, multicenter, multicohort study in patients with RRMM

Key eligibility criteria

- Adults with measurable MM
- ≥3 prior LOT, including a PI and IMiD
- Prior anti-CD38 therapy allowed (90-day washout period)
- Prior BCMA-directed therapies were allowed

Key study objectives

- Part 1: Identify RP2D(s) for each treatment combination
- Part 2: Safety and tolerability at the selected RP2D(s) of each combination
- Antitumor activity, PK/PD

Tec + dara dosing schedules

Dara	Tec SC	Patients enrolled
1800 mg SC (per approved schedule[1]) Cycles 1–2: QW Cycles 3–6: Q2W Cycles 7+: Monthly	**1.5 mg/kg QW**[a]	n = 21
	3 mg/kg Q2W[a]	n = 39
	3 mg/kg QW	n = 5

Analysis cutoff date: April 6, 2022

- Step-up dosing was used for tec
- Premedications[b] (including steroids) limited to step-up doses and first full dose of tec
- 9 patients switched from 1.5 mg/kg SC QW to 3 mg/kg SC Q2W dosing in cycles 4–9

[a]Dose levels expanded in part 2. [b]Glucocorticoid, antihistamine, and antipyretic.
BCMA, B-cell maturation antigen; dara, daratumumab; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics; QW, weekly; Q2W, every other week; RP2D, recommended phase II dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; tec, teclistamab.
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use [package insert]. Horsham, PA: Janssen Biotech, Inc; 2022.

Rodrigues-Otero, et al. EHA 2022. Abstract S188.

TRIMM-2 Tec + Dara: Safety Overview

AE [≥20.0%], n (%)	Tec + dara (N = 65)	
	Any grade	Grade 3/4
Hematologic		
Neutropenia	32 (49.2)	27 (41.5)
Anemia	27 (41.5)	18 (27.7)
Thrombocytopenia	21 (32.3)	16 (24.6)
Nonhematologic		
CRS	44 (67.7)	0
Diarrhea	21 (32.3)	1 (1.5)
Fatigue	19 (29.2)	2 (3.1)
Pyrexia	19 (29.2)	0
Nausea	18 (27.7)	0
Cough	14 (21.5)	0
Headache	13 (20.0)	1 (1.5)
Asthenia	13 (20.0)	1 (1.5)
Decreased appetite	13 (20.0)	0

Tec + dara was well tolerated with no overlapping toxicities

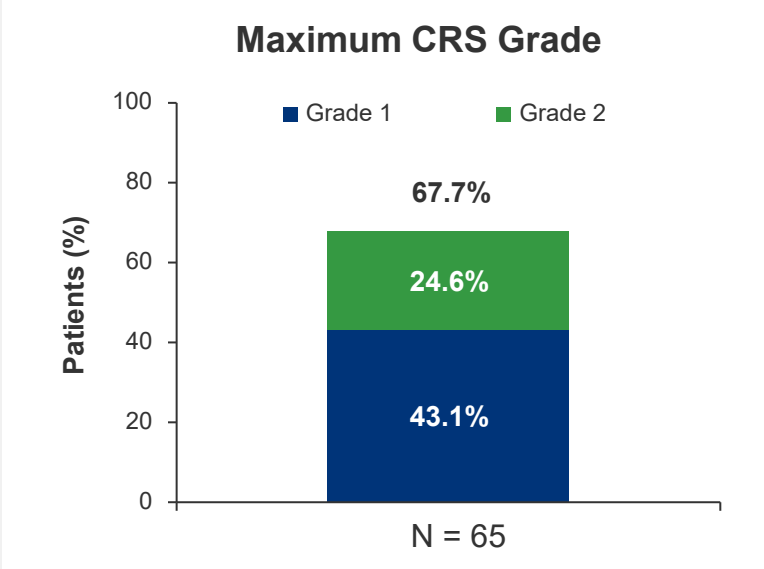
- 44 patients had infections (67.7%; grade 3/4: 27.7%)
- 1 patient had a grade 1 ICANS event during step-up dosing that fully resolved in 1 day

- 4 deaths due to AEs, all unrelated to tec or dara:
  - Bacterial pneumonia (n = 1)
  - Sepsis (n = 1)
  - Hepatic failure (n = 1)
  - COVID-19 (n = 1)

Analysis cutoff date: April 6, 2022.
AE, adverse event; CRS, cytokine release syndrome; dara, daratumumab; ICANS, immune effector cell-associated neurotoxicity syndrome; tec, teclistamab.

TRIMM-2 Tec + Dara: Cytokine Release Syndrome

Parameter	N = 65
Patients with CRS[a], n (%)	44 (67.7)
Grade 1	28 (43.1)
Grade 2	16 (24.6)
Grade ≥3	0
Time to onset [days][b], median (range)	2.5 (1–7)
Duration [days], median (range)	2.0 (1–7)
Patients who received supportive measures[c], n (%)	39 (60.0)
Tocilizumab[d]	21 (32.3)
Steroids	3 (4.6)
Oxygen	4 (6.2)



- All CRS events were grade 1/2 and resolved without treatment discontinuation
- Most CRS events occurred during step-up doses or the first full treatment dose

Analysis cutoff date: April 6, 2022. [a]Graded according to ASTCT criteria. [b]Relative to the most recent dose. [c]A patient could receive >1 supportive therapy. [d]Tocilizumab was allowed for all CRS events.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome.

TRIMM-2 Tec + Dara: Overall Response Rate

Best response, n (%)	Response-evaluable patients[a] (n=51)		
	Dara SC 1800 mg		
	Tec 1.5 mg/kg QW (n = 20)	Tec 3 mg/kg Q2W (n = 27)	Tec 3 mg/kg QW (n = 4)
ORR[b]	15 (75.0)	20 (74.1)	4 (100.0)
CR/sCR	6 (30.0)	3 (11.1)	2 (50.0)
VGPR	8 (40.0)	15 (55.6)	2 (50.0)
PR	1 (5.0)	2 (7.4)	0
SD	3 (15.0)	5 (18.5)	0
PD	2 (10.0)	2 (7.4)	0

- Median follow-up of 8.6 months (range, 0.3–19.6)
- Among 51 response-evaluable patients, ORR was 76.5%
  - VGPR or better in 70.6% of all response-evaluable patients
- ORR of 73.7% (28/38) was achieved in patients with prior anti-CD38 exposure
- Median time to first confirmed response was 1.0 month (range, 0.9–3.5)

[a]Patients have received ≥1 study treatment and ≥1 postbaseline response evaluation. [b]PR or better, includes unconfirmed responses. Collecting urine was not mandatory in patients without measurable disease in the urine, limiting the assessment of some patient responses to PR.
CR, complete response; dara, daratumumab; ORR, overall response rate; PD, progressive disease; PR, partial response; Q2W, every other week; QW, weekly; SC, subcutaneous; sCR, stringent CR; SD, stable disease; tec, teclistamab; VGPR, very good partial response.

Conclusions

Conclusions

- ✓ Bispecific TCEs are showing promising clinical efficacy with durable responses and manageable safety profiles
- ✓ These are off-the-shelf therapies offering some advantages compared with CAR T cells, in particular in patients with rapidly progressive disease
- ✓ Mitigation strategies to prevent high-grade CRS, including step-up dosing and steroid premedication, are effective, and toxicity is manageable, with mostly grade 1 and 2 CRS and very few neurologic complications
- ✓ New targets are emerging, and are critical to rescue patients for whom BCMA therapies fail
- ✓ Trials are ongoing in different settings, in earlier lines of therapy, and in combination with SOC treatments

Thank you!
Gracias!
Obrigada!

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Discussion

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Beyond the Horizon: New and Future Multiple Myeloma Treatment Approaches – CAR Ts in MM

Luciano Costa, MD, PhD

APTITUDE HEALTH®

CAR T-Cell Therapy in Multiple Myeloma

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University of Alabama at Birmingham

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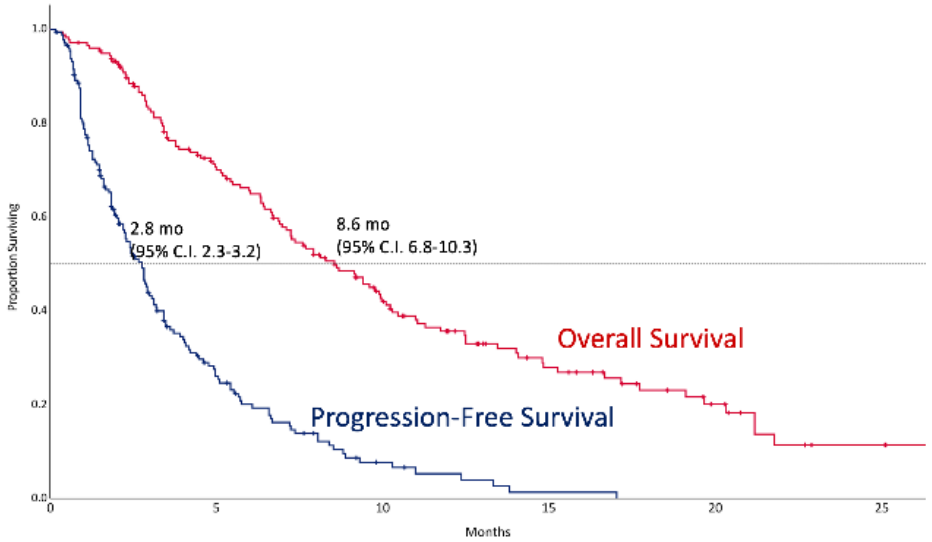
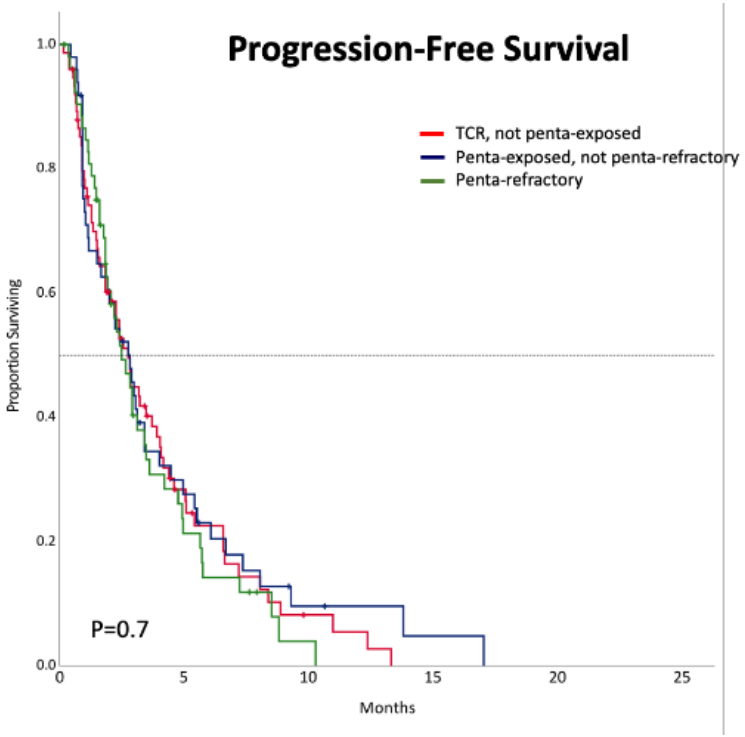
@End_myeloma

Treatment Beyond TCR MM: MAMMOTH Study





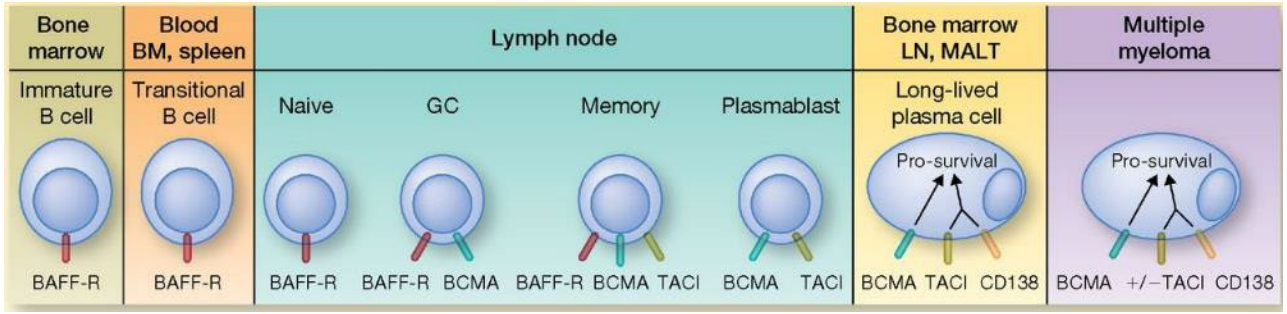
Bal S, et al. *Leukemia*. 2022;36:877-880.

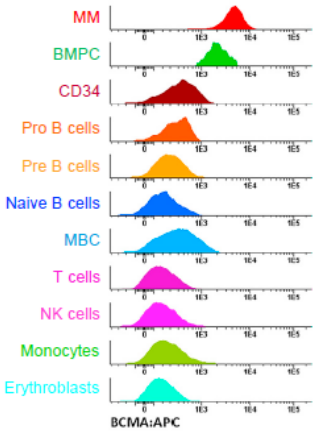
Treatment Beyond TCR MM: MAMMOTH Study

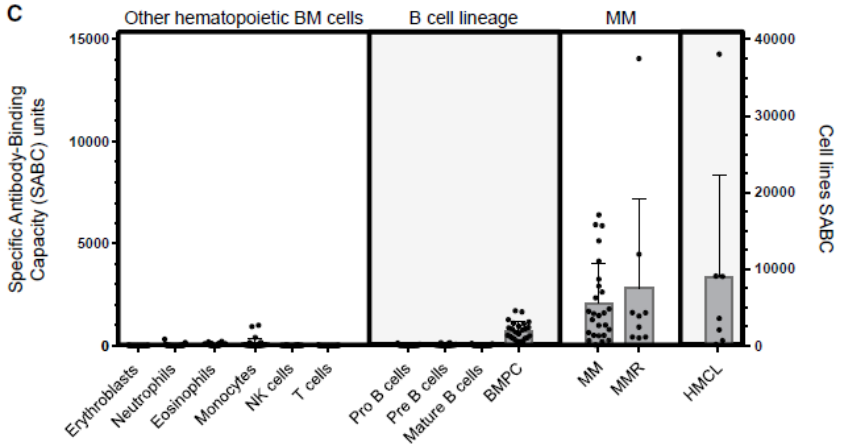
		Next Regimen After MM Becomes TCR			
Characteristic	**All patients**	**Cytotoxic chemotherapy**	**CD38 MoAb-containing**	**Carfilzomib-containing**	**Pomalidomide-containing**
N	177	80	45	42	60
Cytogenetic high-risk	29%	33%	29%	24%	18%
ISS3	28%	26%	27%	33%	32%
Median time diagnosis-TCR (y)	4.8	4.3	5.3	3.8	4.4
N prior lines (range)	5 (3-17)	5.5 (3-12)	5 (3-17)	5 (3-9)	5 (3-10)
Penta-exposed	58%	68%	47%	41%	58%
Penta-refractory	30%	33%	22%	14%	22%
ORR	**30%**	**44%**	**20%**	**31%**	**28%**
Median PFS in mo (95% CI)	2.8 (2.3-3.2)	2.4 (1.9-3.0)	3.1 (2.6-3.5)	4.0 (1.0-7.0)	3.4 (2.3-4.5)
Median OS in mo (95% CI)	8.6 (6.8-10.3)	7.6 (5.4-9.8)	11.0 (8.5-13.5)	9.2 (5.4-13.0)	9.4 (7.1-11.7)

Bal S, et al. *Leukemia*. 2022;36:877-880.

B-Cell Maturation Antigen (BCMA)

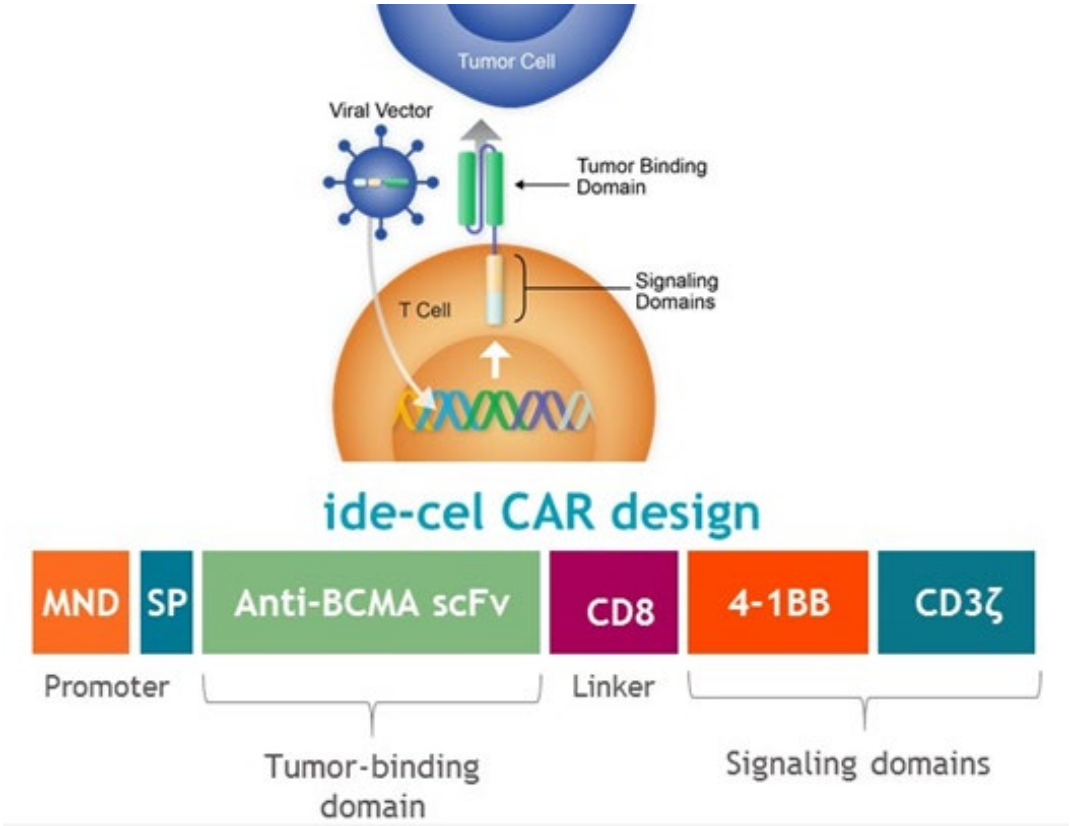






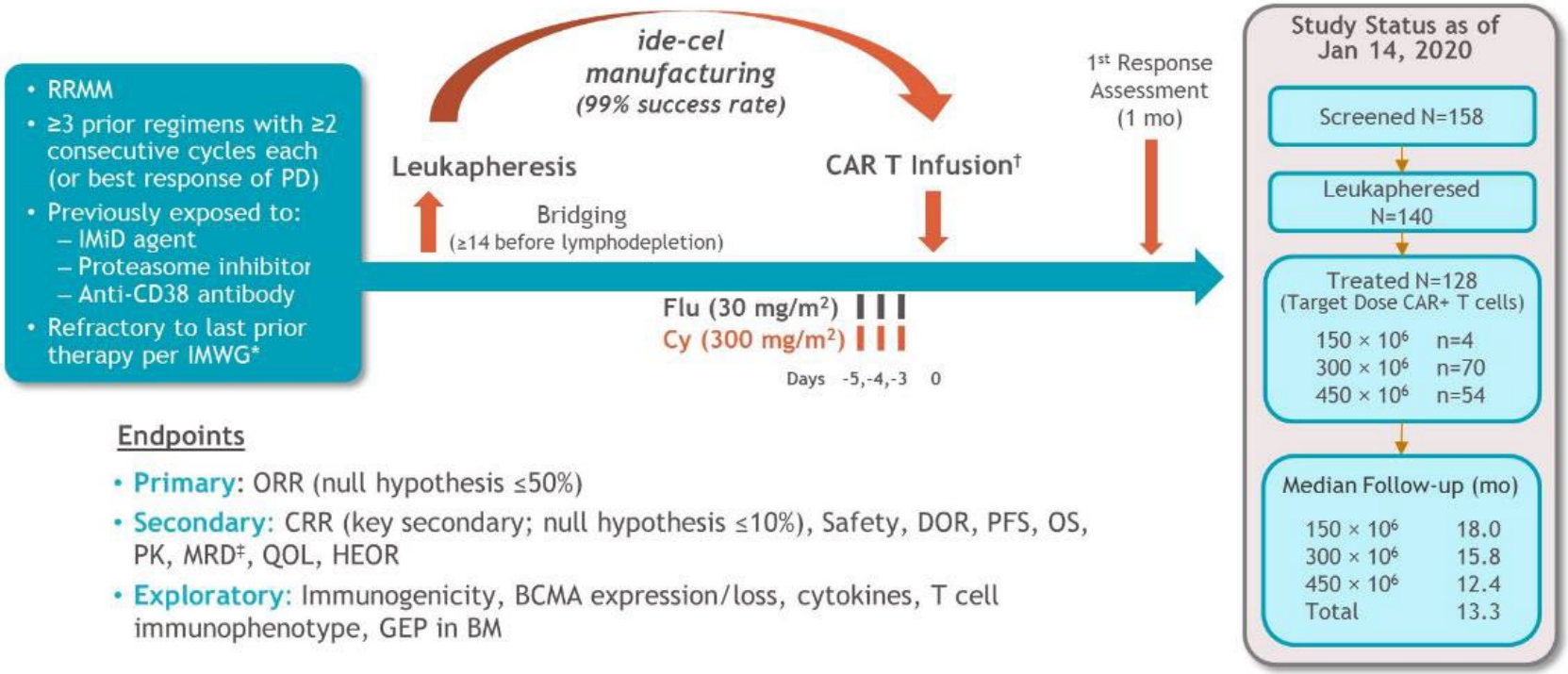
Seckinger A, et al. *Cancer Cell*. 2017;31:396-410.

Ide-Cel



Munshi NC, et al. ASCO 2020. Abstract 8503.

KARMMA Study



Endpoints

- **Primary**: ORR (null hypothesis ≤50%)
- **Secondary**: CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory**: Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

Munshi NC, et al. *N Engl J Med.* 2021;384:705-716.

KARMMA Study

Characteristics		Ide-cel Treated (N=128)
Age, median (range), y		61 (33–78)
Male, %		59
ECOG PS, %	0	45
	1	53
	2	2
R-ISS Stage,* %	I	11
	II	70
	III	16
High-risk cytogenetics [del(17p), t(4;14), t(14;16)],† %		35
High tumor burden (≥50% BMPCs), %		51
Tumor BCMA expression (≥50% BCMA+),‡ %		85
Extramedullary disease, %		39
Time since initial diagnosis, median (range), y		6 (1–18)
No. of prior anti-myeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1	94
	>1	34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab-refractory	94
	Triple-refractory	84

Munshi NC, et al. *N Engl J Med.* 2021;384:705-716.

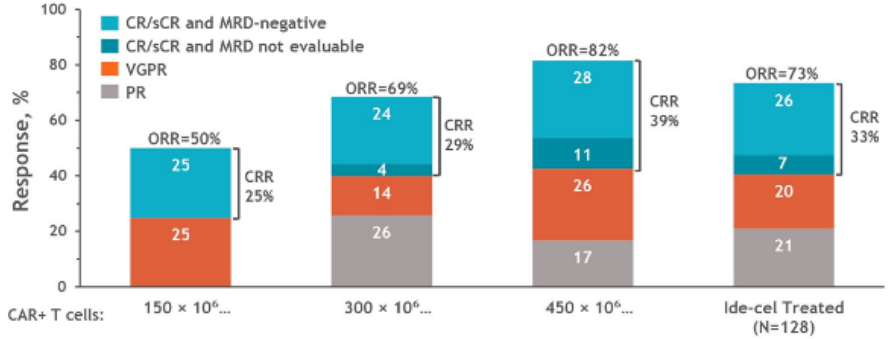
KARMMA Study

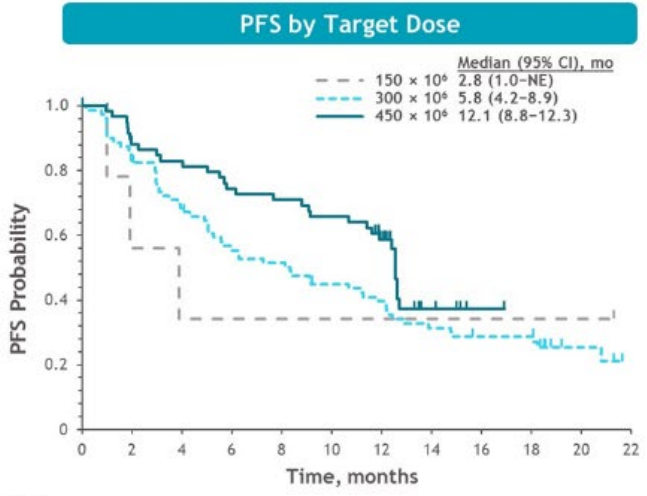
Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Max. grade (Lee Criteria)*				
1/2	2 (50)	49 (70)	49 (91)	100 (78)
3	0	2 (3)	3 (6)	5 (4)
4	0	1 (1)	0	1 (<1)
5	0	1 (1)	0	1 (<1)
Median onset, d (range)	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median duration, d (range)	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab, n (%)	1 (25)	30 (43)	36 (67)	67 (52)
Corticosteroids, n (%)	0	7 (10)	12 (22)	19 (15)

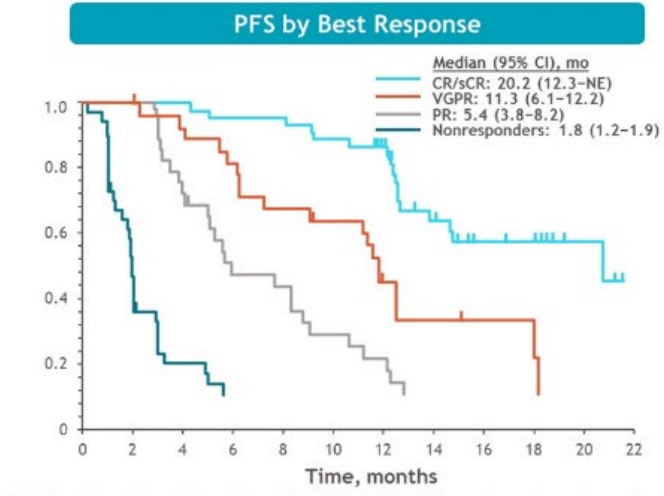
- 3% grade 3 neurotoxicity
- Cytopenias were common; median 2 months for improvement

Munshi NC, et al. *N Engl J Med.* 2021;384:705-716.

KARMMA Study

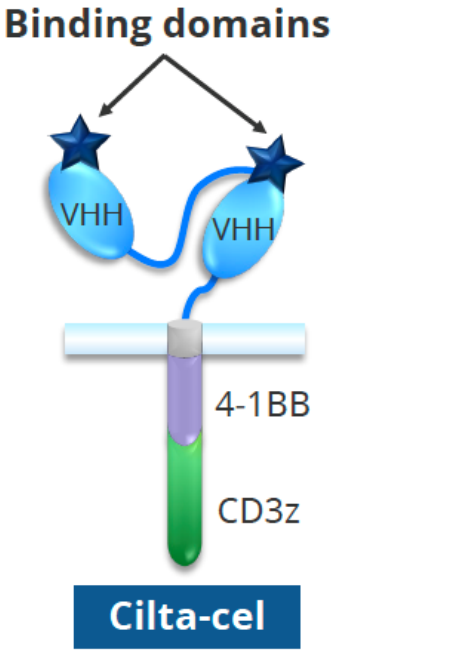




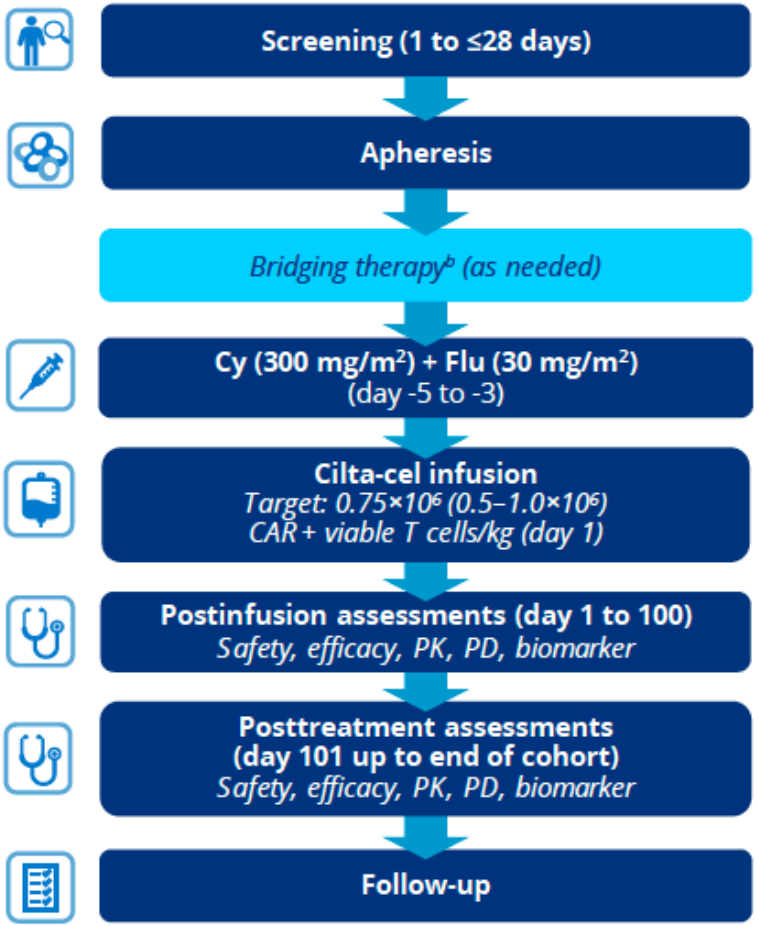


Munshi NC, et al. *N Engl J Med.* 2021;384:705-716.

Cilta-Cel: CARTITUDE-1



2 BCMA-targeting single-domain antibodies designed to confer avidity



Martin T, et al. *J Clin Oncol.* 2022. Epub ahead of print. doi: 10.1200/JCO.22.00842

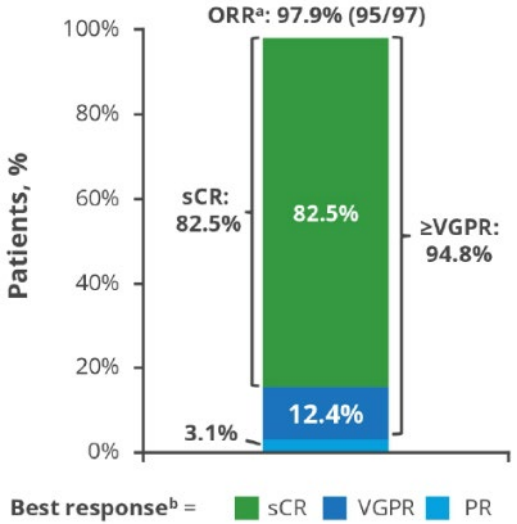
Cilta-Cel: CARTITUDE-1

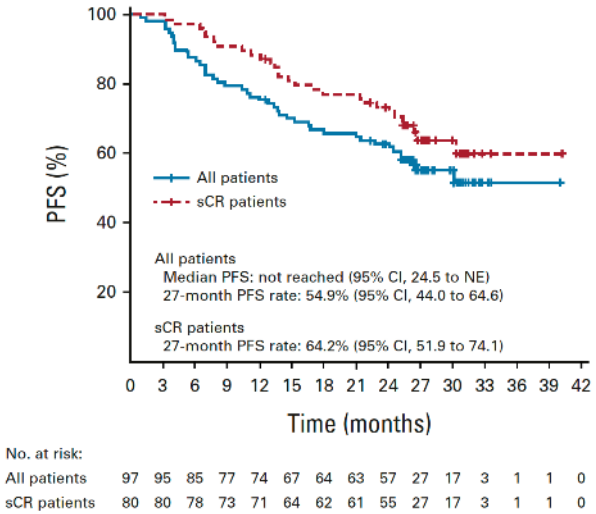
Characteristic	
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Black/African American, n (%)	17 (17.5)
All plasmacytomas,[a] n (%)	19 (19.6)
Extramedullary plasmacytomas, n (%)	13 (13.4)
Bone-based plasmacytomas, n (%)	6 (6.2)
Bone-marrow plasma cells ≥60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6–18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[b]

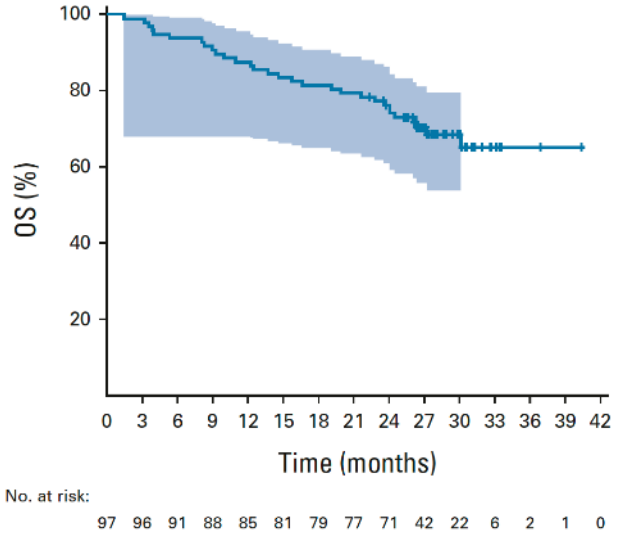
Characteristic	
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-drug refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

Martin T, et al. *J Clin Oncol.* 2022. Epub ahead of print. doi: 10.1200/JCO.22.00842

Cilta-Cel: CARTITUDE-1







Martin T, et al. *J Clin Oncol.* 2022. Epub ahead of print. doi: 10.1200/JCO.22.00842

Cilta-Cel: CARTITUDE-1

	N=97	
	Any grade	Grade 3/4
Hematologic AEs ≥25%, n (%)		
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)
Nonhematologic AEs ≥25%, n (%)		
Metabolism and nutrition disorders		
Hypocalcemia	31 (32.0)	3 (3.1)
Hypophosphatemia	30 (30.9)	7 (7.2)
Decreased appetite	28 (28.9)	1 (1.0)
Hypoalbuminemia	27 (27.8)	1 (1.0)
Gastrointestinal		
Diarrhea	29 (29.9)	1 (1.0)
Nausea	27 (27.8)	1 (1.0)
Other		
Fatigue	36 (37.1)	5 (5.2)
Cough	34 (35.1)	0
AST increased	28 (28.9)	5 (5.2)
ALT increased	24 (24.7)	3 (3.1)

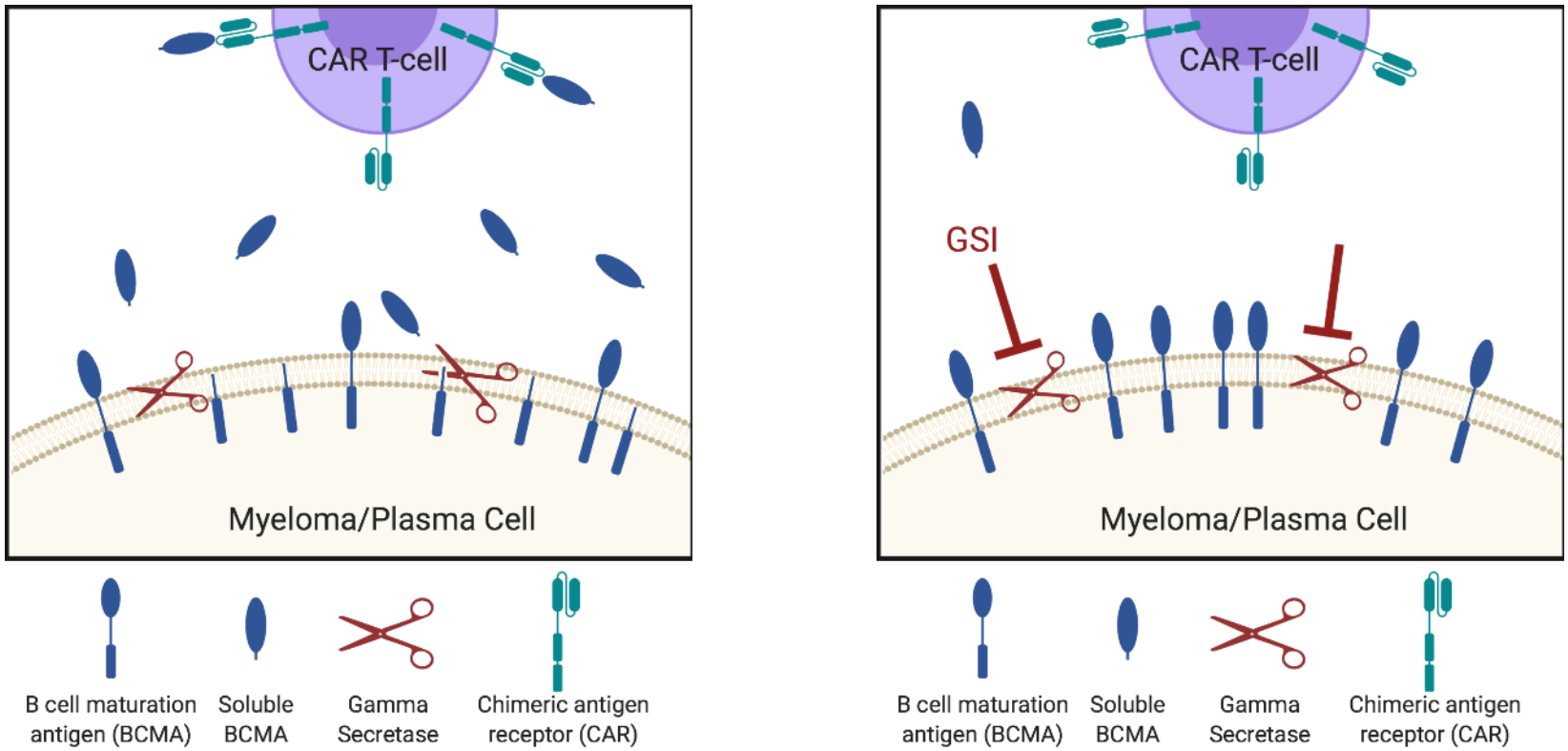
CRS	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]

Of 92 patients with CRS, majority (94.6%) were grades 1/2
CRS resolved in 91 (98.9%) patients within 14 days of onset

	N=97
Total CAR T-cell neurotoxicities, n (%)	
Any Grade	20 (20.6)
Grade ≥3	10 (10.3)
ICANS, n (%)	
Any Grade	16 (16.5)
Grade ≥3	2 (2.1)
Other neurotoxicities,[c] n (%)	
Any Grade	12 (12.4)
Grade ≥3	9 (9.3)

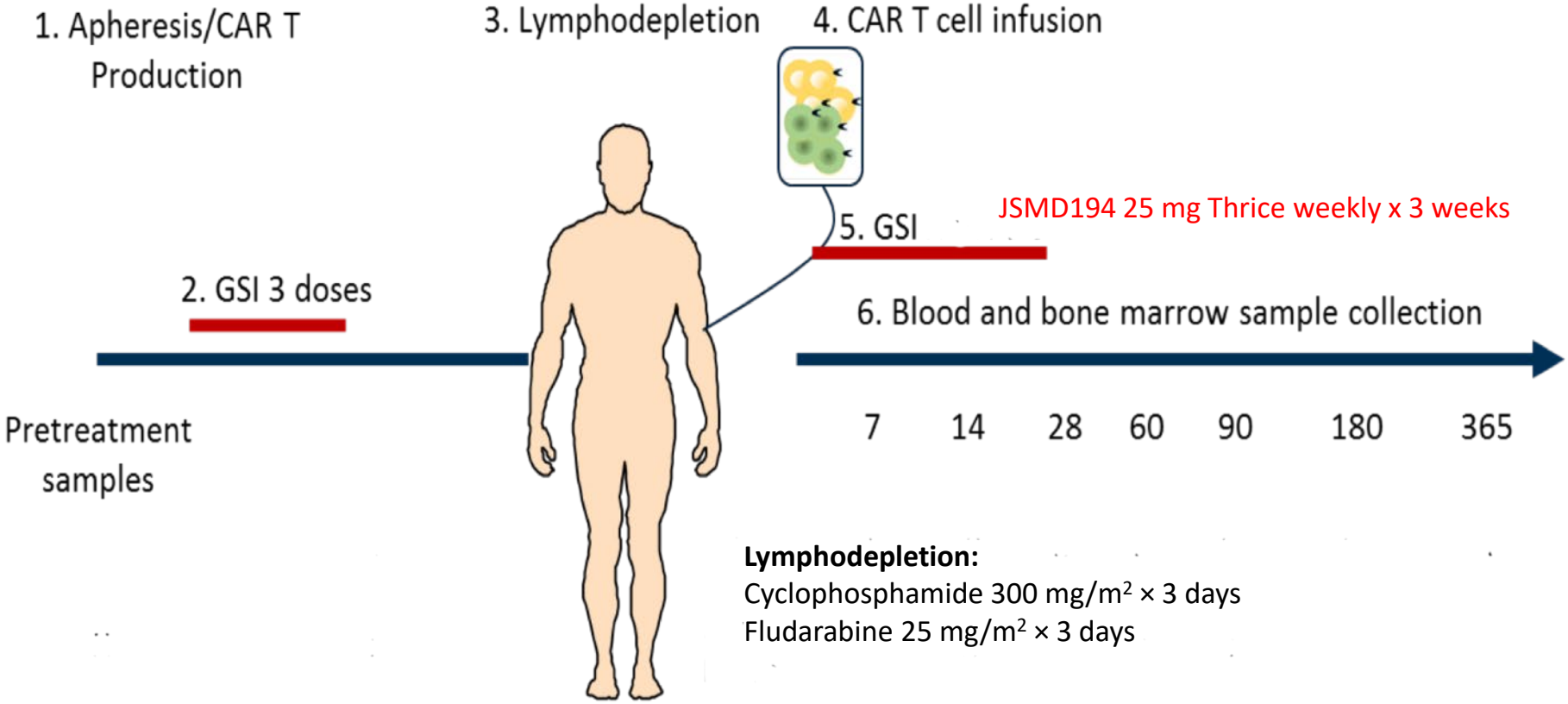
Martin T, et al. ASH 2021. Abstract 549.

Gamma Secretase Cleaves BCMA From Plasma Cells



Pont MJ, et al. *Blood*. 2019;134:1585-1597.

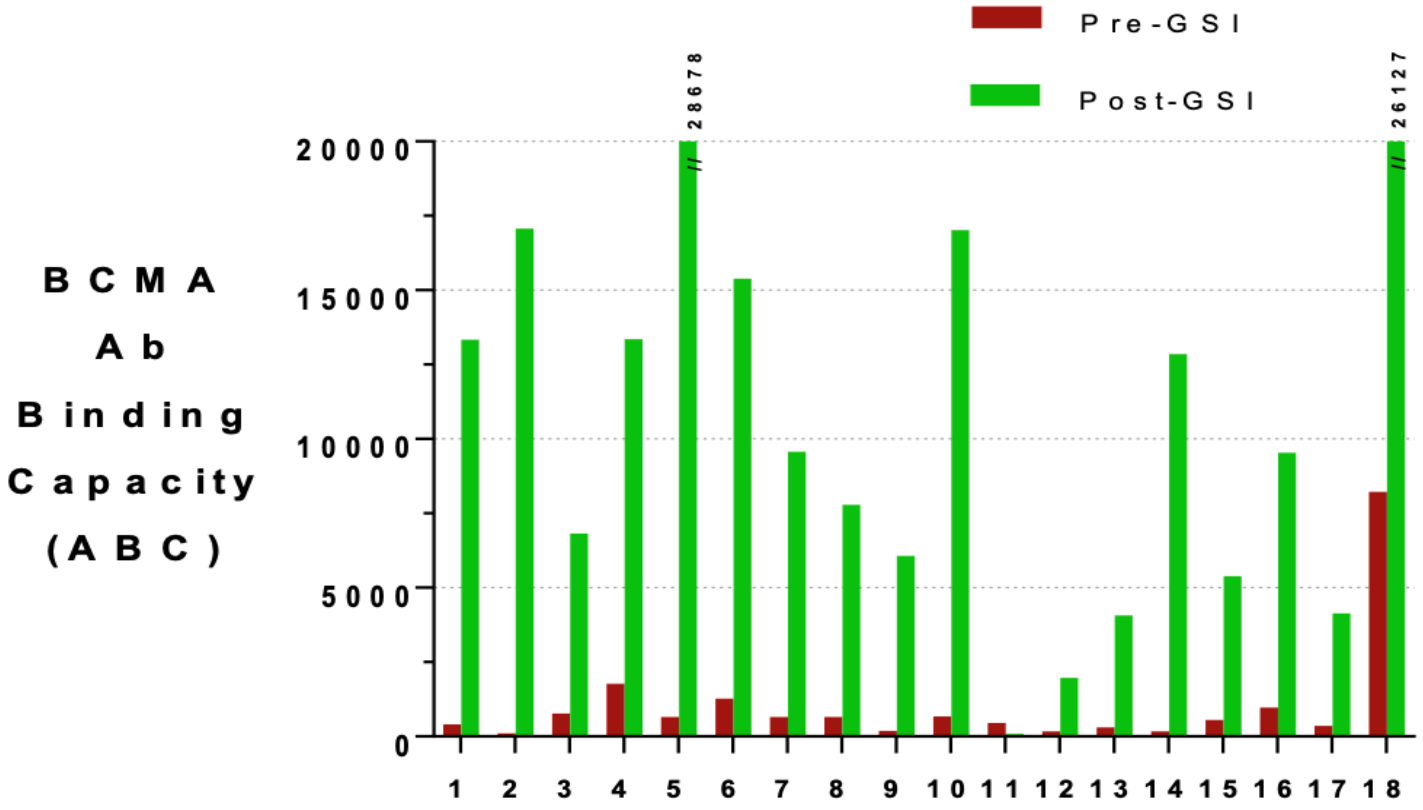
Study Design



Lymphodepletion:
Cyclophosphamide 300 mg/m^2 × 3 days
Fludarabine 25 mg/m^2 × 3 days

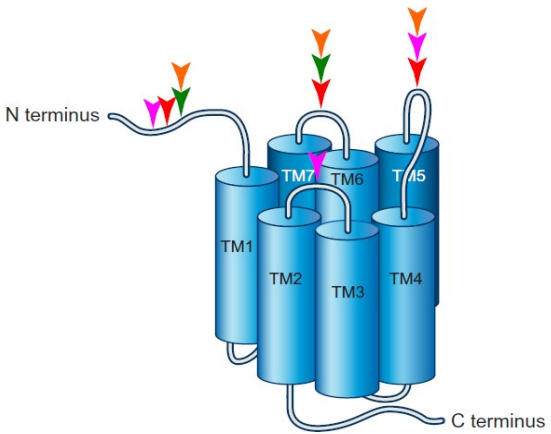
Cowan A, et al. ASH 2021. Abstract 551.

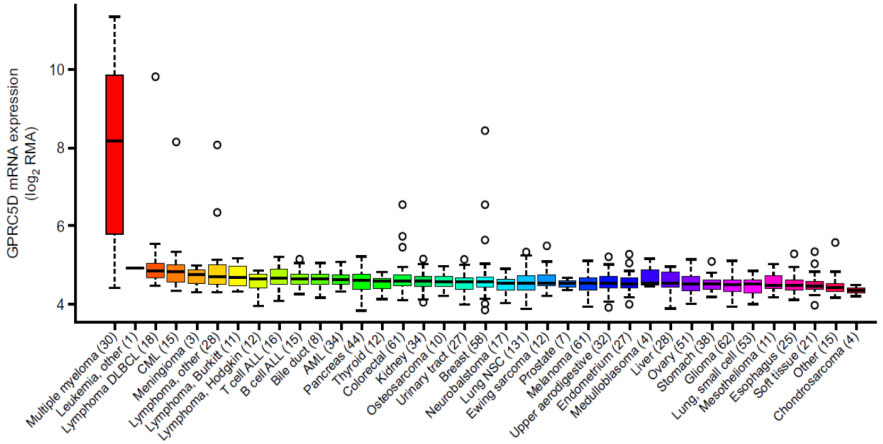
Gamma Secretase Inhibition Increases BCMA Surface Density

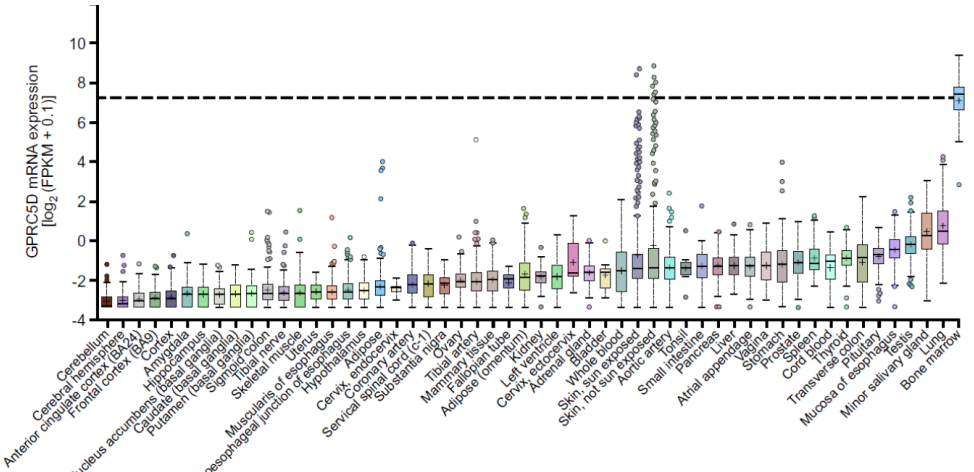


Cowan A, et al. ASH 2021. Abstract 551.

GPRC5D



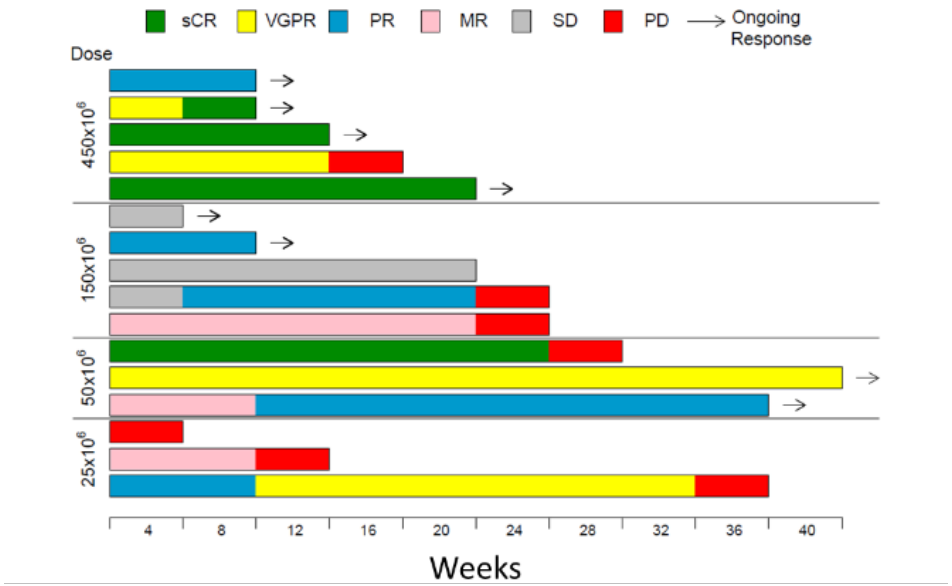




Smith EL, et al. *Sci Transl Med*. 2019;11:eaau7746.

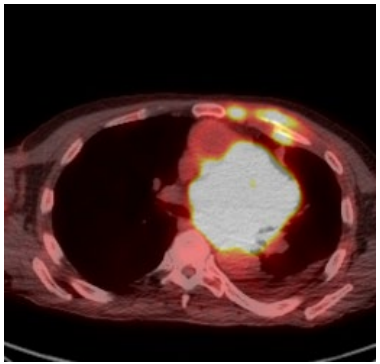
GPRC5D CAR T

- MCARH109, FIH study
- 3+3 design
- Median 8 prior lines of therapy
- 25, 50, 150, 450 × 10^6 viable CAR T cells
- 18 patients treated, 16 with response assessment
- 93% had CRS, grade 3 in 1/12
- 69% ORR

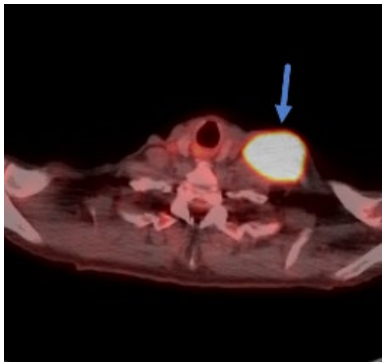


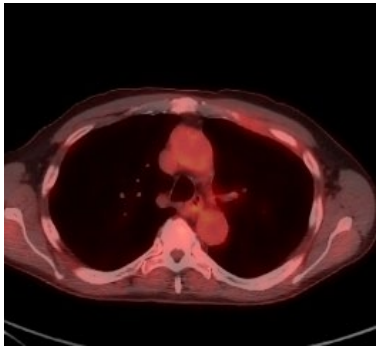
Mailankody S, et al. ASH 2021. Abstract 827.

GPRC5D CAR T

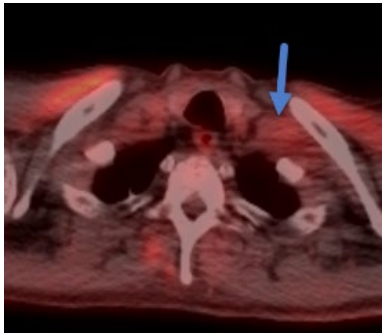


Pretreatment





4-week follow-up



Mailankody S, et al. ASH 2021. Abstract 827.

Future of Cell Therapy in MM

- Better manufacturing, enrichment for memory CAR T cells (BB21217, NEX-T platform)
- Mitigation of CRS
- Increase BCMA expression-γ secretase inhibitors (?)
- CAR T in earlier lines of therapy (KARMMA-3, CARTITUDE-4)
- Upfront use in high-risk NDMM (CARTITUDE-2, KARMMA-4)
- Post-AHCT in high-risk patients
- CAR T followed by maintenance therapy (KARMMA-7)
- Non-BCMA target
  - GPRC5D (CC-95266)
  - CD38/CD138

Thank you!

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Discussion

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Interactive Discussion and Q&A: Treatment Landscape Evolution in Multiple Myeloma

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Interactive Discussion

- How can Latin America utilize new treatment approaches for MM?
- Which will become more widely available in Latin America, bispecifics or CAR T?
- Are clinical trials or earl access programs with novel agents available in the region?

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Session Close – Audience Response Questions

Rafael Fonseca, MD

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Question 1

What treatment belongs to the T-cell engagers category? **[repeated question]**

a) Melflufen
b) Belantamab
c) Ide-cel
d) Selinexor
e) Venetoclax

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Question 2

Which of the following combinations has not been tested in phase III clinical trials in RR MM? **[repeated question]**

a) Dara-Pd
b) Elotuzumab, venetoclax, dexamethasone
c) Bortezomib, pomalidomide, dexamethasone
d) Bortezomib, daratumumab, dexamethasone
e) Carfilzomib, lenalidomide, dexamethasone

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Question 3

Which statements are true for the treatment of myeloma? **[repeated question]**

a) There is a high rate of attrition (loss)

b) Several drug trials show that 2 drugs can be as good as 3 in terms of efficacy

c) Myeloma is a heterogeneous disease with increased rates of *p53* abnormalities with progression

d) All the above

e) 1 and 3

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Thank You!

- Please complete the **evaluation survey** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the www.globalmmacademy.com website
- You can request a certificate of attendance to be sent to you after the meeting

THANK YOU!

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Emerging and Practical Concepts in Multiple Myeloma

THANK YOU FOR YOUR PARTICIPATION!

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