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Global Multiple Myeloma Academy

Global Multiple Myeloma Academy

Emerging and Practical Concepts in Multiple Myeloma

April 9–10, 2021

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Session Open

Rafael Fonseca

APTITUDE HEALTH®

Faculty

Chair

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Mayo Clinic Cancer Center, USA

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Cairo University, Egypt

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Mohamad Mohty MD
Saint-Antoine Hospital and Sorbonne University, Paris, France

Keith Stewart, MD
Princess Margaret Cancer Centre, Canada

Global Multiple Myeloma Academy

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
- Bring in the regional multiple myeloma perspective

Agenda Day 2

10 April 2021, 16.00 – 19.15 CET / 17.00 – 20.15 AST (UTC +3)

Time (UTC +3)	Topic	Speaker
17.00 – 17.10 10 min	**Session Open**	Rafael Fonseca
17.10 – 17.30 20 min	**Identification and Special Considerations for High-Risk Multiple Myeloma** • Risk stratification, prognosis, and treatment choices (15 min, 5-min discussion)	María-Victoria Mateos
17.30 – 17.55 25 min	**Management of Early Relapse of Multiple Myeloma** • Definition, prognosis, and treatment choices (15 min, 10-min discussion)	Rafael Fonseca
17.55 – 18.20 25 min	**Management of Heavily Pretreated Multiple Myeloma** • Optimal use of treatment choices in relapsed/refractory multiple myeloma (excluding T-cell engagers) (15 min, 10-min discussion)	Keith Stewart
18.20 – 18.30 10 min	**Break**	
18.30 – 19.20 50 min	**New and Future Therapies for Multiple Myeloma** • Promising new developments in relapsed/refractory MM • Latest trial updates, and upcoming new strategies (including T-cell engagers) (35 min, 15-min discussion)	Irene Ghobrial
19.20 – 20.00 40 min	**Patient Case Discussion: Relapsed/Refractory Multiple Myeloma** • Treatment challenges in relapsed/refractory MM in the region (10 min) • Cases from the region will be discussed with the faculty – “tumor board approach” (30 min)	Mervat Mattar All faculty
20.00 – 20.15 15 min	**Session Close** • ARS questions	Rafael Fonseca

University of Salamanca

Identification and special considerations for high-risk multiple myeloma: Risk stratification, prognosis, and treatment choices

María-Victoria Mateos
University Hospital of Salamanca
Salamanca, Spain

Conflict of interest

Honoraria derived from lectures and participation in advisory boards from Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Roche, Sanofi, Oncopeptides, Seagen

What is the definition of high-risk MM?

- **Overall survival of 2 years or less despite the use of novel agents → IMWG definition[1]**
- **Progression-related death within 2 years from treatment initiation → P. Moreau[2]**
- **Those patients not being cured? → B. Barlogie[3]**

1. Sonneveld P, et al. *Blood.* 2016;127(24):2955-2962; 2. Moreau P, et al. *J Clin Oncol.* 2014;32(20):2173-2180; 3. Barlogie B, et al. *Blood.* 2014;124(20):3043-3051.

What are factors that determine high risk in a patient with myeloma?

Patient-specific factors

- Age
- Comorbidities, eg, renal failure, spinal cord compression

Disease-specific factors

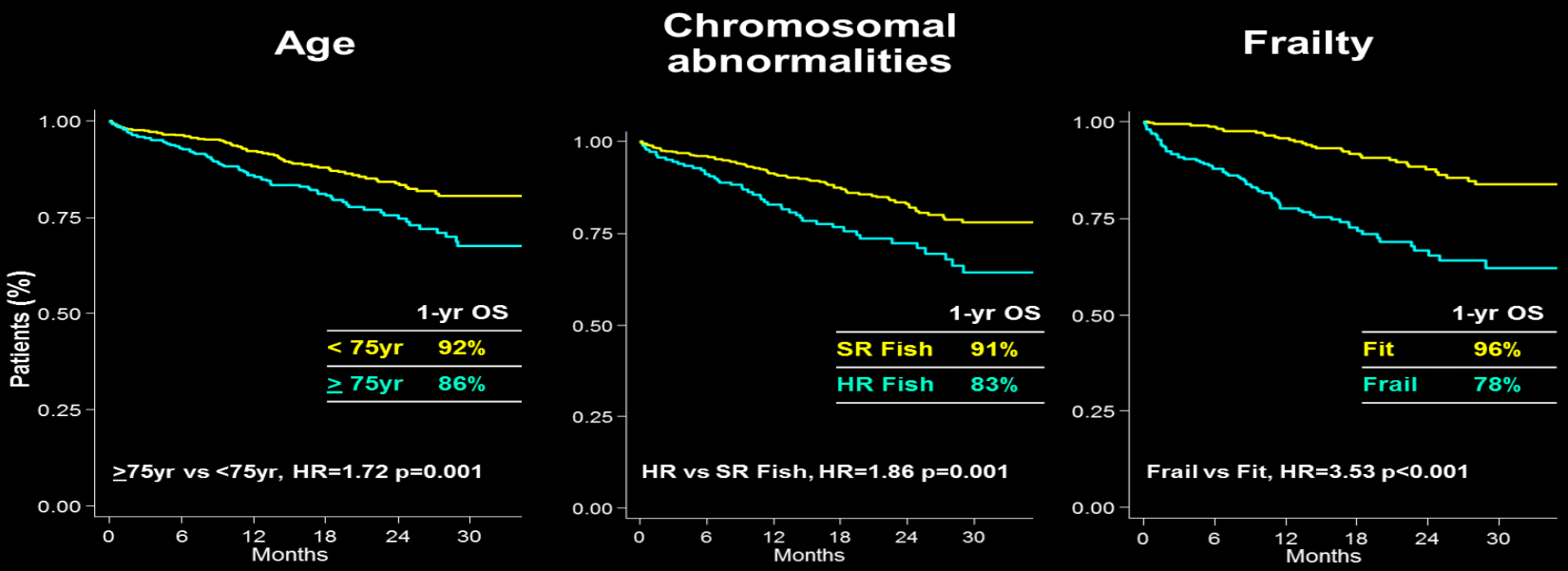
- ISS stage/R-ISS
- Cytogenetic abnormalities
- Extramedullary disease
- Plasma cell leukemia
- Lactate dehydrogenase level

ISS, International Staging System.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple myeloma. Version 5.2021. 2021.

Overall survival

Subgroup analysis in all patients



Fit defined as: score=0 Frail defined as: score≥2
HR Fish: presence of t(4;14) or t(14;16) or del 17q13

Palumbo A, et al. *Blood.* 2015;25:2068-2074.

What are factors that determine high risk in a patient with myeloma?

Patient-specific factors

- Age
- Comorbidities, eg, renal failure, spinal cord compression

Disease-specific factors

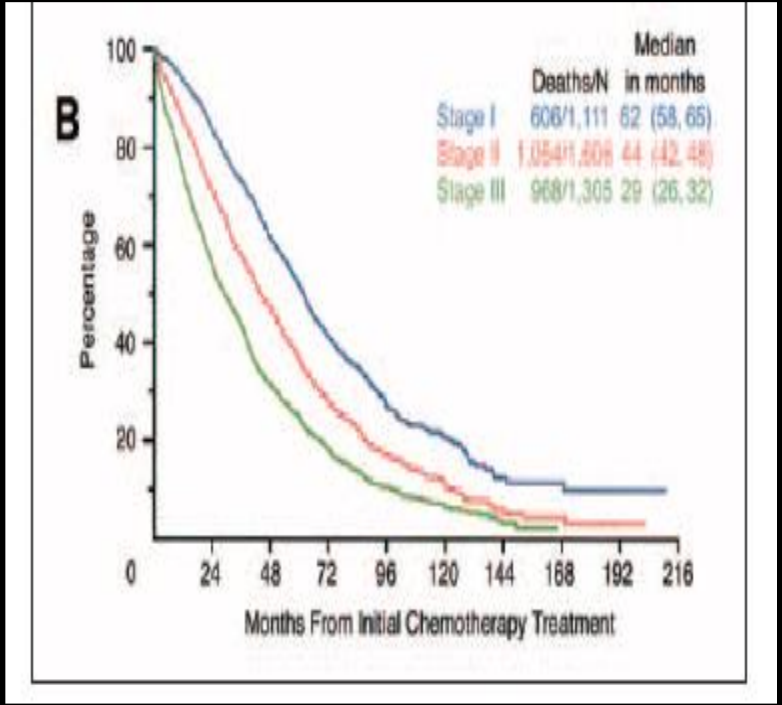
- ISS stage/R-ISS
- Lactate dehydrogenase level
- Cytogenetic abnormalities
- Extramedullary disease
- Plasma cell leukemia
- Response to treatment

International Staging System for MM

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;23:3412-3420.

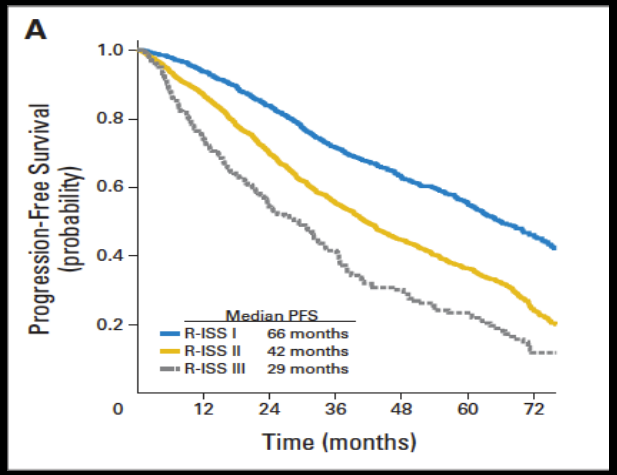
ISS III, high LDH, and t(4;14) and/or del(17p) as a prognostic index for OS

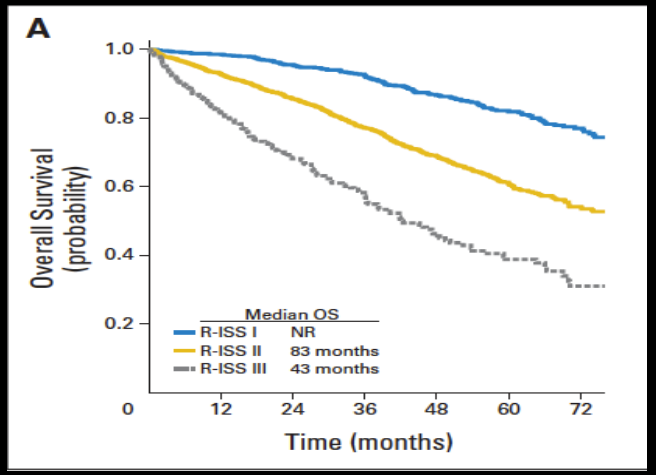
Score	Definition	Percentage of overall population	Outcome
0	**Absence of adverse factors** (neither high LDH, nor ISS III, nor t[4;14] and/or del[17p])	57%	4-year OS: 84%
1	**Presence of only 1 adverse factor** (either high LDH, or ISS III, or t[4;14] and/or del[17p])	32%	4-year OS: 73%
2	**Presence 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.

Revised International Staging System

R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH





High-risk CA includes the presence of del(17p) and/or t(4;14) and/or t(14;16).

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

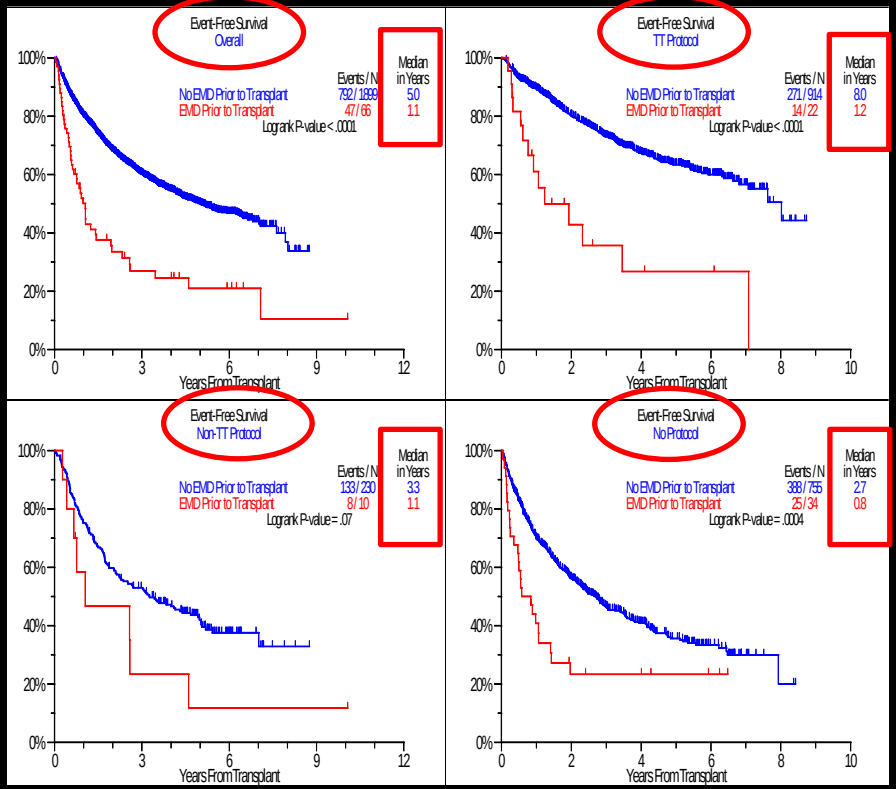
Extramedullary disease

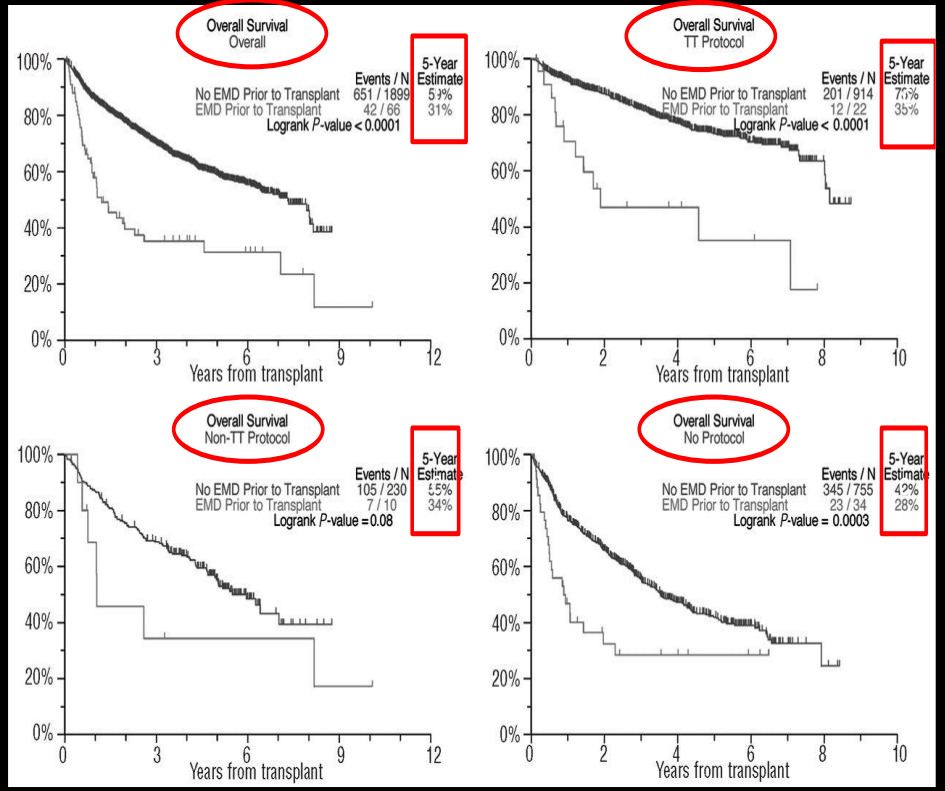
EMM entities	Definition	Clinical presentation
Extramedullary disease[1]	Soft-tissue plasmacytoma or PC infiltration of an anatomical site distant from the bone marrow. Secondary to a hematogenous spread	Mainly affect the liver, skin, CNS, pleural effusion, kidneys, lymph nodes, pancreas,..

- **Incidence: At diagnosis, 1.7-3.5%** [2]
  At relapse, up to 10%
- **There is no evidence that the incidence of plasmacytomas increases at relapse after allo trx or after exposure to novel agents-based combinations.**[3]
- **However, a better control of medullary disease with novel drugs can result into a more prolonged survival with a higher risk of extramedullary progression.**
- **To consider that, sometimes, plasmacytomas can develop on surgical scars.**

1. Touzeau C, Moreau P. *Blood.* 2016;127(8):971-976; 2. Beksac M, et al. *Haematologica.* 2020;105(1):201-208; 3. Bladé J, et al. *J Clin Oncol.* 2011;29(28):3805-3812.

PFS/OS in patients with EMM disease at diagnosis by PET-CT





Usmani SZ, et al. *Haematologica*. 2012;97:1761-1767.

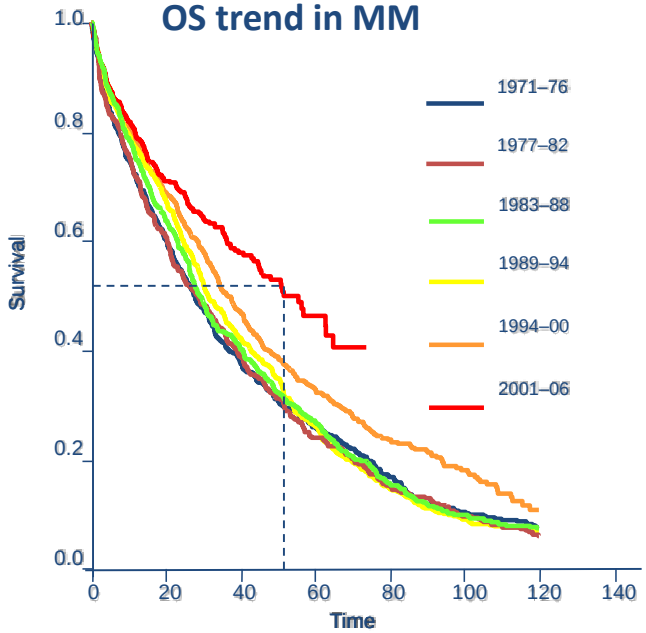
Plasma cell leukemia

EMM entities	Definition	Clinical presentation
Plasma cell leukemia [1]	Aggressive variant of myeloma characterized by the presence of circulating plasma cells (>20% and/or absolute count >2 X 10^9/L).	Could be considered as EMM because of blood involvement. Extramedullary disease is also very common in PCL patients.

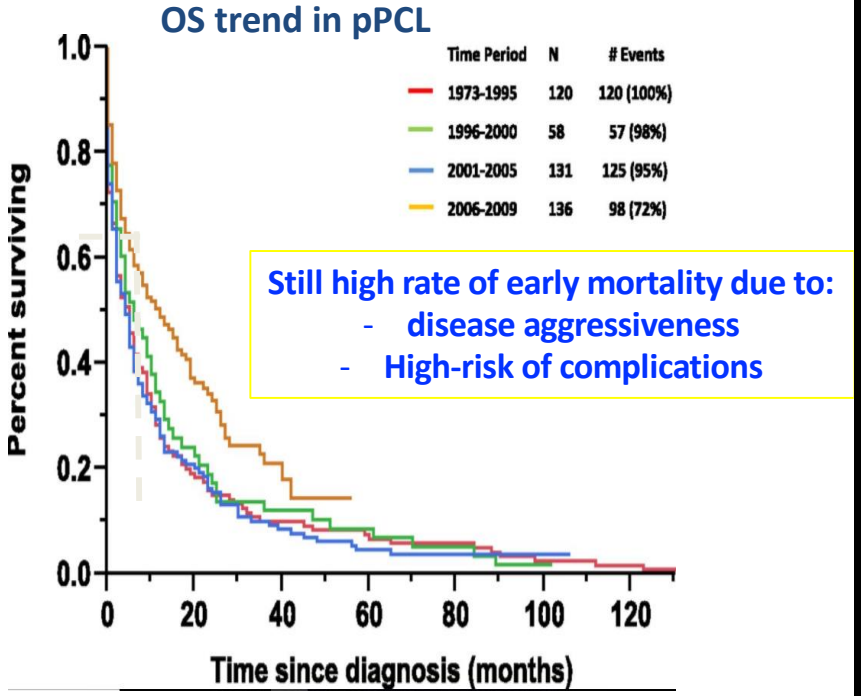
- **Primary PCL:** no previous history of MM; <1-4% of all MM (crude incidence 0.04-0.05 /100.000 persons per year in EU) [2]
- **Secondary PCL:** leukemic transformation of relapsed refractory MM; (1% of all MM, about 12% of MM with high tumor burden) [2]
- **Diferential diagnosis with reactive plasmacytosis as well as myeloma with circulating PCs** [3]

1. Touzeau C, Moreau P. *Blood.* 2016;127(8):971-976; 2. Suska A, et al. *Clin Hematol Int*. 2020;2(4):133-142; 3. Albarracin F, Fonseca R. *Blood Rev.* 2011;25:107-112.

Plasma cell leukemia: Outcomes compared with MM



2001-2006: median OS 50 months



Still high rate of early mortality due to:
- disease aggressiveness
- High-risk of complications

The presence of high-risk CA in pPCL confers a poorer prognosis

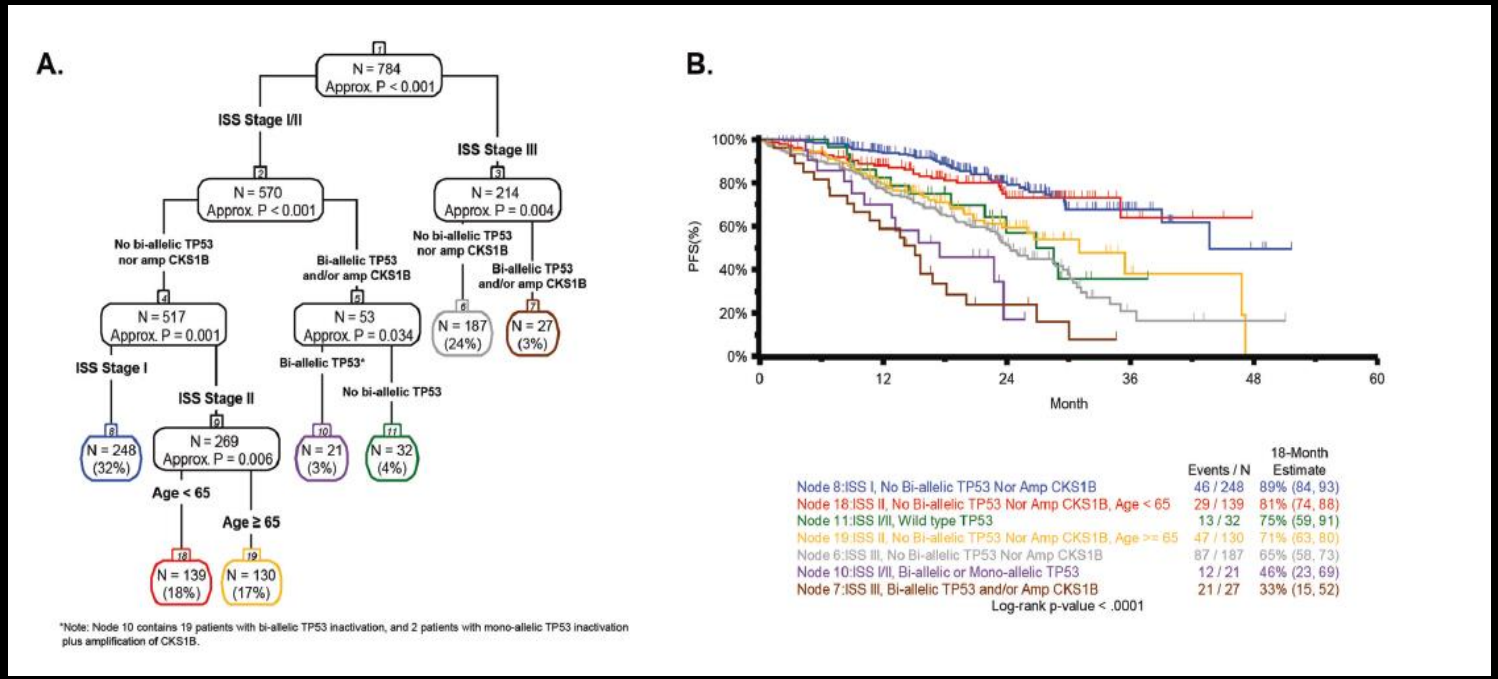
Kumar SK, et al. *Blood.* 2009;111:2516-2520; Gonsalves WI, et al. *Blood.* 2014;124(6):907-912.

Cytogenetic abnormalities

- **FISH routine testing should include at least t(4;14) and del(17p), 1q, and 1p. It is also possible to include t(14:16)**
- **It is relevant to know the mutational status for *TP53***
- **Concerning other mutations, huge heterogeneity is present**
- **CA may differ in first and later relapse because of clonal evolution, which may influence the effect of salvage treatment**
- **Clinical classifications may combine these lesions with ISS, serum LDH, or HR gene expression signatures**

Sonneveld P, et al. *Blood.* 2016;127(24):2955-2962.

A high-risk, double-hit group of NDMM identified by genomic analysis



A high-risk subgroup was defined by recursive partitioning using either a) bi-allelic *TP53* inactivation or b) amplification (≥4 copies) of *CKS1B* (1q21) on the background of International Staging System III, composing 6.1% of the population (median PFS = 15.4 months; OS = 20.7 months)

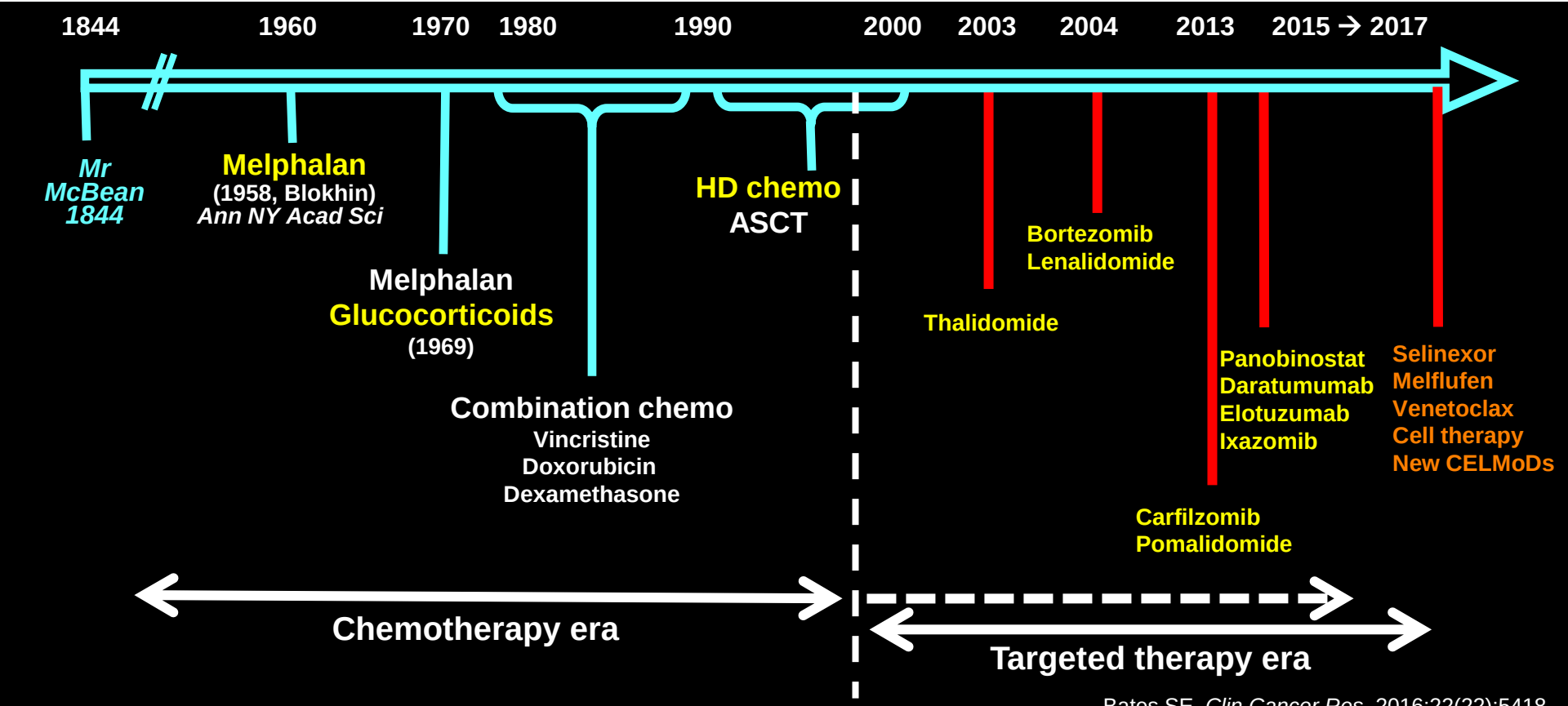
Walker B, et al. *Leukemia.* 2019;33(1):159-170.

What are the therapeutic options for patients with high-risk features?

What is, in your opinion, the most relevant approach for the management of MM patients with high-risk features?

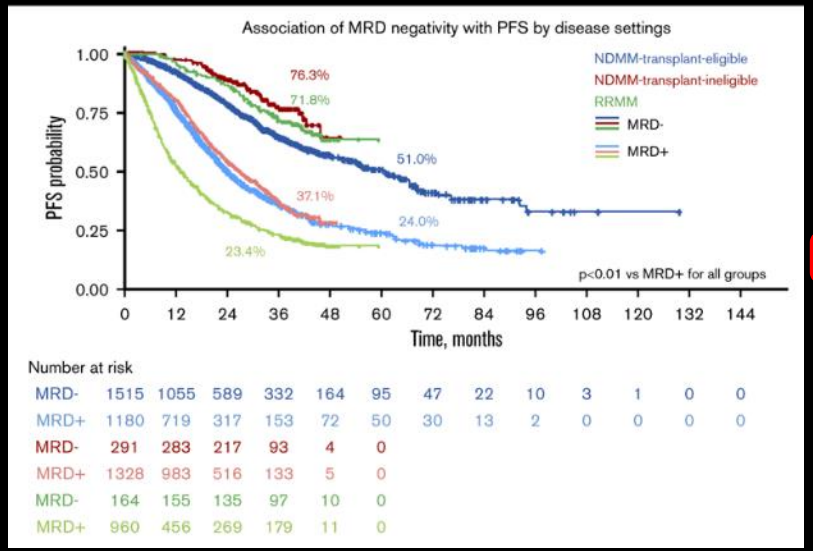
1. To use novel agent-based combinations
2. To try to achieve minimal residual disease negativity
3. To use combinations based on alkylators and conventional chemotherapy
4. Answer 1 and 2 are correct

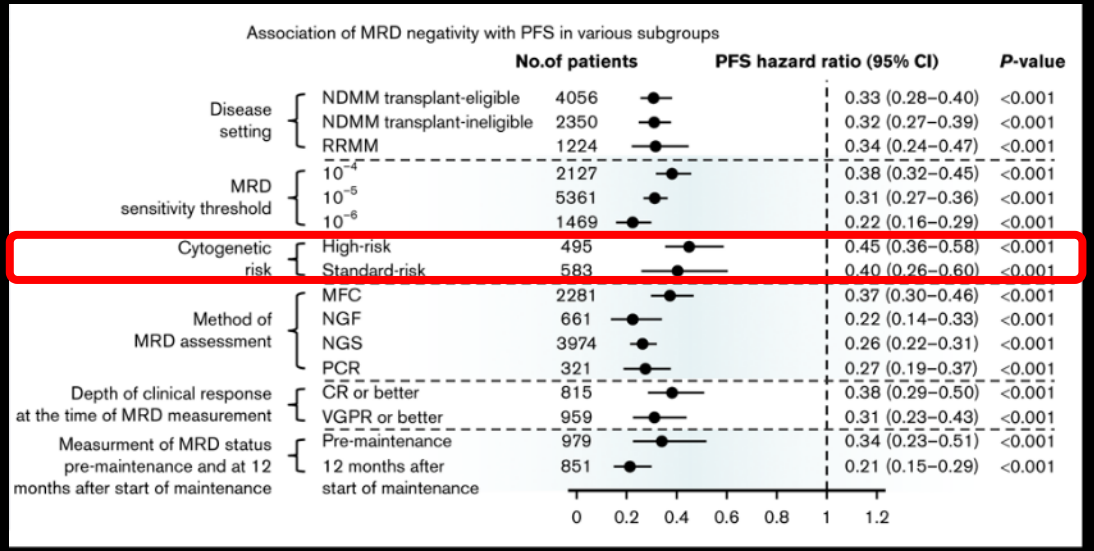
Treatment of MM



Bates SE. *Clin Cancer Res.* 2016;22(22):5418.

MRD as predictor across MM patient subgroups including HR





MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; RRMM, relapsed refractory multiple myeloma.

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

What are factors that determine high risk in a patient with myeloma?

Patient-specific factors

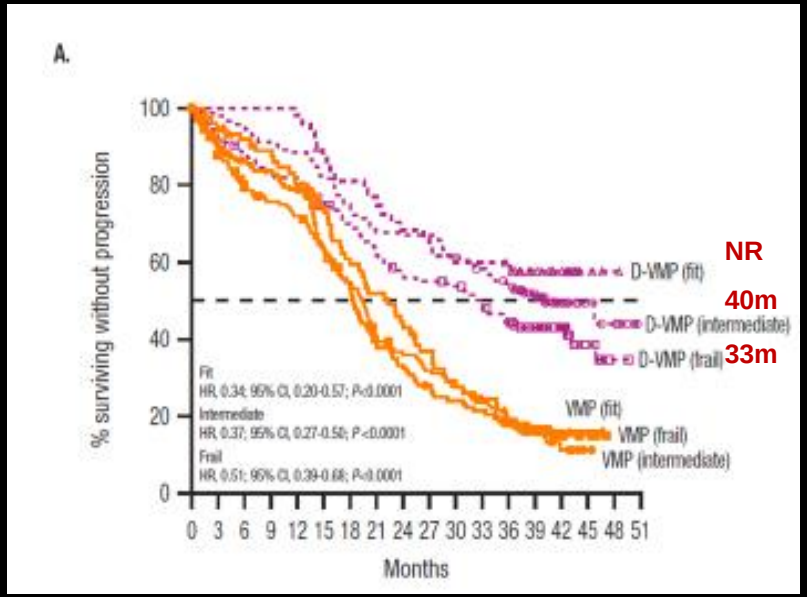
- **Age**
- **Comorbidities**, eg, renal failure, spinal cord compression

Disease-specific factors

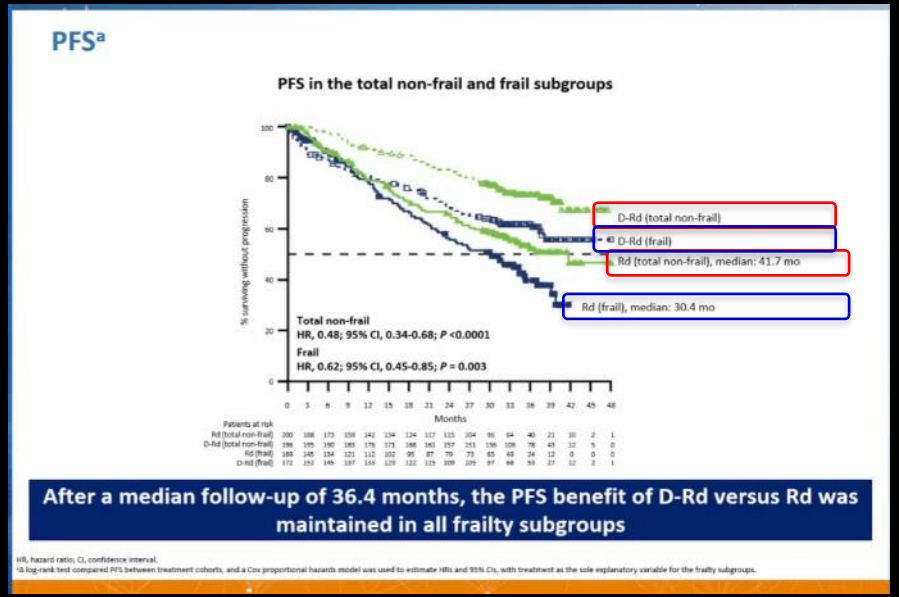
- ISS stage/R-ISS
- Cytogenetic abnormalities
- Extramedullary disease
- Plasma cell leukemia
- Lactate dehydrogenase level

How do novel combinations improve the outcomes of frail NDMM patients?

ALCYONE trial: Dara-VMP vs VMP (33% of frail patients)



MAIA trial: Dara-Rd vs Rd (30% of frail patients)



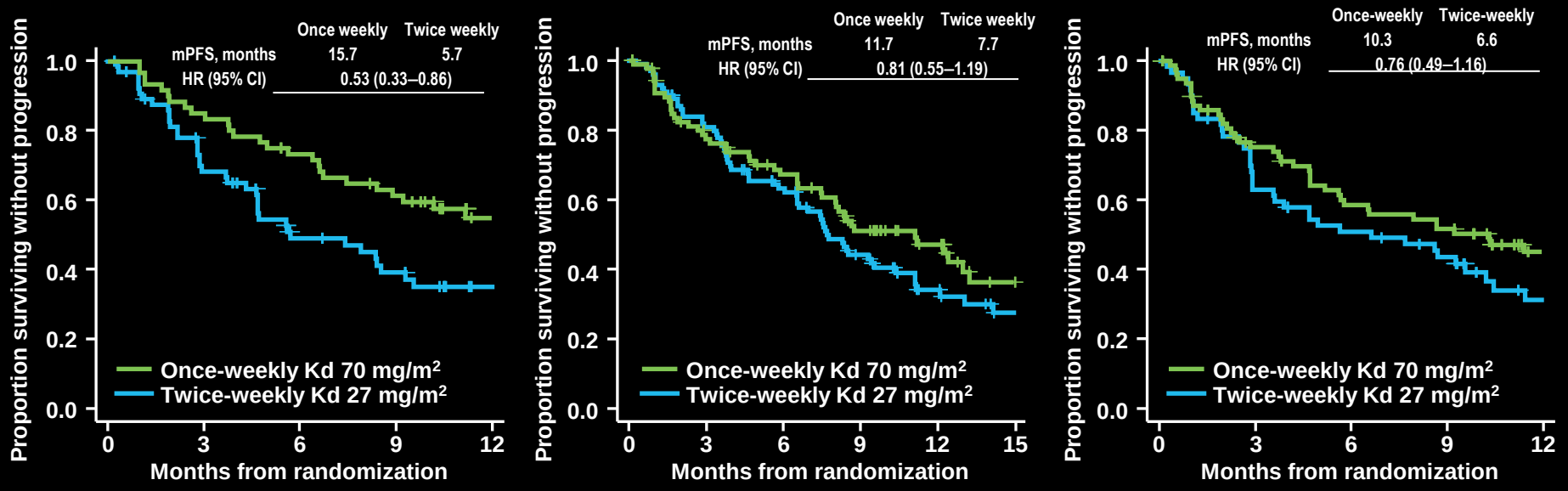
The addition of daratumumab improved the outcomes of frail patients.
Frailty evaluated through the use of chronologic age, ECOG, and Charlson comorbidity index.

Mateos MV. Submitted; Zamagni E, et al. European Myeloma Network 2021 Virtual Meeting.

How do novel combinations improve the outcomes of frail RRMM patients?

In **ARROW**, median PFS was 11.2 mo for K once weekly vs 7.6 mo for K twice weekly, with HR of 0.69 (95% CI: 0.54-0.83)

Fit	Intermediate	Frail

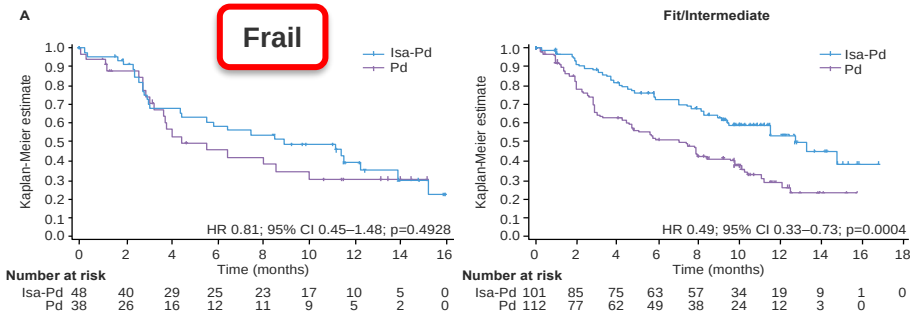


Mateos MV. 17th International Myeloma Workshop. Boston, MA, 2019.

How do novel combinations improve the outcomes of frail, more heavily treated RRMM patients?

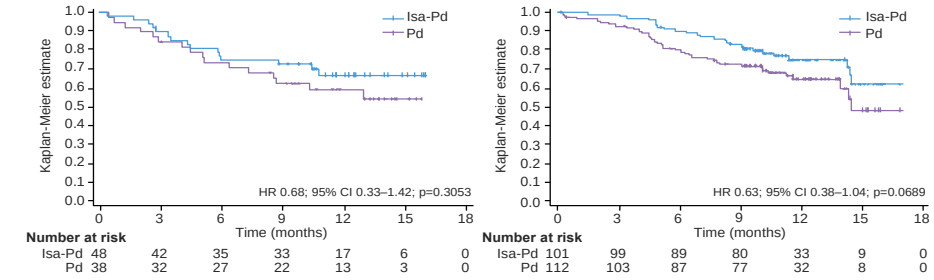
In **ICARIA**, median PFS was 11.5 mo for ISA-Pd vs 6.5 mo for Pd, with HR of 0.59

Median progression-free survival (PFS) with Isa-Pd vs Pd



- In frail patients was 9.0 vs 4.5 months (hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.45–1.48; log-rank p=0.4928).
- In fit/intermediate patients was 12.7 vs 7.4 months (HR 0.49; 95% CI 0.33–0.73; log-rank p=0.0004).

Median overall survival (OS) with Isa-Pd vs Pd



- 66.9% (95% CI 50.8–78.7) vs 58.8% (95% CI 41.0–72.9) in frail patients.
- 75.0% (95% CI 64.5–82.8) vs 64.5% (95% CI 53.9–73.3) in fit/intermediate patients.

Schjesvold F, et al. ASH 2020. Abstract/Poster 1411.

What are factors that determine high risk in a patient with myeloma?

Patient-specific factors

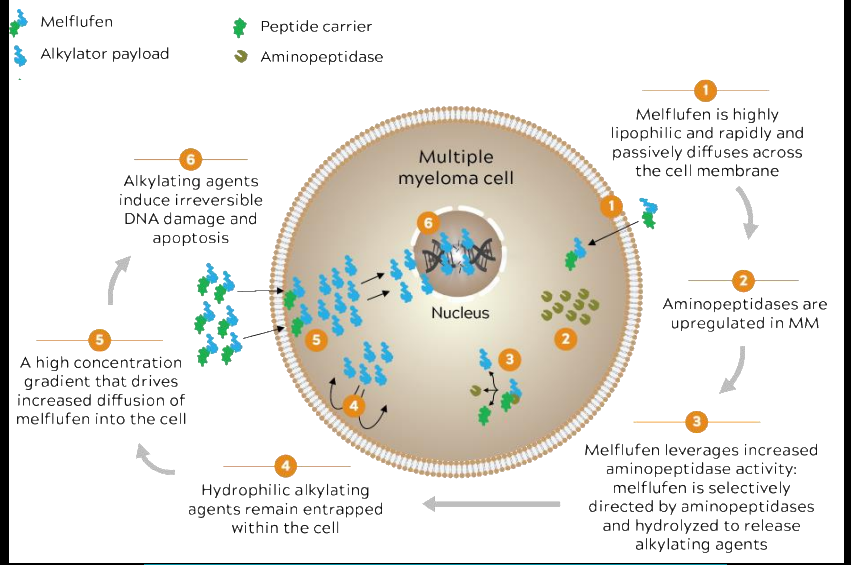
- Age
- Comorbidities, eg, renal failure, spinal cord compression

Disease-specific factors

- ISS stage/R-ISS
- Cytogenetic abnormalities
- **Extramedullary disease**
- Plasma cell leukemia
- Lactate dehydrogenase level

Melflufen plus Dex in RRMM with EMD: Subanalysis from the HORIZON clinical trial

Melphalan flufenamide (melflufen) is an investigational first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**[1-5]

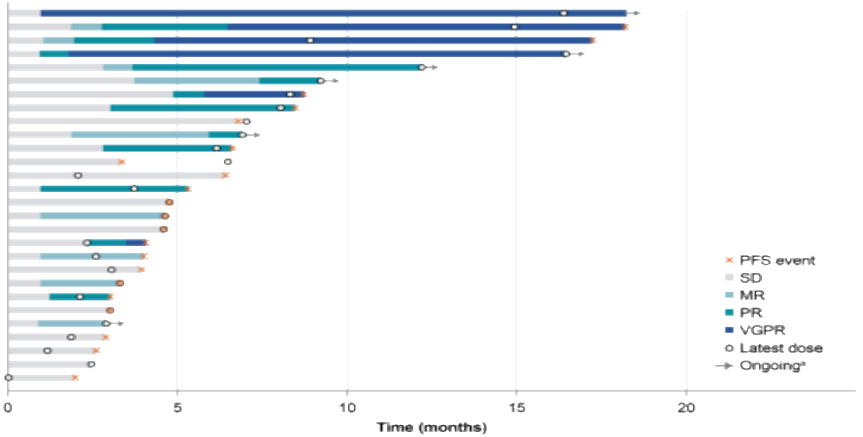


Outcome[6]	Overall Population (N=157)
ORR (95% CI), %	**29 (22-37)**
OS, median (95% CI), mo	**11.6 (9.3-15.4)**
PFS, median (95% CI), mo	**4.2 (3.4-4.9)**
DOR (≥PR), median (95% CI), mo	5.5 (3.9-7.6)

ORR and CBR For Patients Within the EMD Group

	ORR, % (95% CI)	CBR, % (95% CI)
Bone-related plasmacytoma (n=28)	25 (10.7-44.9)	32 (15.9-52.4)
Soft-tissue plasmacytoma (n=27)	22 (8.6-42.3)	30 (13.8-50.2)

Swim-Lane Plot for Patients With EMD Who Achieved ≥SD



Median treatment duration was 12 weeks (range, 4-79) in the EMD group and 18 weeks (range, 4-99) in the non-EMD group.

Richardson P, et al. ASH 2020. Abstract 3214.

Efficacy of BCMA CAR T Ide-cel on the basis of baseline features

Deep and durable responses were observed in patients with more aggressive disease features.
128 RRMM patients were included in karMMa-2 trial and 39% presented with EMD.

Efficacy outcomes	High-risk subgroups												All Ide-cel treated
	Extramedullary disease		Cytogenetic risk		Tumour burden		Bridging therapy		R-ISS disease stage		No. prior regimens/year		
	With (n = 50)	Without (n = 78)	High (n = 45)	Not high (n = 66)	High (n = 65)	Low (n = 57)	With (n = 112)	Without (n = 16)	Stage III (n = 21)	Stage I/II (n = 104)	>1 (n = 60)	≤1 (n = 68)	(N = 128)
ORR, % (95% CI)	70 (55.4–82.1)	76 (64.6–84.7)	69 (55.4–82.4)	80 (70.7–89.9)	71 (58.2–81.4)	77 (64.2–87.3)	71 (62.1–79.6)	88 (61.7–98.4)	48 (25.7–70.2)	80 (70.8–87.0)	65 (51.6–76.9)	81 (69.5–89.4)	73 (65.8–81.1)
CRR, % (95% CI)	24 (13.1–38.2)	38 (27.7–50.2)	31 (17.6–44.6)	38 (26.2–49.6)	29 (18.6–41.8)	37 (24.4–50.7)	34 (25.3–43.5)	25 (7.3–52.4)	10 (1.2–30.4)	38 (29.1–48.5)	30 (18.8–43.2)	35 (24.1–47.8)	33 (24.7–40.9)
Median D0R,[a] months (95% CI)	9.2 (5.4–11.3)	11.1 (9.9–16.7)	10.7 (6.5–NE)	10.9 (8.0–13.5)	10.4 (6.1–11.3)	11.0 (9.2–16.7)	10.9 (9.0–11.4)	9.1 (4.0–13.5)	6.9 (1.9–10.3)	11.0 (10.0–11.4)	10.5 (9.0–11.3)	11.0 (6.5–11.4)	10.7 (9.0–11.3)
Median PFS, months (95% CI)	7.9 (5.1–10.9)	10.4 (4.9–12.2)	8.2 (4.8–11.9)	10.4 (5.4–12.2)	7.5 (4.9–11.3)	10.4 (5.6–12.3)	8.8 (5.5–11.6)	8.5 (3.4–14.4)	4.9 (1.8–8.2)	11.3 (6.1–12.2)	8.9 (3.1–11.1)	8.6 (5.8–12.2)	8.8 (5.6–11.6)

Ide-cel was approved by FDA on 26 March, 2021.

[a]Duration among responders.

Raje NS, et al. Presented at ASH 2020. Abstract 3234.

What are factors that determine high risk in a patient with myeloma?

Patient-specific factors

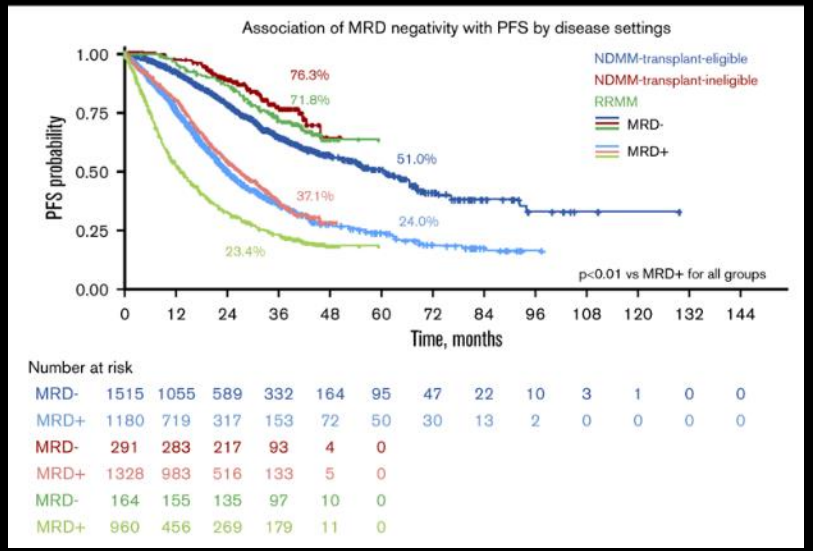
- Age
- Comorbidities, eg, renal failure, spinal cord compression

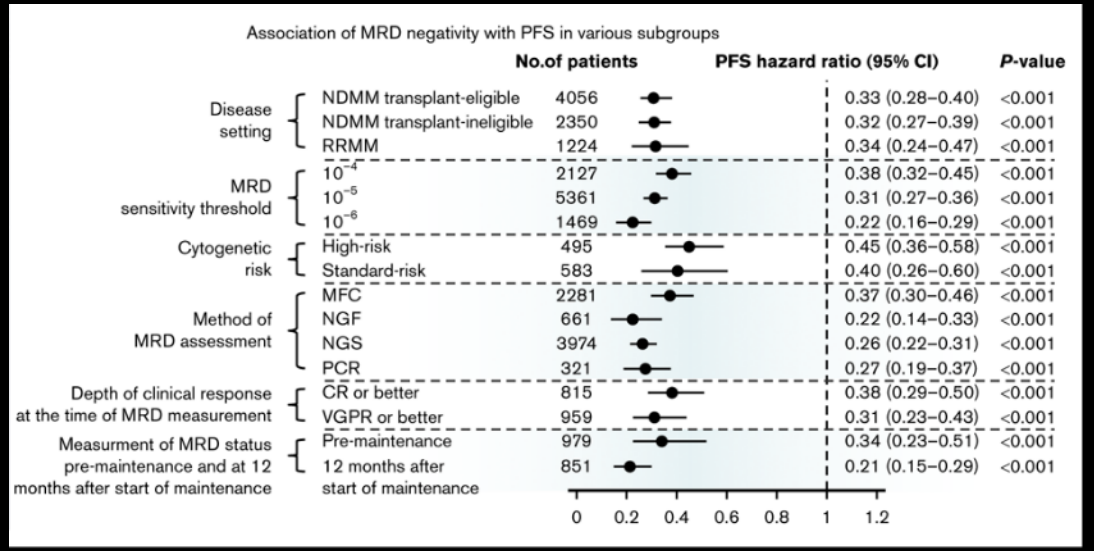
Disease-specific factors

- **ISS stage/R-ISS**
- **Cytogenetic abnormalities**
- Extramedullary disease
- **Plasma cell leukemia**
- Lactate dehydrogenase level

Response to treatment

MRD as predictor across MM patient subgroups





MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; RRMM, relapsed refractory multiple myeloma.

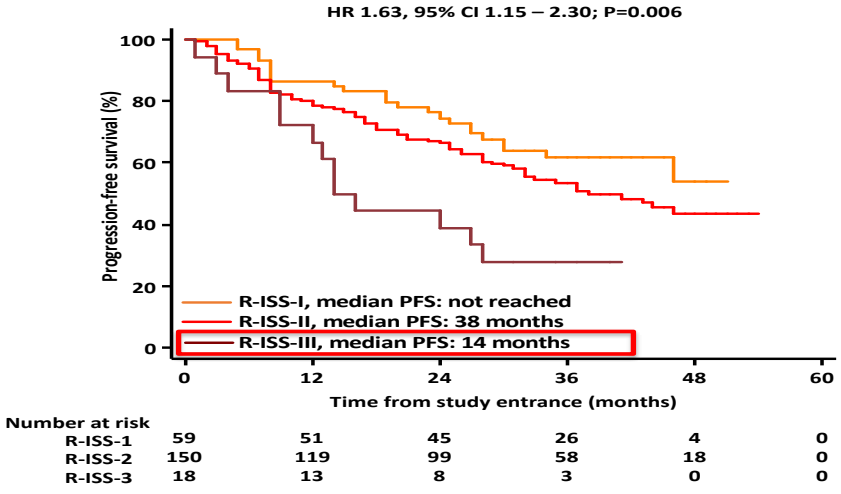
Munshi N, et al. *Blood Adv*. 2020;4(23):5988-5999.

MRD negativity is able to overcome the poor prognosis defined by the R-ISS system

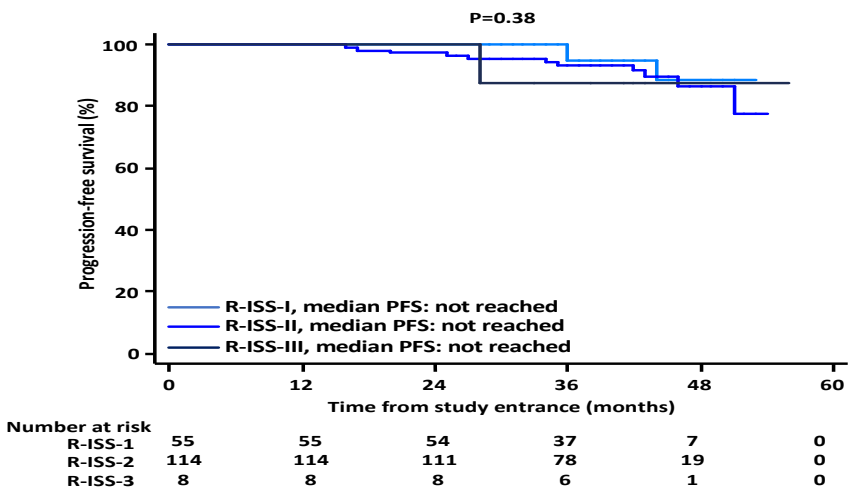
RVD × 6c → ASCT → RVD × 2c → Rd +/– ixazomib

Risk is dynamic: patients with adverse prognosis may shift into a favorable one upon achieving deep responses to treatment

MRD-positive



MRD-negative



The best way to overcome high-risk cytogenetics is through the achievement of MRD-negativity

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

Management of MM in the newly diagnosed transplant candidate patient

Induction

Three-drug–based combinations

- ***VTD-Dara***
- *VCD*
- *VRD*
- *VTD*

ASCT

MEL200 as standard conditioning regimen

Consolidation

Similar to induction to upgrade the response depending on the number of induction cycles

Maintenance

Len single agent

Bortezomib in high risk

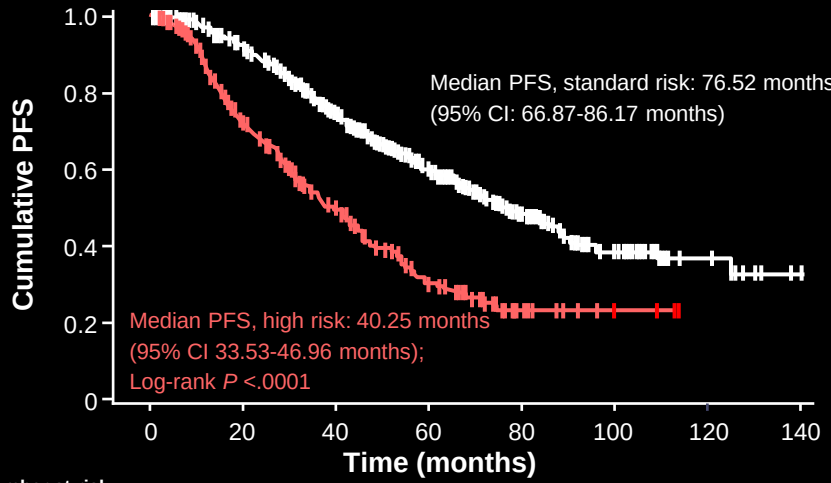
According to the ESMO[1] and NCCN[2] guidelines

ASCT, autologous stem cell transplant; PAD, bortezomib, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone; VTD-dara, bortezomib, thalidomide, dexamethasone, daratumumab.

1. Dimopoulos MA, et al. *HemaSphere.* 2021;5(2):e528;
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple myeloma. Version 5.2021. 2021.

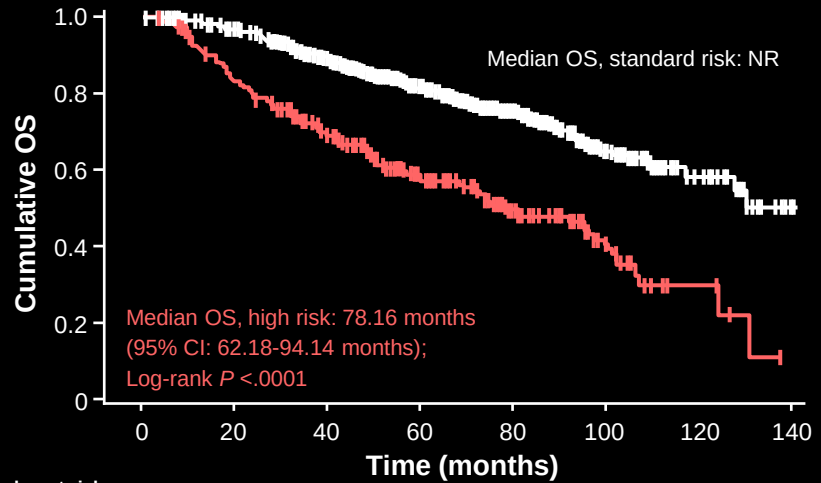
Real-world outcomes of RVd induction in transplant by standard- and high-risk status

1000 consecutive NDMM patients treated with RVd as continuous therapy (75.1% patients received upfront ASCT)



Number at risk

Standard risk	503	314	159	75	27	6	1
High risk	154	87	33	9	2	0	0



Number at risk

Standard risk	550	394	240	133	56	14	1
High risk	193	134	79	37	14	4	0

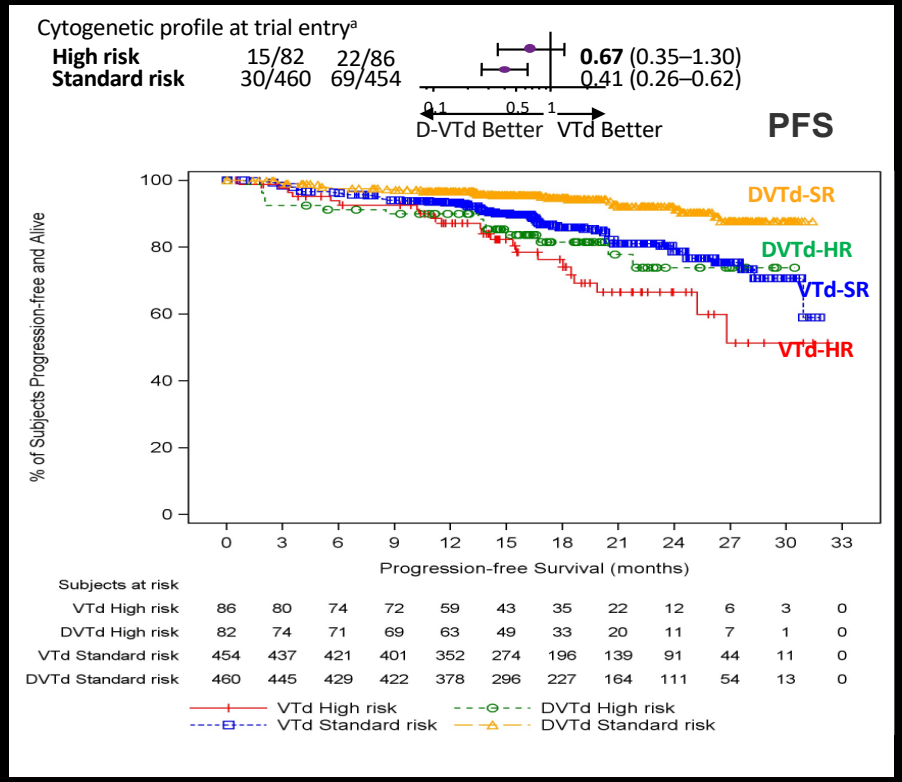
Patients	Median PFS (months)	Median OS (months)	OS rates (5 years)	OS rates (10 years)
High risk	40.3	78.2	57%	29%
Standard risk	76.5	NR	81%	58%

VRd is not approved in EU for transplant-eligible NDMM patients (approved for transplant-ineligible patients).
Risk defined by IMWG criteria. IMWG, International Myeloma Working Group.

Joseph N, et al. *J Clin Oncol.* 2020;38(17):1928-1937.

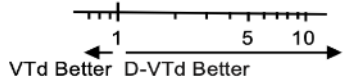
Dara-VTD vs VTD as induction and consolidation in TE NDMM: Results from the phase 3 CASSIOPEIA trial (n = 1085) – HR subgroups

In the ITT population: sCR/MRD– rate/median PFS was 29% vs 20%/64% vs 44%/93% vs 85% at 18 mo



Probability of MRD– achievement with D-VTd vs VTd

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)

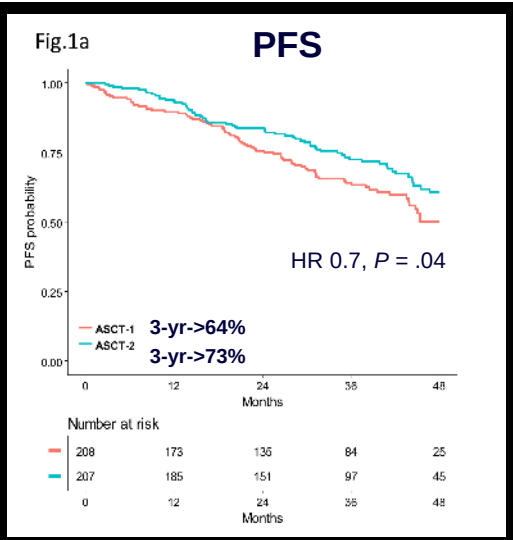


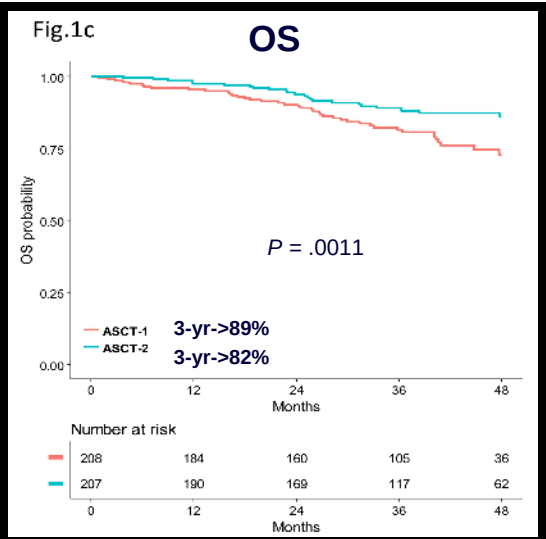
Moreau P, et al. *Lancet.* 2019;394:29-38.

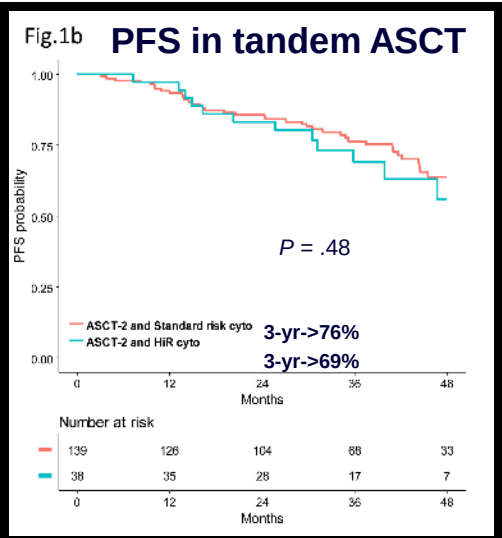
Tandem ASCT in high-risk NDMM patients

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

VCD × 4c → HDM ½ → 2R → Observ → Len maintenance







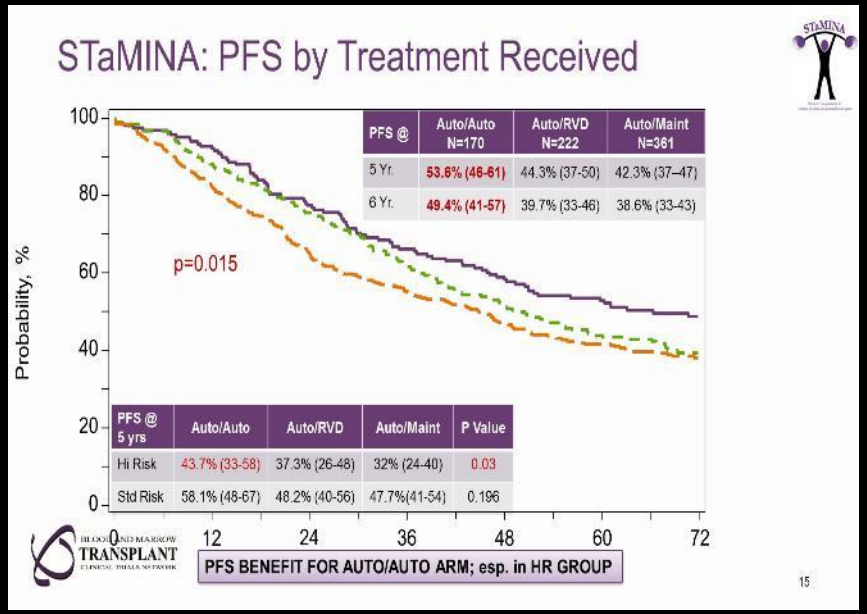
ASCT-2 was superior to ASCT-1 in terms of prolonged PFS and OS in the overall population and seems to be able to overcome the poor prognosis of patients with advanced R-ISS and HiR CA.

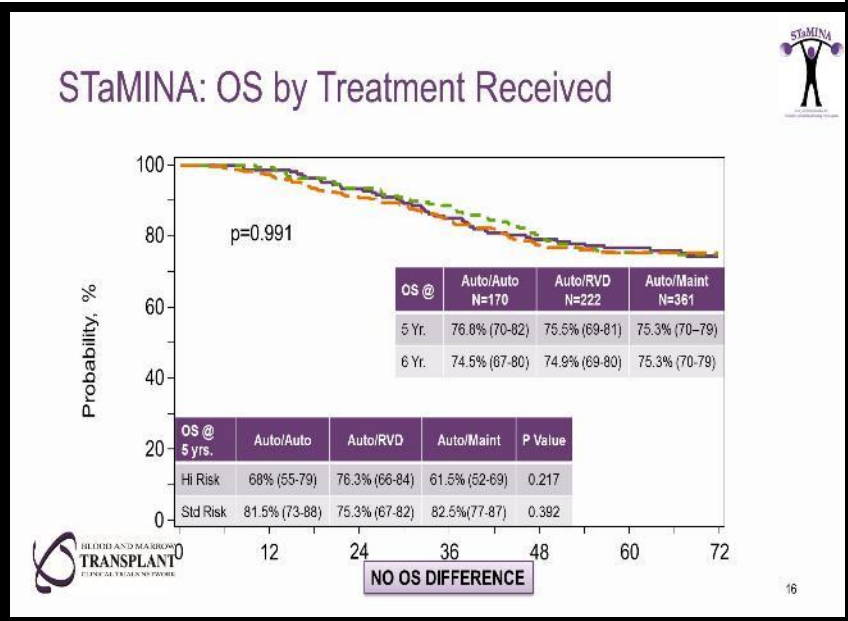
Cavo M, et al. ASH 2017. Oral presentation.

Tandem ASCT in high-risk NDMM patients

Induction -> HDM 1R

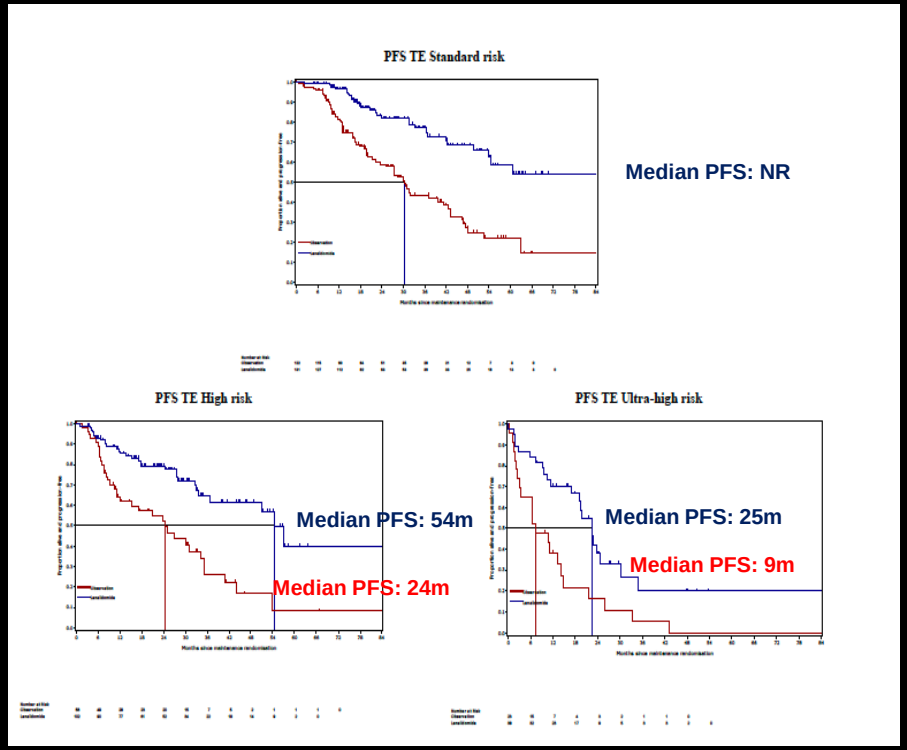
- **No consol → Len maint**
- **RVD × 4c → Len maint**
- **HDM → Len maint**

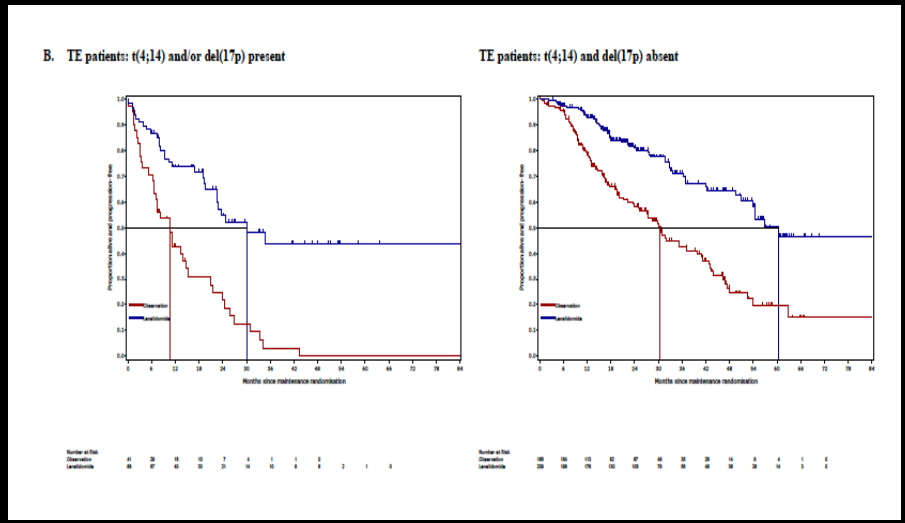




Hari P, et al. ASCO 2020.

Lenalidomide as maintenance in HR-NDMM transplant eligible: Myeloma XI trial

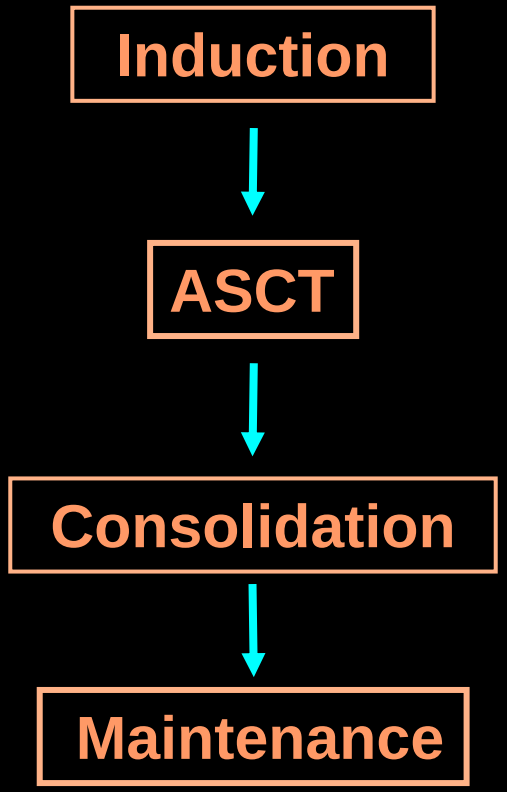




Lenalidomide improves the outcome of patients with HR or ultra HR, but does not overcome its poor prognosis.

Jackson G, et al. *Lancet Oncol.* 2019;20(1):57-73.

Management of HR-MM in the newly diagnosed transplant candidate patient



Three-drug–based combinations

- ***VTD-Dara***
- *VCD*
- *VRD*
- *VTD*
- ***What about carfilzomib?***

Tandem MEL200 as standard conditioning regimen

Similar to induction to upgrade the response depending on the number of induction cycles

Len single agent
Len-Dara
Len-carfilzomib

According to the ESMO[1] and NCCN[2] guidelines

ASCT, autologous stem cell transplant; PAD, bortezomib, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone; VTD-dara, bortezomib, thalidomide, dexamethasone, daratumumab.

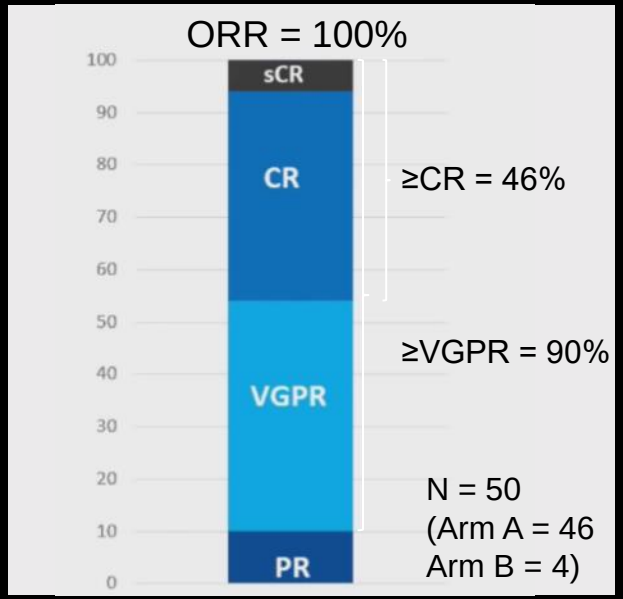
1. Dimopoulos MA, et al. *HemaSphere*. 2021;5(2):e528;
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple myeloma. Version 5.2021. 2021.

Phase 2 GMMG-CONCEPT study: Interim analysis of isatuximab + carfilzomib-lenalidomide-dexamethasone in high-risk NDMM

Isa-KRd induction, consolidation, and maintenance; TE patients undergo ASCT after 6 cycles induction

- TE (Arm A; n = 117) and TNE (Arm B; n = 36) patients
- Median (range) age: 58 (42–82) years
- **High risk: del(17p); t(4;14); t(14;16) or >3 copies 1q21 AND ISS stage II or III**

Best response during induction (6 cycles)



Safety: Most common TEAEs

Hematologic TEAEs, n=50	Grade 3 or 4 N (%)
Leukopenia	13 (26%)
Neutropenia	17 (34%)
Lymphopenia	14 (28%)
Anemia	5 (10%)
Thrombocytopenia	7 (14%)

Non-Hematologic TEAEs, n=50	Any Grade N (%)	Grade 3 or 4 N (%)
URI	9 (18%)	0
Pyrexia	6 (12%)	0
Rash	8 (16%)	0
Peripheral sensory neuropathy	8 (16%)	0 (2%)
Nasopharyngitis	5 (10%)	0
Hypertension	6 (12%)	6 (12%)
Cardiac failure	2 (4%)	2 (4%)
Infusion Reaction	16 (32%)	0

- **MRD–, 20/33 (61%) evaluable TE patients during induction**

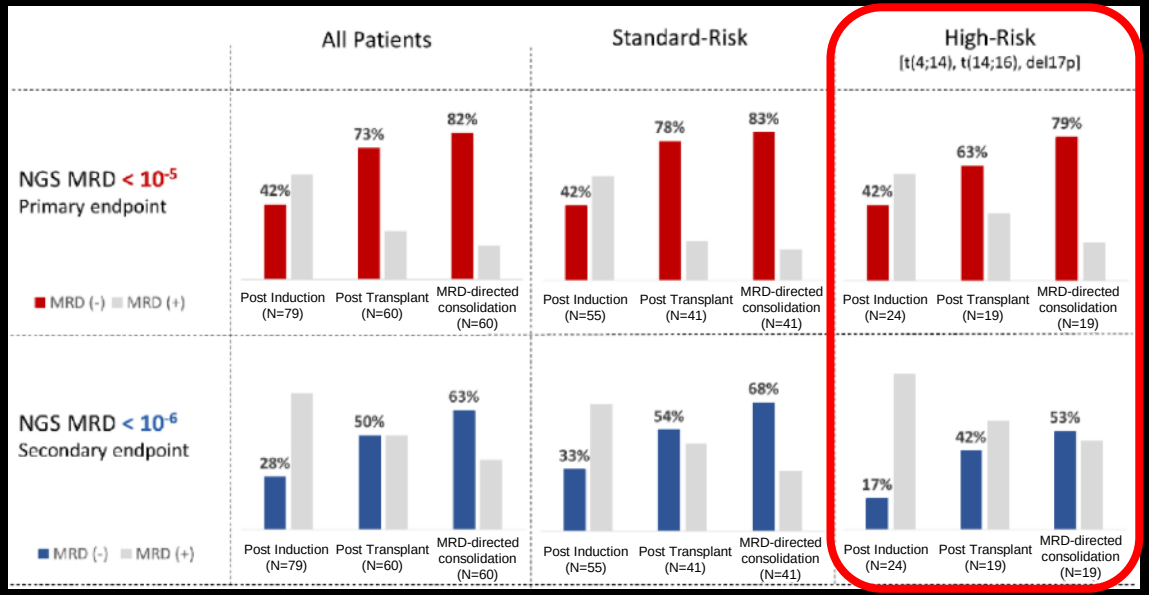
CR, complete response; PR, partial response; sCR, stringent complete response; TEAE, treatment-emergent adverse event; TE, transplant eligible; TNE, transplant non-eligible; URI, upper respiratory tract infection; VGPR, very good partial response.

Weisel K, et al. EHA 2020. Abstract S204.

Phase 2 MASTER study: Daratumumab + carfilzomib-lenalidomide-dexamethasone induction and MRD response-adapted consolidation in NDMM

D-KRd induction (4 cycles), D-KRd consolidation (4 + 4 cycles), and R maintenance

- Median age: 61 years
- **High risk: 29%**
- **≥VGPR after induction: 91%; ≥CR post-ASCT and MRD-guided consolidation: 92%**



Safety: Most common TEAEs

Common AEs	Grade 3 or 4 (%)
Neutropenia	25
Lymphopenia	23
Infection	12
Anemia	11

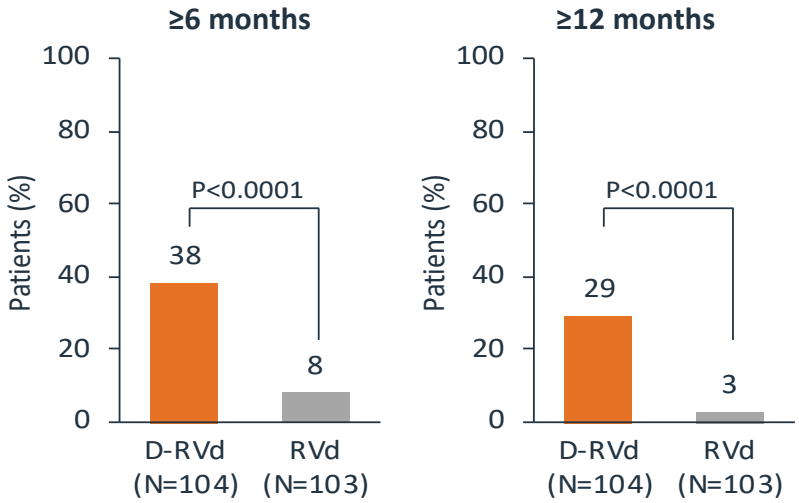
Optimal approach but . . . will it be a valid approach to stop therapy on the basis of MRD in HR subgroup of pts?

AE, adverse event; MRD, minimal residual disease; NGS, next-generation sequencing.
Costa L, et al. EHA 2020. Abstract EP928.

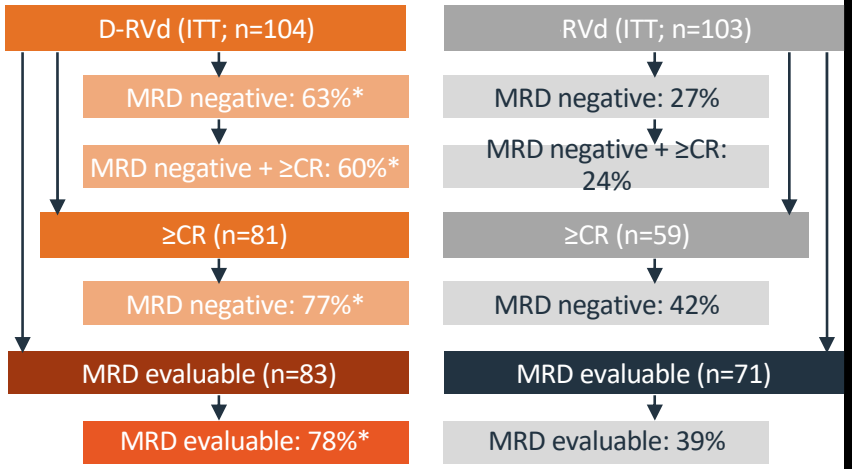
New options for maintenance in HR-NDMM transplant eligible

RVd +/– Dara → ASCT → RVd +/– Dara → maintenance with R +/– Dara

MRD negativity at ≥6 and ≥12 months



MRD negativity at 12-month maintenance cutoff



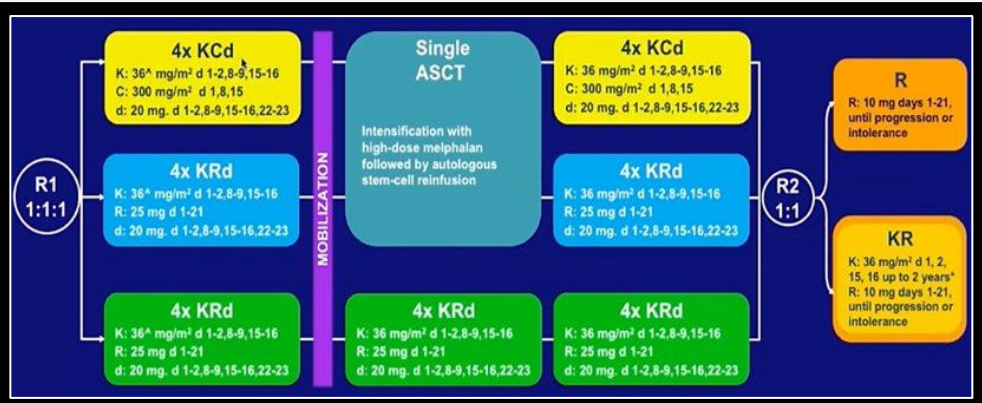
*P<0.0001 for all comparisons

MRD– and sustained over time higher with Dara-R as maintenance will improve the outcome in HR patients.

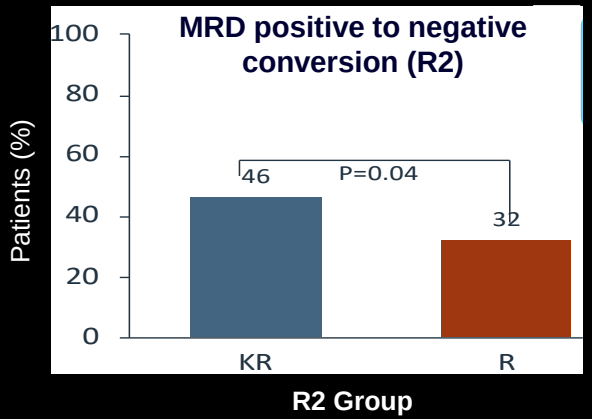
CR, complete response; D-RVd, daratumumab, lenalidomide, bortezomib, dexamethasone; ITT, intention to treat; MRD, minimal residual disease; RVD, lenalidomide, bortezomib, dexamethasone; sCR, stringent CR.

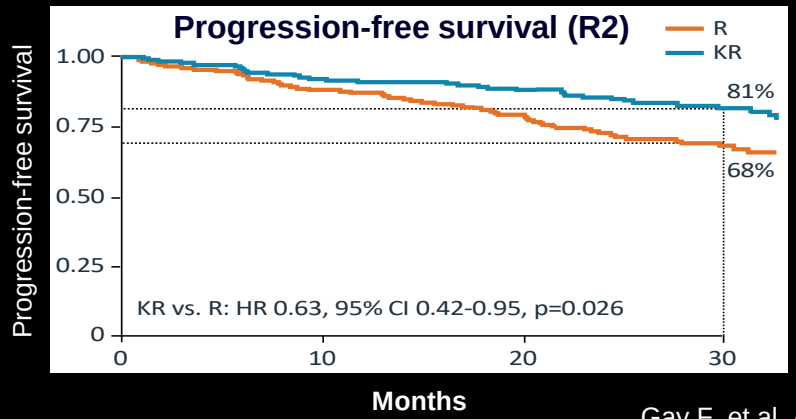
Kaufman JL, et al. ASH 2020. Abstract 549 (oral presentation).

New options for maintenance in HR-NDMM transplant eligible



- KR maintenance improves PFS compared with R in all patients
- No significant toxicity signal
- Disadvantages: 4 days of infusion, HR still does worse than SR

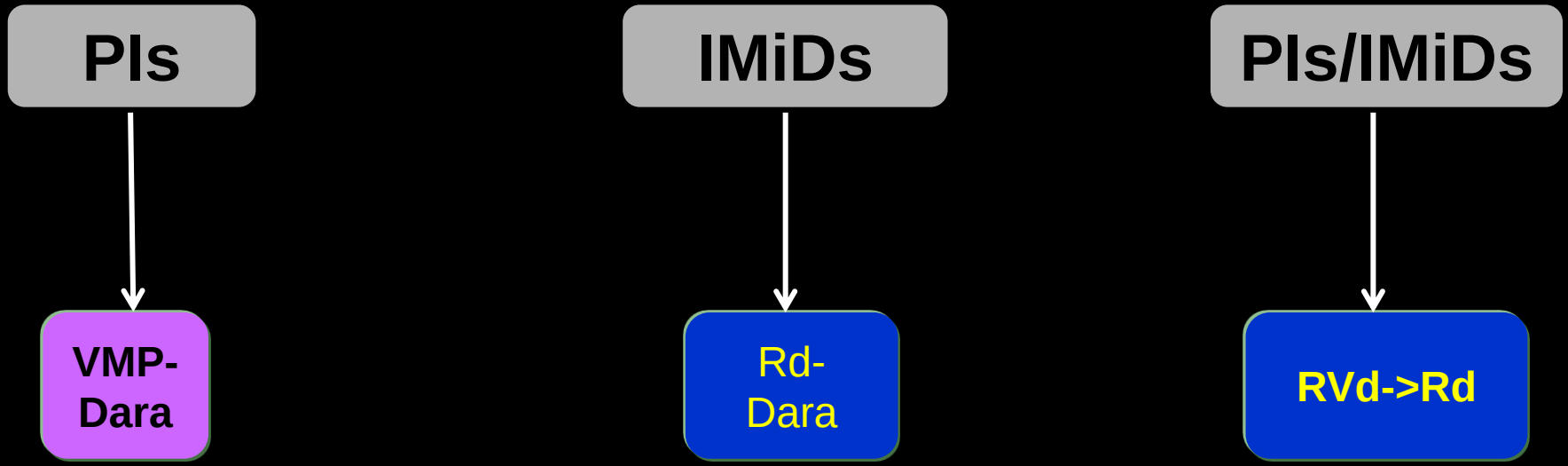




Median follow-up from Random 2:
31 (26-36) months

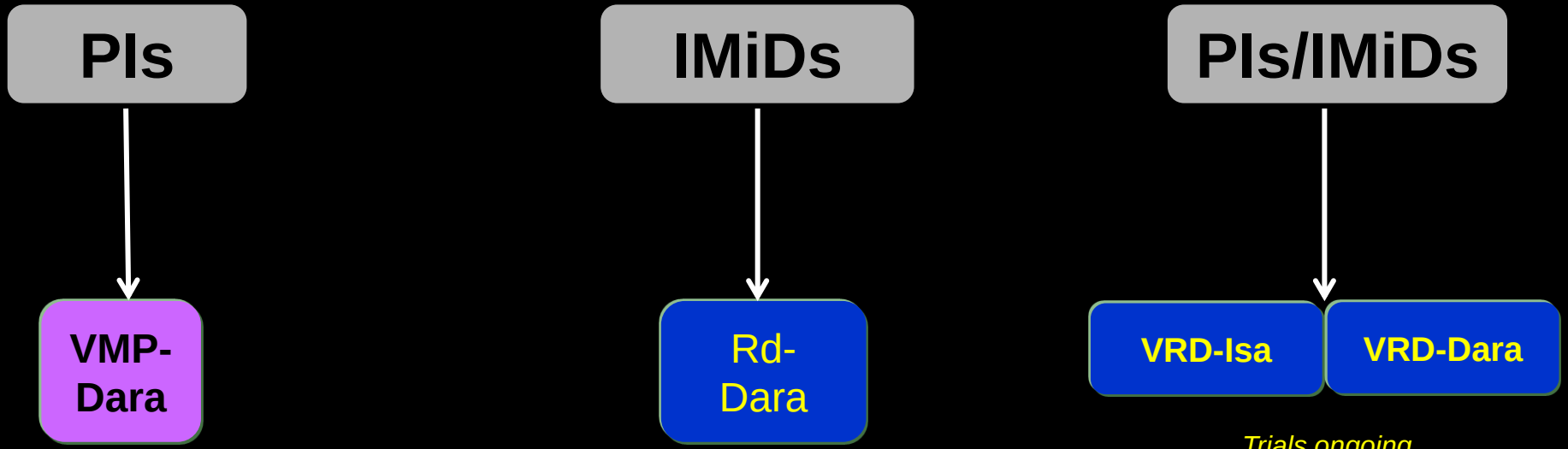
Gay F, et al. ASH 2020 Virtual Meeting. Abstract 141.

Management of MM in the non-transplant candidate ND patient



1. Mateos MV, et al. *N Engl J Med.* 2018;378:518-528; 2. Facon T, et al. *N Engl J Med.* 2019;380:2104-2115; 3. Durie B, et al. *Lancet.* 2017;389:519-527.

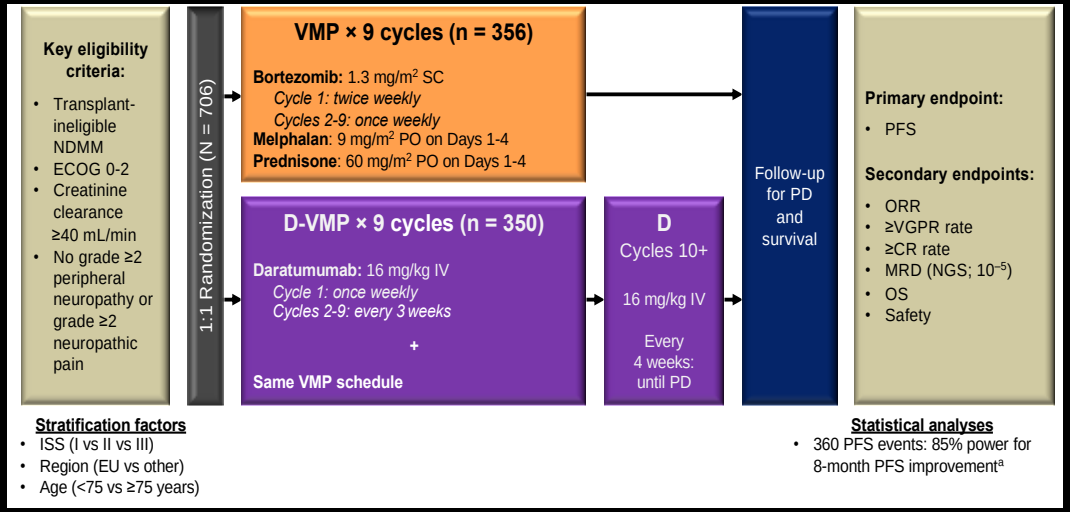
Management of MM in the HR-ND non–transplant-eligible patient

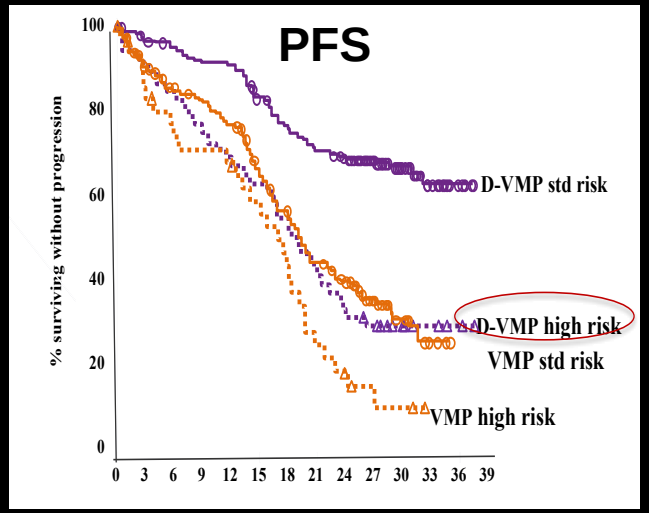


mAbs as part of the upfront setting for every NDMM non-transplant eligible

1. Mateos MV, et al. *N Engl J Med.* 2018;378:518-528; 2. Facon T, et al. *N Engl J Med.* 2019;380:2104-2115.

Dara-VMP vs VMP in HR-NDMM non-transplant eligible





- Dara added to VMP does not overcome the poor prognosis of the presence of high-risk CA
- This effect is especially observed after the first 12 mo when patients received only Dara
- In order to improve the outcome, something else should be added to Dara maintenance
- Patients with HR and achieving MRd negativity could potentially benefit

ORR: 91% vs 74%
CR: 45% vs 25%
PFS: 36.4 vs 19.3 mo
OS at 42 mo: 75 vs 67%
15% with HR CA

Mateos MV, et al. *N Engl J Med.* 2018;378:518-528.

Dara-Rd vs Rd in HR-NDMM non-transplant eligible

Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥30 mL/min

1:1 Randomization

D-Rd (n = 368)
Daratumumab (16 mg/kg IV)[a]
Cycles 1-2: QW
Cycles 3-6: Q2W
Cycles 7+: Q4W until PD
R: 25 mg PO daily on Days 1-21 until PD
d: 40 mg[b] PO or IV weekly until PD

Rd (n = 369)
R: 25 mg PO daily on Days 1-21 until PD
d: 40 mg[b] PO or IV weekly until PD

Primary endpoint:
- PFS

Key secondary endpoints[c]:
- ≥CR rate
- ≥VGPR rate
- MRD-negative rate (NGS; 10^{-5})
- ORR
- OS
- Safety

ORR: 93% vs 81%
CR: 48% vs 25%
PFS at 28 mo: 71% vs 56%
15% with HR CA

Efficacy

- After a median follow-up of 36.4 months, median PFS was NR with D-Rd versus 33.8 months with Rd (HR, 0.56; 95% CI, 0.44-0.71; *P*<0.0001; **Figure 2**)
  - The estimated 36-month PFS rate was 68% with D-Rd versus 46% with Rd (**Figure 2**)

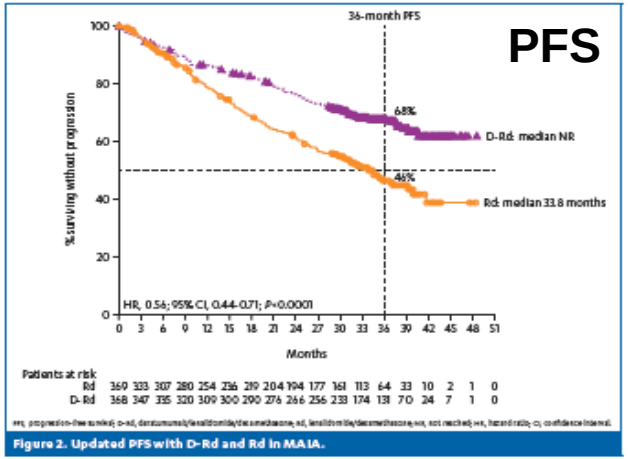
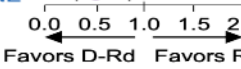


Figure 2. Updated PFS with D-Rd and Rd in MAIA.

	Rd n/N	Rd Median	D-Rd n/N	D-Rd Median	HR (95% CI)
Baseline hepatic function					
Normal	186/340	33.8	125/335	NE	0.50 (0.40-0.63)
Impaired	13/29	35.1	16/31	29.2	1.06 (0.51-2.21)
ISS staging					
I	39/103	51.2	28/98	NE	0.60 (0.37-0.97)
II	92/156	29.7	61/163	NE	0.46 (0.34-0.64)
III	68/110	24.2	52/107	42.4	0.59 (0.41-0.85)
Type of MM					
IgG	117/231	38.7	91/225	NE	0.67 (0.51-0.88)
Non-IgG	49/76	23.5	26/74	NE	0.36 (0.22-0.58)
Cytogenetic risk at study entry					
High risk	28/44	29.6	23/48	45.3	0.57 (0.33-1.00)
Standard risk	153/279	34.4	99/271	NE	0.48 (0.38-0.62)
ECOG PS score					
0	68/123	39.6	42/127	NE	0.45 (0.31-0.67)
1	92/187	35.1	72/178	NE	0.61 (0.45-0.84)
≥2	39/59	23.5	27/63	NE	0.52 (0.31-0.85)



Kumar S, et al. ASH 2020. Abstract 2276.

Phase 2 study: Carfilzomib-lenalidomide-Dex vs carfilzomib-thalidomide-Dex induction and carfilzomib maintenance (n = 60 pts)

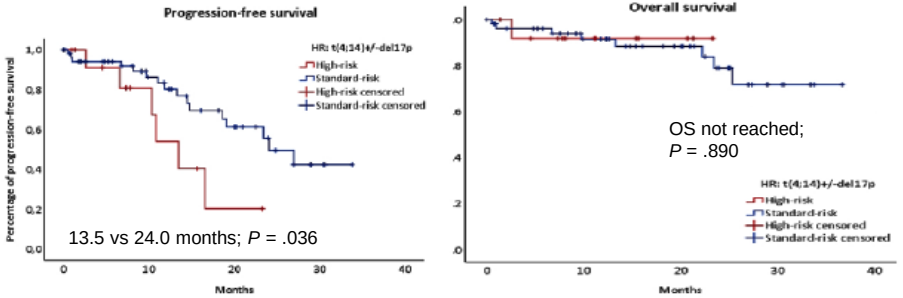
- Median age: 75 years
- Median follow-up: 15.7 months

Response rate by risk group

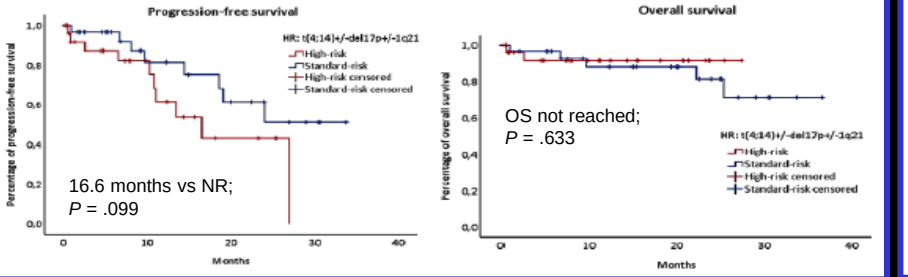
Response	SR patients without HR (n=49)	HR patients (n=11)	SR patients without HR ± 1q21 (n=29)	HR ± 1q21 (n=20)
ORR	93.9%	100%	89.6%	100%
PR	16.3%	27.3%	17.2%	20.0%
VGPR	38.8%	36.4%	48.3%	25.0%
CR	38.8%	36.4%	24.1%	55.0%

- MRD negativity: 18/40 (45%) patients

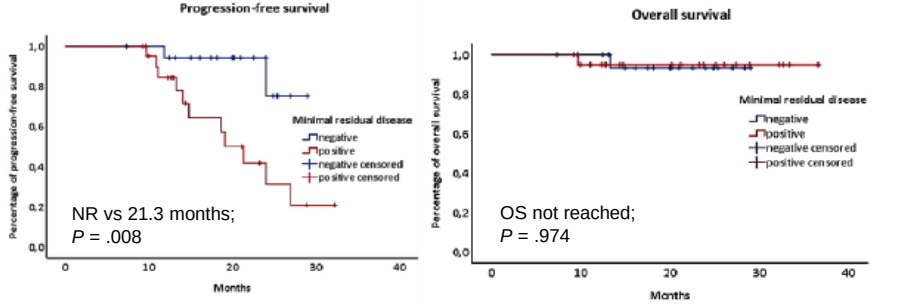
PFS was shorter in HR patients; no difference in OS was seen



PFS and OS did not differ between patients with and without HR cytogenetics ± 1q21



PFS was shorter in MRD+ patients; no difference in OS was seen



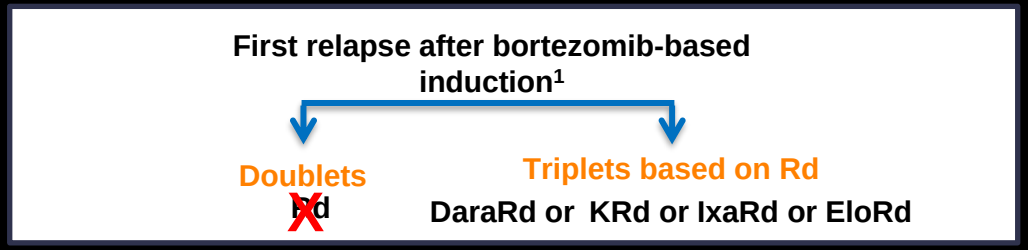
CR, complete response; HR, high risk; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SR, standard risk; VGPR, very good partial response.

Ludwig H, et al. EHA 2020. Abstract EP961.

Management of first relapses in HR-MM patients

First line

- **Bortezomib-based combinations**
- **Len naive or exposed, but sensitive**



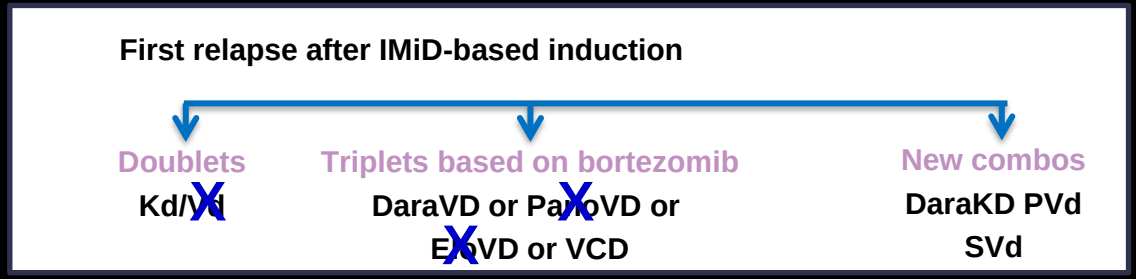
Efficacy	POLLUX DaraRd vs Rd[2,3]	ASPIRE KRd vs Rd[4,5]	ELOQUENT-2 ERd vs Rd[6]	TOURMALINE-MM1 IRd vs Rd[7]
PFS HR (95% CI)	**0.44 (0.35–0.55)** **44.5 vs 17.5 mo**	**0.69 (0.57–0.83)** **26.3 vs 17.6 mo**	**0.71 (0.59–0.86)** **19.4 vs 14.9 mo**	**0.74 (0.59–0.94)** **20.6 vs 14.7 mo**
OS HR (95% CI)	0.63 (0.42–0.95)	0.79 (0.63–0.99) 48 vs 40 mo	0.78 (0.63–0.96) 48.3 vs 39.6 mo	NE
PFS in high-risk subgroup	**26.8 vs 8.3**	**23.1 vs 13.9**	**15.2 vs 7.4**	**21.4 vs 9.7**
PIs plus IMiDs seem to be the most effective combos in HR				

1. Moreau P, et al. *Ann Oncol.* 2017;28(suppl 4):iv52-iv61; 2. Bahlis NJ, et al. ASH 2018. Abstract 1996, poster presentation; 3. Usmani SZ, et al. ASH 2016. Abstract 1151, oral presentation; 4. Stewart AK, et al. *N Engl J Med.* 2015;372:142-152; 5. Siegel DS, et al. *J Clin Oncol.* 2018;36(8):728-734; 6. Dimopoulos MA, et al. *Cancer.* 2018;124(20):4032-4043; 7. Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634.

Management of first relapses in HR-MM patients

First line

- **Bortezomib-based combinations**
- **Len exposed and refractory**



Efficacy	ENDEAVOR [1] (n = 929) Kd vs Vd	CASTOR [2] (n = 499) DaraVd vs Vd	CANDOR [3] (n = 466) DaraKd vs Kd	OPTIMISMM [4] (n = 559) PVd vs Vd	BOSTON [5] (n = 402) SVd vs Vd
PFS HR (95% CI)	0.53 (0.44 – 0.63) 18.7 vs 9.4 m	0.31 (0.25 – 0.40) 16.7 vs 7.1 m	0.59 (0.45–0.78) 28.6 vs 15.2	0.61 (0.49–0.77) 11.2 vs 7.1	0.67 13.9 vs 9.4
OS HR (95% CI)	0.79 (0.65–0.96) 47.6 vs 40 m	--	--	--	--
PFS in high-risk subgroup	8.8 vs 6.0	12.6 vs 6.2	15.6 vs 5.6	HR 0.56 in favor of PVd	HR 0.67 in favor of SVd (0.38 in del[17])

1. Dimopoulos M, et al. *Lancet Oncol.* 2016;17:27-38; 2. Palumbo A, et al. *N Engl J Med.* 2016;375:754-766; 3. Dimopoulos M, et al. *Lancet.* 2020;396:186-197; 4. Richardson PG, et al. *Lancet Oncol.* 2019;20(6):781-794; 5. Grosicki S, et al. *Lancet.* 2020;396:1563-1573.

48-yr-old NDMM IgG-κ with anemia and lytic lesions with no HR CA. RVd → ASCT (CR, MRD–) → R maintenance; relapse occurred 1 year later. How would you define this patient?

1. Standard-risk patient, candidate for anti-CD38 mAbs
2. Functional high-risk patient, candidate to receive a different approach
3. I will consult an expert on how to proceed
4. I will do a PET-CT to see if the patient presents EMD

Is this enough?

We need to do better, because the conventional and novel strategies including anti-CD38 mAbs improve but do not overcome the poor prognosis of HR features

Better identification

- What about functional high-risk patients?
- Improve scientific knowledge and understanding

New and disruptive approaches

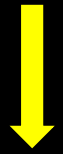
- Cell therapy

Mateos MV. Personal communication.

Functional high-risk MM patients

Early relapse (<1–2 years post-first line)

Regardless of age and the presence of high-risk features



Classical approach

"Overcome drug resistance"

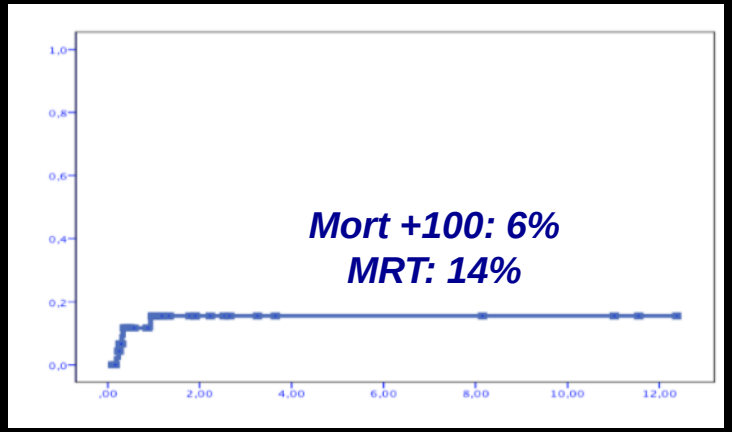
Combination of non–cross-resistant agents

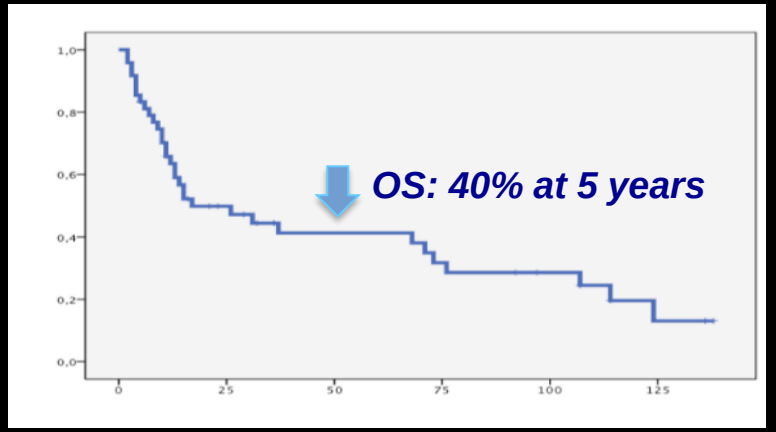
VDL-PACE/VRD/VRD-Cyclo/RAD/ . . . → RIC-Allo

San Miguel, JF. *J Clin Oncol*. 2009;27(34):5676-5677.

Allogeneic transplant in MM: Local experience

- Retrospective study, n = 48 pts
- RIC-allo in 98%, 73% in ≥RP





SLP of approximately 1 year
Chronic GVHD is an independent prognostic factor for PFS/OS

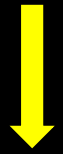
Allo-transplant can be a therapeutic option in selected patients, but it is key to do immunosuppression manipulation (withdrawal, DLI, . . .) in order to develop graft-versus-myeloma.

López Godino O, et al. EBMT 2014. Abstract PH-P534.

Functional high-risk MM patients

Early relapse (<1–2 years post-first line)

Regardless of age and the presence of high-risk features



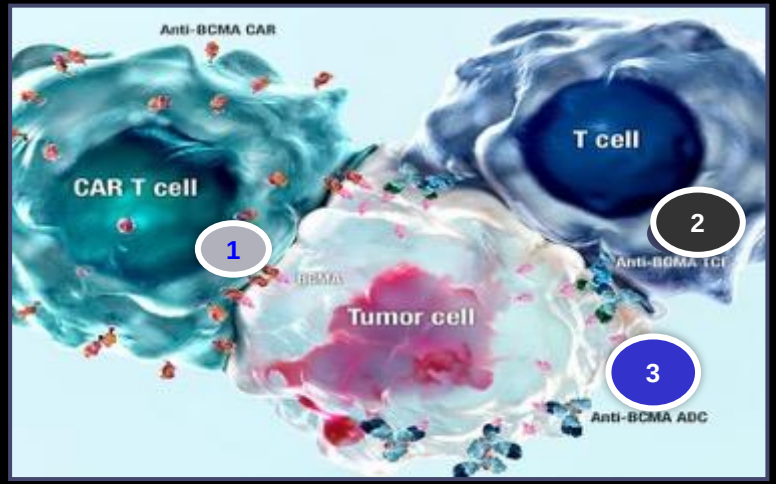
Modern approach

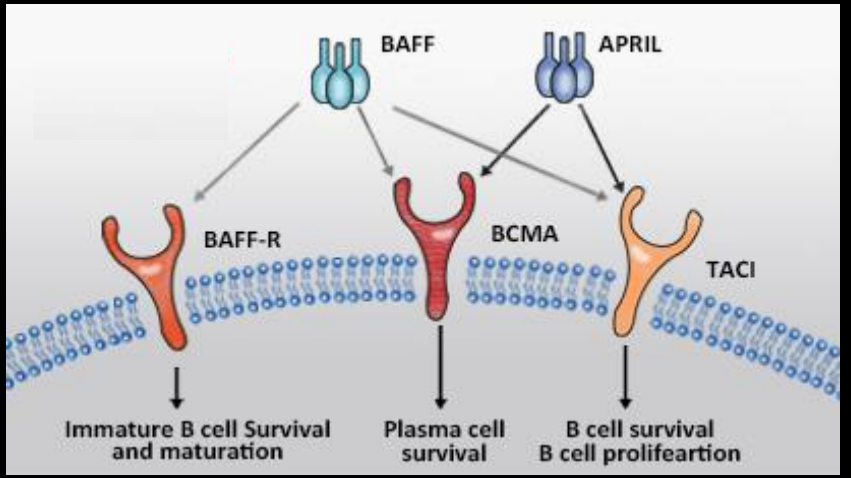
"Overcome drug resistance"

Cell therapy through CAR T cells or bispecific mAbs

Mateos MV. Personal communication.

BCMA as a target in MM





1. **CAR T-cell therapy (CAR T)**
2. **T-cell engager antibody (TCE)**
3. **Antibody-drug conjugate (ADC)**

BCMA is extensively studied and is an approved target[1,2]

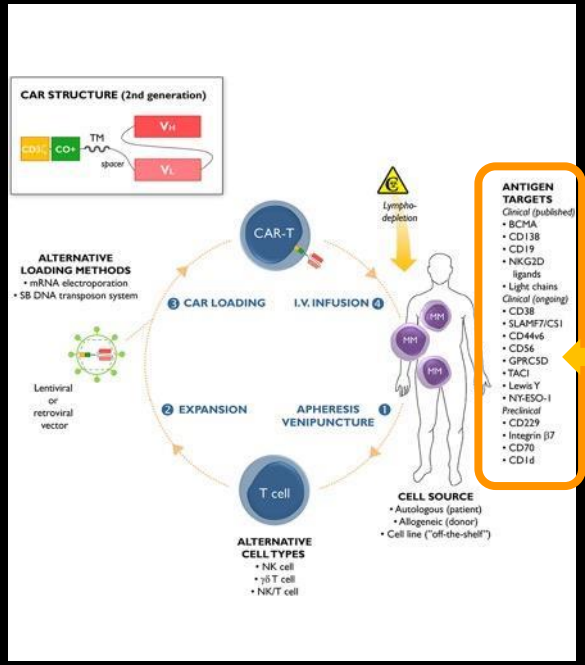
Belantamab mafodotin monotherapy is an ADC approved for patients with RRMM with ≥4 prior therapies, whose disease is refractory to ≥1 PI, IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy[1]

CAR T, chimeric antigen receptor T-cell therapy; IMiD, immunomodulatory agent; mAb, monoclonal antibody; PI proteasome inhibitor.

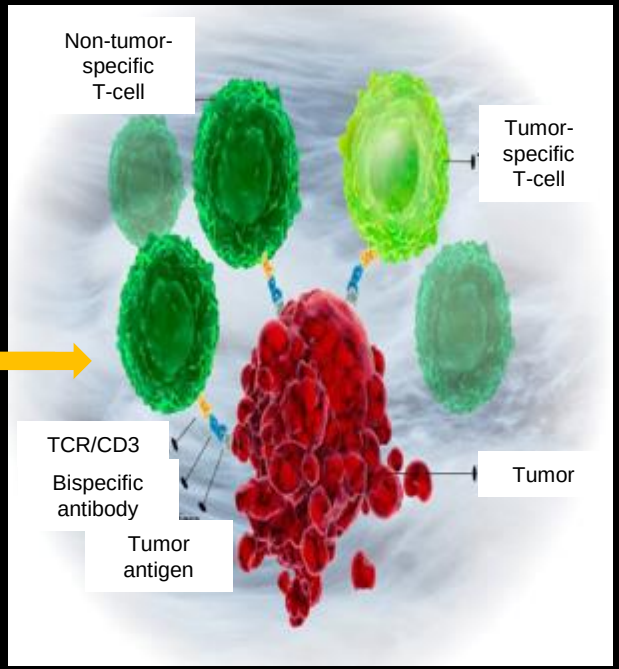
1. https://www.ema.europa.eu/en/documents/product-information/blenrep-epar-product-information_en.pdf;
2. Yu B, et al. *J Hematol Oncol.* 2020;doi:10.1186/s13045-020-00962-7.

Targets other than BCMA are currently being investigated

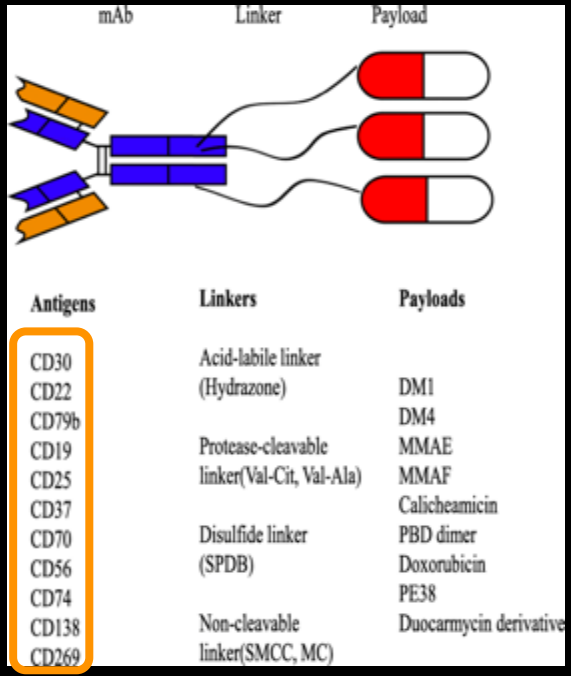
CAR T targets[1]



Bispecific antibodies[2]



ADC targets*[3]



*In MM and lymphoid malignancies.

1. Timmers M, et al. *Front Immunol*. 2019;doi:10.3389/fimmu.2019.01613; 2. Dahlén E, et al. *Ther Adv Vaccines Immunol*. 2018;6(1)3-17; 3. Yu B, et al. *J Hematol Oncol.* 2019;doi:10.1186/s13045-019-0786-6.

Disease morbidity and risk-assessment influence the choice of cell therapy

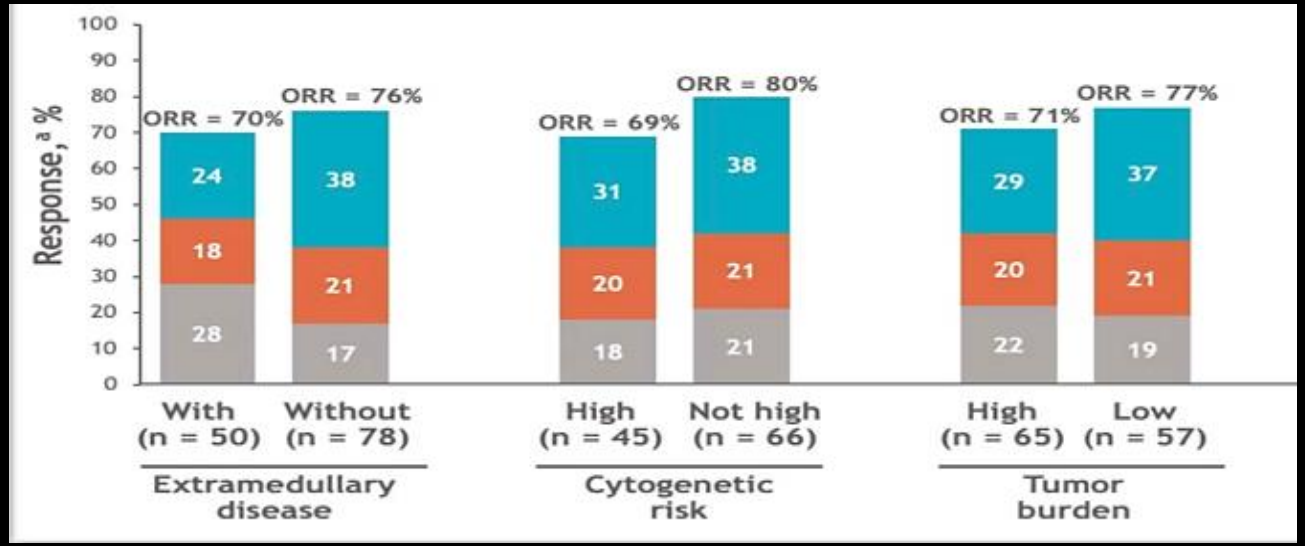
	Ide-cel[1] (all treated) (N = 128)	Cilta-cel[2] (N = 97)
Follow-up, median	13.3 mo (0.2–21)	12.4 mo (1.5–24.9)
Prior lines of therapy, median (range)	6 (3–16)	6 (3–18)
Triple refractory	84%	87%
Extramedullary disease (EMD)	39%	13%
High-risk cytogenetics	35%	24%
High tumor burden	51%	22%

EMD and/or high-risk cytogenetics and/or high tumor burden should not influence the choice of cell therapy

[a]High tumor burden cut-offs ≥50% for ide-cel vs ≥60% for cilta-cel treated-patients.

1. Munshi NC, et al. *J Clin Oncol*. 2020;28(15): abstract 8503 (oral presentation); 2. Madduri D, et al. ASH 2020. Oral presentation.

Ide-cel, CAR T bb2121, KarMMa pivotal phase 2 trial: Efficacy across different patient subgroups



- Median PFS was ≥7.5 months in patients who had a high tumor burden, bridging therapy, and ≥1 prior regimen per year
- Median DOR was ≥9.2 months in all high-risk groups examined, except patients with R-ISS stage III

CAR T, chimeric antigen receptor T-cell therapy; CR, complete response; DOR, median duration of response; ORR, overall response rate; PFS, median progression-free survival.

Raje N, et al. ASH 2020. Abstract 3234 (poster presentation).

Disease morbidity and risk-assessment influence the choice of cell therapy

	Teclistamab[1] (N = 149)	AMG 701[2] (N = 82)	PF-3135[3] (N = 18)	REGN5458[4] (N = 49)	TNB-383B[5] (N = 58)	Talquetamab[6] (N = 157)	Cevostamab[7] (N = 53)
Prior lines of therapy, median (range)	6 (2-14)	6 (2-25)	6.6 (1.7-16.8)	5 (2-17)	6 (3-15)	6 (2-20)	6 (2-15)
Triple refractory	81%	62%	30%	100%	64%	82%	72%
Extramedullary disease (EMD)	12%	25%	UK	UK	UK	20%	17%
High-risk cytogenetics	32%	UK	27%	UK	UK	13%	88%
High tumor burden	25%	UK	UK	UK	UK	22%	UK

Short follow-up for all trials

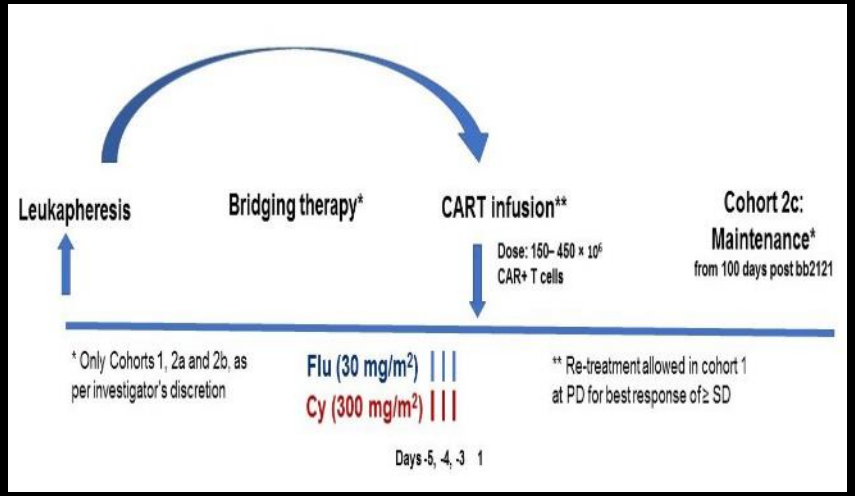
ORR across the studies range from 62%–83% and no subgroup analyses have been conducted

ORR, overall response rate; UK, unknown.

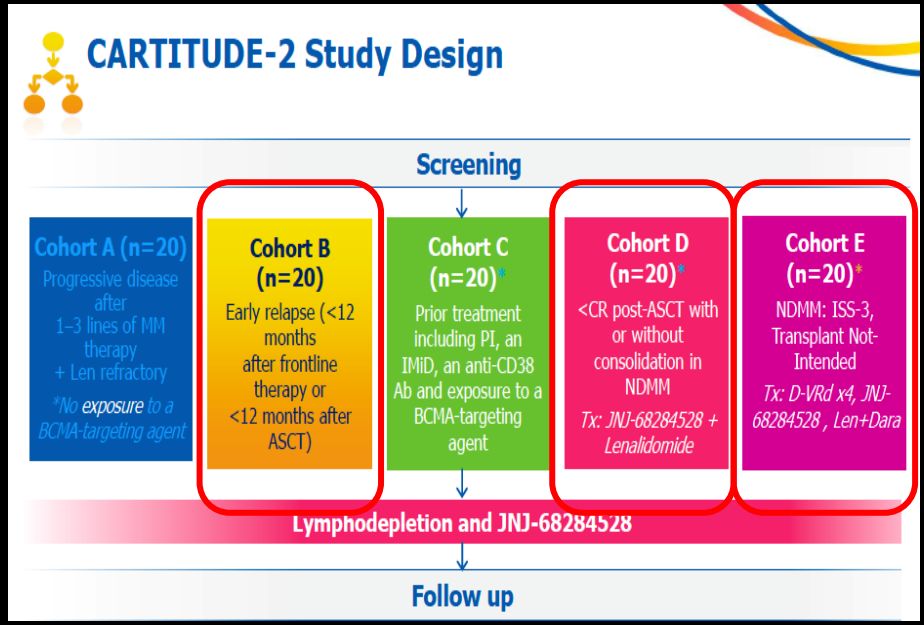
1. Garfall AL, et al. ASH 2020. Abstract 180; 2. Harrison SJ, et al. ASH 2020. Abstract 181; 3. Lesokhin AM, et al. ASH 2020. Abstract 3206; 4. Madduri D, et al. ASH 2020. Abstract 291; 5. Rodriquez C, et al. ASH 2020. Abstract 293; 6. Chari A, et al. ASH 2020 Virtual Meeting. Abstract 290; 7. Cohen AD, et al. ASH 2020 Virtual Meeting. Abstract 292.

BCMA-CAR T cells under investigation in HR-MM pts

Ide-cel: bb2121-MM-002



Cilta-cel



MM R-ISS 3 after 1PL and

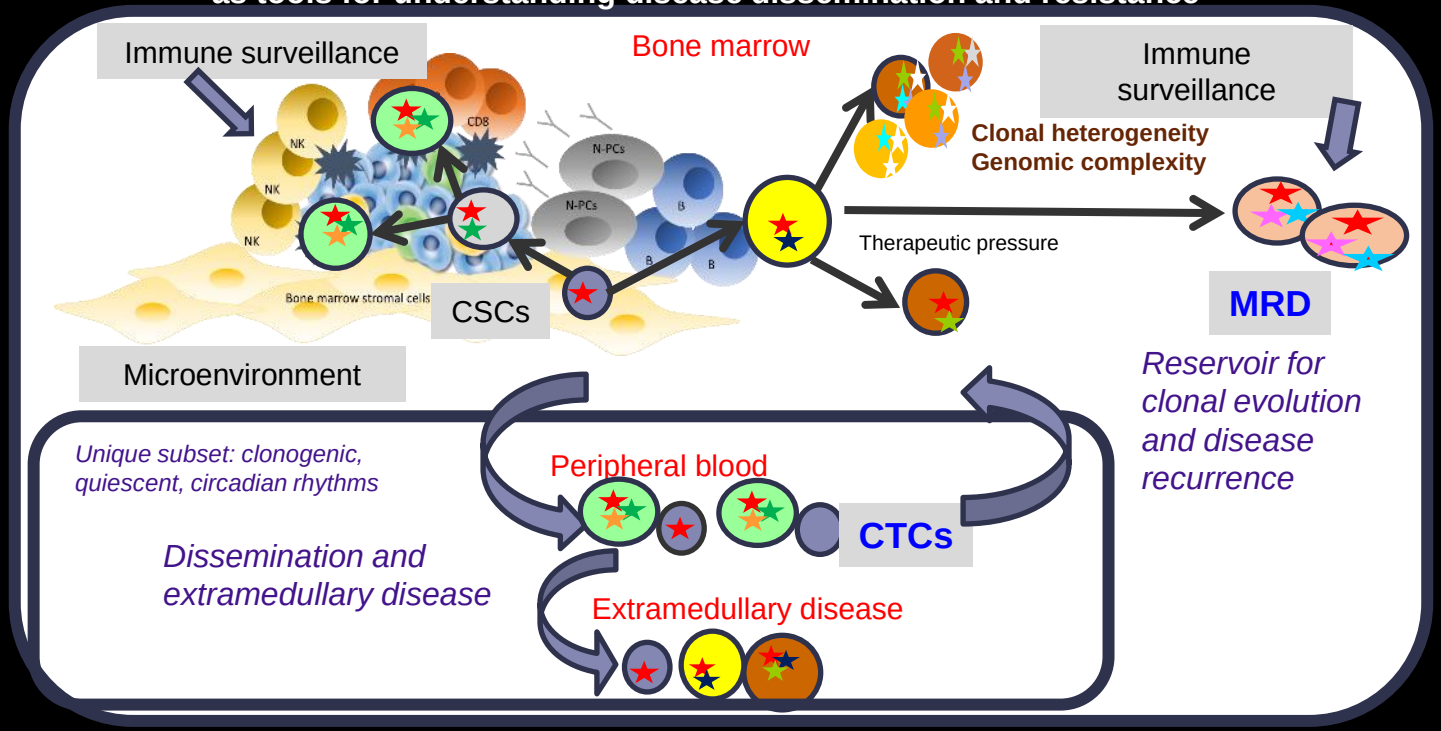
- **PD <18 mo from start 1L (TE)**
- **PD <18 mo from start 1L (TIE)**
- **<VGPR 70–110 days from ASCT**

Raje N et al. *N Engl J Med.* 2019;380:1726-1737; ClinicalTrials.gov Identifier: NCT04133636.

How to improve scientific knowledge?

***To identify signatures of high-risk clones*: circulating PC and MRD**

as tools for understanding disease dissemination and resistance



Next-generation sequencing, transcriptome . . . to well characterize the high-risk clones

Conclusions

- We need to continue improving
- Conventional and novel drugs improve but do not overcome the poor prognosis of high-risk features
- Areas for improvement
  - Better identification such as functional high risk and generation of scientific knowledge around the high-risk subgroups
  - New approaches such as cell therapy that can be promising for these patients
  - Trials focused on high-risk MM patients
- Strong correlation between prognosis in HR and MRD-negativity achievement

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

MAYO CLINIC

Rafael Fonseca, MD
Interim Executive Director Mayo Clinic Cancer Center

MM Early Relapse – 2021

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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Disclosures

- **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**
- **Believe in stem cell transplant**

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Early RR MM Question

- **Which of the following is not true in the treatment of relapsed MM?**
  1. **In a direct comparison in RR MM, carfilzomib showed superiority over bortezomib**
  2. **The addition of daratumumab to bortezomib and dexamethasone does not improve outcomes**
  3. **Adding oral proteasome inhibitors can augment the depth of response to lenalidomide and dexamethasone**
  4. **Cyclophosphamide can be combined effectively with proteasome inhibitors in RR MM**
  5. **Both lenalidomide and pomalidomide can be combined with daratumumab**

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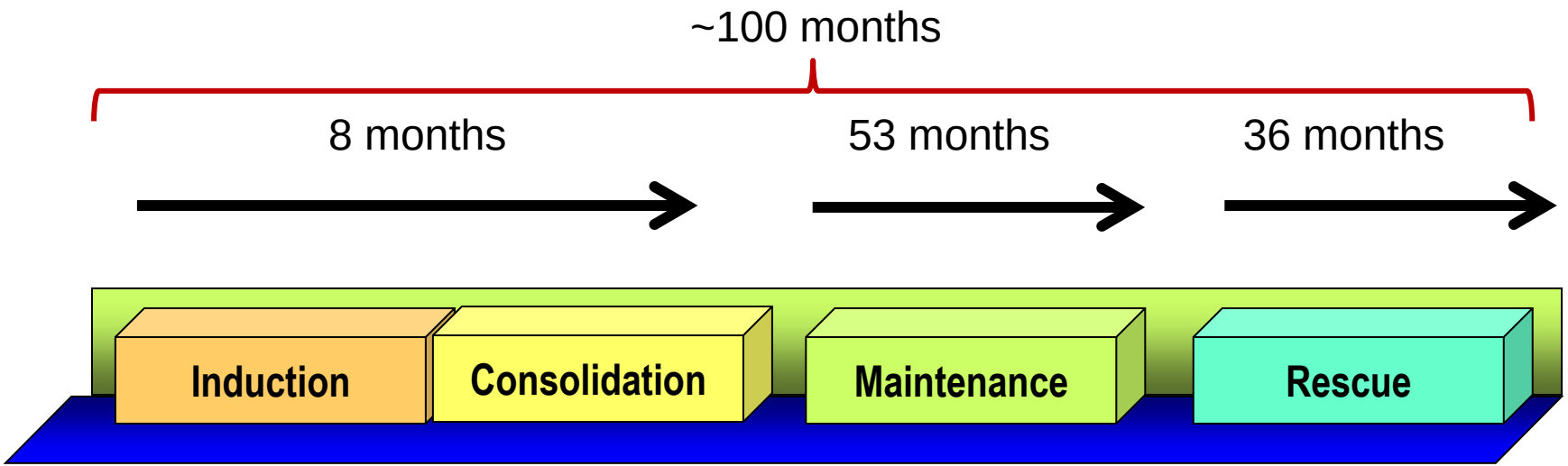
Multiple Myeloma Treatment Lines 2021



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Fonseca R, unpublished.

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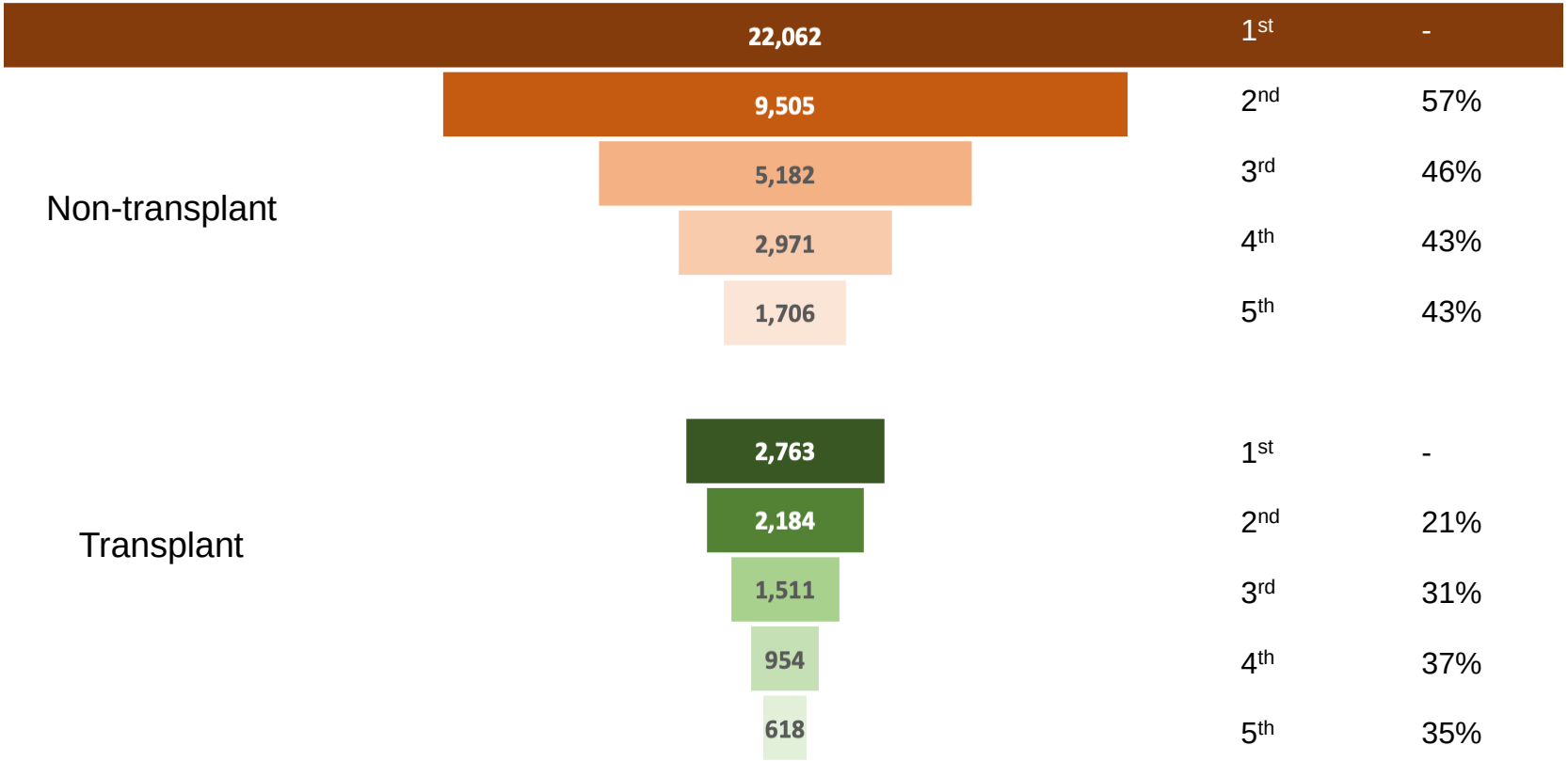
Attrition With Subsequent Treatment



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

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Key Numbers to Remember

- **VD: 9**
- **RD: 17**

@rfonsi1, fonseca.rafael@mayo.edu

Fonseca R, unpublished.

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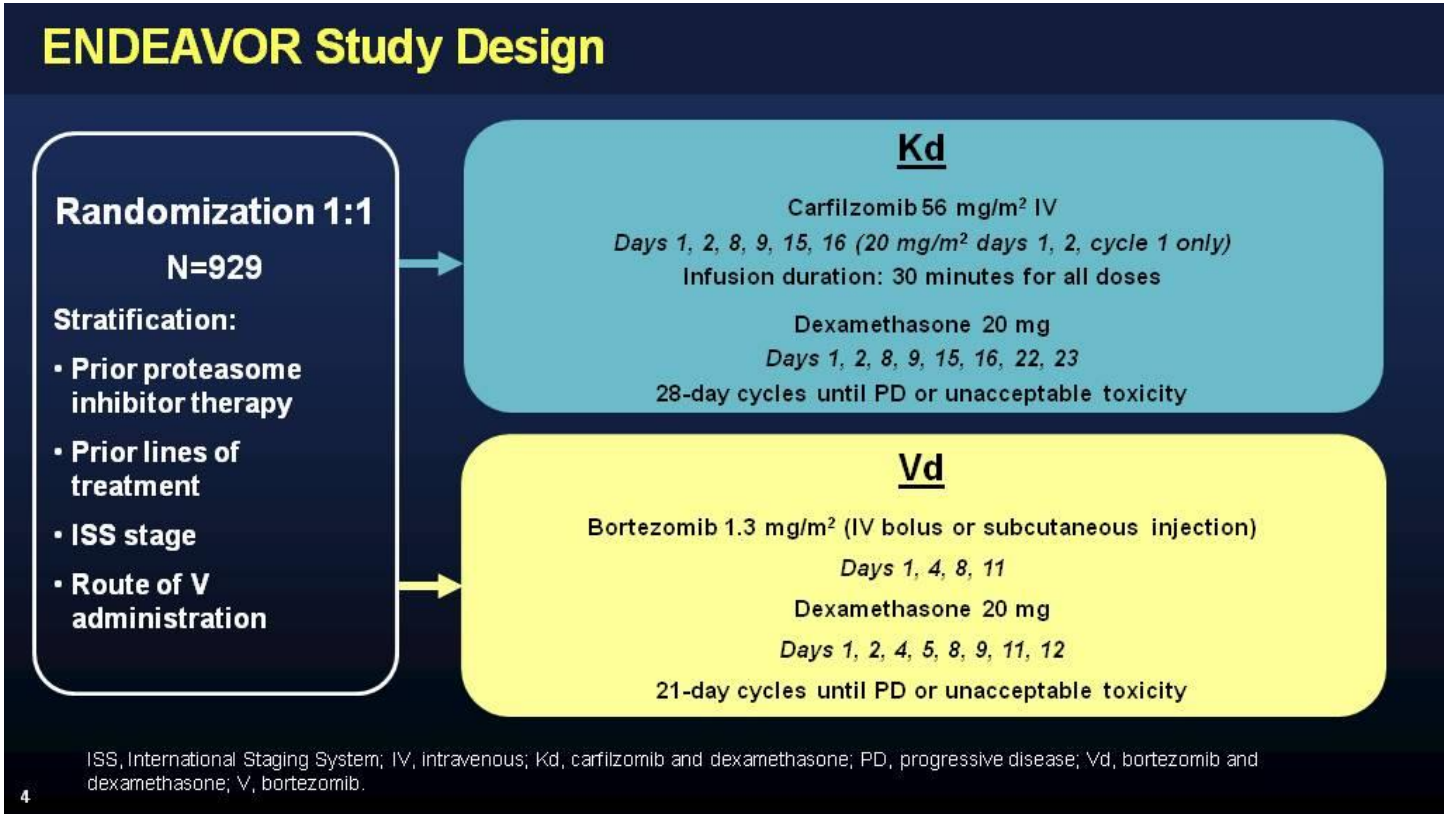
ENDEAVOR: Kd vs Vd



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Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38.

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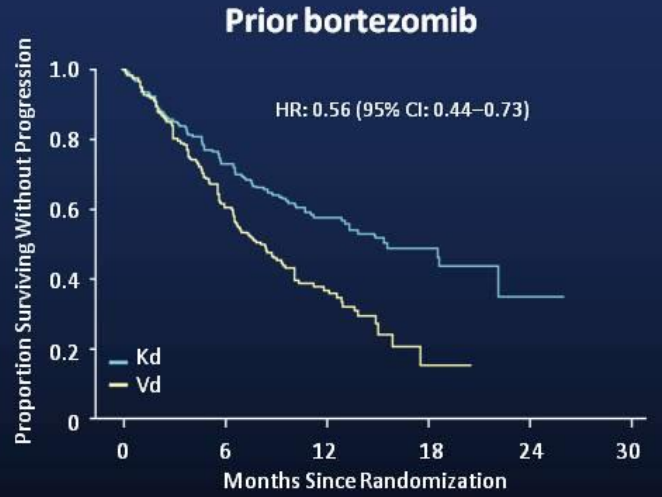
ENDEAVOR: Kd vs Vd

Progression-Free Survival and Overall Response Rates by Prior Bortezomib Exposure



	Kd (n=214)	Vd (n=213)
Median PFS, mo	NE	11.2
ORR, % (95% CI)	84 (78–88)	65 (59–72)

	Kd (n=250)	Vd (n=252)
Median PFS, mo	15.6	8.1
ORR, % (95% CI)	71 (65–77)	60 (54–66)

CI, confidence interval; HR, hazard ratio; Kd, carfilzomib and dexamethasone; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

20

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Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38.

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GEM-KyCydex: Objectives

Multicenter, open-label, randomized phase II trial

Randomization 1:1

N=198

- RRMM patients after 1-3 prior lines of therapy
- Prior therapy with PIs was allowed
- Patients refractory to PIs were not allowed
- CrCl >30 mlx minute
- LVEF > 50%

KyCydex

- Carfilzomib 70 mg/m^2 IV
  Days 1, 8 and 15 (20 mg/m^2 day 1 cycle 1 only)
  Infusion duration: 30 minutes for all doses
- Dexamethasone 40 mg weekly: 20 mg the day of Ky and 20 mg the day after.
- Cyclophosphamide 300 mg/m^2 IV
  Days 1, 8 and 15

28-day cycles until PD or unacceptable toxicity

Kydex

- Carfilzomib 70 mg/m^2 IV
  Days 1, 8 and 15 (20 mg/m^2 day 1 cycle 1 only)
  Infusion duration: 30 minutes for all doses
- Dexamethasone 40 mg weekly: 20 mg the day of Ky and 20 mg the day after.

28-day cycles until PD or unacceptable toxicity

Dex 20 mg weekly for pts older than 75.

Primary endpoint

- Progression-free survival

Secondary endpoints

- ORR and the different response categories
- TTP
- OS
- Safety profile

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Mateos MV, et al. *Blood.* 2020;136(suppl 1):8-9.

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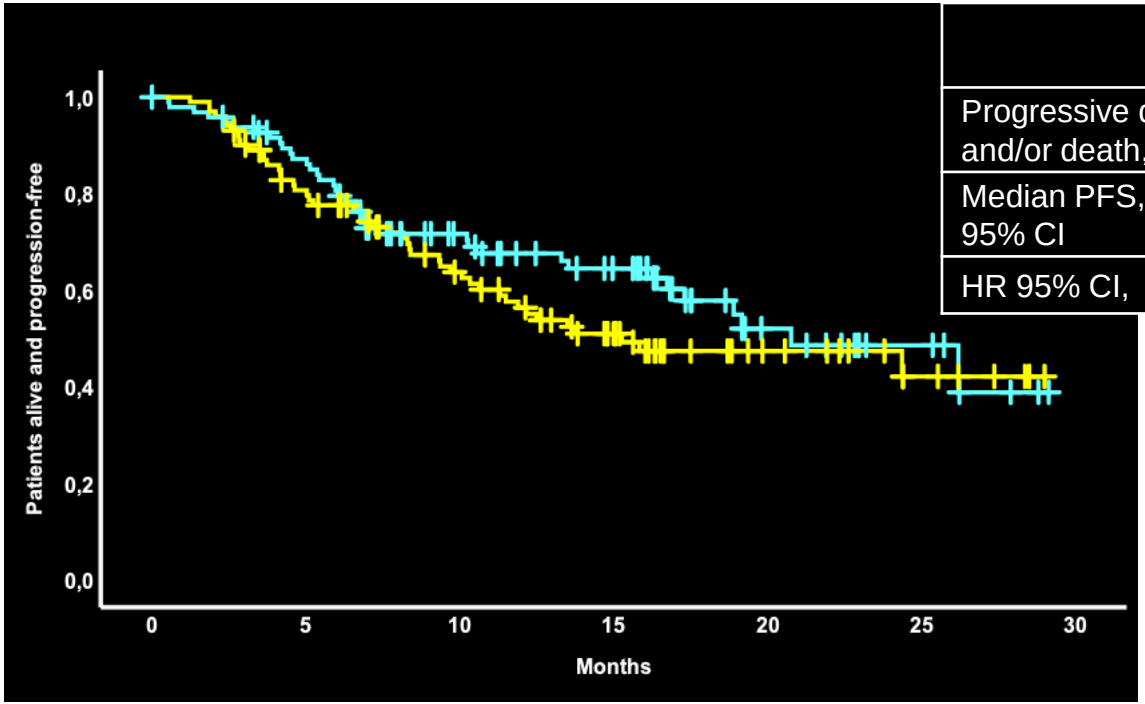
GEM-KyCydex: PFS

Median follow-up: 15.6 (1.3–29)



	KyCydex (n = 97)	Kydex (n = 101)
Progressive disease and/or death, n(%)	38 (39%)	47 (47%)
Median PFS, months, 95% CI	**20.7 (14.5–27.0)**	**15.2 (5.1–25.4)**
HR 95% CI, *P* value	1.2 (0.8–1.9), .24	

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Mateos MV, et al. *Blood.* 2020;136(suppl 1):8-9.

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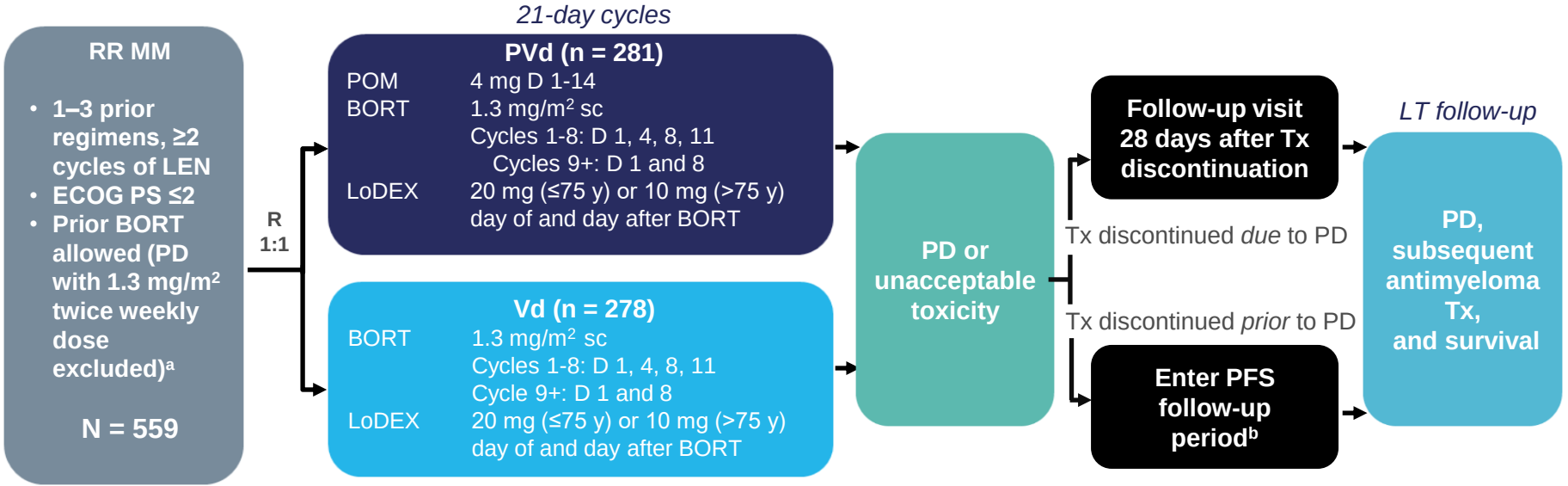
Phase III OPTIMISMM Study Design



- **Stratification**
  - **Age (≤75 y vs >75 y)**
  - **Prior regimens (1 vs >1)**
  - **β2-microglobulin at screening (<3.5 mg/L vs ≥3.5 to ≤5.5 mg/L vs >5.5 mg/L)**
- **Study endpoints**
  - **Primary: PFS**
  - **Secondary: OS, ORR by IMWG criteria, DOR, safety**
  - **Key exploratory: TTR, PFS2, efficacy analysis in subgroups**
- **Data cutoff: October 26, 2017**

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Richardson PG, et al. ASCO 2018. Abstract 8001.

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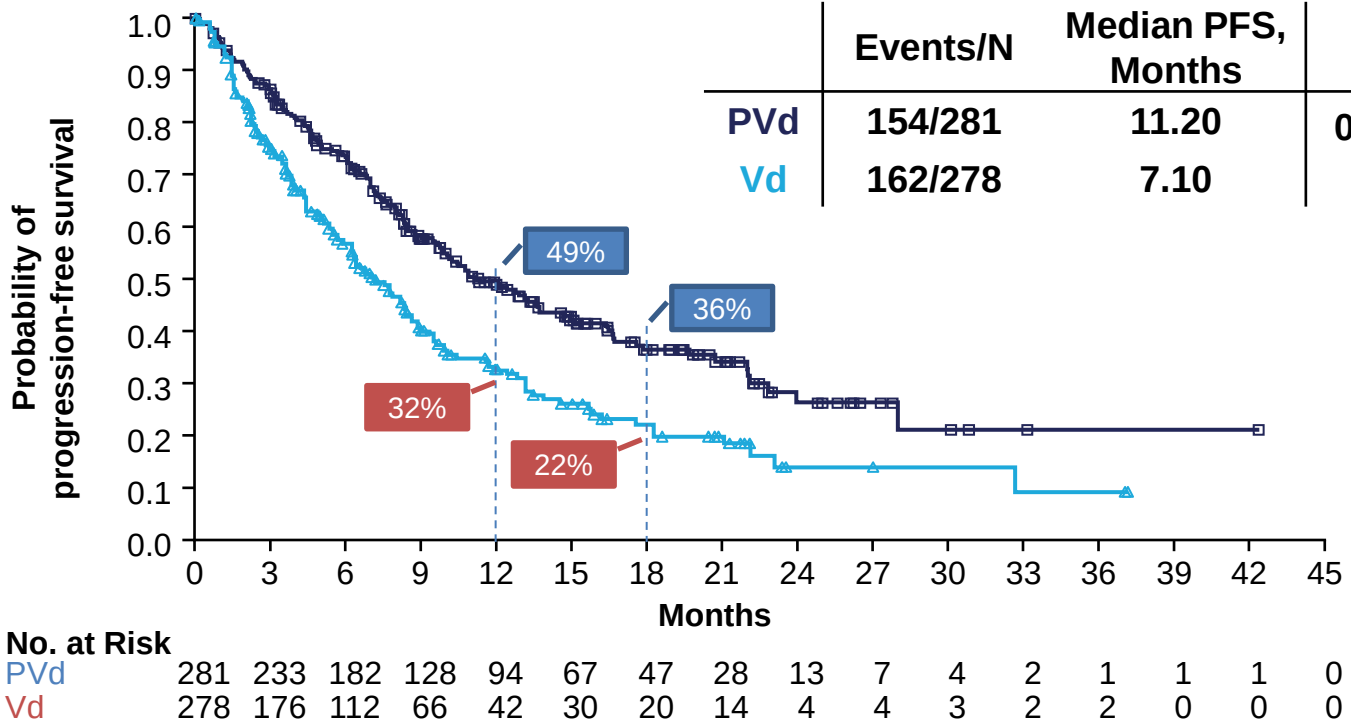
Progression-Free Survival (ITT)

	Events/N	Median PFS, Months	HR (95% CI) *P* Value
PVd	154/281	11.20	0.61 (0.49-0.77)
Vd	162/278	7.10	<.0001



- **PVd reduced the risk of progression and death by 39% compared with Vd**

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Richardson PG, et al. ASCO 2018. Abstract 8001.

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TOURMALINE-MM1: Len-Dex ± Ixazomib

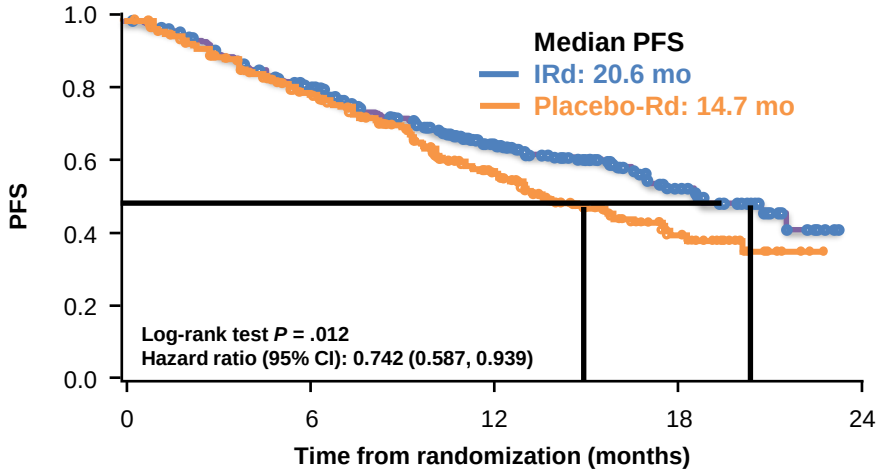
Ixazomib 40 mg d1, 8, 15
Lenalidomide 25 mg d1-21
Dexamethasone d1, 8, 15, 22

Placebo d1, 8, 15
Lenalidomide 25 mg d1-21
Dexamethasone d1, 8, 15, 22

Cycles repeated until disease progression or unacceptable toxicity

Primary Endpoint: PFS

Secondary Endpoints:
OS, OS in high-risk pts with del(17)



Risk Group	IRd	Rd	HR
	Median PFS, mo	Median PFS, mo	
Standard	20.6	15.6	0.640*
High	21.4	9.7	0.543
Patients with del(17p)	21.4	9.7	0.596
Patients with t(4;14) alone	18.5	12.0	0.645

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Moreau P, et al. *N Engl J Med*. 2016;374:1621-1634.

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ASPIRE: Len-Dex ± Carfilzomib

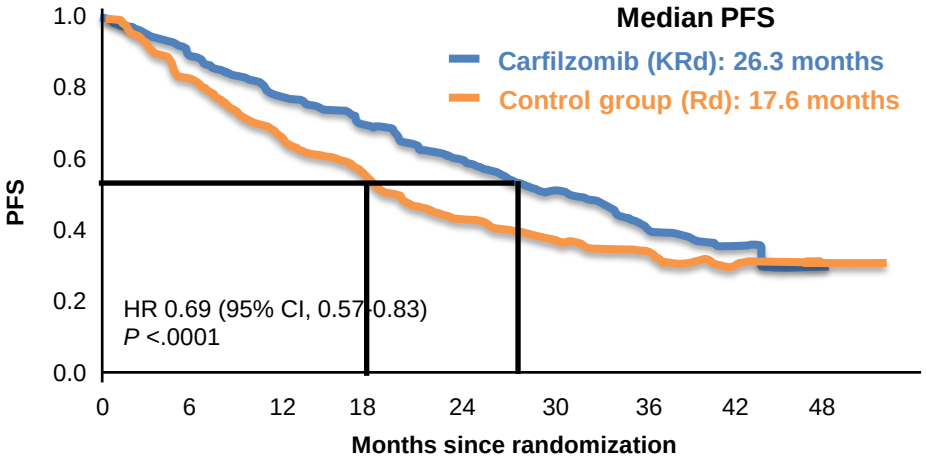
- **Carfilzomib 20 mg/m² (27 mg/m²)**
  - Cycle 1-12: d 1, 2, 8, 9, 15, 16
  - Cycles 13-18: d 1, 2, 15
- **Lenalidomide 25 mg** d1-21
- **Dexamethasone 40 mg** d1, 8, 15, 22

- **Lenalidomide** 25 mg d1-21
- **Dexamethasone** d1, 8, 15, 22

After cycle 18, Len-Dex was continued until POD or toxicity

Primary Endpoint: PFS

Secondary Endpoints: OS, ORR, duration of response, HRQOL, safety



Risk Group by FISH	KRd (n = 396)		Rd (n = 396)		HR	*P* Value
	n	Median PFS, mo	n	Median PFS, mo		
High	48	23.1	52	13.9	0.70	.083
Standard	147	29.6	170	19.5	0.66	.004

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Stewart AK, et al. *N Engl J Med*. 2015;372:142-152.

MAYO CLINIC

CASTOR Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

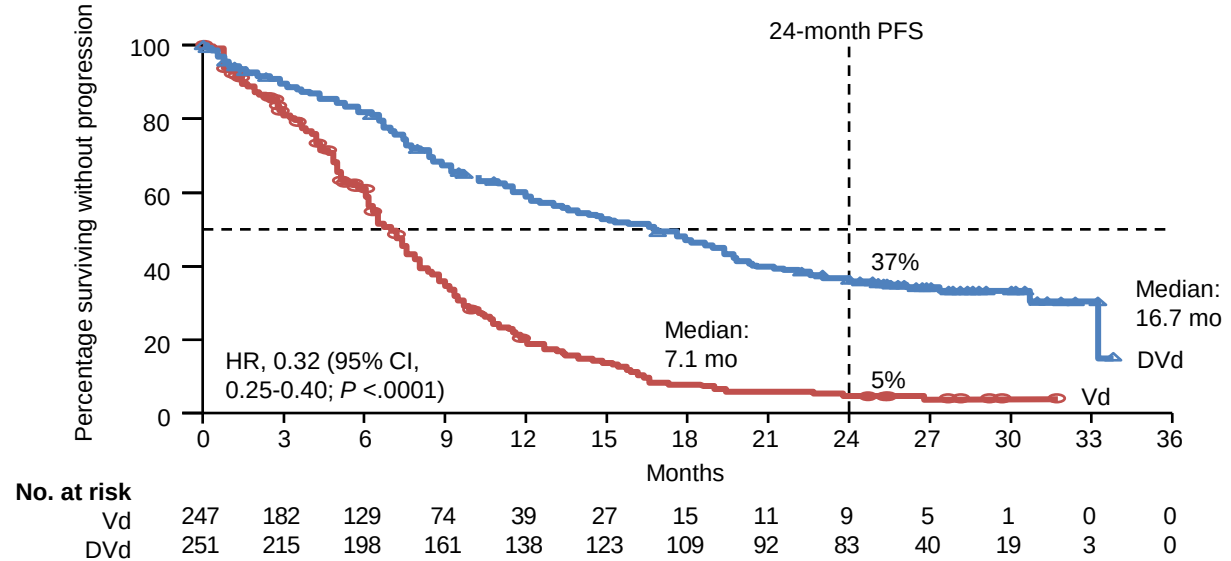
Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

Palumbo A, et al. *N Engl J Med*. 2016;375:754-766.

MAYO CLINIC

Updated PFS in the ITT Population

- **PFS was significantly prolonged with DVd compared with Vd (median: 16.7 vs 7.1 months; HR, 0.32; 95% CI, 0.25-0.40; *P* <.0001; Figure)**



PFS, progression-free survival; ITT, intent-to-treat; DVd, daratumumab-bortezomib-dexamethasone; Vd, bortezomib-dexamethasone; HR, hazard ratio.

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Mateos M, et al. *Blood*. 2018;132(suppl 1): abstract 3270.

MAYO CLINIC

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*

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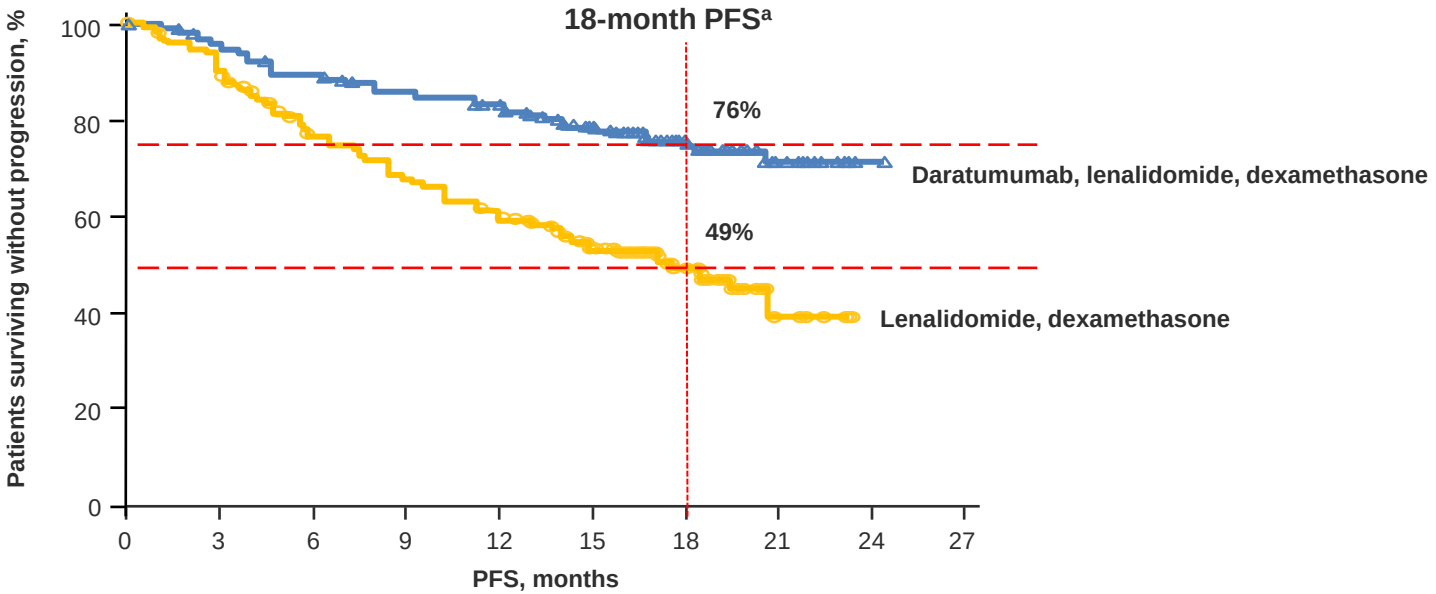
Dimopoulos MA, et al. *N Engl J Med*. 2016;375:1319-1331.

MAYO CLINIC

Updated PFS for POLLUX Trial



Median (range) follow-up:
17.3 (0-24.5) months

Median PFS

DRd: not reached; Rd: 17.5 months

HR 0.37 (95% CI, 0.28-0.50; *P* <.0001)

HR, hazard ratio.
[a]Kaplan-Meier estimates.
Clinical cutoff: June 30, 2016.

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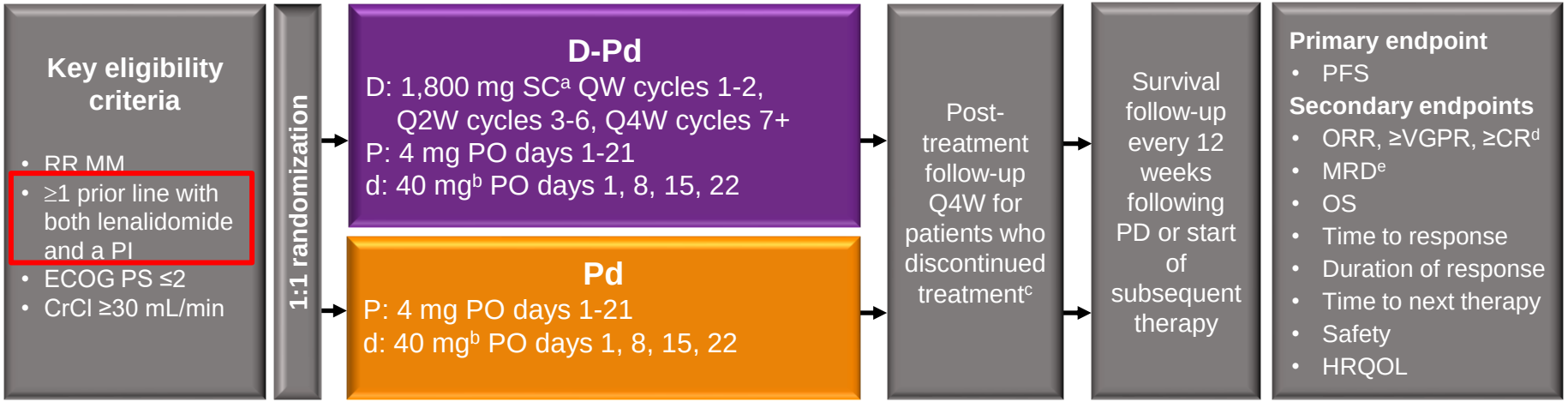
Dimopoulos MA, et al. *N Engl J Med*. 2016;375:1319-1331.

MAYO CLINIC

APOLLO Study Design



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

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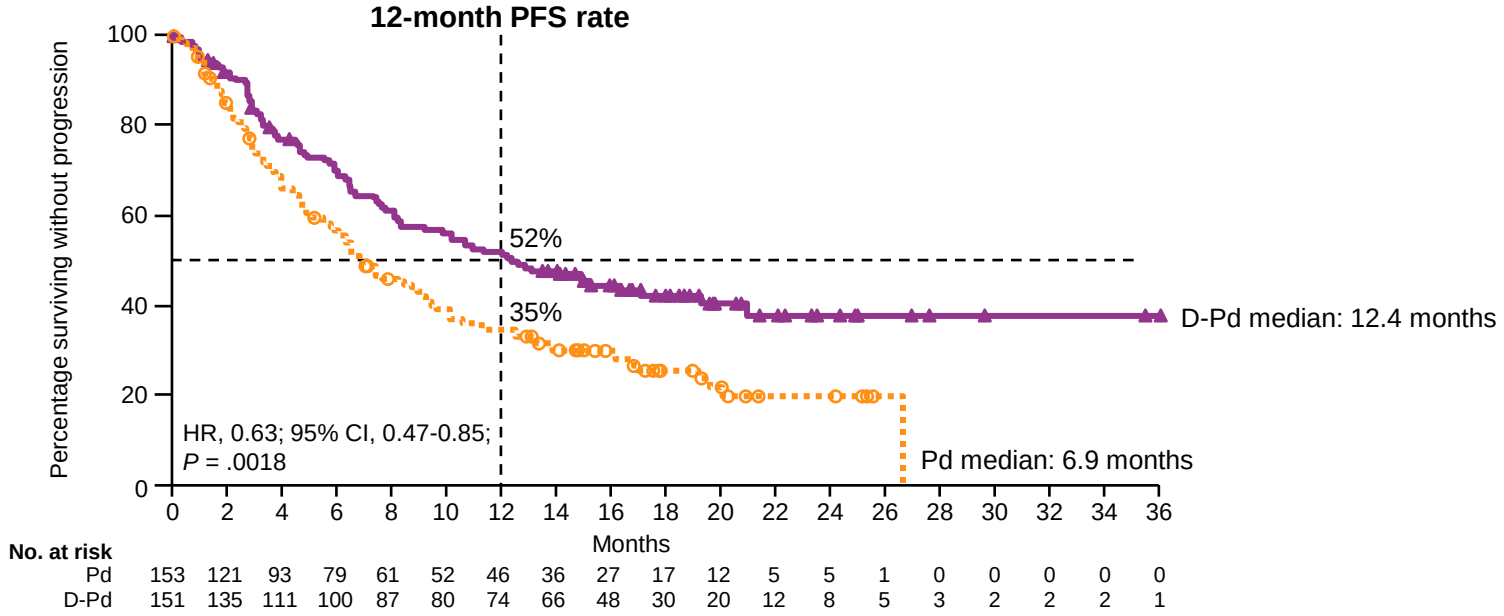
Dimopoulos MA, et al. ASH 2020. Abstract 412.

MAYO CLINIC

APOLLO PFS (FU 16.9 mo)



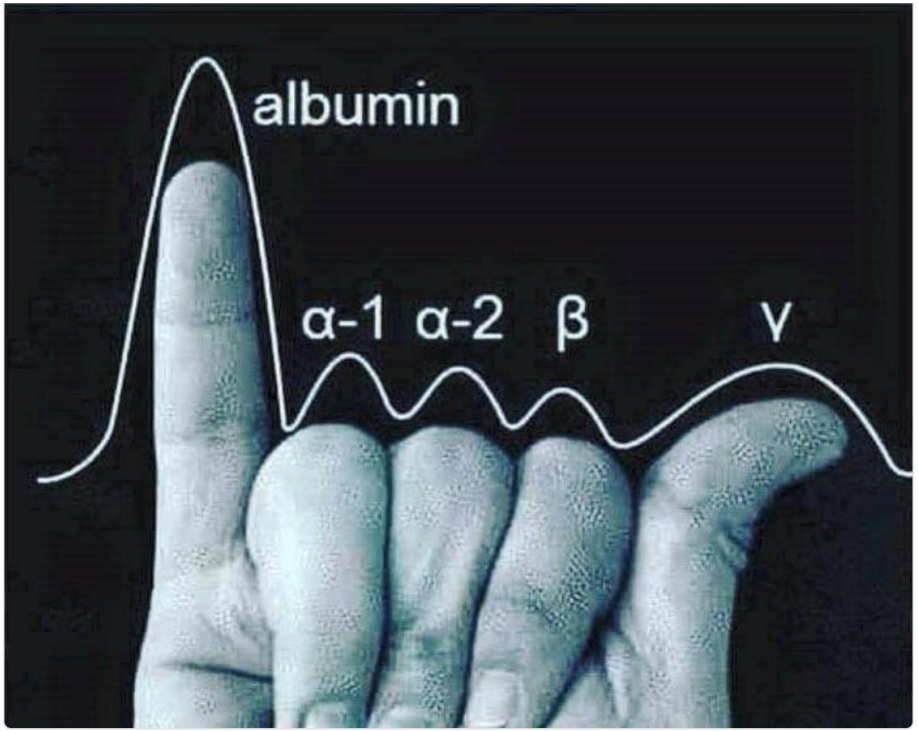
- Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

@rfonsi1, fonseca.rafael@mayo.edu

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

MAYO CLINIC

Thank you!



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MAYO CLINIC

Early RR MM Question

- **Which of the following is not true in the treatment of relapsed MM?**
  1. **In a direct comparison in RR MM, carfilzomib showed superiority over bortezomib**
  2. **The addition of daratumumab to bortezomib and dexamethasone does not improve outcomes**
  3. **Adding oral proteasome inhibitors can augment the depth of response to lenalidomide and dexamethasone**
  4. **Cyclophosphamide can be combined effectively with proteasome inhibitors in RR MM**
  5. **Both lenalidomide and pomalidomide can be combined with daratumumab**

@rfonsi1, fonseca.rafael@mayo.edu

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

Treatment of Relapsed Multiple Myeloma

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

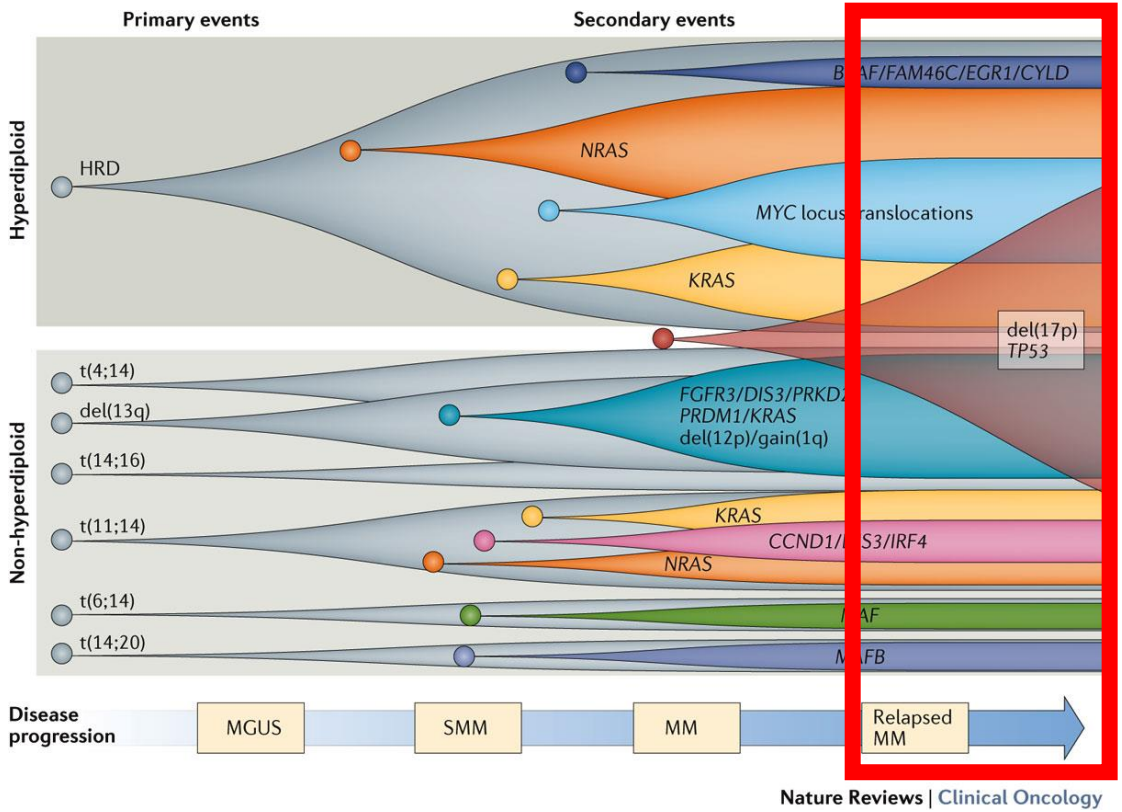
What approximate percentage of MM patients are estimated to survive long enough to receive third-line therapy?

1. 90%
2. 80%
3. 65%
4. 50%
5. 40%

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

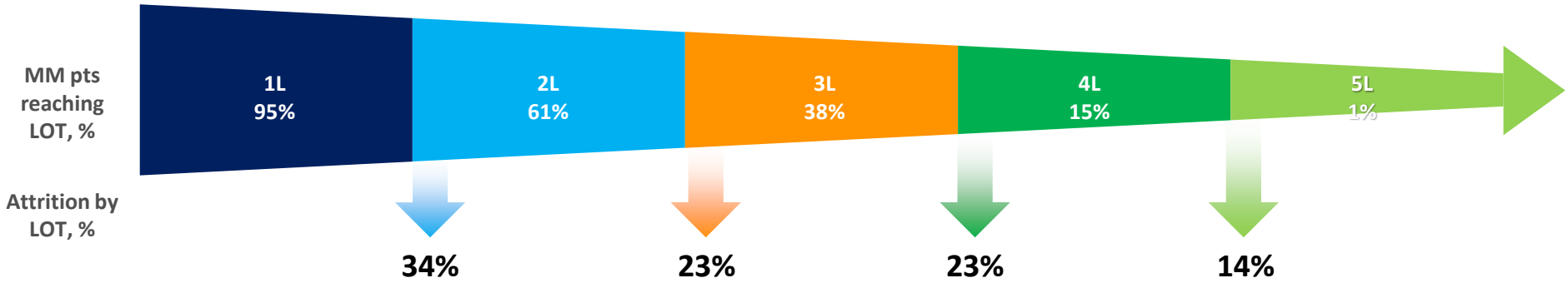
1. Ocular toxicity can be reduced by starting with graduated dosing
2. A less common but significant toxicity is early onset cytokine release syndrome
3. The response rate is 30%–35% partial response or better
4. The response rate in first relapse is 72%
5. Ocular toxicity is manageable with steroid 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



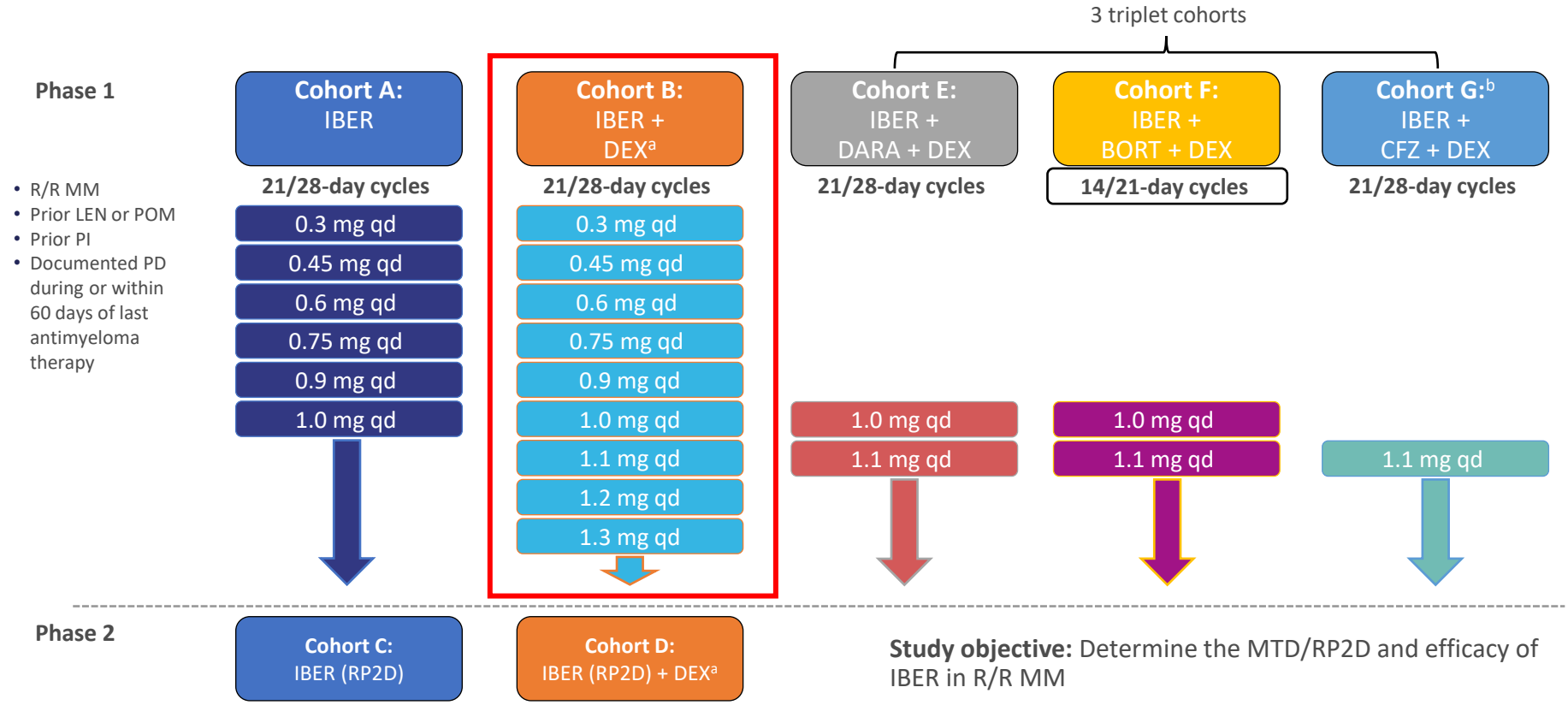
In every new LOT, ~15%–35% of patients are lost

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

What to Do After Lenalidomide and Pomalidomide?

IMIDS

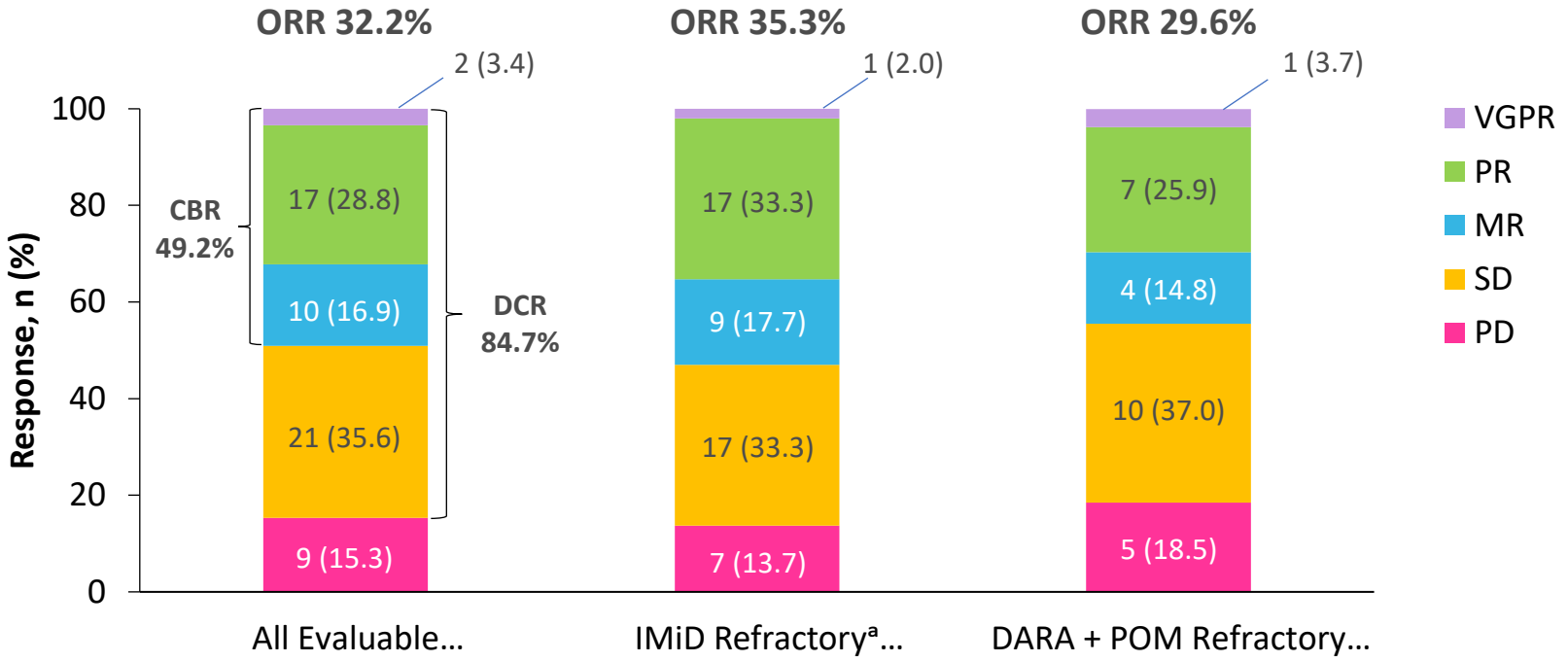
Iberdomide MM-001 Phase 1b/2a Trial: Study Design



[a]DEX given at a dose of 40 mg (20 mg in patients aged >75 years) on days 1, 8, 15, and 22 of each 28-day cycle. [b]CFZ dosed once weekly (Cohort G1) or twice weekly (Cohort G2).
CFZ, carfilzomib; DEX, dexamethasone; MTD, maximum tolerated dose; PD, progressive disease; PI, proteasome inhibitor; qd, once daily; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

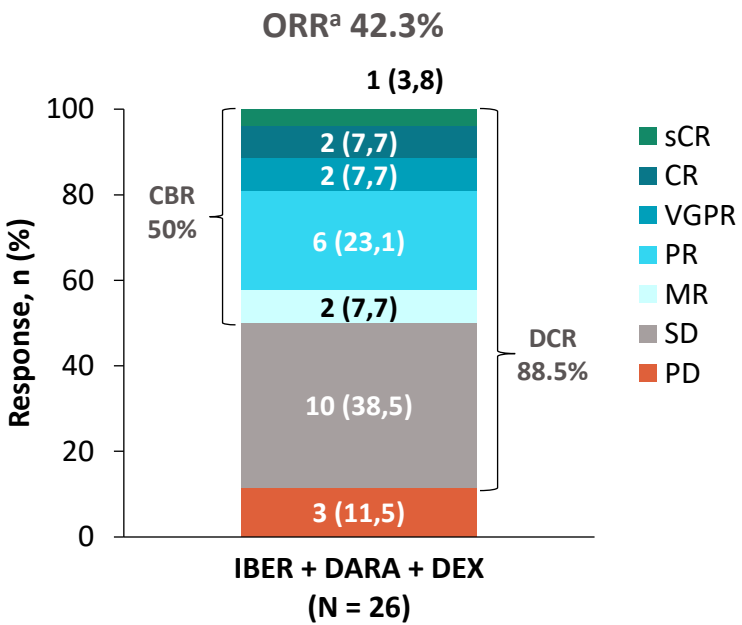
Lonial S, et al. ASCO 2019. Abstract 8006.

Response

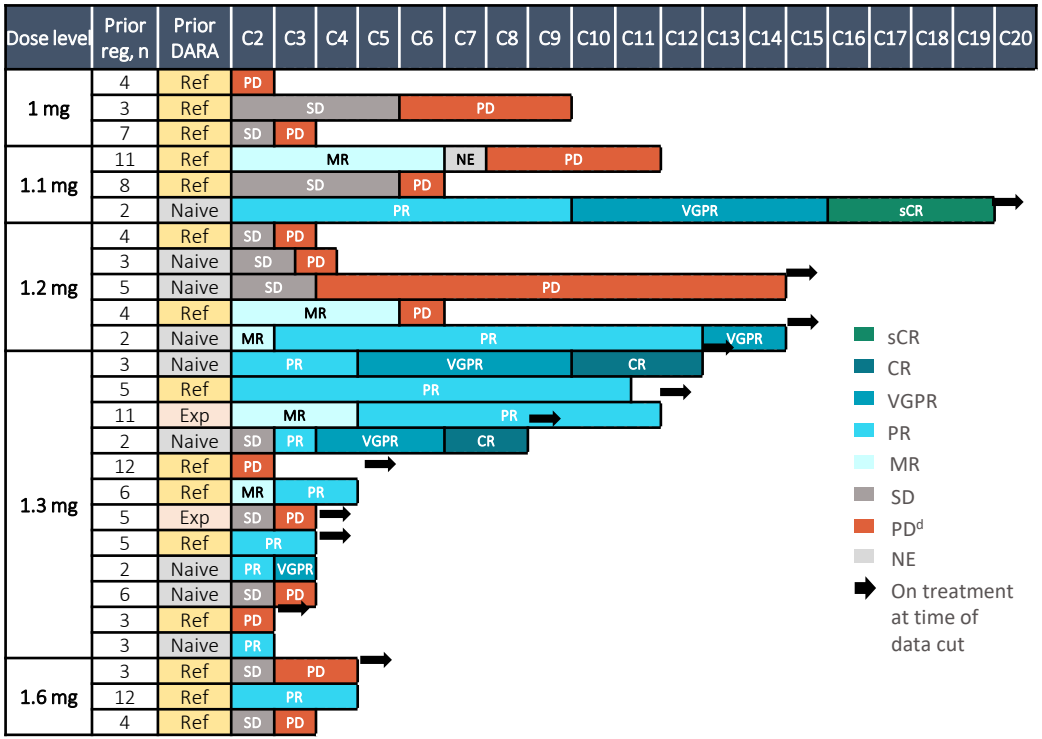


Evaluable patients include those who have received ≥1 dose of IBER, had measurable disease at baseline, and ≥1 postbaseline response assessment.
[a]Includes LEN and POM.
CBR, clinical benefit rate; DCR, disease control rate; MR, minimal response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.
Lonial S, et al. ASCO 2019. Abstract 8006.

Best Response: IBER + DARA + DEX Cohort



- In the IBER + DARA + DEX cohort,[b] 26 patients were IMiD refractory, 15 were anti-CD38 refractory (all DARA), and 13 were triple-class refractory[c]



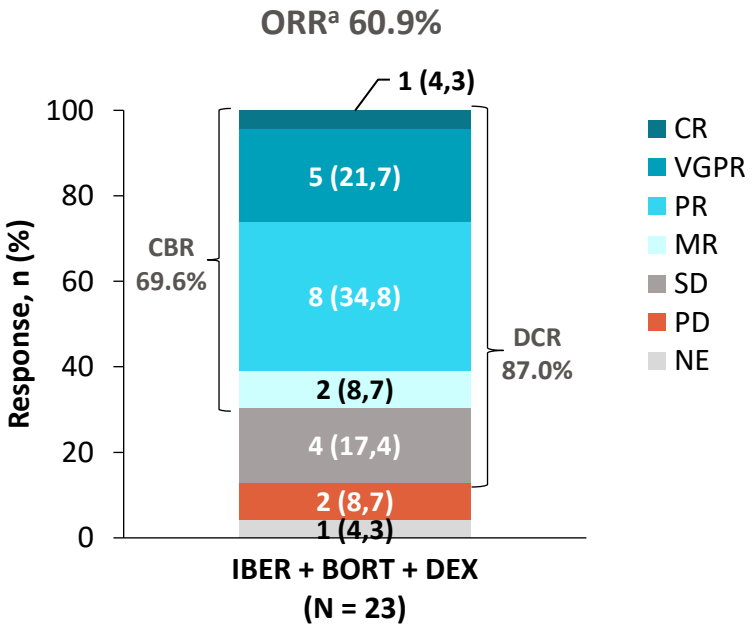
- Median time to response was 4.1 (range 4.0–12.0) weeks

[a]PR or better. [b]Full analysis population (N = 27). [c]Defined as refractory to ≥1 IMiD, 1 PI, and 1 anti-CD38 mAb. [d]One patient in the 1.2-mg group and 2 patients in the 1.3-mg group had an unconfirmed PD as of the data cutoff date.

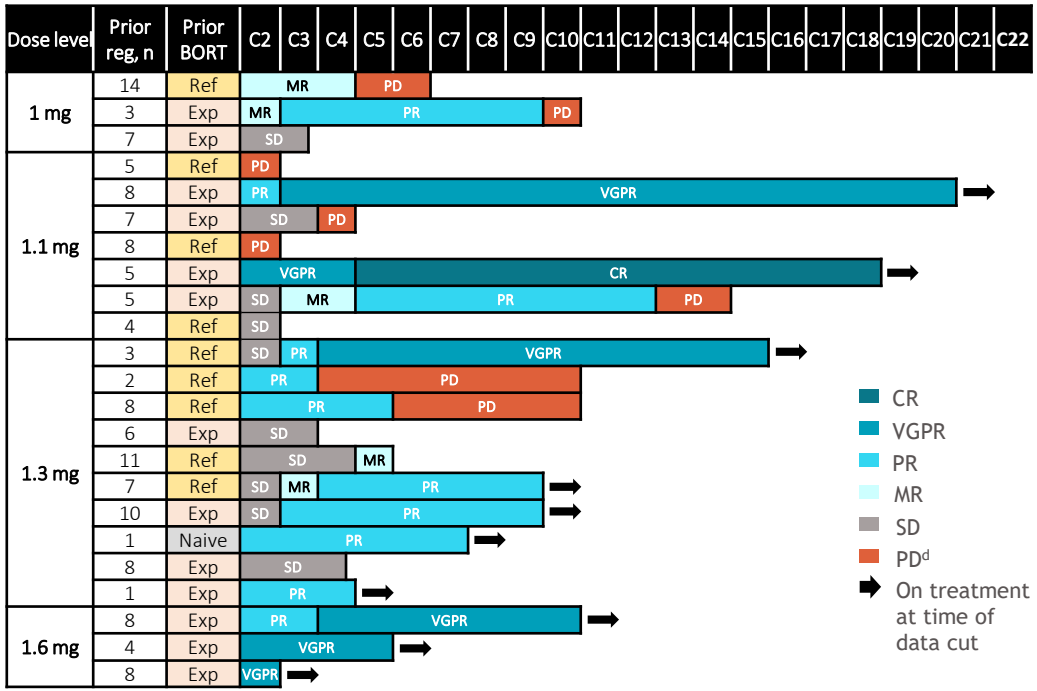
CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; Exp, exposed; MR, minimal response; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; Ref, refractory; reg, regimen; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

van de Donk NWCJ, et al. ASH 2020. Abstract 724.

Best Response: IBER + BORT + DEX Cohort



- In the IBER + BORT + DEX cohort,[b] 18 patients were IMiD refractory, 15 were PI refractory, 9 were BORT refractory, and 9 were triple-class refractory[c]

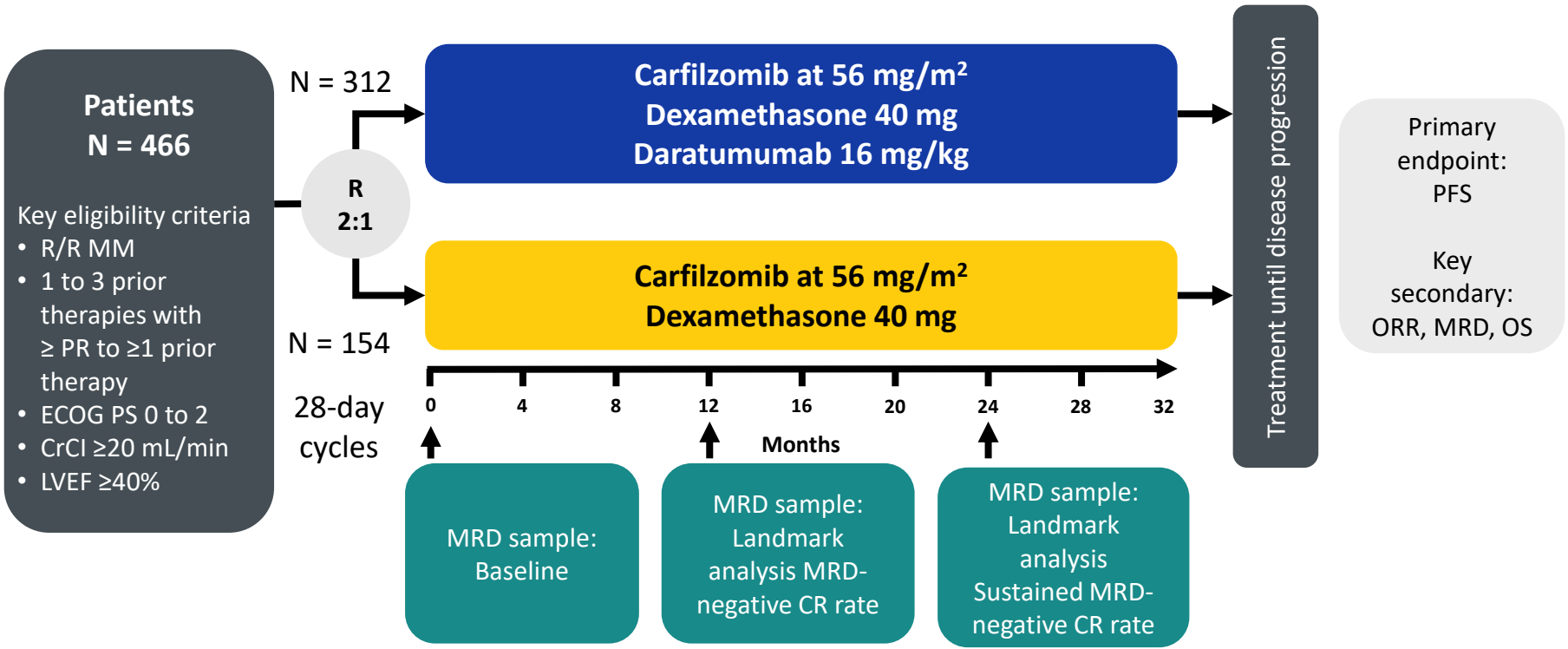


- Median time to response was 3.6 (range 3.0–13.1) weeks

[a]PR or better. [b]Full analysis population (N = 23). [c]Defined as refractory to ≥1 IMiD, 1 PI, and 1 anti-CD38 mAb. [d]One patient in the 1.1-mg group had an unconfirmed PD as of the data cutoff date.
van de Donk NWCJ, et al. ASH 2020. Abstract 724.

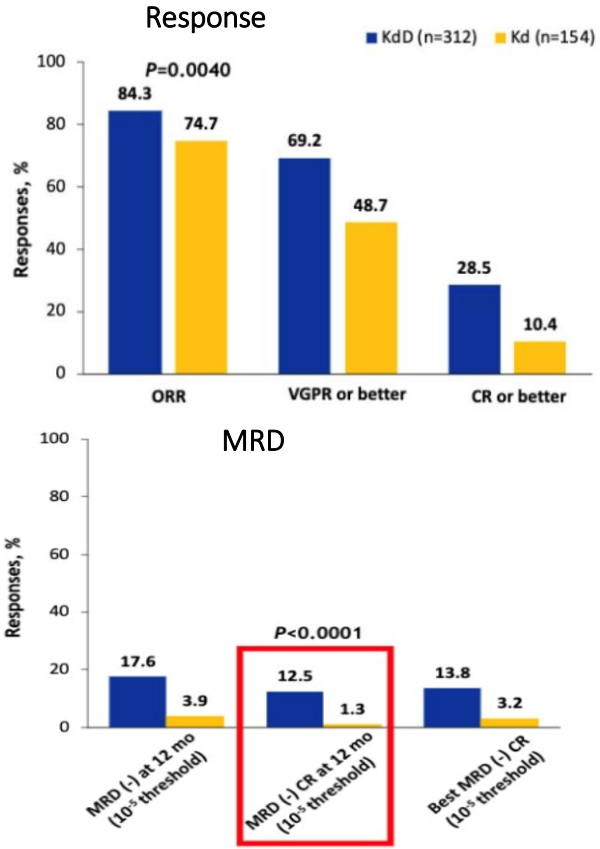
NOVEL COMBINATIONS?

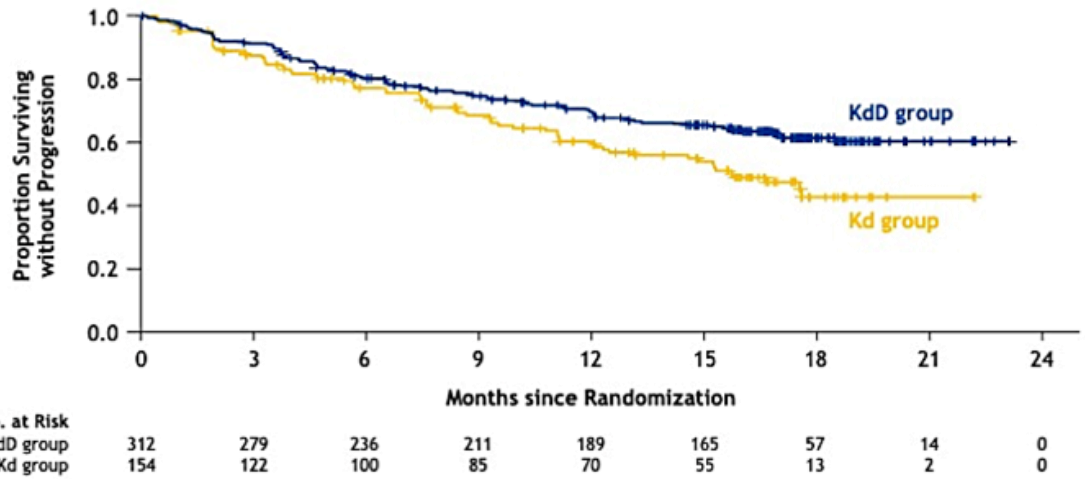
CANDOR: CAR-DARA-DEX vs CAR-DEX



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	

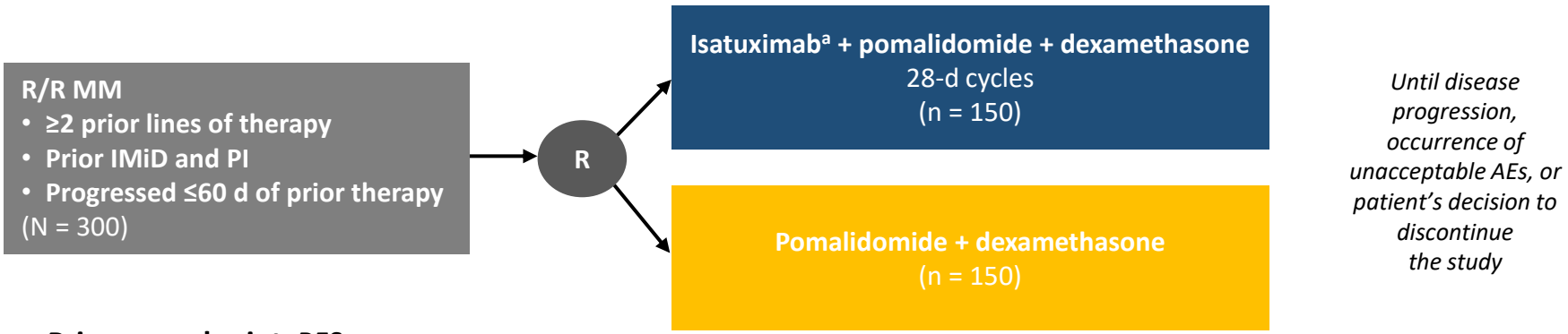
Usmani SZ, et al. ASH 2019. Abstract LBA6.

CANDOR: AEs of Interest

AE, n (%)	CAR-DARA-DEX (n = 308)		CAR-DEX (n = 153)	
	All grades	Grade ≥3	All grades	Grade ≥3
Acute renal failure	18 (5.8)	9 (2.9)	12 (7.8)	10 (6.5)
Cardiac failure	23 (7.5)	12 (3.9)	16 (10.5)	13 (8.5)
Ischemic heart disease	13 (4.2)	9 (2.9)	5 (3.3)	4 (2.6)
Respiratory tract infection	225 (73.1)	89 (28.9)	84 (54.9)	24 (15.7)
Peripheral neuropathy	53 (17.2)	3 (1.0)	13 (8.5)	0
Hypertension	98 (31.8)	55 (17.9)	44 (28.8)	21 (13.7)
IRR (on same day as any K)	126 (40.9)	38 (12.3)	43 (28.1)	8 (5.2)
DARA-related infusion reactions	56 (18.2)	7 (2.3)	0	0
Viral infections	63 (20.5)	19 (6.2)	22 (14.4)	3 (2.0)

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

Phase 3 ICARIA-MM Study: Isatuximab + Pomalidomide-Dexamethasone in R/R MM[1,2]

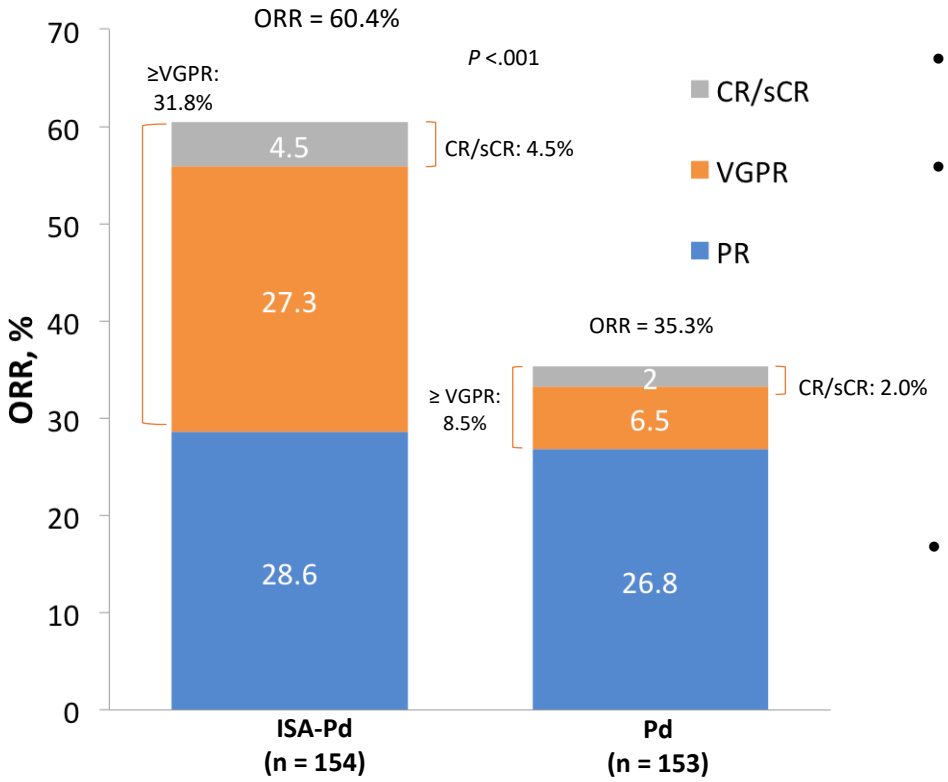


- **Primary endpoint:** PFS
- **Key secondary endpoints:** ORR, OS, safety

[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



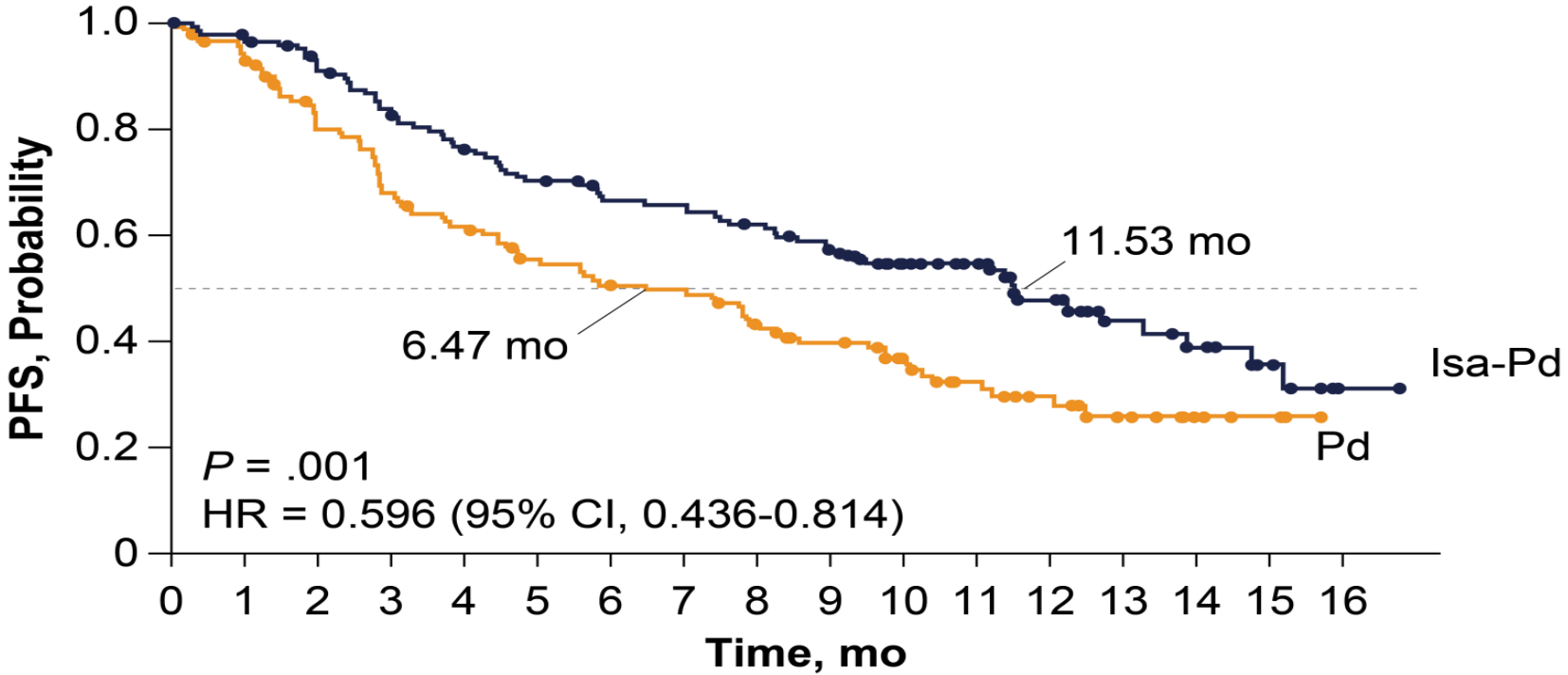
- Median time to first response: ISA-Pd = 35 days vs Pd = 58 days
- True CR rate in ISA-Pd underestimated because of ISA interference with M-protein measurement

	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)[1]



No. at Risk

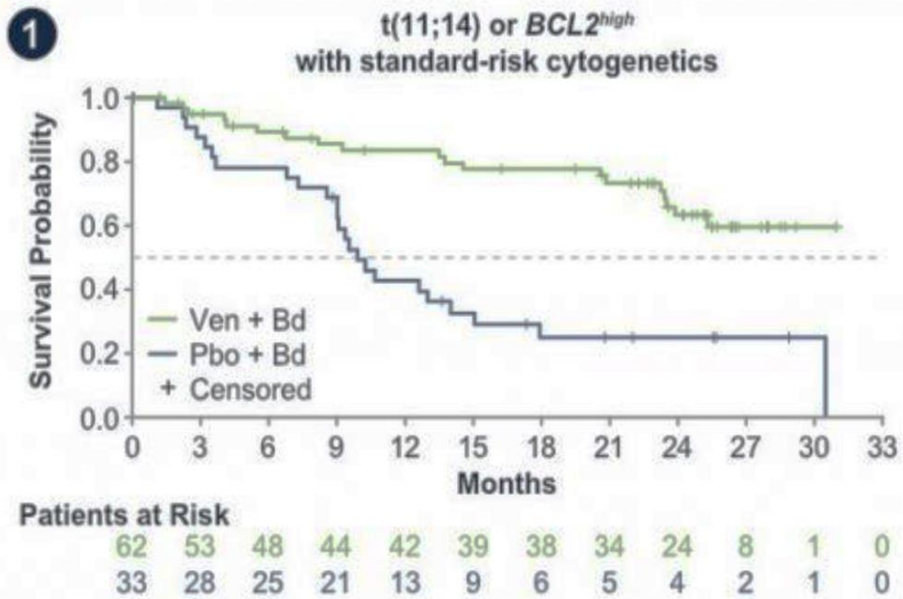
Isa-Pd	154	129	106	89	81	52	30	14	1
Pd	153	105	80	63	51	33	17	5	0

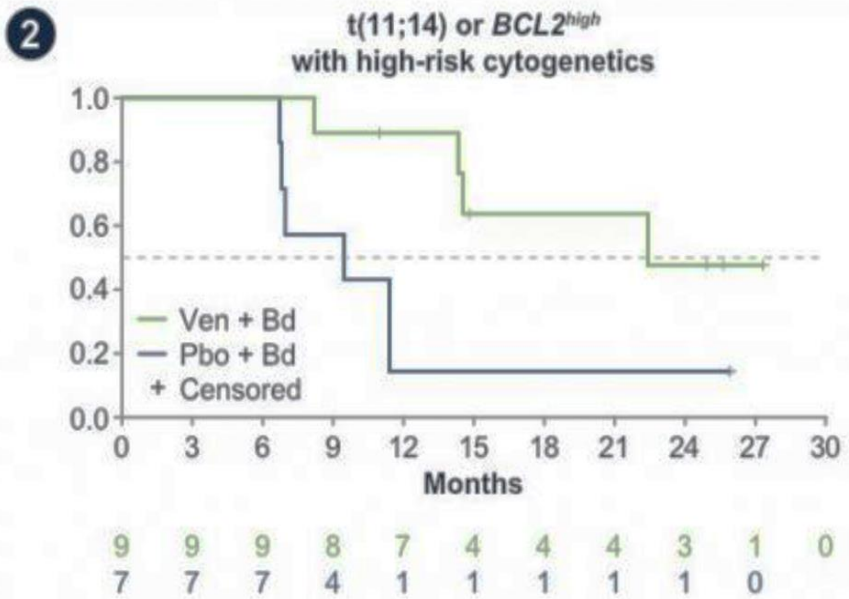
1. Richardson PG, et al. ASCO 2019. Abstract 8004.

NEW SMALL MOLECULES

Venetoclax-Bortezomib-DEX Highly Active in t(11;14) or High BCL-2

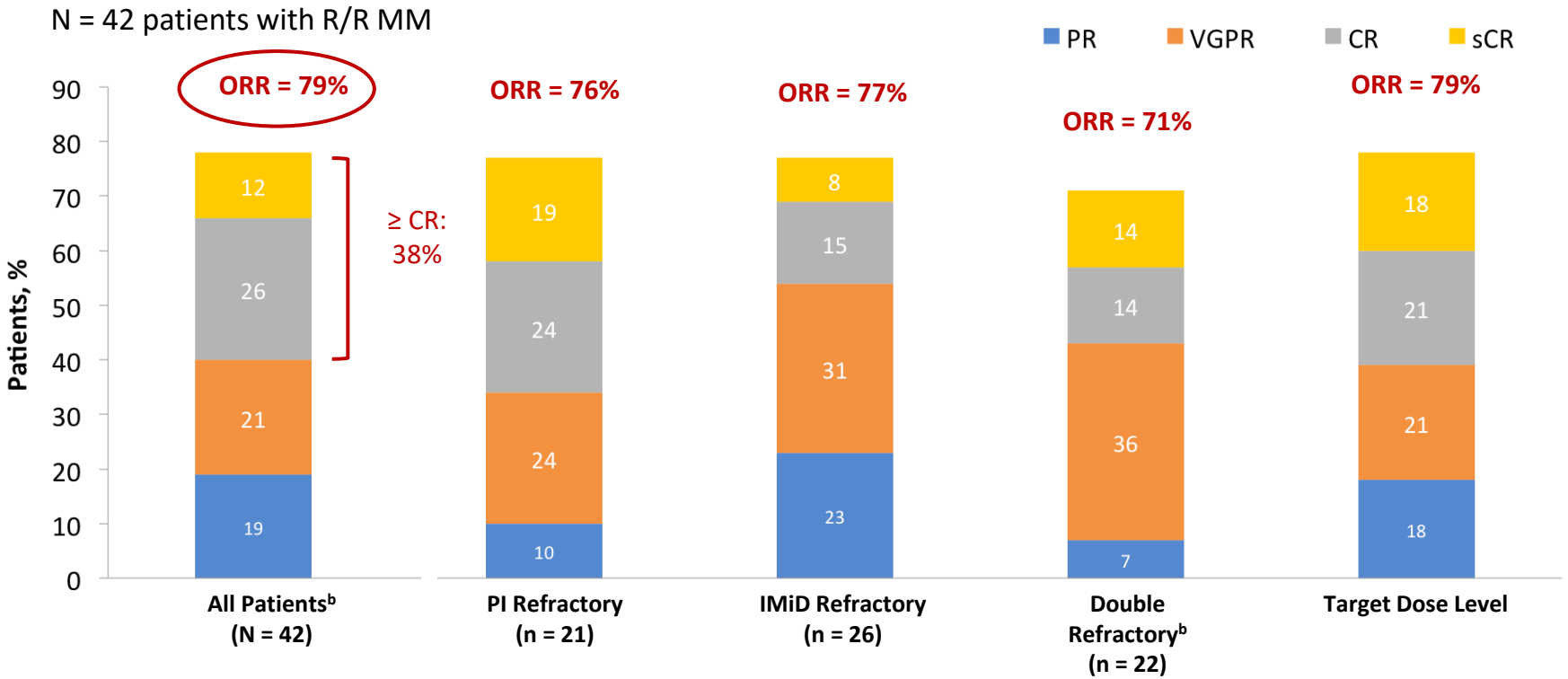
Figure 4. Investigator-Assessed PFS by *BCL2* Gene Expression and Cytogenetic Risk Status





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

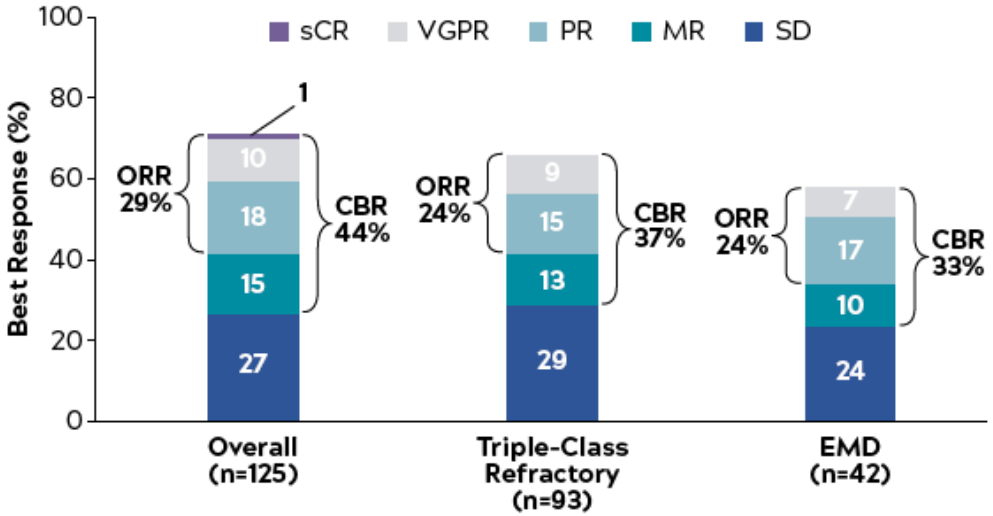
. . . And With Carfilzomib-Dexamethasone[a]



[a]Data cutoff: September 17, 2018. [b]One patient died within the first 2 weeks of dosing; no data available.
Costa LJ, et al. ASH 2018. Abstract 303.

HORIZON: Melflufen

- Patients with R/R MM refractory to pomalidomide or anti-CD38 mAb or both
- ≥2 prior lines of therapy including an IMiD and a PI
- ECOG PS ≤2



TEAE	Grade 3, n (%)	Grade 4, n (%)
Anemia	56 (36)	1 (1)
Neutropenia	47 (31)	54 (35)
Thrombocytopenia	32 (21)	74 (48)
↓ WBC	13 (8)	15 (10)
Pneumonia	11 (7)	2 (1)
Febrile neutropenia	6 (4)	2 (1)
Lymphopenia	6 (4)	2 (1)
Leukopenia	4 (3)	6 (4)

Mateos MV, et al. ASH 2019. Abstract 1883.

Melflufen + Dexamethasone in Combination With Daratumumab: Overall Response (N = 33)

Subgroup	Best Confirmed Response, Patients, n							Patients, %	
	>CR	VGPR	PR	MR	SD	PD	NA	ORR	CBR
Melflufen 30 mg (n = 6)	0	4	1	0	0	0	1[a]	83	83
Melflufen 40 mg (n = 27)	2	6	11	1	2	1	4[b]	70	74
Total (N = 33)	**2**	**10**	**12**	**1**	**2**	**1**	**5**	**73**	**76**

- ORR in patients was similar for both cohorts
  - 30 mg: 83%
  - 40 mg: 70%
  - 30 + 40 mg: 73%

[a]One patient had an unconfirmed PD in the 30-mg dose cohort.
[b]Four patients had unconfirmed responses in the 40-mg dose cohort: 2 PD, 1 SD, and 1 PR.
Data cutoff date: 19 October 2020.
CBR, clinical benefit rate; CR, complete response; MR, minor response; NA, not assessed; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.
Mateos MV, et al. ASH 2019. Abstract 1883.

STORM Part II Study Design

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.

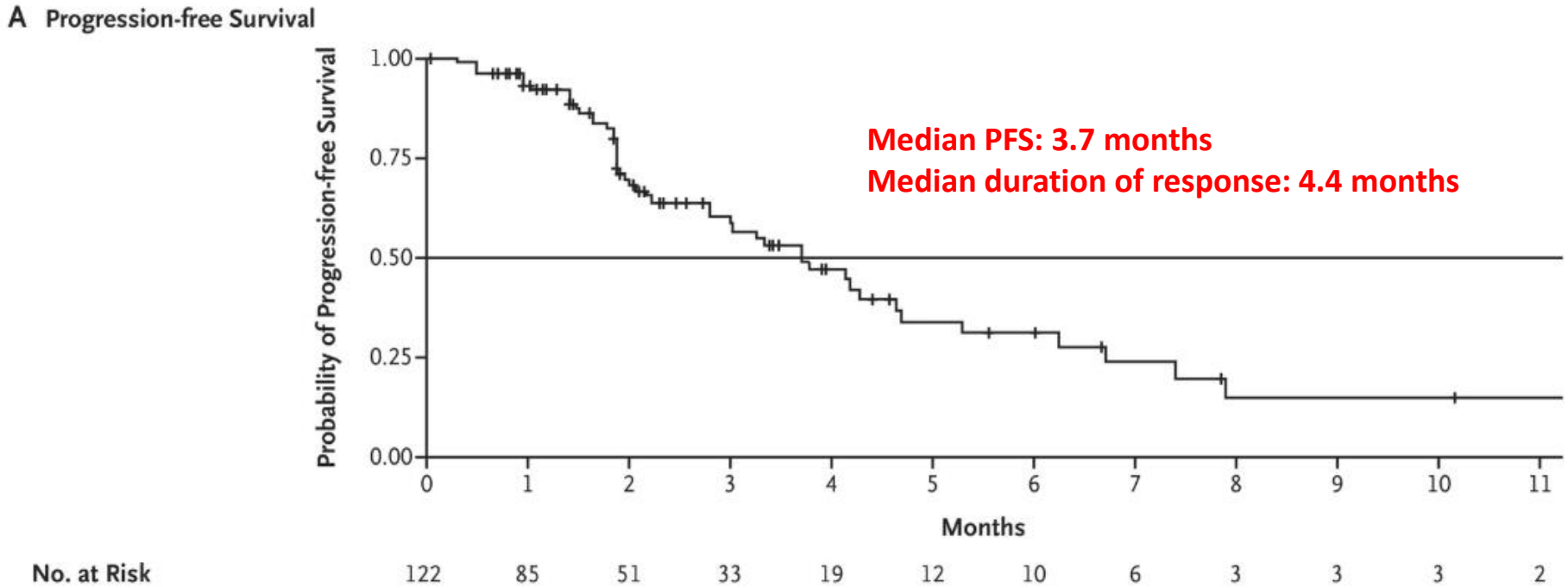
Phase 2 STORM Trial: Response Assessment

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

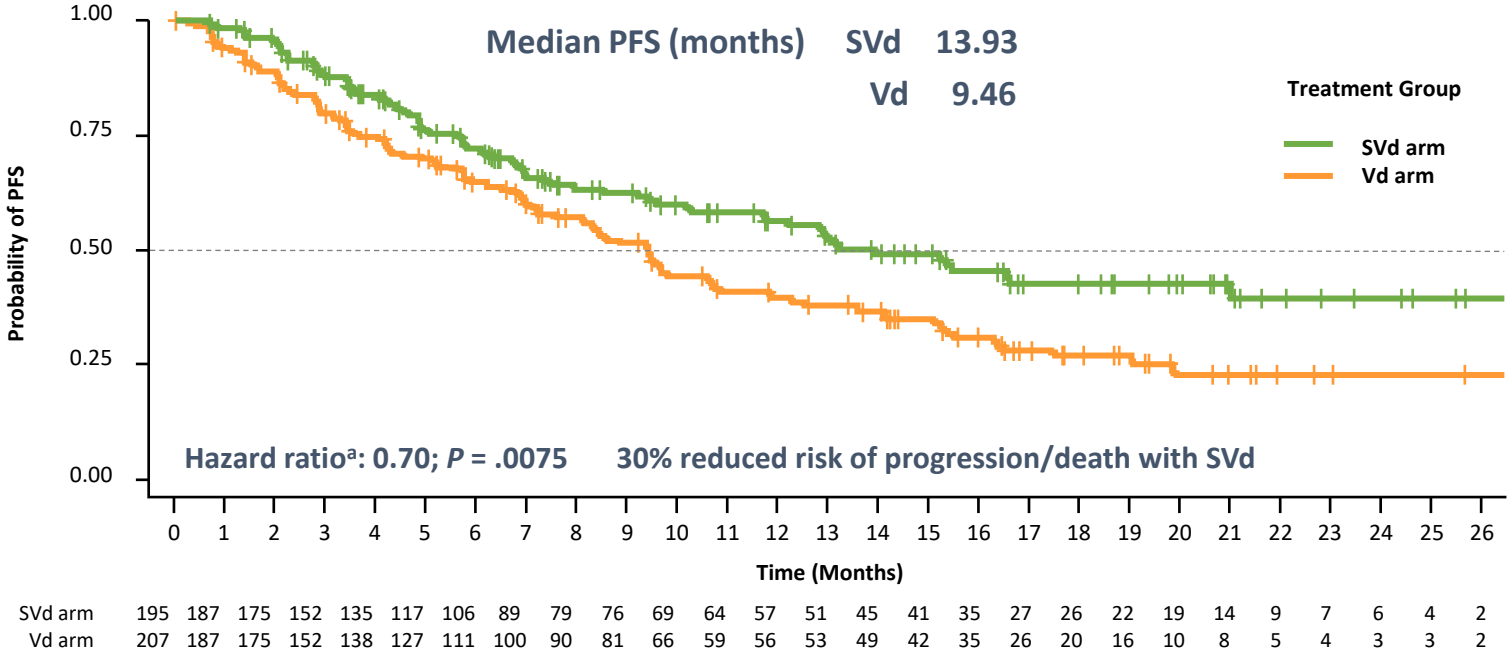
- Hematologic, GI related, constitutional symptoms, and hyponatremia
- Typically responsive to dose modification and standard supportive care agents

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*

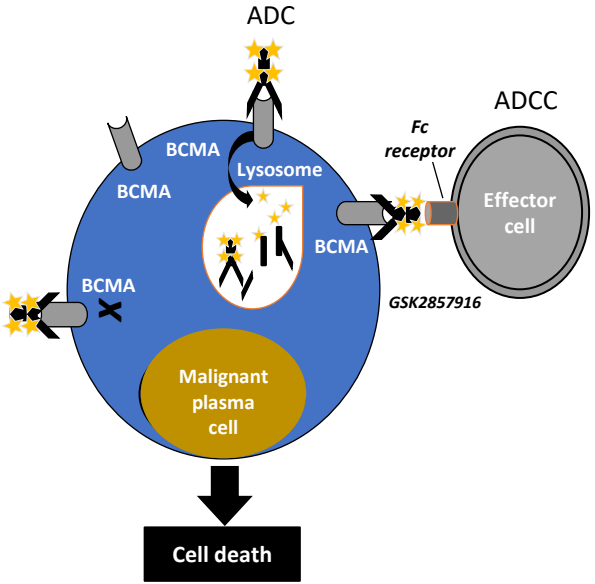
	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-hematological (%)				
Nausea	50.3	7.7	9.8	0
Fatigue	42.1	13.3	18.1	1.0
Decreased Appetite	35.4	3.6	5.4	0
Diarrhea	32.3	6.2	25.0	0.5
Peripheral Neuropathy†	32.3	4.6	47.1	8.8
Upper Respiratory Tract Infection‡	29.2	3.6	21.6	1.5
Weight 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



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

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

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
- 2 deaths were potentially treatment related
  - Sepsis in the 2.5-mg/kg cohort and hemophagocytic lymphohistiocytosis in the 3.4-mg/kg cohort

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

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
- Iberdomide > pomalidomide > lenalidomide
- Save selinexor and melflufen for “no other options”
- Belamaf very active, but eye toxicity limiting
- Venetoclax t(11;14)

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

1. 90%
2. 80%
3. 65%
4. 50%
5. 40%

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

1. Ocular toxicity can be reduced by starting with graduated dosing
2. A less common but significant toxicity is early onset cytokine release syndrome
3. The response rate is 30%–35% partial response or better
4. The response rate in first relapse is 72%
5. Ocular toxicity is manageable with steroid eye drops

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Break

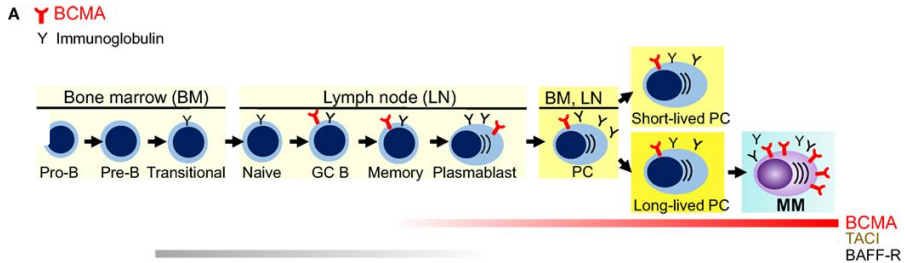
APTITUDE HEALTH®

Promising New Developments in Relapsed MM: Updates From ASH 2020

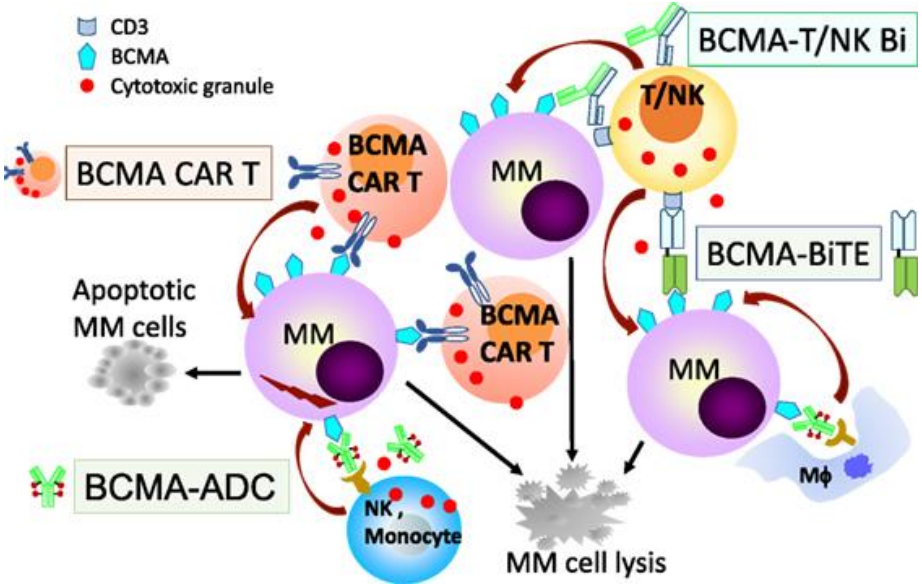
Irene Ghobrial, MD
Lavine Family Chair of Preventative Cancer Therapy
Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, MA

Dana-Farber
Cancer Institute

BCMA in Multiple Myeloma



- Expressed on late memory B cells committed to PC differentiation and PCs
- Important for survival of long-lived PCs
- γ-secretase cleaves BCMA from the cell surface, yielding soluble BCMA



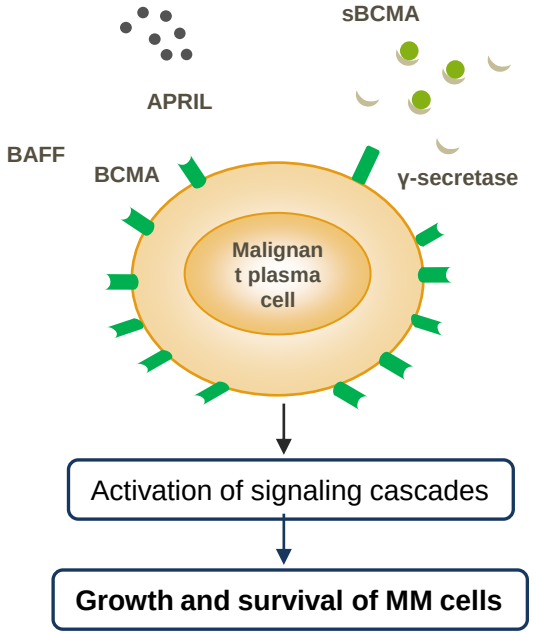
Rationale for Targeting BCMA

BCMA is a cell surface protein expressed on late-stage B cells and plasma cells but virtually absent on naive and memory B cells[1-3]

BCMA is highly expressed on malignant plasma cells in all patients with MM[3-5]

- BCMA ligands, BAFF and APRIL, are detected in increased levels in the circulation of patients with MM[3,5]

BCMA is essential for the proliferation and survival of malignant plasma cells[3]

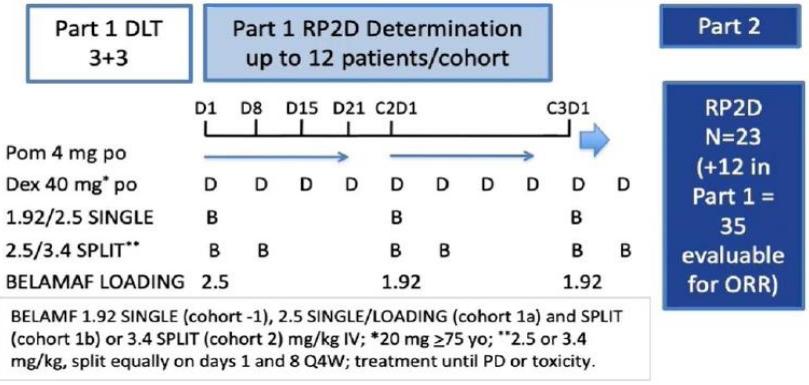


1. Tai YT, et al. *Immunotherapy*. 2015;7(11):1187-1199; 2. Ryan MC, et al. *Mol Cancer Ther*. 2007;6(11):3009-3018;
3. Cho SF, et al. *Front Immunol*. 2018;9:1821; 4. Novak AJ, et al. *Blood*. 2004;103(2):689-694; 5. Tai YT, et al. *Blood*. 2014;123(20):3128-3138.

Comparing Options

	CAR T	Bispecifics	ADCs
Treatment logistics	Specialized center; need to wait for production	TBA, likely community friendly, off-the-shelf Need for long acting	Community friendly, off-the-shelf
Length of treatment	~2 months	??	Possibly limited cycles
Toxicities	CRS, neurotoxicity, cytopenias	CRS, pneumonia	Corneal, thrombocytopenia
Cost	? $400K	? But have to consider length of treatment	$24K/month

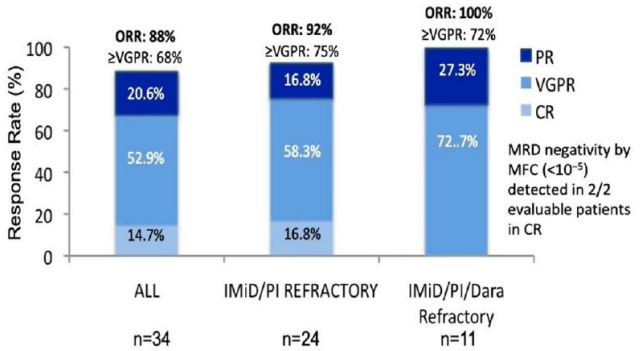
Belantamab Mafodotin in Combination With Pomalidomide and Dexamethasone for RR MM: Dose-Finding Study (Part 1)



Characteristic	n=37 (%)
Age, median (range), years	64 (36-81)
ISS Stage I/II/III	17 (45.9%)/16 (43.2%)/1 (2.7%)
High-risk cytogenetics*	9/19 (47%)
Number of prior lines of therapy, median (range)	3 (1-5)
Autologous Stem Cell Transplant (ASCT)	24 (64.9%)
LEN exposed LEN refractory	37 (100%) 33 (89.2%)
PI exposed Bortezomib Carfilzomib PI refractory	37 (100%) 36 (97.3%) 13 (35.1%) 30 (81.1%)
DARA exposed DARA refractory	16 (43.2%) 16 (43.2%)
LEN and PI refractory	27 (73%)
LEN, PI, and DARA refractory	13 (35.1%)

TEAE	Any Grade	≥ Grade 3
Keratopathy	28 (75.7%)	19 (51.4%)
Neutropenia	21 (56.8%)	15 (40.5%)
Thrombocytopenia	18 (48.6%)	12 (32.4%)
Decreased visual acuity	17 (45.9%)	6 (16.2%)
Fatigue	15 (40.5%)	4 (10.8%)

Response Rates

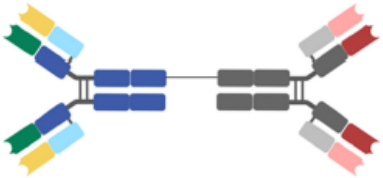


Outcome (median)	All	IMiD/PI Refractory	IMiD/PI/Dara Refractory
Follow-up, months (range)	7.8 (1.9, 20.3)	7.8 (1.9, 18.9)	7.4 (2.1, 16.1)
PFS, months (95% CI)	NR (10.8, -)	NR (10.8, NR)	11.1 (4.9, NR)

Bispecific Antibodies: Many Different Platforms

Bispecific T-cell Engager or BiTE (Amgen)

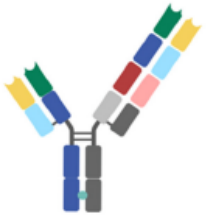
Dual Affinity Re-Targeting or DART (Janssen, MacroGenics)



Tandem diabodies or TandAb (Affimed)

BsAb armed activated T cells or BAT (mostly academic)

T-cell dependent BsAb Xmab (Xencor, Glenmark, Amgen)



CrossMAb (Celgene, Roche)

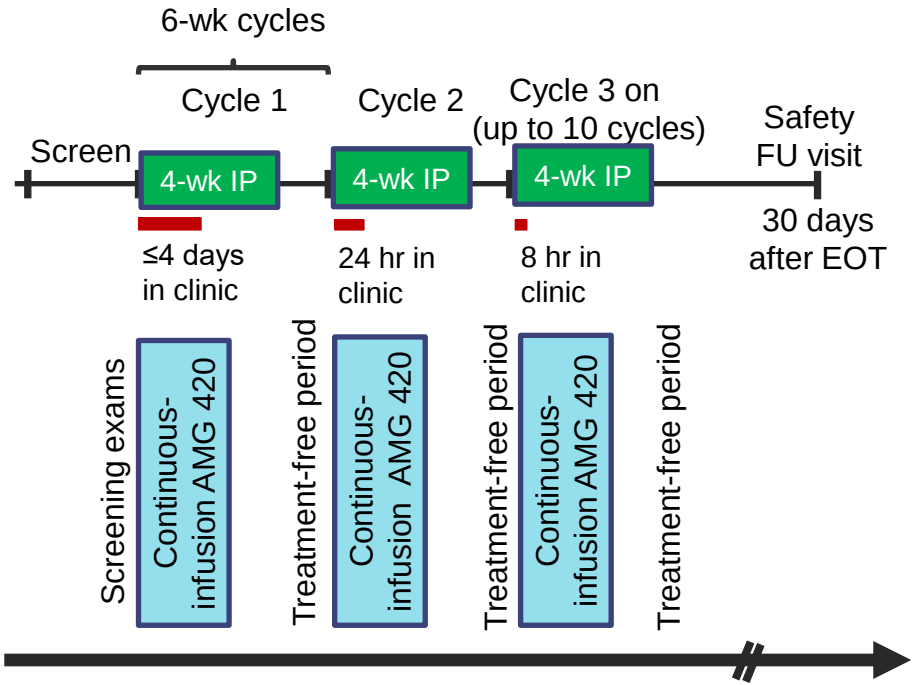
Duobody (Genmab)

Trifunctional Antibody or TriFAb

Adapted from Lejeune M, et al. *Front Immunol.* 2020;11:762.

AMG 420 Phase I Study: Design

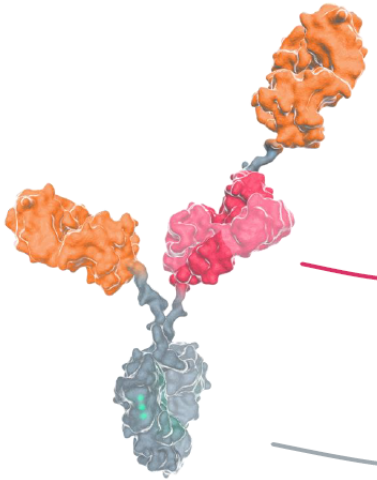
Relapsed/Refractory Multiple Myeloma, ≥2 Prior Lines of Therapy, ≥1 IMID, ≥1 PI



- **First-in-human (FIH) phase I dose-escalation study of AMG 420 for up to 10 cycles**
- **Single-patient cohorts [0.2–1.6 µg/day (d)] were followed by cohorts of 3–6 patients (3.2–800 µg/d)**
- **Objectives**
  - Safety
  - Maximum tolerated dose (MTD)
  - Antitumor activity

CC-93269 Key Engineering Characteristics

- CC-93269 is a humanized 2+1 IgG1-based TCE that binds to BCMA on myeloma cells and to CD3ε on T cells, enabling specific and tight BCMA binding[1,2]



Anti-BCMA (bivalent)[1–5]
Bivalent binding to BCMA in a 2+1 format for superior potency, tumor targeting, and retention

Anti-CD3ε (monovalent)[1–5]
Head-to-tail geometry of BCMA- and CD3ε-binding Fab domains using a flexible linker

Heterodimeric FcγR-silent Fc[1–6]
No binding to FcγR and C1q to minimize infusion-related reactions and binding to FcRn retained for IgG-like PK

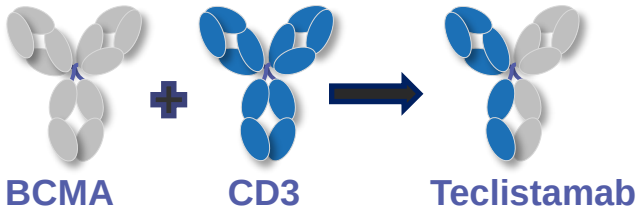
- CC-93269 induces tumor regression in animal models of myeloma and promotes myeloma cell death in primary patient bone marrow aspirates[1,2]

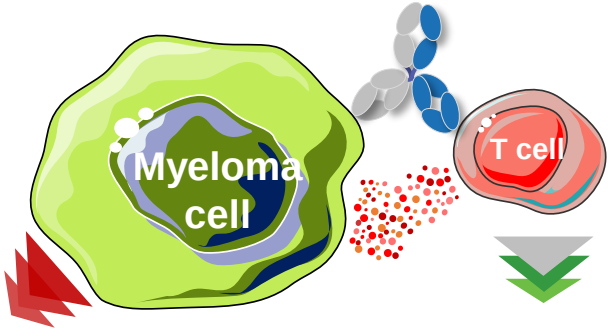
BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; Fab, antigen-binding fragment; FcγR, Fc gamma receptor; FcRn, neonatal Fc receptor; Ig, immunoglobulin; PK, pharmacokinetics; TCE, T-cell engager.

1. Seckinger A, et al. *Cancer Cell.* 2017;31:396-410; 2. Vu DM, et al. *Blood.* 2015;128: abstract 2998; 3. Klein C, et al. *Cancer Res.* 2017;77: abstract 3629; 4. Bacac M, et al. *Clin Cancer Res.* 2016;22:3286-3297; 5. Lehmann S, et al. *Clin Cancer Res.* 2016;22:4417-4427; 6. Schlothauer T, et al. *Protein Eng Des Sel.* 2016;29:457-466.

Teclistamab for Patients With RR MM: Updated Phase I Results

BCMA × CD3 Bispecific Antibody





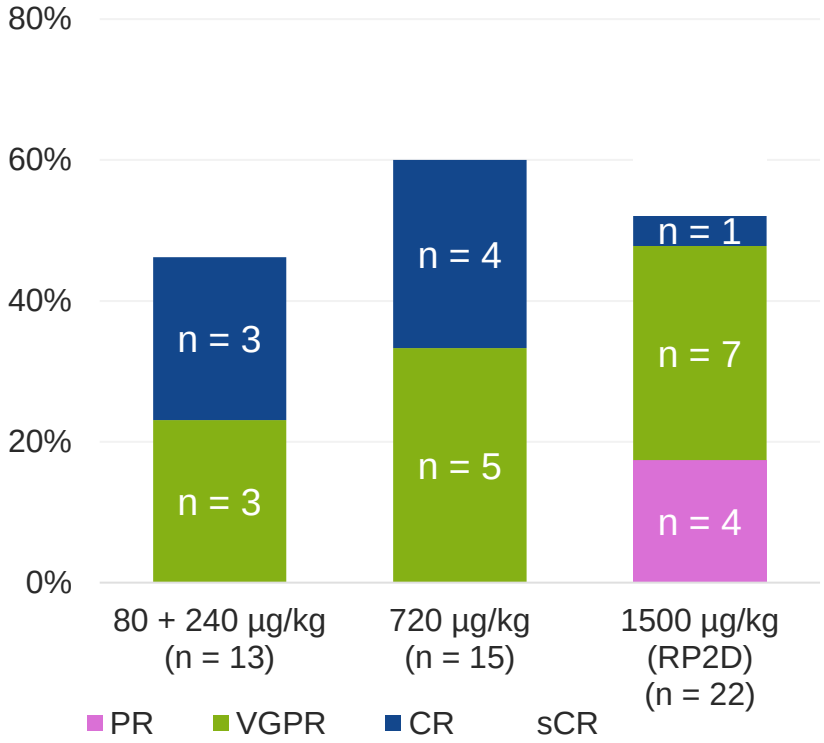
Cell death

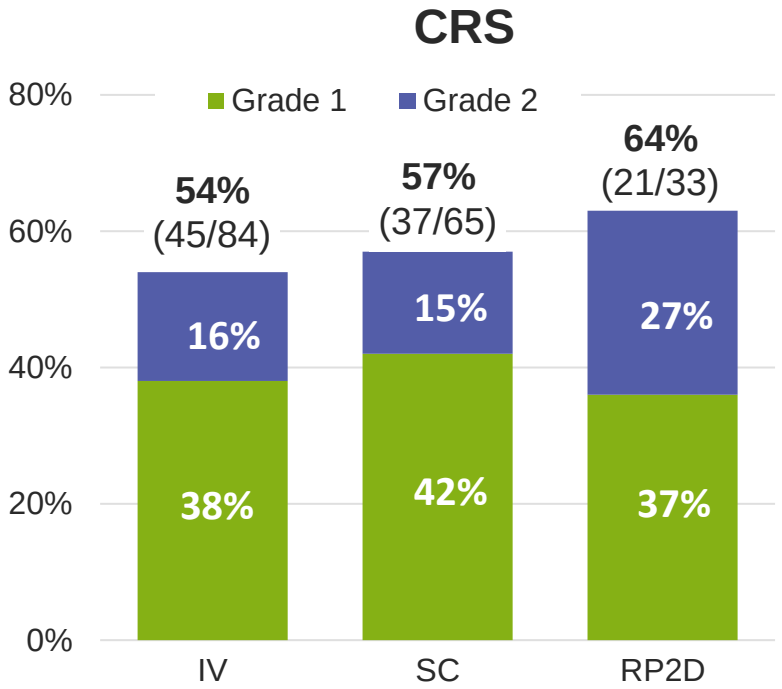
T-cell activation
Cytokine secretion
Cytotoxicity

Characteristic, n (%)	Total N = 149	1500 µg/kg SC (RP2D) n = 33
Median prior lines of therapy (range)	6 (2–14)	5 (2–11)
Triple-class exposed	143 (96)	33 (100)
Penta-drug exposed	102 (69)	21 (64)
Refractory status		
Carfilzomib	99 (66)	22 (67)
Pomalidomide	115 (77)	24 (73)
Anti-CD38	138 (93)	32 (97)
Triple-class refractory	121 (81)	28 (85)
Penta-drug refractory	58 (39)	12 (36)
Refractory to last line of therapy	136 (91)	29 (88)

Teclistamab for Patients With RR MM: Updated Phase I Results

BCMA × CD3 Bispecific Antibody



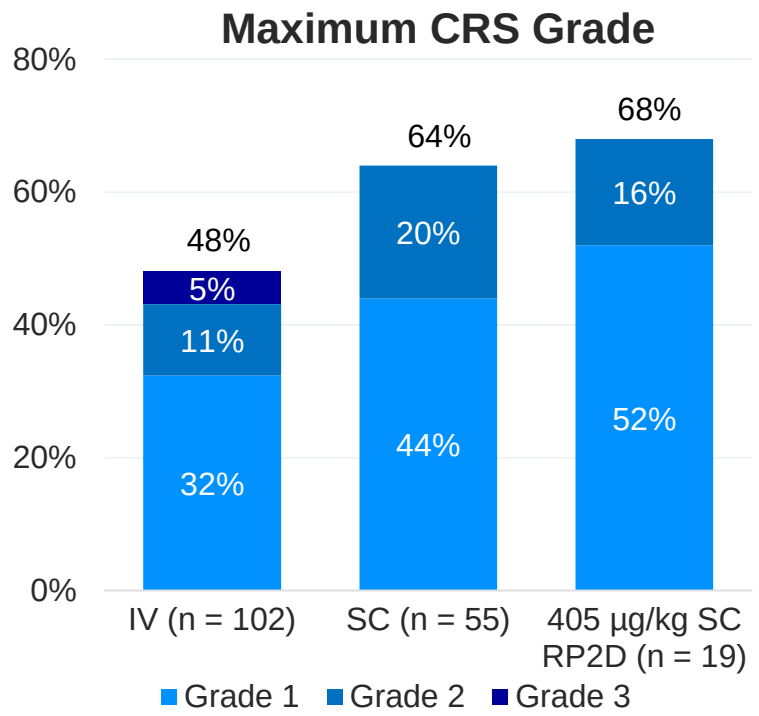


PR, partial response; VGPR, very good partial response; CRS, cytokine release syndrome; IV, intravenous; SC, subcutaneous; RP2D, recommended phase II dose.

Phase I First-in-Human Study of Talquetamab in Patients With RR MM

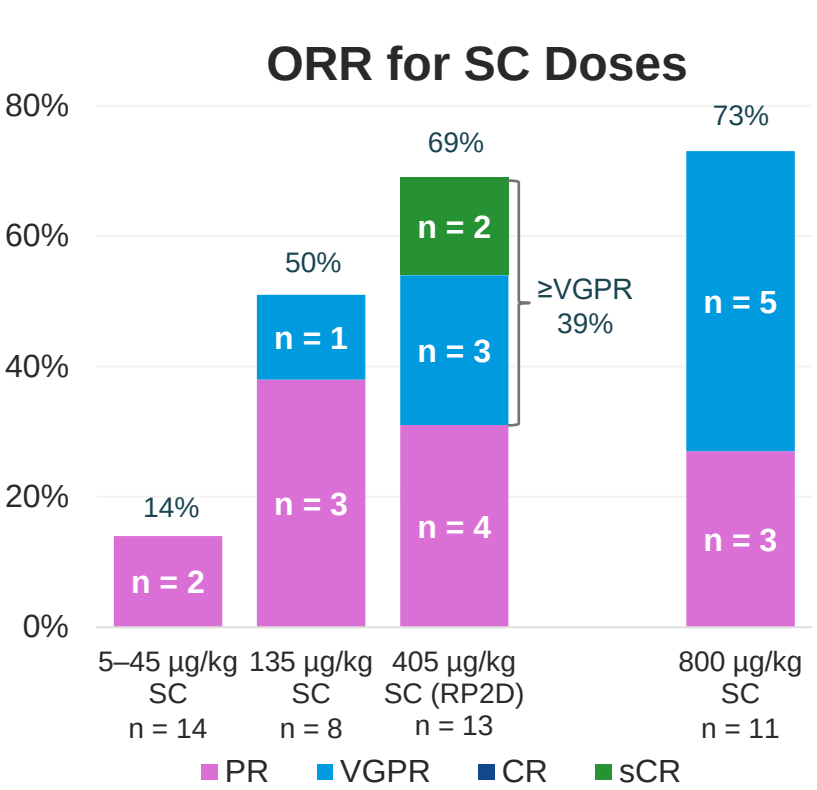
G Protein-Coupled Receptor Family C Group 5 Member D (GPRC5D) × CD3 Bispecific Antibody

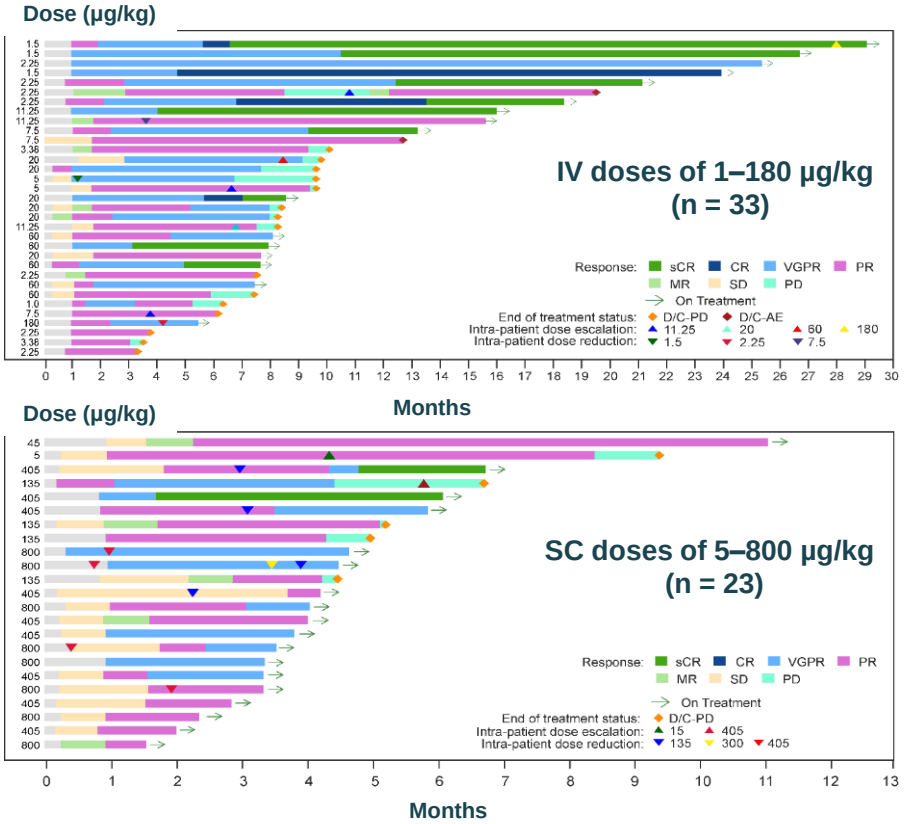
Characteristic, n (%)	Total (N = 157)	405 µg/kg SC RP2D (n = 19)
Median prior lines of therapy (range)	6 (2–20)	4.5 (2–14)
Triple-class exposed	155 (99)	18 (95)
Penta-drug exposed	120 (76)	13 (68)
Prior anti-BCMA therapy	27 (17)	3 (16)
Refractory status		
Carfilzomib	105 (67)	11 (58)
Pomalidomide	119 (76)	15 (79)
Anti-CD38	149 (95)	18 (95)
Triple-class	128 (82)	13 (68)
Penta-drug	51 (33)	4 (21)
Refractory to last line of therapy	136 (87)	15 (79)



CRS, cytokine release syndrome; IV, intravenous; SC, subcutaneous; RP2D, recommended phase II dose.

Talquetamab: Overall Response Rate and DOR



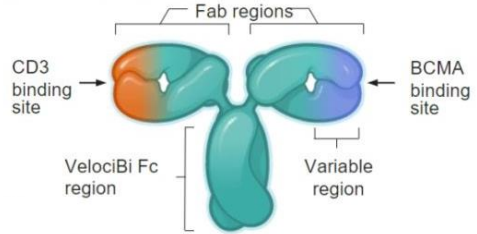


PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; IV, intravenous; SC, subcutaneous; RP2D, recommended phase II dose.

REGN5458 Induces Deep and Durable Responses in Patients With RR MM

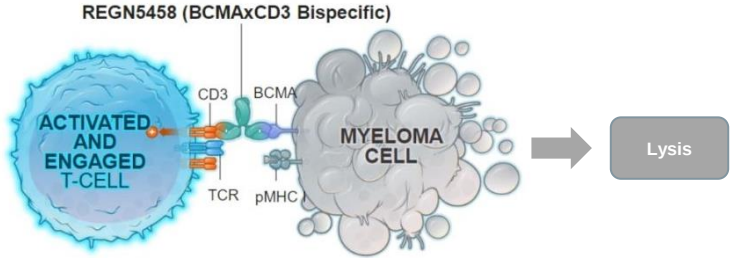
BCMA × CD3 Bispecific Monoclonal Antibody

REGN5458 molecular structure

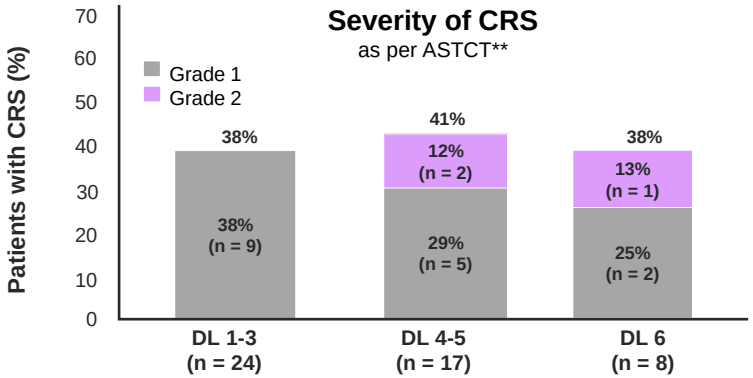


REGN5458
A BCMA × CD3 bispecific antibody discovered using *VelociBi™*

REGN5458 mechanism of action



Prior Systemic Treatment	Total (N = 49)
Median prior lines of therapy, n (range)	5 (2-17)
Refractory, n (%)	
Triple refractory	49 (100)
Penta-refractory	28 (57)
Refractory status, n (%)	
Carfilzomib	39 (80)
Pomalidomide	45 (92)
Anti-CD38 antibody	49 (100)
Refractory to last line of therapy,* n (%)	30 (61)



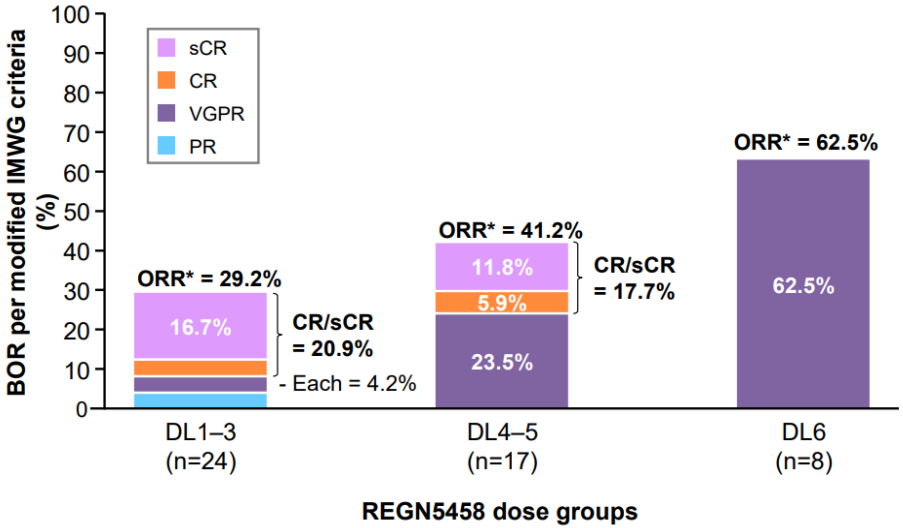
*Relapse or lack of response within 60 days; **Highest severity of CRS per ASTCT from each patient included.
DL, dose level; CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy.

REGN5458 Induces Deep and Durable Responses in Patients With RR MM

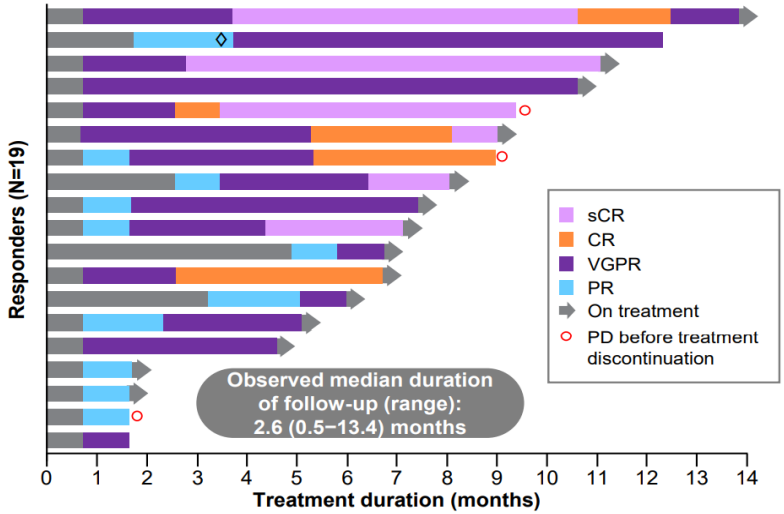
BCMA × CD3 Bispecific Monoclonal Antibody

Efficacy

Intent-to-treat analysis



Duration of Response



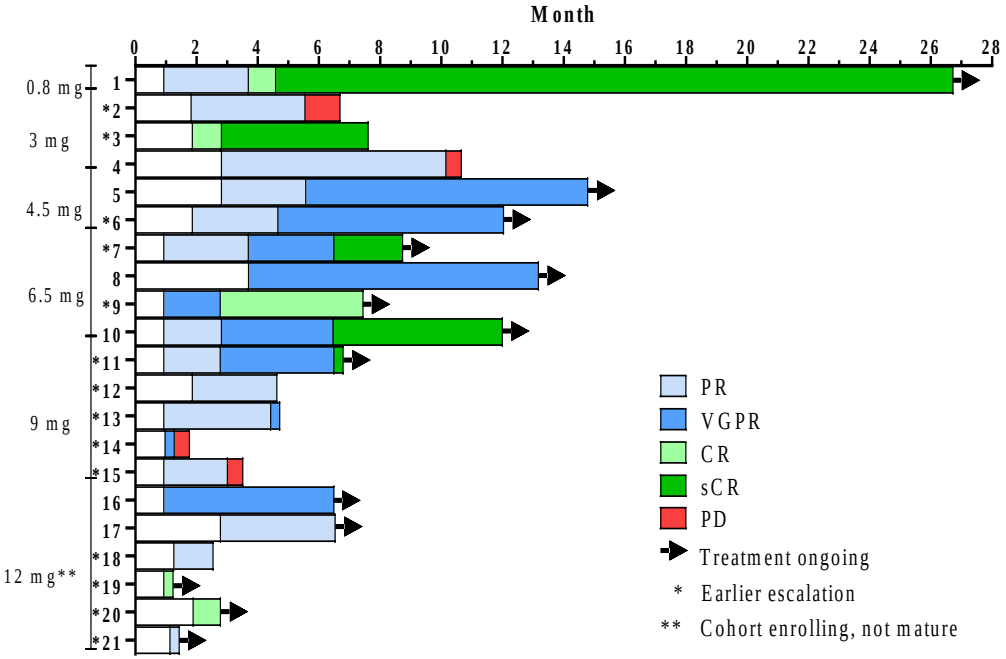
BOR, best overall response; IMWG, International Myeloma Working Group; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; PD, progressive disease.

AMG 701 for Patients With RR MM: Phase I First-in-Human Study

Anti-BCMA Half-Life Extended Bispecific T-Cell Engager

Feature	Description
Inclusion	MM relapsed/refractory to ≥3 prior lines, including PI, IMiD, and anti-CD38 Ab*
Exclusion	Non-secretory disease Auto/allo stem cell transplant within 3 or 6 months, respectively Prior treatment with anti-BCMA agent
Treatment	Weekly IV infusions in 4-week cycles until disease progression
Premedication	8 mg dexamethasone or equivalent in first 2 cycles†
Dosing	Step-dosing schedules were tested

Characteristic	N = 85
Male, n (%)	44 (52%)
Age, median (min-max), years	64 (34-83)
Disease duration, median (min-max), years	5.6 (0.5-15.1)
ISS stage I/II/III	21%/48%/26%*
Extramedullary disease	25%
Bone marrow plasma cells at baseline, median (min-max)	10% (0%-94%)
Prior lines of therapy, median (min-max)	6 (2-25)
Prior stem cell transplant, any	82%
Auto/allo	80%/11%
Triple-exposed/triple-refractory (PI, IMiD, and anti-CD38 Ab)	93%/62%



Phase I MagnetisMM-1 Trial: Preliminary Safety and Efficacy BCMA-CD3 Bispecific Antibody Elranatamab (PF-06863135)

MM patients refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody (n = 18) received subcutaneous doses of elranatamab at 80, 130, 215, and 360 µg/kg weekly

- 22% had received prior BCMA-targeted ADC or CAR T therapy

Safety

TEAEs	All Events N (%)	Grade 3-4 N (%)
CRS	11 (61%)	-
Anemia	9 (50%)	8 (44%)
Thrombocytopenia	7 (39%)	5 (28%)
Injection site reaction	6 (33%)	-
Lymphopenia	6 (33%)	6 (33%)
Neutropenia		4 (22%)
Bone pain		2 (11%)

Efficacy

- ORR = 33% overall and 75% at the top 2 dose levels (215 and 360 µg/kg)
- 2 patients achieved a best response of PR, VGPR, and sCR each
- 7 patients had best response of stable disease

Elranatamab demonstrated a manageable safety profile and promising efficacy in RR MM and has been granted **FDA Fast Track Designation**

ADC, antibody-drug conjugate; CRS, cytokine release syndrome; ORR, objective response rate; PR, partial response; VGPR, very good partial response; sCR, stringent complete response.

Phase II MagnetisMM-3 Trial: Design

Objective: To evaluate whether elranatamab can provide clinical benefit in relapsed/refractory multiple myeloma

Key eligibility criteria

- RR MM, refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody
  - **Cohort A:** (n = 90) Prior BCMA-directed ADC or CAR T therapy
  - **Cohort B:** (n = 60) No prior BCMA-directed therapy

Elranatamab

Weekly 76 mg subQ injection following a priming dose of 44 mg

Primary endpoint

- ORR at 2 years

Key secondary endpoints

- DOR
- MRD-negativity rate
- PFS
- OS
- Safety

FPI Feb 2021

RR MM, relapsed/refractory multiple myeloma; PI, proteasome inhibitor; IMiD, immunomodulatory drug; ORR, objective response rate; subQ, subcutaneous; DOR, duration of response; MRD, minimal residual disease; PFS, progression-free survival; OS, overall survival; FPI, first patient in.

Initial Clinical Activity and Safety of BFCR4350A in RR MM

FcRH5/CD3 T-Cell–Engaging Bispecific Antibody

In dose escalation, pts receive BFCR4350A by IV infusion in 21-day cycles (Q3W). In Arm A, a single step-up dose is used in cycle 1 to mitigate the risk for CRS, with the step dose (0.05–3.6 mg) given on C1D1 and the target dose (0.15–132 mg) given on C1D8, and on D1 of each subsequent cycle.

BFCR4350A monotherapy demonstrates promising activity in heavily pretreated RR MM, with deep and durable responses observed in pts with HR cytogenetics, triple-class refractory disease, and/or prior exposure to anti-CD38 mAbs, CAR Ts, or ADCs.

Table: Summary of best overall response by investigator assessment at the active dose level (3.6/20mg) and above*†

	≥3.6/20mg N=29	3.6/20mg N=3	3.6/40mg N=6	3.6/60mg N=7	3.6/90mg N=9	3.6/132mg N=4
ORR‡	15 (51.7%)	2 (66.7%)	4 (66.7%)	1 (14.3%)	6 (66.7%)	2 (50.0%)
sCR	3 (10.3%)	0	2 (33.3%)	1 (14.3%)	0	0
CR	3 (10.3%)	0	0	0	1 (11.1%)	2 (50.0%)
VGPR	4 (13.8%)	0	0	0	4 (44.4%)	0
PR	5 (17.2%)	2 (66.7%)	2 (33.3%)	0	1 (11.1%)	0

*by IMWG uniform response criteria 2016; †April 13, 2020 data cut-off; ‡pts with best overall response of sCR, CR, VGPR or PR

CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent CR; VGPR, very good PR

Initial Results of a Phase I Study of TNB-383B in RR MM

BCMA × CD3 Bispecific T-Cell–Redirecting Antibody

Patients have been treated with escalating doses of TNB-383B infused IV over 1–2 hours Q3W (without step-up dosing). The primary objectives are to determine the safety/tolerability and clinical pharmacology of TNB-383B and to identify the MTD/RP2D.

Table 1: Demographics and Disease Characteristics

	0.025 - 1.8 mg	≥ 5.4 mg	Total
Subjects	N = 15	N = 23	N = 38
Male	10 (67%)	11 (48%)	21 (55%)
Female	5 (33%)	12 (52%)	17 (45%)
Median Age (Range)	72 (56-83)	68 (37-78)	68 (37-83)
Median Prior Lines of Therapy (Range)	8 (4-12)	7 (4-13)	7 (4-13)

Table 2: Response Summary

	0.025 - 1.8 mg	≥ 5.4 mg	Total
Subjects	N = 15	N = 23	N = 38
ORR	2 (13%)	12 (52%)	14 (37%)
sCR/CR	0 (0.0%)	3 (13%)	3 (7.9%)
VGPR	1 (6.7%)	3 (13%)	4 (11%)
PR	1 (6.7%)	6 (26%)	7 (18%)
Median DOR in weeks (Range)	24 (21-27)	9 (3-21)	9 (3-27)

BCMA and Other Targets

BCMA BsAbs	Phase of Study	NCT#
AMG 701	Phase I	NCT03287908
PF-06863135	Phase I	NCT03269136
REGN5458	Phase I/II	NCT03761108
TNB-383B	Phase I	NCT03933735
RO7297089	Phase I	NCT04434469

Novel BsAb	Target	Phase of Study	NCT#
Talquetamab	GPRC5D	Phase I	NCT03399799
AMG 424	CD38	Phase I	NCT03445663
GBR 1342	CD38	Phase I	NCT03309111
BFCR4350A	FCRH5	Phase I	NCT03275103

BsAb, bispecific antibody.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

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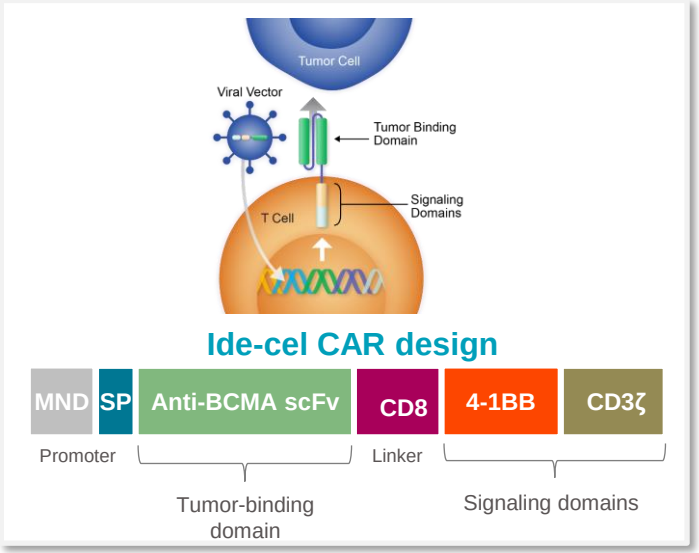
Introduction and Objectives

- **Outcomes remain poor in triple-class–exposed RR MM patients who progress on IMiD® agents, proteasome inhibitors (PIs), and anti-CD38 antibodies, and there is no standard of care**
  - Deep and durable responses uncommon[1-3]
  - Median PFS of 3-4 mo; median OS of 9.3 mo[4]
- **Ide-cel, a BCMA-directed CAR T-cell therapy, showed promising tolerability and efficacy in RR MM patients in the phase I CRB-401 study[5]**
  - Evaluated doses of 50−800 × 10^6 CAR+ T cells
  - ORR = 85%; CRR = 45%; median PFS = 11.8 mo; median DOR = 10.9 mo
  - Grade ≥3 CRS or neurotoxicity observed in 6% of patients

Objective: To present efficacy and safety data from the pivotal phase II KarMMa trial of ide-cel in RR MM*



Ide-cel CAR T-Cell Design

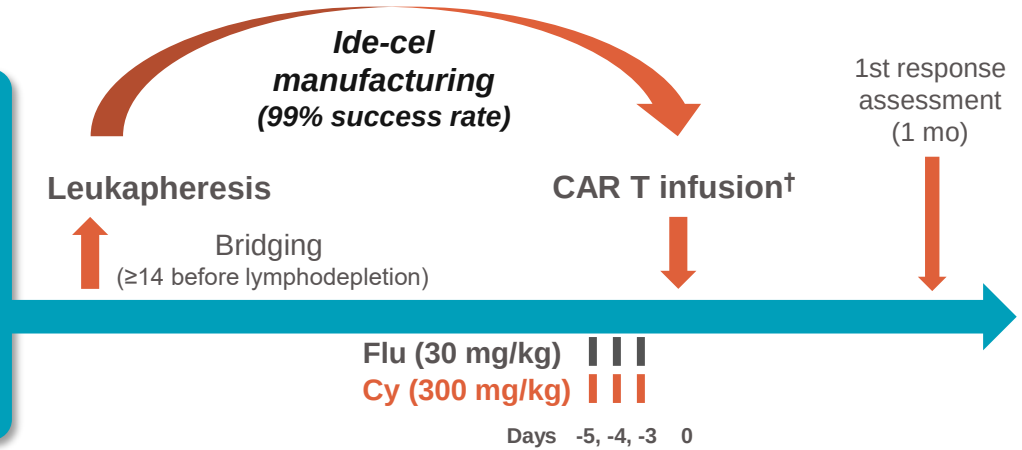
- **Autologous** T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- Targeting domain: **anti-BCMA**
- Co-stimulatory domain: **4-1BB**
- T-cell activation domain: **CD3ζ**

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRR, complete response rate; IMiD, immunomodulatory drug; ORR, overall response rate; PFS, progression-free survival; RR MM, relapsed and refractory multiple myeloma; TM, transmembrane. *Data presented are updated from the protocol-specified primary analysis dataset.

1. Braggio E, et al. *Cancer Cell.* 2015;28:678-.e1. 2. Rasche L, et al. *Cancer Treat Rev.* 2017;55:190-199. 3. Nijhof IS, et al. *Drugs.* 2018;78:19-37. 4. Gandhi UH. *Leukemia.* 2019;33:2266-2275. 5. Raje NS, et al. *N Engl J Med.* 2019;380:1726-1737.

Phase II Pivotal KarMMa Study

- RR MM
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG*



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

Study Status as of Jan 14, 2020

Screened N = 158

Leukapheresed N = 140

Treated N = 128
(Target dose CAR+ T cells)

150×10^6	n = 4
300×10^6	n = 70
450×10^6	n = 54

Median Follow-up (mo)

150×10^6	18.0
300×10^6	15.8
450×10^6	12.4
Total	13.3

*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. †Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.
CRR, complete response ratio; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory imide drugs; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.

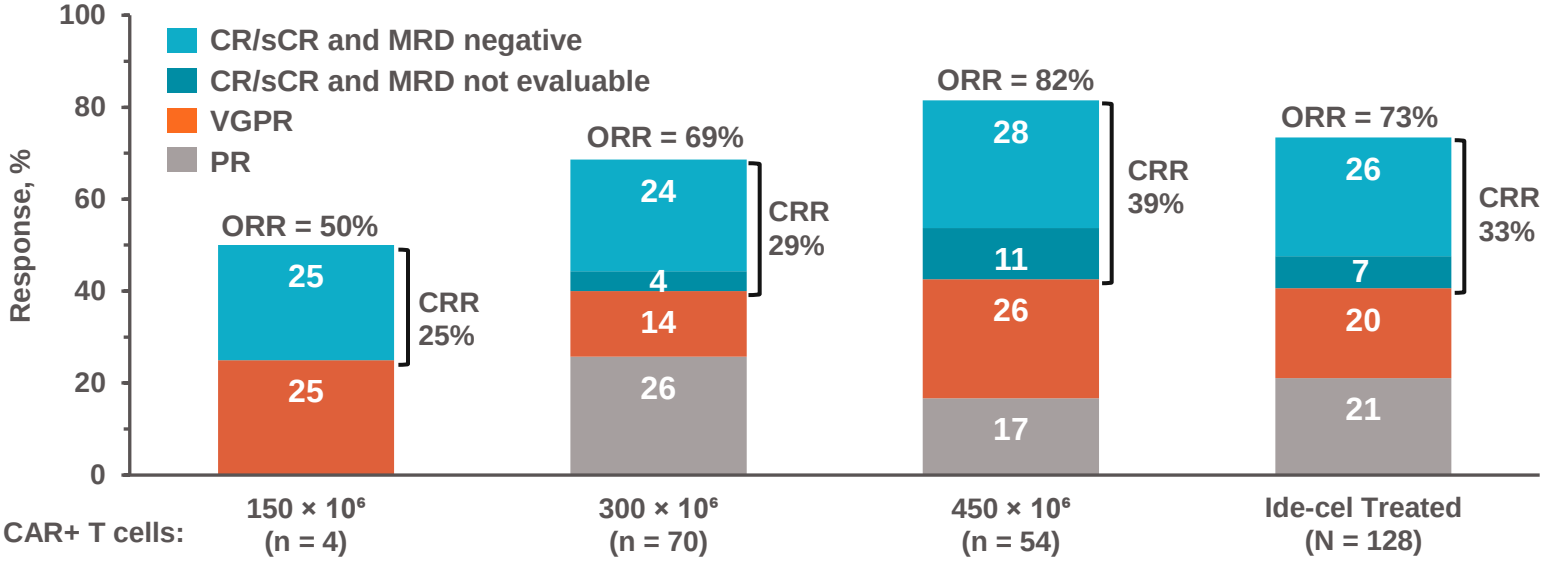
Baseline Demographics and Clinical Characteristics

Characteristics		Ide-cel Treated (N = 128)
Age, median (range), y		61 (33–78)
Male, %		59
ECOG PS, %	0 1 2	45 53 2
R-ISS Stage,* %	I II III	11 70 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 antimyeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1 >1	94 34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab refractory Triple refractory	94 84

- Patients were heavily pretreated, refractory to last line per IMWG criteria, and mostly refractory to all 3 major MM drug classes
- The majority had high tumor burden and more than one-third had extramedullary disease and high-risk cytogenetics
- Tumor BCMA expression identified by IHC in all patients
- Most patients (88%) received bridging therapy during CAR T-cell manufacturing
  - Only 5% of patients responded (5 PR, 1 VGPR) to bridging therapy

Data cutoff: 14 Jan 2020. *R-ISS stage was assessed at enrollment; unknown for 3 patients. †Baseline cytogenetics not evaluable/missing for 17 patients; 45 patients (35%) had 1q amp abnormality. ‡No minimum tumor BCMA expression required for study entry.
Ab, antibody; BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cells; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; MM, multiple myeloma; PR, partial response; R-ISS, revised International Staging System; SCT, stem cell transplant; VGPR, very good PR.

Best Overall Response

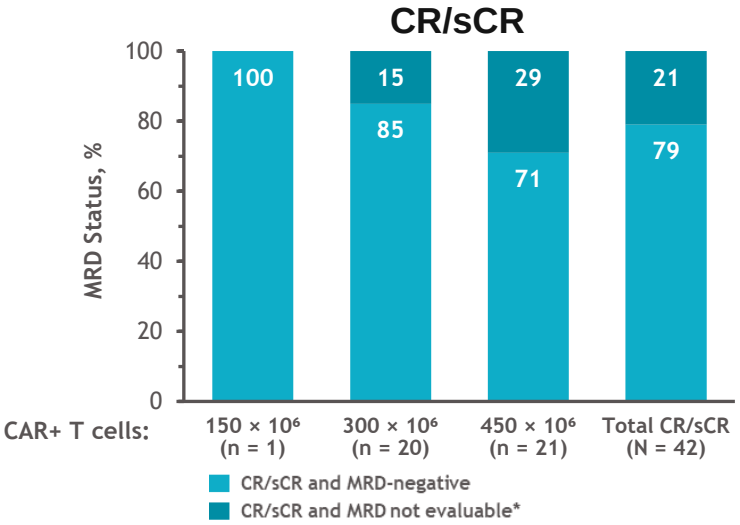


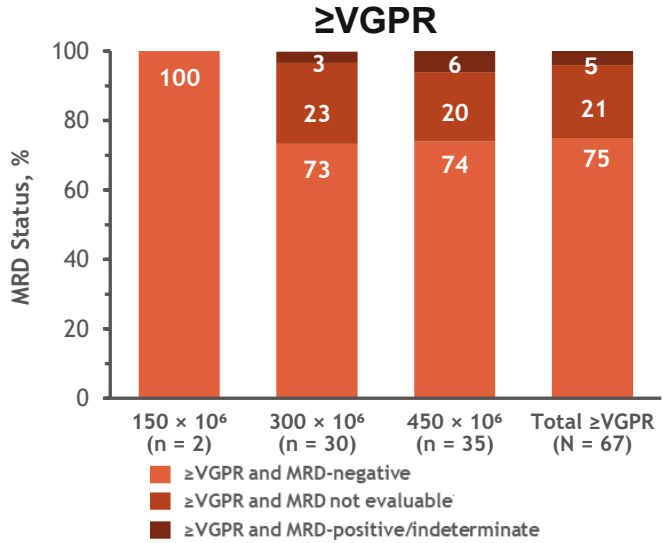
- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel–treated population
  - *ORR of 73% (95% CI, 65.8−81.1; P <.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7−40.9; P <.0001)*
- Median time to first response of 1.0 mo (range, 0.5−8.8); median time to CR of 2.8 mo (range, 1.0−11.8)
- Median follow-up of 13.3 mo across target dose levels

Data cutoff: 14 Jan 2020. MRD negative defined as $<10^{-5}$ nucleated cells by next-generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered. Values may not add up due to rounding. **P* value at the primary data cutoff with same ORR and 95% CI.
CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (≥PR); PR, partial response; VGPR, very good PR.

MRD Negativity

Target dose, CAR+ T cells	150 × 10^6	300 × 10^6	450 × 10^6	Total
All ide-cel treated	n = 4	n = 70	n = 54	n = 128
MRD negative and ≥CR, n (%) [95% CI]	**1 (25)** [0.6–80.6]	**17 (24)** [14.8–36.0]	**15 (28)** [16.5–41.6]	**33 (26)** [18.5–34.3]
MRD negative and ≥VGPR, n (%) [95% CI]	**2 (50)** [6.8–93.2]	**22 (31)** [20.9–43.6]	**26 (48)** [34.4–62.2]	**50 (39)** [30.6–48.1]

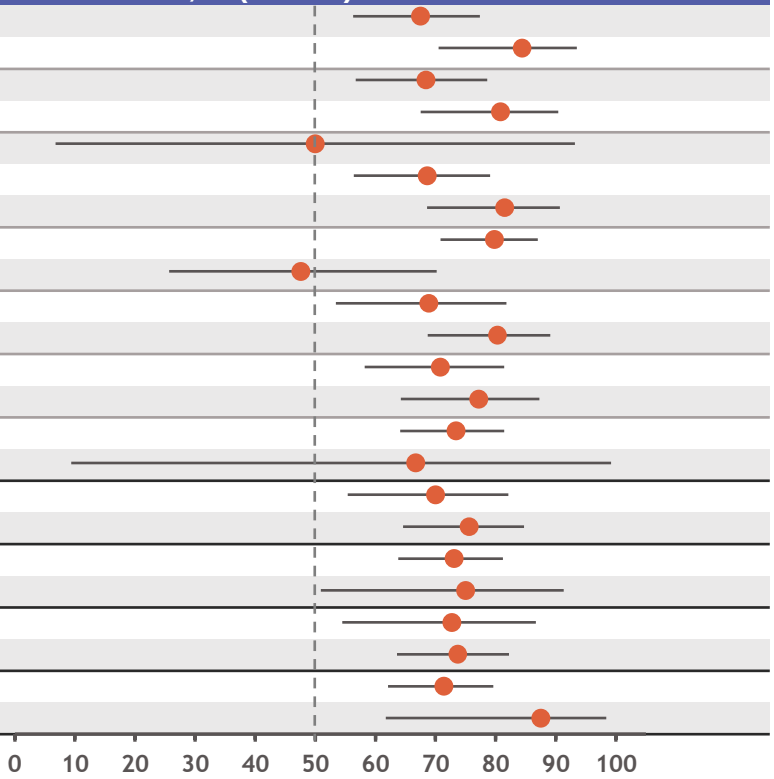




Data cutoff: 14 Jan 2020. MRD negative defined as <10^{-5} nucleated cells by next-generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered. Values may not add up due to rounding. *Of 42 patients with ≥CR, 8 were not evaluable for MRD and 1 had values outside the 3-mo window prior to CR/sCR.
CR/sCR, complete response/stringent CR; MRD, minimal residual disease; VGPR, very good partial response.

Clinically Meaningful Efficacy (ORR) Observed Across Subgroups

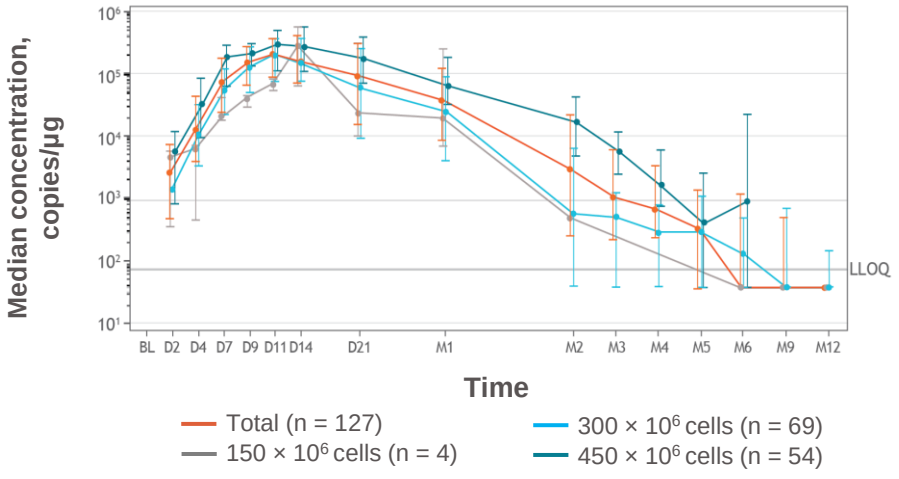
Subgroup		N	ORR, % (95% CI)
Age group, years	<65	83	
	≥65	45	
Sex	Male	76	
	Female	52	
Ide-cel target dose level, CAR+ T cells	150 × 10^6	4	
	300 × 10^6	70	
	450 × 10^6	54	
R-ISS stage at enrollment	I or II	104	
	III	21	
High-risk cytogenetics del(17p), t(4;14), t(14;16)	Yes	45	
	No	66	
Tumor burden at baseline, BMPCs, %	≥50%	65	
	<50%	57	
Tumor BCMA expression	≥50%	109	
	<50%	3	
Extramedullary disease	Yes	50	
	No	78	
Triple refractory*	Yes	108	
	No	20	
Penta-refractory†	Yes	33	
	No	95	
Bridging therapy	Yes	112	
	No	16	



Data cutoff: 14 Jan 2020. *Defined as refractory to an IMiD agent, PI, and CD-38 antibody. †Defined as refractory to 2 IMiD agents, 2 PIs, and 1 anti-CD38 antibody. BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; R-ISS, revised International Staging System.

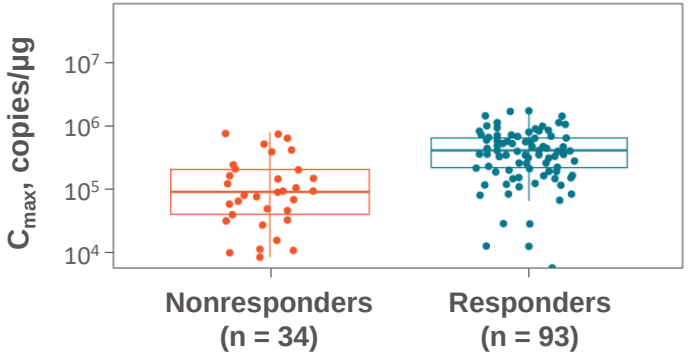
CAR+ T-Cell Expansion, Persistence, and Peak Exposure

CAR+ T-Cell Expansion and Persistence



	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12
Evaluable patients, n	118	100	49	27	11
Patients with detectable vector, n (%)	117 (99)	75 (75)	29 (59)	10 (37)	4 (36)

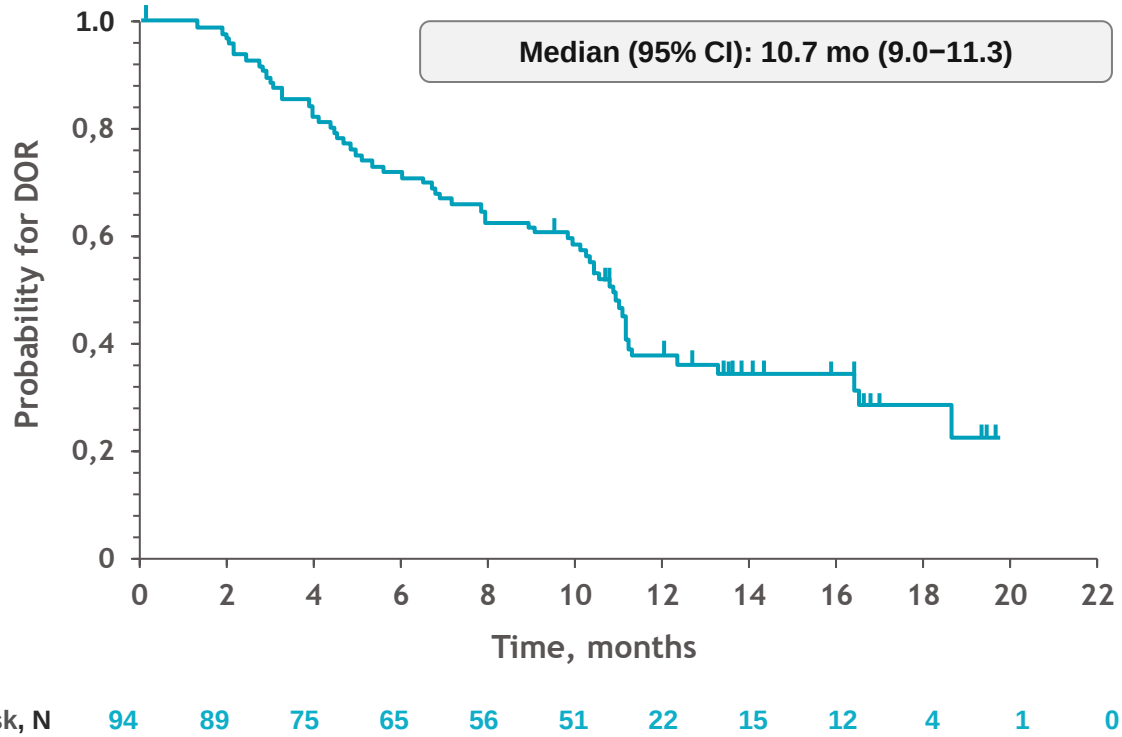
Peak Vector Copies in Responders (≥PR) vs Nonresponders (<PR)



- Median peak CAR+ T-cell expansion was at 11 d
- Median expansion increased at higher target doses with overlapping profiles
- Peak exposure higher in responders than nonresponders
- Durable persistence was observed up to 1 y

Data cutoff: 19 April 2019. Pharmacokinetic (PK) analysis population (N = 127). One patient died on day 4 and had no evaluable PK samples and was therefore excluded. Error bars represent interquartile range. BL, baseline; C_{max}, maximum concentration; LLOQ, lower limit of quantitation; M, month.

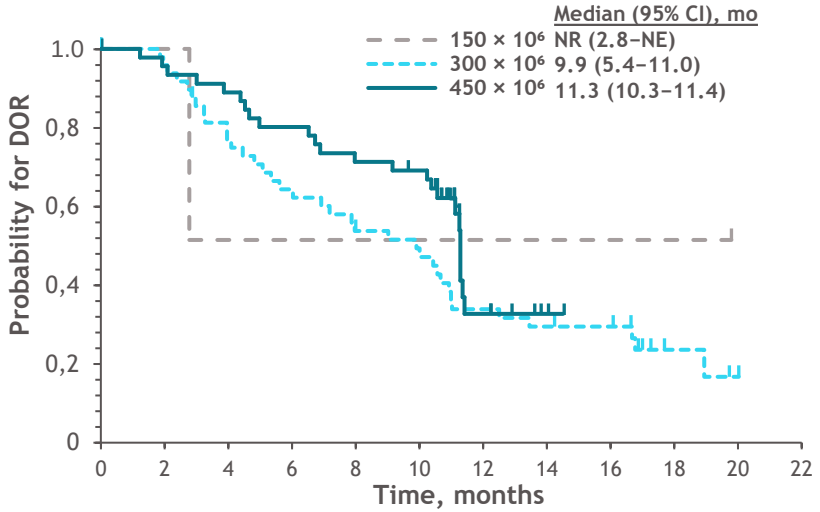
Duration of Response



Data cutoff: 14 Jan 2020. DOR is measured from the start of first partial response or better. DOR, duration of response.

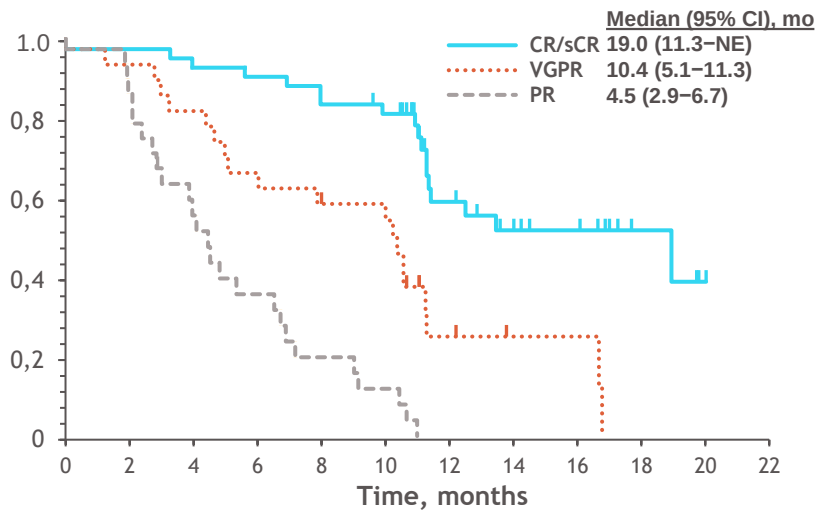
Duration of Response by Target Dose and Best Response

DOR by Target Dose



At risk, N											
150 × 10⁶	2	2	1	1	1	1	1	1	1	1	0
300 × 10⁶	48	45	35	29	24	21	14	12	11	3	1	0
450 × 10⁶	44	42	39	35	31	29	7	2	0	0	0

DOR by Best Response

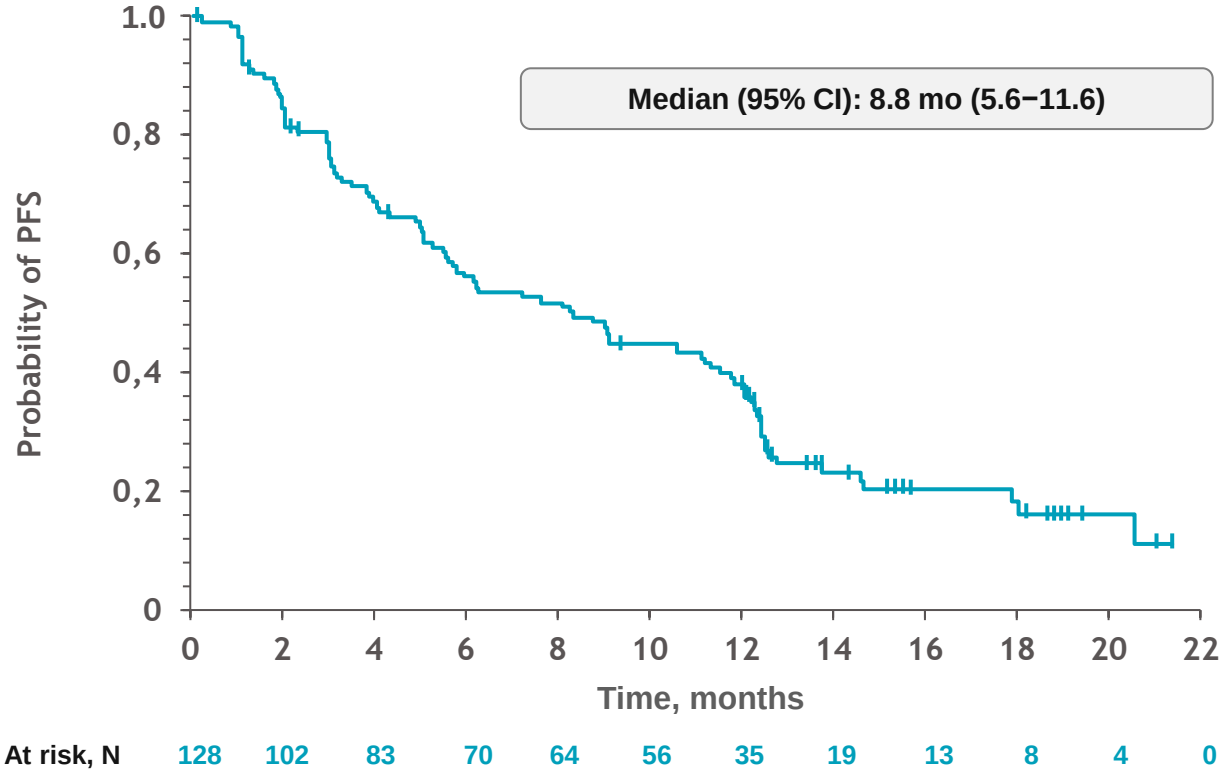


At risk, n												
CR/sCR	42	42	40	39	36	34	18	13	10	4	1	0
VGPR	25	24	21	17	15	14	4	2	2	0	0
PR	27	23	14	9	5	3	0	0	0	0	0

- Durable responses were observed across all target doses; median DOR of 11.3 mo at 450 × 10^6 CAR+ T cells
- DOR increased with depth of response; median DOR of 19 mo in patients achieving CR/sCR

Data cutoff: 14 Jan 2020. CR/sCR, complete response/stringent CR; DOR, duration of response; NE, not estimable; NR, not reached; PR, partial response; VGPR, very good PR.

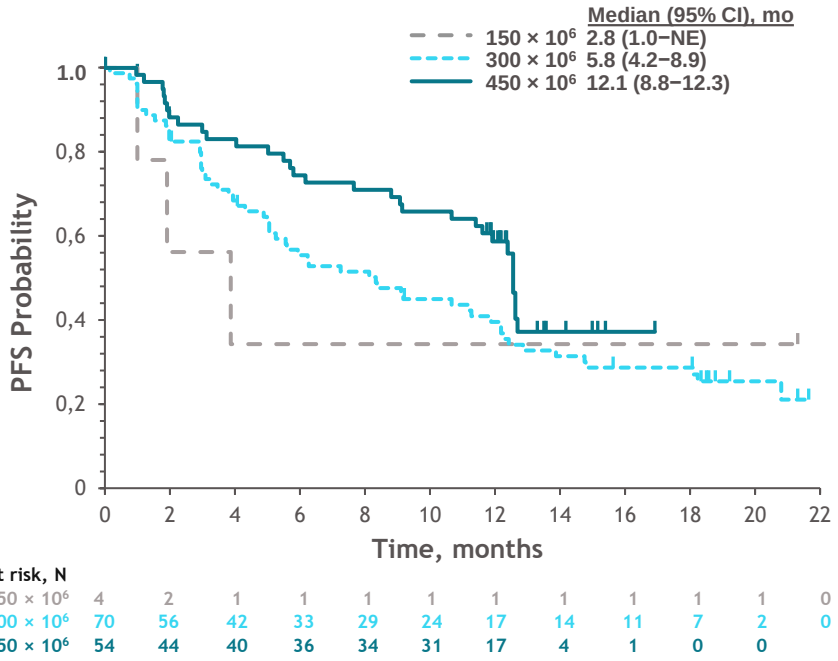
Progression-Free Survival



Data cutoff: 14 Jan 2020. PFS, progression-free survival.

Progression-Free Survival

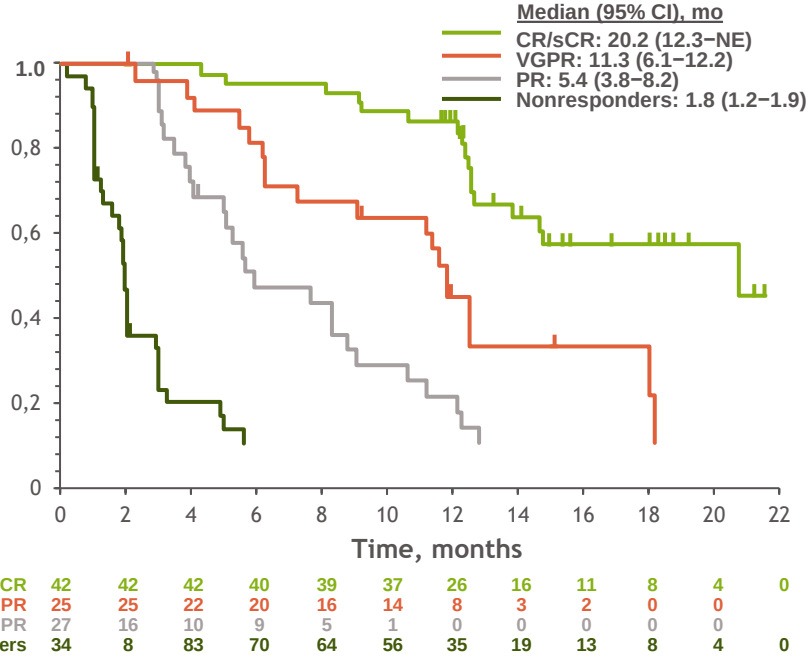
PFS by Target Dose



At risk, N												
150 × 10⁶	4	2	1	1	1	1	1	1	1	1	1	0
300 × 10⁶	70	56	42	33	29	24	17	14	11	7	2	0
450 × 10⁶	54	44	40	36	34	31	17	4	1	0	0	

- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10^6 CAR+ T cells

PFS by Best Response

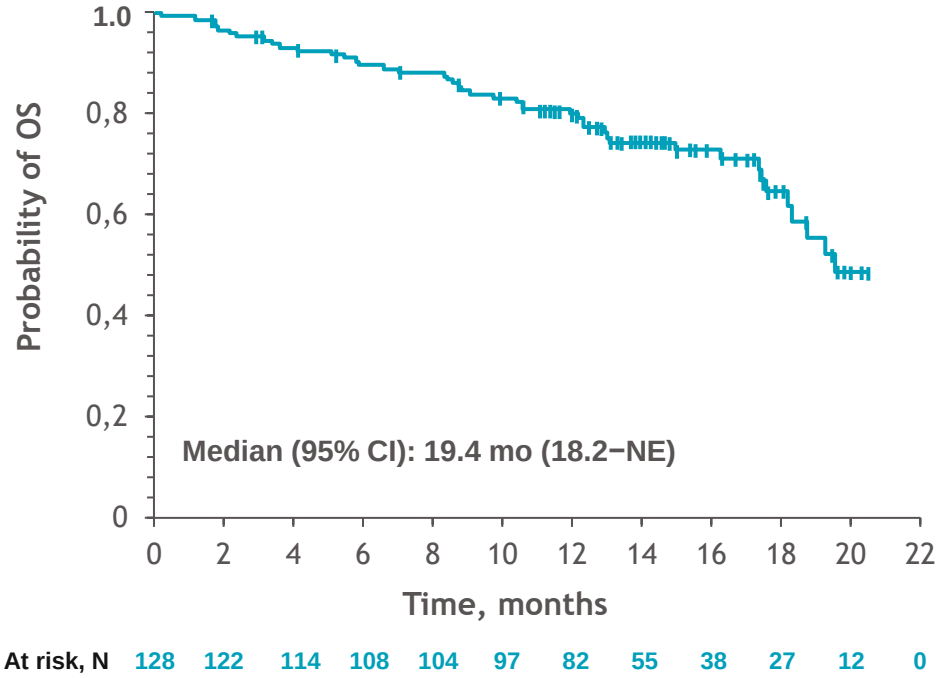


CR/sCR	42	42	42	40	39	37	26	16	11	8	4	0
VGPR	25	25	22	20	16	14	8	3	2	0	0	
PR	27	16	10	9	5	1	0	0	0	0	0	
Nonresponders	34	8	83	70	64	56	35	19	13	8	4	0

- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

Data cutoff: 14 Jan 2020. NE, not estimable; PFS, progression-free survival.

Overall Survival



- 78% of all ide-cel–treated patients were event free at 12 mo
- Survival data are immature with 66% of patients censored overall; 72% at target dose of 450 × 10^6 CAR+ T cells

Data cutoff: 14 Jan 2020. NE, not estimable; OS, overall survival.

Incidence and Management of CRS

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)

- CRS frequency increased with dose, but mostly low-grade
- ≤6% grade 3 or higher CRS events at all target doses, including one grade 5 event
- CRS treated with corticosteroids was infrequent (≤22%) at all target doses

Data cutoff: 14 Jan 2020. Siltuximab was used to manage CRS in 1 patient who was treated with 300 × 10^6 CAR+ T cells. Anakinra was used to manage CRS in 1 patient who was treated with 300 × 10^6 CAR+ T cells.
*CRS graded according to Lee criteria [Lee DW, et al. *Blood.* 2014;124(2):188-195].
CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute.

Incidence and Management of Neurotoxicity

Target Dose, × 10^6 CAR+ T Cells	150 (n = 4)	300 (n = 70)	450 (n = 54)	Ide-cel Treated (N = 128)
≥1 NT event, n (%)	0	12 (17)	11 (20)	23 (18)
Max. grade (CTCAE)*				
1	0	7 (10)	5 (9)	12 (9)
2	0	4 (6)	3 (6)	7 (5)
3	0	1 (1)	3 (6)	4 (3)
Median onset, d (range)	NA	3 (1−10)	2 (1−5)	2 (1−10)
Median duration, d (range)	NA	3 (2−26)	5 (1−22)	3 (1−26)
Tocilizumab, n (%)	NA	0	3 (6)	3 (2)
Corticosteroids, n (%)	NA	2 (3)	8 (15)	10 (8)

- NT mostly low-grade and was similar across target doses
- Incidence of grade 3 NT events was uncommon (≤6%) at all target doses; no grade 4 or 5 events
- NT managed with corticosteroids was infrequent (≤15%) at all target doses

Data cutoff: 14 Jan 2020. CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute; NT, neurotoxicity (investigator-identified).
*Investigator-identified NT events were graded according to the NCI CTCAE v4.03.

Most Common Adverse Events

AE,* n (%)	Ide-cel Treated (N = 128)	
	Any grade	Grade ≥3
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	35 (27)	34 (27)
Gastrointestinal		
Diarrhea	45 (35)	2 (2)
Nausea	37 (29)	0
Other		
Hypokalemia	45 (35)	3 (2)
Fatigue	43 (34)	2 (2)
Hypophosphatemia	38 (30)	20 (16)
Hypocalcemia	34 (27)	10 (8)
Pyrexia	32 (25)	3 (2)
Hypomagnesemia	30 (23)	0
Decreased appetite	27 (21)	1 (<1)
Headache	27 (21)	1 (<1)
Hypogammaglobulinemia	27 (21)	1 (<1)
Cough	26 (20)	0
CRS†	107 (84)	7 (5)

- Cytopenias were common; not dose related
- Median time to recovery of grade ≥3 neutropenia and thrombocytopenia was 2 mo (95% CI, 1.9−2.1) and 3 mo (95% CI, 2.1−5.5), respectively
- Delayed recovery (>1 mo) of grade ≥3 neutropenia in 41% of patients and thrombocytopenia in 48%‡
- Infections (including bacterial, viral, fungal) were common (69%); not dose related
- 5 deaths (4%) within 8 wk of ide-cel infusion
  - 2 following MM progression
  - 3 from AEs (CRS, aspergillus pneumonia, GI hemorrhage)
- 1 additional death from AE (CMV pneumonia) within 6 mo, in the absence of MM progression

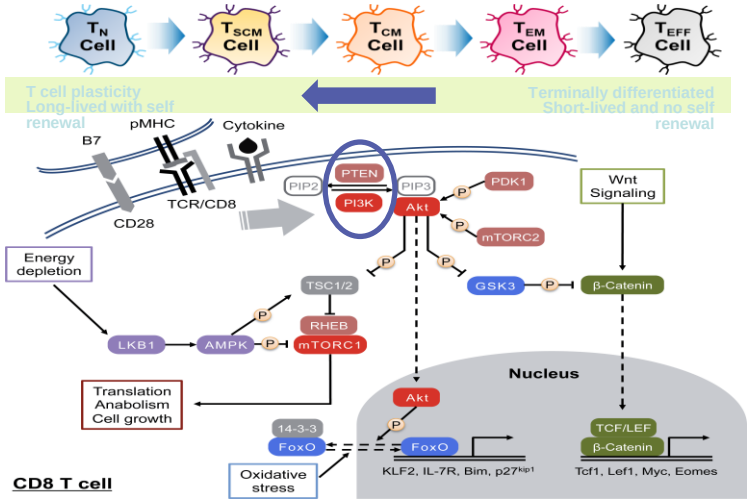
Data cutoff: 14 Jan 2020. AE, adverse event; CMV, cytomegalovirus; CRS, cytokine release syndrome; GI, gastrointestinal.
*Events reported in 20% or more patients. †Clustered term including the preferred term; uniformly graded per Lee DW, et al. Includes 2 patient with grade 5 CRS event was observed.
‡Includes patients with grade 3/4 cytopenia at 1 mo post-infusion.

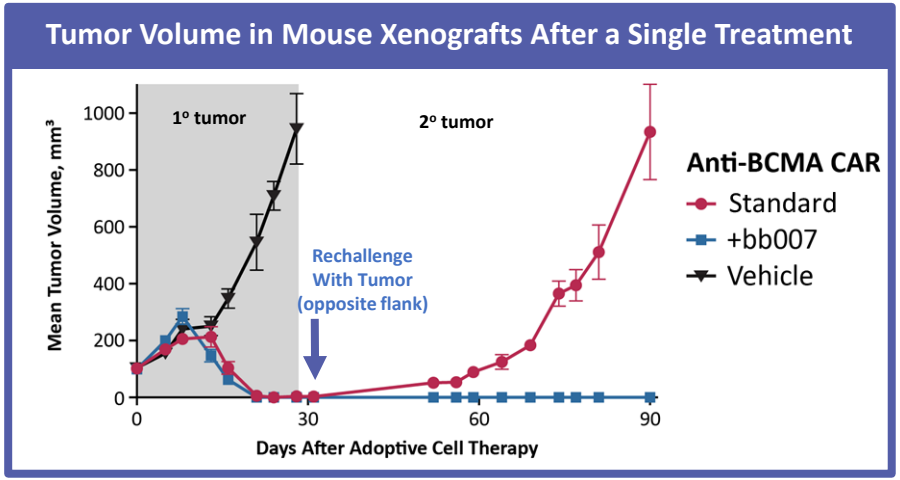
Conclusions

- Ide-cel demonstrated frequent, deep, and durable responses in heavily pretreated, highly refractory RR MM patients in the pivotal KarMMa trial
  - Both primary and key secondary endpoints were met: ORR of 73% and CRR of 33%
  - Median DOR was 10.7 mo and median PFS was 8.8 mo in all ide-cel–treated patients
  - Median DOR was 19.0 mo and median PFS was 20.2 mo in patients achieving CR/sCR
  - Median OS was 19.4 mo among all ide-cel–treated patients
- Efficacy was highest at the target dose of 450 × 10^6 CAR+ T cells
  - ORR of 82% including 39% CRR; median DOR and PFS of 11.3 mo and 12.1 mo, respectively
- Ide-cel was tolerable across the dose range
  - The frequency of grade ≥3 CRS or investigator-identified NT ≤6% at target dose of 450 × 10^6 CAR+ T cells
- Results support a favorable benefit-risk profile for ide-cel across the target dose range of 150 to 450 × 10^6 CAR+ T cells
- KarMMa efficacy results were compared with real-world treatment outcomes in a similar triple-class–exposed RR MM population; multiple efficacy endpoints were significantly improved with ide-cel (Jagannath S, et al. ASCO 2020. Abstract 8525)
- Ide-cel provides an attractive option for treatment of triple-class–exposed (to IMiD agents, PIs, and anti-CD38 antibodies) RR MM

Building on bb2121: bb21217

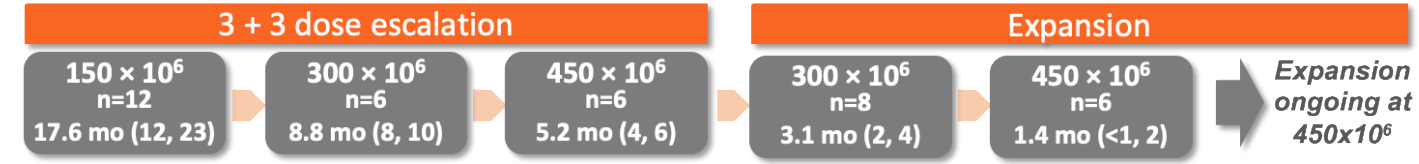
- bb21217 uses the same CAR construct as bb2121
- bb21217 is cultured with a PI3 kinase inhibitor, bb007, to enrich for T cells displaying a memory-like phenotype





- Opposite-flank tumor rechallenge resulted in no tumor growth in mice treated with bb007-cultured CAR T cells, suggesting longer persistence of antitumor effect

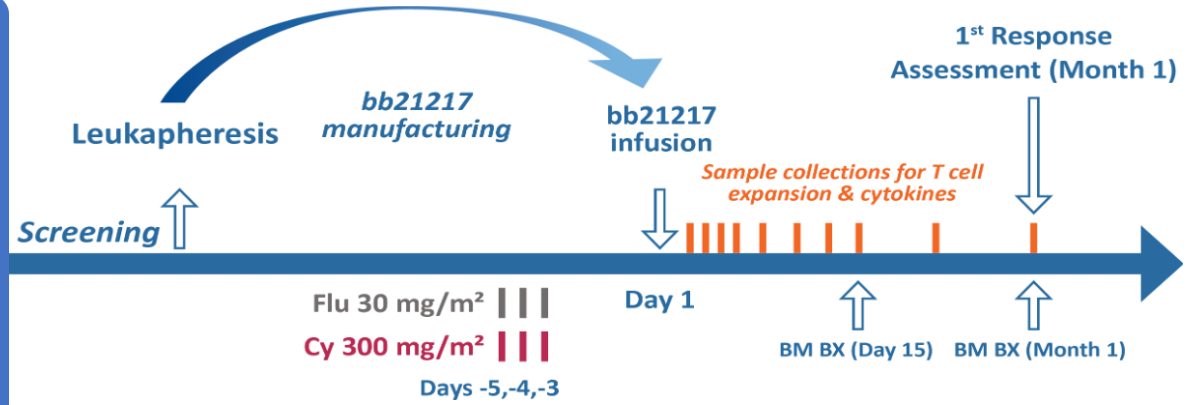
bb21217 Phase I Study: Design

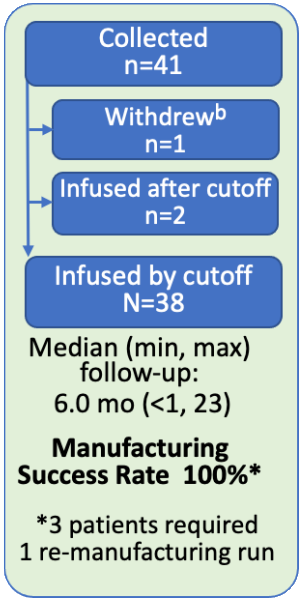


N ≈ 74

- R/R MM
- ≥3 prior regimens
- Prior IMiD and PI required
- In escalation only ≥50% BCMA expression required
- In expansion only prior αCD38 exposure and refractory to last line required

NCT03274219





Primary endpoints: AEs, DLTs
Other endpoints: Response[c], PFS, OS, MRD, CAR+ T cell expansion and persistence

CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T-Cell Therapy, in Relapsed/Refractory Multiple Myeloma

Deepu Madduri[1], Jesus G Berdeja[2], Saad Z Usmani[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], A Keith Stewart[7], Parameswaran Hari[8], Myo Htut[9], Elizabeth O'Donnell[10], Nikhil C Munshi[11], David Avigan[12], Abhinav Deol[13], Alexander Lesokhin[14], Indrajeet Singh[15], Enrique Zudaire[15], Tzu-Min Yeh[16], Alicia J Allred[15], Yunsi Olyslager[17], Arnob Banerjee[15], Jenna D Goldberg[16], Jordan M Schecter[16], Carolyn C Jackson[16], William Deraedt[17], Sen Hong Zhuang[16], Jeffrey Infante[16], Dong Geng[18], Xiaoling Wu[18], Marlene J Carrasco-Alfonso[18], Muhammad Akram[18], Farah Hossain[18], Syed Rizvi[18], Frank Fan[19], Sundar Jagannath[1], Yi Lin[20], Thomas Martin[21]

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https://epg-digital.com/u/ASH2020-Madduri
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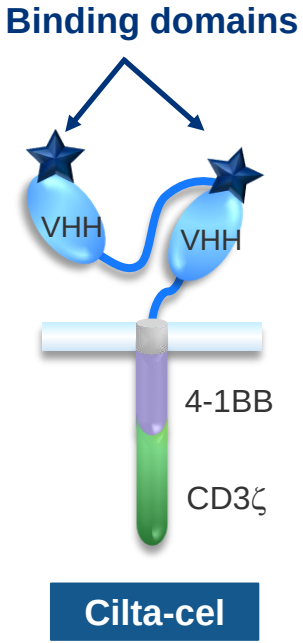
CARTITUDE-1: Introduction

Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T-cell therapy

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

In the phase Ib portion of the CARTITUDE-1 study, cilta-cel yielded deep, durable responses with a manageable safety profile in patients with relapsed/refractory MM[1]

Here, we report initial results from the combined phase Ib/II CARTITUDE-1 study of cilta-cel[2]



BCMA, B-cell maturation antigen; MM, multiple myeloma; VHH, single variable domain on a heavy chain.

1. Berdeja J, et al. *J Clin Oncol.* 2020;38(suppl): abstract 8505; 2. Madduri D, et al. ASH 2020. Presentation 177.

CARTITUDE-1: Phase Ib/II Study Design

Primary objectives

Phase Ib: Characterize the safety of cilta-cel and confirm the recommended phase II dose

Phase II: Evaluate the efficacy of cilta-cel by ORR

Key eligibility criteria

Progressive MM per IMWG criteria

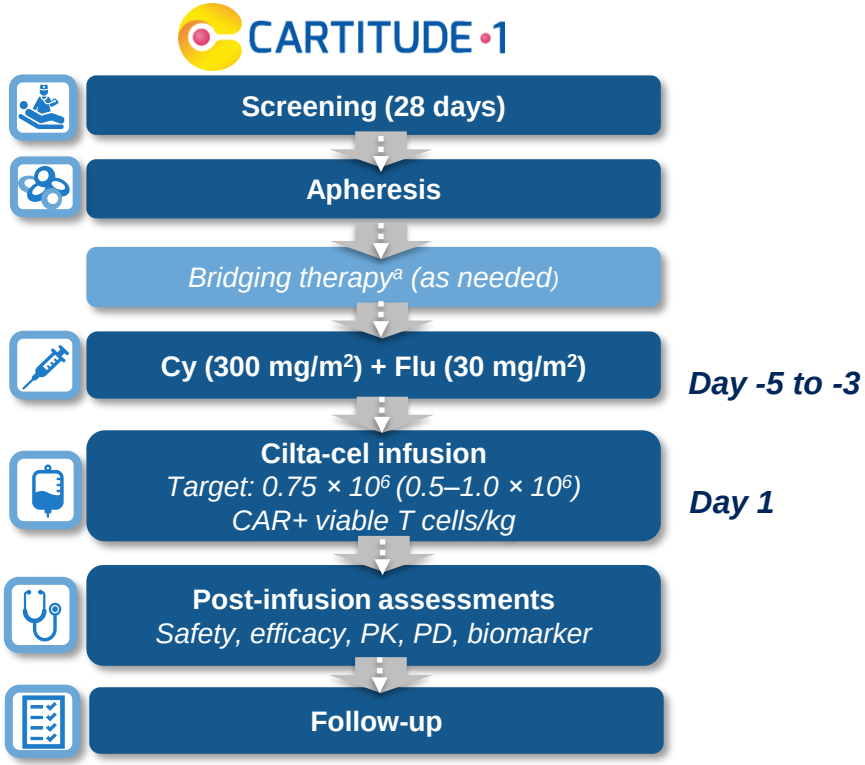
ECOG PS ≤1

Measurable disease

≥3 prior therapies or double refractory

Prior PI, IMiD, anti-CD38 therapy

Median administered dose: 0.71 × 10^6 (0.51–0.95 × 10^6) CAR+ viable T cells/kg



CAR, chimeric antigen receptor; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics.
[a]Treatment with previously used agent resulting in at least stable disease.
ClinicalTrials.gov number, NCT03548207; 01 Sept 2020 data cutoff.

CARTITUDE-1: Hematologic AEs and Infections

AEs ≥20%, n (%)	N = 97	
	Any Grade	Grade 3/4
Hematologic	97 (100)	96 (99.0)
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)

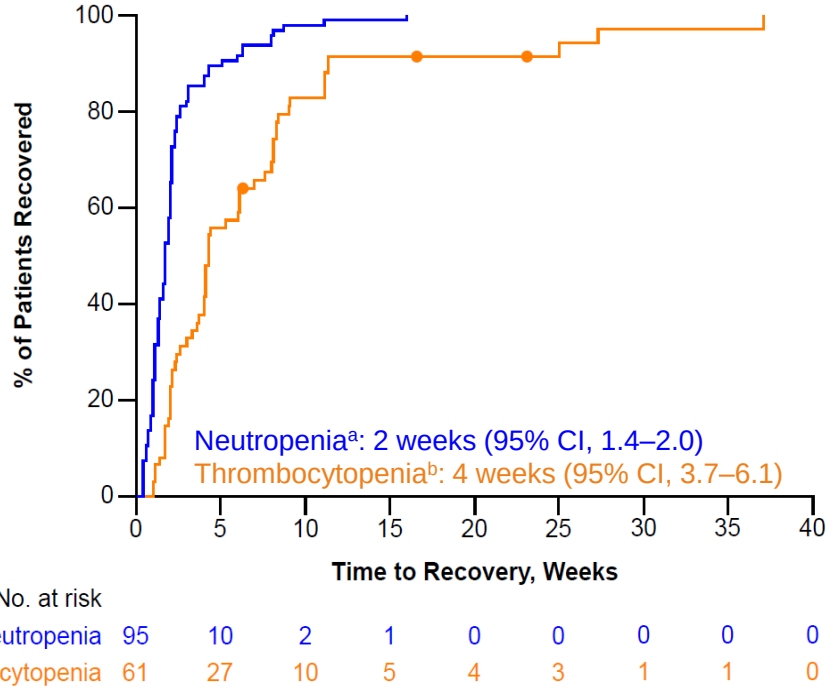
Late recovery (>1 month) of grade 3/4 cytopenias from first onset

- Neutropenia[a]: 10.3%
- Thrombocytopenia[b]: 25.8%

Any-grade infections: 57.7%

- Grade 3/4: 19.6%
  - Pneumonia: 8.2%
  - Sepsis: 4.1%

Median Time to Recovery of Grade 3/4 Cytopenias From First Onset



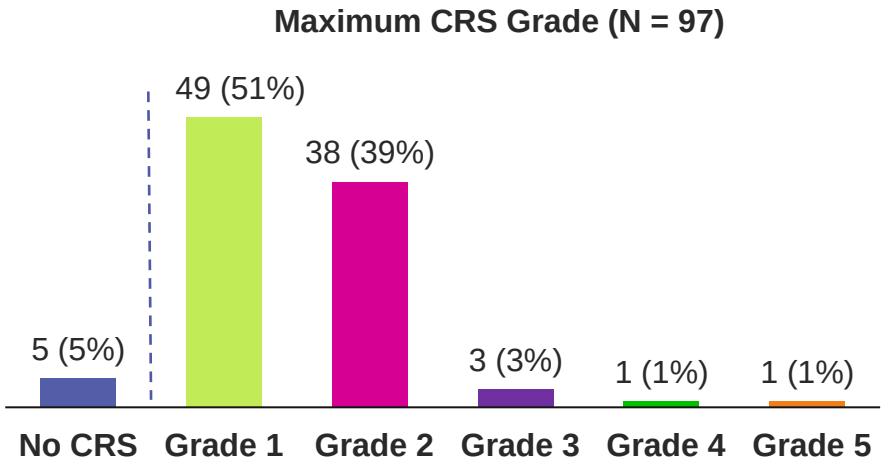
AE, adverse event.

[a]Recovery of grade 3/4 neutropenia defined as the first incidence of absolute neutrophils count ≥1000 cells/μL after the onset; recovery does not take into account treatment for neutropenia; [b]Recovery of grade 3/4 thrombocytopenia defined as the first incidence of platelets count ≥50,000 cells/μL after the onset; recovery does not take into account treatment for thrombocytopenia.

CARTITUDE-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]
Supportive measures, n (%)	88 (90.7)
Tocilizumab	67 (69.1)
Corticosteroids	21 (21.6)
Anakinra	18 (18.6)
Vasopressor used	4 (4.1)
Intubation/mechanical ventilation	1 (1.0)
Other	
Cyclophosphamide	1 (1.0)
Etanercept	1 (1.0)

Cilta-cel CAR+ T cells showed maximum peripheral expansion at a median of 13 days (range, 9–55)



Of 92 patients with CRS, majority (94.6%) were grades 1/2

CRS onset

- Day 4 or later: 89.1% (n = 82)
- Day 6 or later: 73.9% (n = 68)

CRS resolved in 91 (98.9%) patients within 14 days of onset

ASTCT, American Society for Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis

[a]CRS was graded using Lee et al. (*Blood* 2014) in the phase Ib portion of the study and ASTCT in phase II; in this combined analysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase Ib portion; [b]The patient with 97-day duration died due to CRS/HLH.

CARTITUDE-1: Neurotoxicity

Total CAR T-cell neurotoxicities

- Any grade: 20 (20.6%)
- Grade ≥3: 10 (10.3%)

ICANS

- Any grade: 16 (16.5%)
- Grade ≥3: 2 (2.1%)

Other neurotoxicities[a]

- Any grade: 12 (12.4%)
- Grade ≥3: 9 (9.3%)

	ICANS	Other Neurotoxicities[a]
Time to onset, median (range) days	8 (3–12)	27 (11–108)
Time to recovery, median (range) days	4 (1–12)	75 (2–160)

Other Neurotoxicities[a]

- **Occurring after resolution of CRS and/or ICANS**
- Among 12 patients
  - 5 had AEs including movement and/or neurocognitive changes
  - 7 had AEs including nerve palsy, peripheral motor neuropathy

Outcomes for CAR T-Cell Neurotoxicities

ICANS resolved in all patients

Other neurotoxicities resolved in 6 patients, and did not resolve in 6 patients

- 1 patient has ongoing neurotoxicity
- 1 patient died from complications of neurotoxicity
- 4 patients died due to other causes

No additional movement and neurocognitive AEs were seen in the CARTITUDE development program

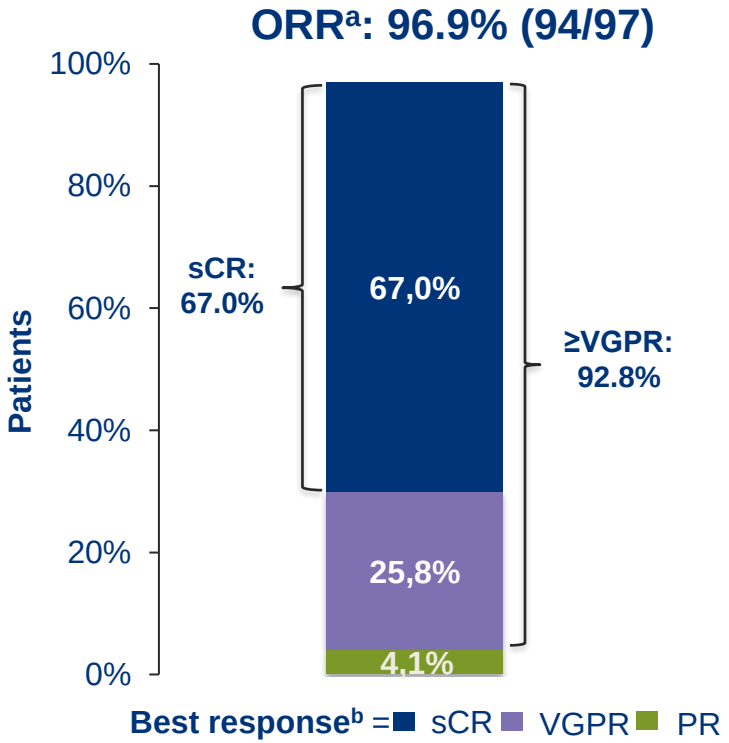
AE, adverse event; CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
[a]Events not reported as ICANS (ie, onset after a period of recovery from CRS and/or ICANS).

CARTITUDE-1: Deaths

	N = 97	Time of Death Post–cilta-cel Infusion, Days
Total deaths during the study, n	14	45–694
Due to progressive disease	5	253–694
AEs unrelated to treatment (n = 3)		
Pneumonia	1	109
Acute myelogenous leukemia[a]	2	418; 582
AEs related to treatment (n = 6)		
Sepsis and/or septic shock	2	45; 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

AE, adverse event; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndrome.
[a]One patient with acute myelogenous leukemia had MDS and a cytogenetic profile consistent with MDS (del20q [present prior to cilta-cel infusion], loss of 5q); the other had prostate cancer and squamous cell carcinoma of the scalp.

CARTITUDE-1: ORR and MRD Assessment



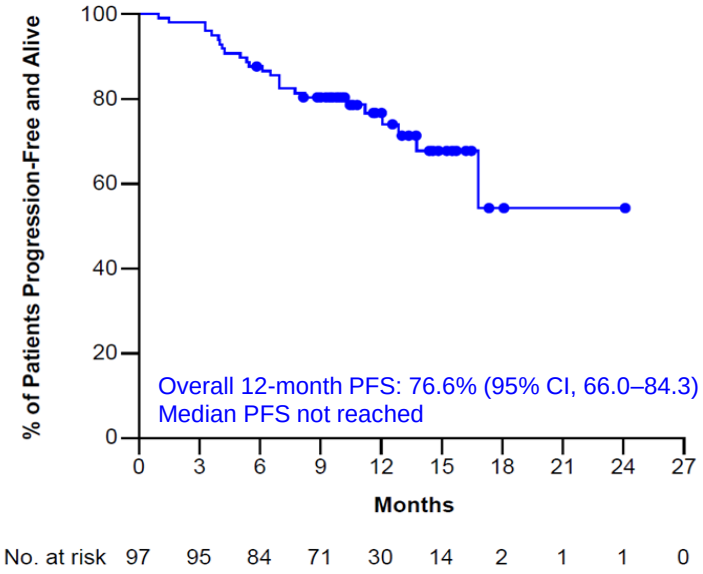
	N	Frequency in Evaluable Patients n = 57[c]	Frequency in All Treated n = 97[d]
Overall MRD–	53	93.0%	54.6%
MRD– and sCR	33	57.9%	34.0%
MRD– and ≥VGPR	49	86.0%	50.5%

- Median time to first response: 1 month (0.9–8.5)
- Responses ongoing in 70 (72.2%) patients
- Of evaluable patients, 93.0% achieved MRD 10^{-5} negativity
  - Median time to MRD 10^{-5} negativity: 1 month (0.8–7.7)
- Among patients with 6 months individual follow-up, most had cilta-cel CAR+ T cells below the level of quantification (2 cells/µL) in peripheral blood

CAR, chimeric antigen receptor; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response. [a]PR or better, independent review committee assessed. [b]No patient had CR or stable disease as best response. [c]MRD was assessed in evaluable samples at 10^{-5} threshold by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine; patients were not evaluable primarily due to lack of an identifiable clone in the baseline bone marrow sample. [d]All treated patients.

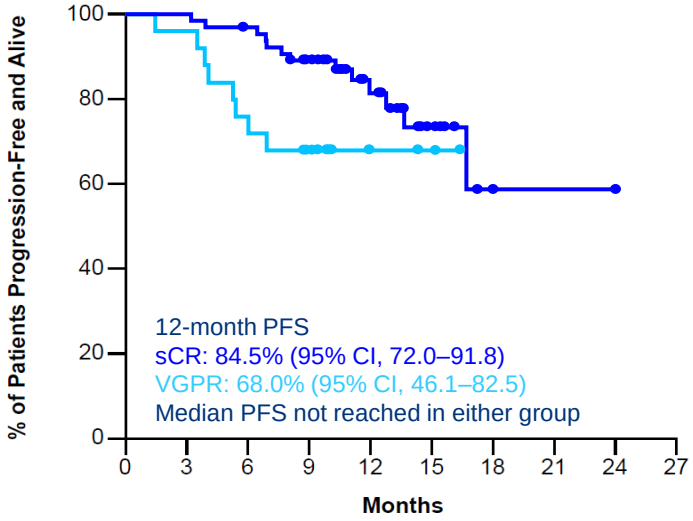
CARTITUDE-1: PFS

Overall PFS



No. at risk	97	95	84	71	30	14	2	1	1	0

PFS by sCR and VGPR



No. at risk										
sCR	65	65	62	53	27	12	2	1	1	0
VGPR	25	24	19	15	3	2	0	0	0	0

At median duration of follow-up of 12.4 months (range, 1.5–24.9), median PFS has not been reached
12-month PFS rate: 76.6% (95% CI, 66.0–84.3)
12-month OS rate: 88.5% (95% CI, 80.2–93.5)

OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

BCMA CAR T-Cell Studies: Baseline Characteristics

	bb2121 Ph I[1]	bb21217 Ph I[2]	JNJ-4528 Ph Ib/II[3]	Orva-Cel Ph I/II[4]
No. apheresed	140	41	35	NR
No. treated	128	38	29	62
Median age	61 (33–78)	62 (33–74)	60 (50–75)	61 (33–77)
High-risk CGs	35%	34%	27%	41% (incl +1q)
EMM	39%	NR	10%	23%
Median lines of prior therapy	6 (3–16)	6 (3–17)	5 (3–18)	6 (3–18)
Triple-class refractory	84%	63%	86%	94%
Bridging therapy	88%	NR	NR	63%

1. Munshi, NC, et al. *N Engl J Med*. 2021;384:705-716; 2. Berdeja JG, et al. ASH 2019. Abstract 927; 3. Madduri D, et al. ASH 2020. Presentation 177;
4. Mailankody S, et al. *J Clin Oncol*. 2020;38(suppl): abstract 8504.

BCMA CAR T-Cell Studies: Safety

	bb2121 Ph II[1]	bb21217 Ph I[2]	JNJ-4528 Ph Ib/II[3]	Orva-Cel Ph I/II[4]
Cytokine release syndrome				
All grades	84%	66%	93%	89%
Grade 3/4/5	4%/<1%/<1%	5%/0%/3%	7%	3%
Median onset, days	1 (1–12)	3 (1–20)	7 (2–12)	2 (1–4)
Median duration	5 (1–63)	4 (1–28)	4 (2–64)	4 (1–10)
Neurotoxicity				
All grades	18%	24%	10%	13%
Grade 3/4/5	3%/0%/0%	5%/3%/0%	3%	3%
Median onset, days	2 (1–10)	7 (3–24)	NR	4 (1–6)
Median duration	3 (1–26)	NR	NR	4 (1–10)

1. Munshi, NC, et al. *N Engl J Med*. 2021;384:705-716; 2. Berdeja JG, et al. ASH 2019. Abstract 927; 3. Madduri D, et al. ASH 2020. Presentation 177;
4. Mailankody S, et al. *J Clin Oncol*. 2020;38(suppl): abstract 8504.

BCMA CAR T-Cell Studies: Safety

	bb2121 Ph II[1]	bb21217 Ph I[2]	JNJ-4528 Ph Ib/II[3]	Orva-Cel Ph I/II[4]
Hematologic AEs				
Neutropenia				
All grades	91%	NR	100%	90%
Grade 3/4	89%	82%	100%	90%
Thrombocytopenia				
All grades	63%	NR	86%	52%
Grade 3/4/5	52%	55%	69%	47%
Infections				
All grades	69%	NR	NR	40%
Grade 3/4/5	NR	18%	NR	13%

1. Munshi, NC, et al. *N Engl J Med*. 2021;384:705-716; 2. Berdeja JG, et al. ASH 2019. Abstract 927; 3. Madduri D, et al. ASH 2020. Presentation 177;
4. Mailankody S, et al. *J Clin Oncol*. 2020;38(suppl): abstract 8504.

BCMA CAR T-Cell Studies: Efficacy

	bb2121 Ph II[1]			bb21217 Ph I[2]			JNJ-4528 Ph Ib/II[3]	Orva-Cel Ph I/II[4]		
Cell dose	150	300	450	150	300	450	0.75×10^6 / kg	300	450	600
Median follow-up, mo	13.3			17.6	4.0	3.3	11.5 (3.0–17.0)	9.5	8.8	2.3
Response rate										
ORR	50%	69%	82%	83%	43%	57%	100%	95%	89%	92%
CR	25%	29%	39%	33%	0%	14%	86%	37%	42%	29%
MRD										
Evaluable for MRD, n				7	6	4	21	11	11	3
MRD– (%)	50%	31%	48%	100%	83.3 %	100%	85.7%	72.7 %	90.9 %	100%
Median DOR, mo	NR	9.9	11.3	11.3	NR	NR	NR	NR	NR	NR
Median PFS	2.8	5.8	12.1	NR	NR	NR	NR	9.3	NR	NR

1. Munshi, NC, et al. *N Engl J Med*. 2021;384:705-716; 2. Berdeja JG, et al. ASH 2019. Abstract 927; 3. Madduri D, et al. ASH 2020. Presentation 177;
4. Mailankody S, et al. *J Clin Oncol*. 2020;38(suppl): abstract 8504.

BCMA CAR T-Cell Studies: CAR T-Cell Persistence

	bb2121 Ph II[1]			bb21217 Ph I[2]			JNJ-4528 Ph Ib/II[3]	Orva-Cel Ph I/II[4]		
Cell dose	150	300	450	150	300	450	0.75×10^6/kg	300	450	600
Detectable CAR T cells at 6 mo	59%			80%			40% at 90 days	67%	71%	--

1. Munshi, NC, et al. *N Engl J Med*. 2021;384:705-716; 2. Berdeja JG, et al. ASH 2019. Abstract 927; 3. Madduri D, et al. ASH 2020. Presentation 177;
4. Mailankody S, et al. *J Clin Oncol*. 2020;38(suppl): abstract 8504.

Other Targets

CD19
SLAMF7
CD44v6
CD138
CD38
GPRC5D
Kappa LCs
CD56

Case Study

A 61-year-old previously healthy male is found to have symptomatic (hypercalcemia, anemia, lytic lesions) IgG kappa MM, R-ISS stage 3 (ISS3, normal LDH, del 17p in 65% PC). He is being treated in a community practice

- He received RVD induction followed by high-dose melphalan ASCT with lenalidomide and ixazomib maintenance. One-and-a-half years later he has serologic PD and new lytic lesions
- He received daratumumab-carfilzomib-dexamethasone and after 12 months has serologic progression
- He received pomalidomide, cyclophosphamide, and dexamethasone and now 6 months later is progressing

Antimyeloma Agents

Steroids	Conventional Chemo	CELMoDs	Proteasome Inhibitors	HDAC Inhibitor	Immunologic Approaches	XPO Inhibitor
Prednisone	X Melphalan	Thalidomide	X Bortezomib	Panobinostat	X Daratumumab (anti-CD38)	Selinexor
Dexamethasone	Melflufen	X Lenalidomide	X Carfilzomib		Isatuximab (anti-CD38)	
	Cyclophosphamide	X Pomalidomide	X Ixazomib		Elotuzumab (anti-CS1)	
	Liposomal doxorubicin	Iberdomide			Belantamab (anti-BCMA + MMAF)	
	DCEP/D-PACE	CC-92480				
	METRO28					
	Carmustine					
	Bendamustine					
Off Label						
		Ruxolitinib	Venetoclax			
			Nelfinavir			

Case Study (continued)

- CBC WBC 4.0/ANC 1.3/Hg 9.0/plt 85
- Chem CrCl 50, calcium normal
- MM M spike 0.4, FLC kappa 125 mg/L, BJP 50 mg/d
- PET-CT multifocal FDG avidity but without cortical damage
- What would you do now with this patient with penta-refractory MM?

Question 1

What would you do now with this patient with penta-refractory MM?

1. 96-hour infusional therapy (VDCEP/VDPACE)
2. Salvage transplant
3. Selinexor
4. Belantamab
5. Enroll in melflufen study
6. Enroll in iberdomide or CELMoD study
7. Enroll in BCMA-CAR T study
8. Enroll in BCMA–T-cell engager study
9. Other

Case Study (continued)

- CBC WBC 4.0/ANC 1.3/Hg 9.0/plt 85
- Chem CrCl 25, calcium normal
- MM M spike 0.4, FLC kappa 3000 mg/L, BJP 1500 mg/d
- PET-CT multifocal FDG avidity but without cortical damage

- What would you do now with this patient with penta-refractory MM where findings developed over 3–4 weeks?

Question 2

What would you do now with this patient with penta-refractory MM where findings developed over 3–4 weeks?

1. 96-hour infusional therapy (VDCEP/VDPACE)
2. Salvage transplant
3. Selinexor
4. Belantamab
5. Enroll in melflufen study
6. Enroll in iberdomide or CELMoD study
7. Enroll in BCMA-CAR T study
8. Enroll in BCMA–T-cell engager study
9. Other

Case Study (continued)

While receiving carfilzomib, the patient developed difficult-to-control HTN and concomitant CHF with finding of multivessel coronary artery disease. Currently on medical management with EF 35% and dyspnea on exertion; ECOG 2

- CBC WBC 4.0/ANC 1.3/Hg 9.0/plt 85
- Chem CrCl 50, calcium normal
- MM M spike 0.4, FLC kappa 125 mg/L, BJP 50 mg/d
- PET-CT multifocal FDG avidity but without cortical damage

- What would you do now with this patient with penta-refractory MM?

Question 3

What would you do now with this patient with penta-refractory MM?

1. 96-hour infusional therapy (VDCEP/VDPACE)
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Case Study (continued)

- CBC WBC 4.0/ANC 1.3/Hg 9.0/plt 85
- Chem CrCl 50, calcium normal
- MM M spike 0.4, FLC kappa 125 mg/L, BJP 50 mg/d
- PET-CT multifocal FDG avidity but without cortical damage

- What would you do now with this patient with penta-refractory MM who is s/p fludarabine cyclophosphamide + anti-BCMA CAR T and has serologic and paramedullary disease progression on PET-CT within 5 months?

Question 4

What would you do now with this patient with penta-refractory MM who is s/p fludarabine cyclophosphamide + anti-BCMA CAR T and has serologic and paramedullary disease progression on PET-CT within 5 months?

1. 96-hour infusional therapy (VDCEP/VDPACE)
2. Salvage transplant
3. Selinexor
4. Belantamab
5. Enroll in melflufen study
6. Enroll in iberdomide or CELMoD study
7. Enroll in BCMA-CAR T study
8. Enroll in BCMA–T-cell engager study
9. Other

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Discussion

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Patient Case Discussion: Relapsed/Refractory Multiple Myeloma

All Faculty

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Relapsed/Refractory Myeloma

Treatment Challenges in the Region

Mervat Mattar, MD

Professor, Clinical Hematology Unit,

Cairo University

MM Gets Harder to Treat With Each Relapse[1,2]

Despite advances in myeloma care, MM remains an incurable disease, and almost all patients relapse after treatment[1,2]

As patients move along the treatment pathway . . .

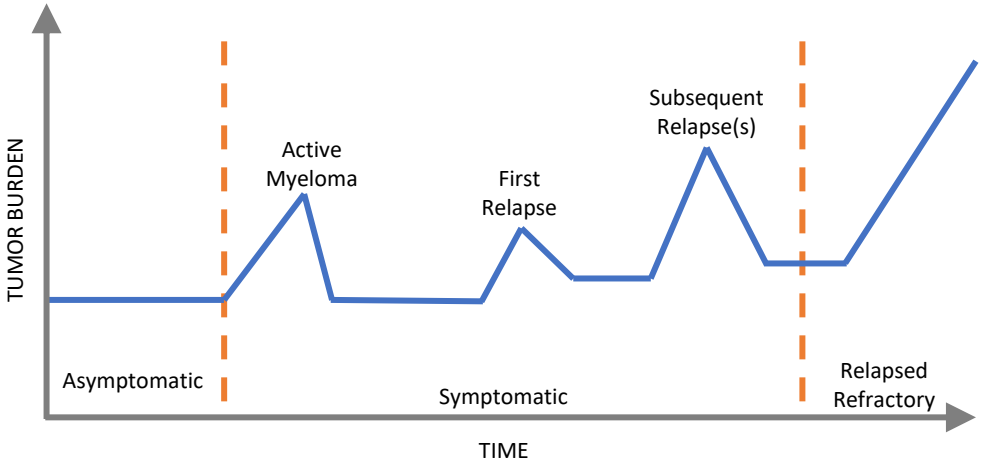


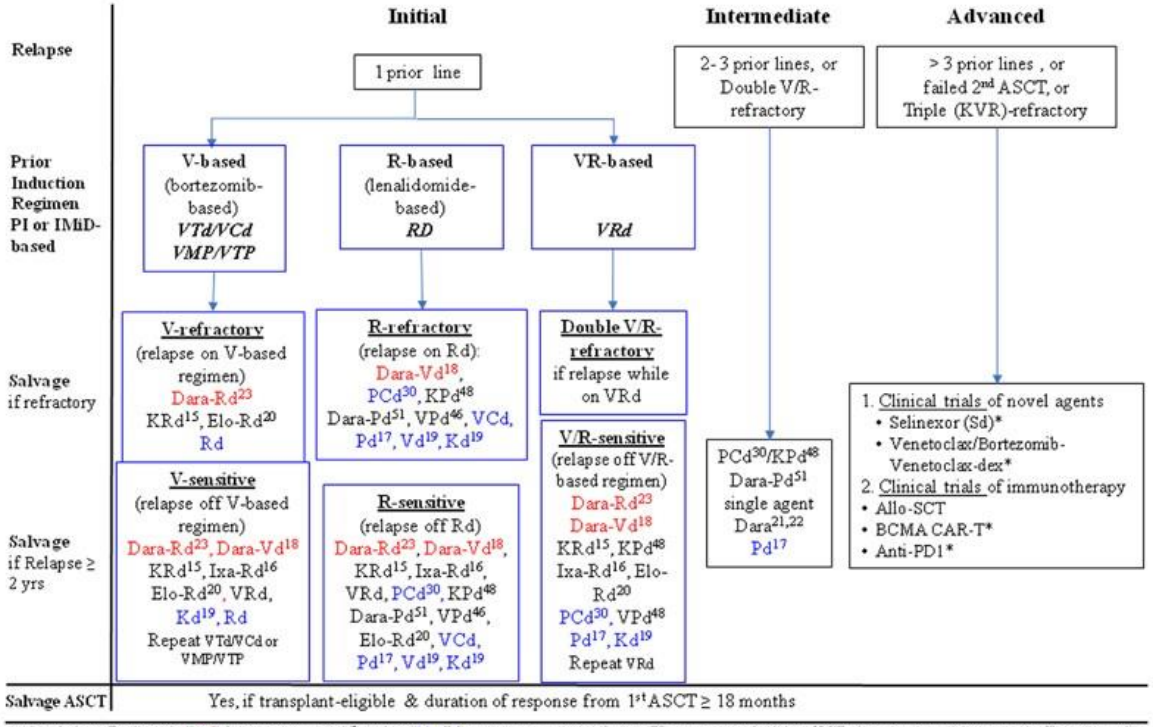
Figure adapted from Kurtin et al. 2013.[3]

Frequency and burden of **comorbidities and disease-related complications** increase[1,2]

Many patients do not reach their next line of therapy[2]

1. Cejalvo MJ, et al. *Expert Rev Hematol*. 2017;10:383-392; 2. Yong K, et al. *Br J Haematol.* 2016;175:12:252-264; 3. Kurtin SE. *J Adv Pract Oncol.* 2013;4(suppl 1):5-14.

RR MM Treatment



Abbreviations: Regimen in "red" font: most potent, 1st choice; "blue" font: less expensive regimens; PI: proteasome inhibitor, IMiD: immunolomodulatory agent; V: bortezomib; R: lenalidomide; VTd: bortezomib-thalidomide-dexamethasone, VCd: bortezomib-cyclophosphamide-dexamethasone, VMP: bortezomib-melphalan-prednisolone, VTP: bortezomib-thalidomide-prednisolone, VRd: bortezomib-lenalidomide-dexamethasone, Rd: lenalidomide-dexamethasone, Kd: carfilzomib-dexamethasone, KRd: carfilzomib-lenalidomide-dexamethasone, Ixa-Rd: ixazomib-lenalidomide-dexamethasone, Dara-Rd: daratumumab-lenalidomide-dexamethasone, Elo-Rd: Elotumumab-lenalidomide-dexamethasone, Pd: pomalidomide-dexamethasone; PCd: pomalidomide-cyclophosphamide-dexamethasone, KPd: carfilzomib-pomalidomide-dexamethasone, Dara-Pd: daratumumab-pomalidmide-dexamethasone, SCT: stem cell transplantation, CAR-T: chimeric antigen receptor T cell, *: ongoing clinical trials, number in superscript: reference in the manuscript

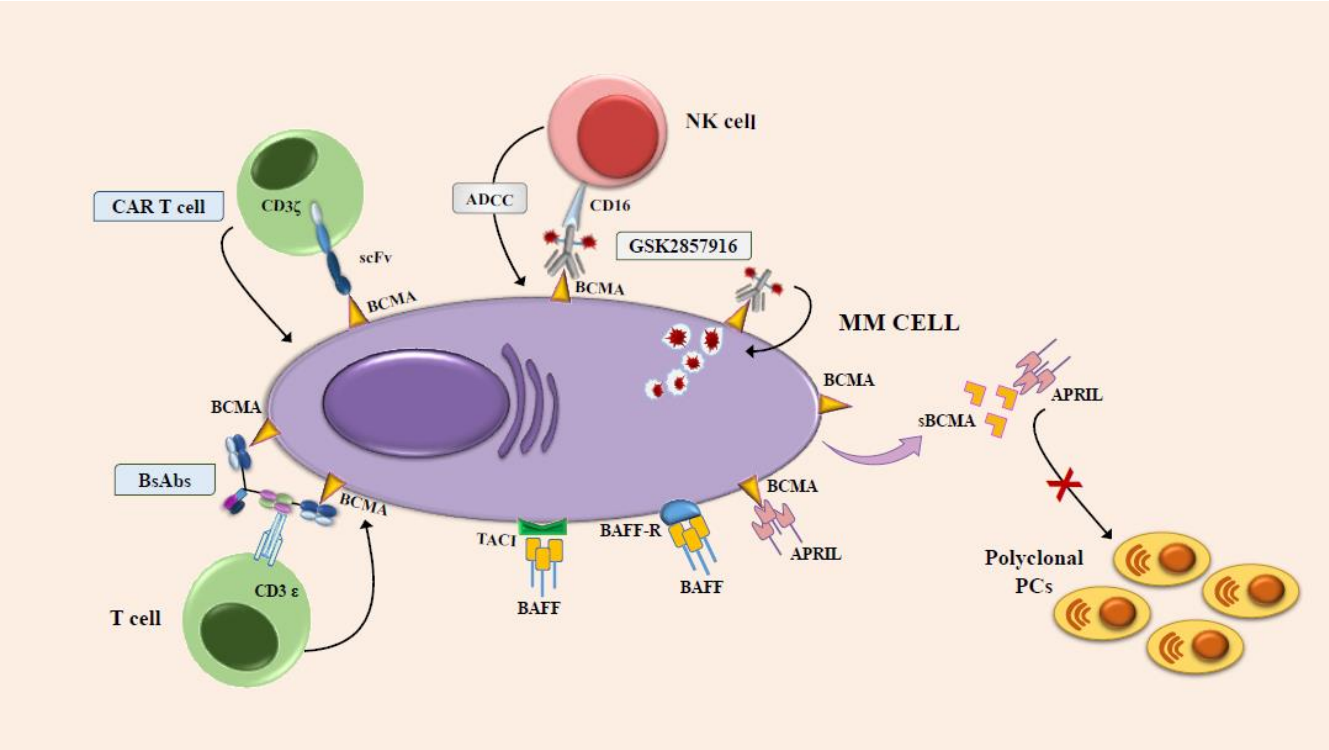
Chim CS, et al. *Leukemia*. 2018;32:252-262.

RR MM: New Medications = Better Survival

	Daratumumab*[1]		Carfilzomib[2]		Panobinostat[3,4]		Pomalidomide[5]		Venetoclax[6]	
N	DVd vs Vd 498		Kd vs Vd 929		FVd vs Vd 768		PVd vs Vd 559		VenVd vs Vd 194 vs 97	
Efficacy	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**
Median follow up, mos	47		37.5		NR		16		18.7	
ORR	85%	63%	76%	63%	55%	61%	82%	50%	82%	68%
≥CR	30%	10%	13%	6%	11%	6%	16%	4%	13%	6%
Median PFS, mos	16.7	7.1	18.7	9.4	12	8.08	11	7	23.2	11.4
PFS HR (95% CI)	0.31 (0.25–0.39)		0.53 (0.44–0.65)		0.63 (0.52–0.76)		0.61 (0.49–0.77)		0.60 (0.43–0.82)	
Median OS, mos	NR	NR	47.6	40.0	40.3	35.8	NR	NR	33.5	NR
OS HR (95% CI)	NR		0.79 (0.65–0.96)		0.94 (0.78–1.14)		NR		1.46 (0.91–2.34)	

1. Weisel K, et al. *Blood*. 2019;134: abstract 3192; 2. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38; 3. San Miguel JF, et al. *Lancet Oncol*. 2014;15:1195-206; 4. San Miguel JF, et al. *Lancet Haematol*. 2016;3:e505-e515; 5. Richardson PG, et al. *Lancet Oncol.* 2019;20:781-794; 6. Kumar S, et al. *J Clin Oncol*. 2020;38: abstract 8509.

Novel Approaches To Myeloma Therapy



Dalla Palma B, et al. *J Clin Med.* 2020; 9(9): 3022.

Regional Challenges

- Poor performance status of repeatedly treated patients
- Associated comorbidities: high incidence of hypertension and diabetes
- CAR T-cell therapy: yet to begin
- Hope for a better outcome for our patients

Thank you

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Relapsed/Refractory Multiple Myeloma Patient Case

Case 1

Dr Ni Ni Aung

Consultant Hematologist

North Tees and Hartlepool NHS Trust

United Kingdom

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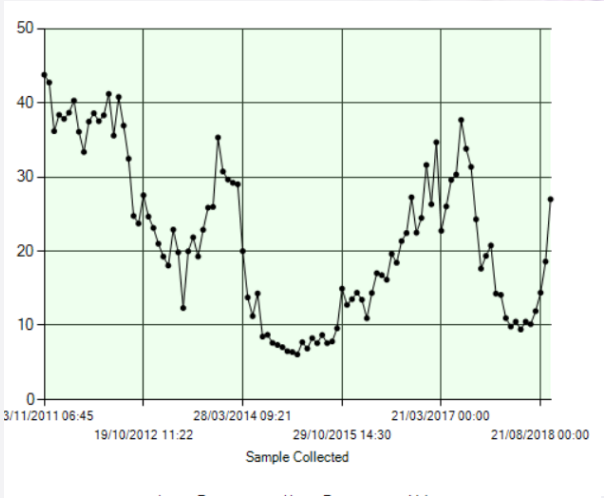
Patient History and Frontline Therapy

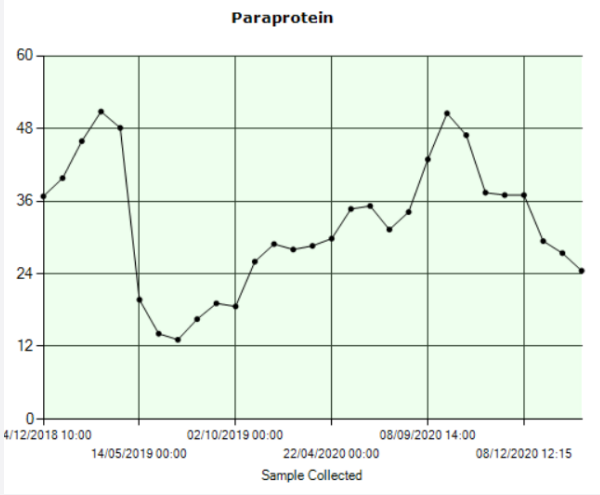
- Mr AG, 52 years old at diagnosis
- Diagnosed with myeloma in Oct 2011
- Presented with 2-year history of episodic lumbar and thoracic back pain
  - FBC: Hb 107 g/L, WBC 3.9 × 10^9/L, N 2.2, L 1.1, Plt 210; Cr 100, urea 11.4, Na 131, K 4.2, LFTs normal, Ca normal, Alb 37
  - Ig A 0.08 g/L, IgM 0.07 g/L, monoclonal band IgG K 43.78 g/L. FLC K 20.47 mg/L, L 0.76, K:L 26.9; BJP negative, ß2m 5.03 mg/L
  - Plasma cells 40%
  - MRI spine: abnormal marrow signals and multiple compression fractures
  - SS: multiple lytic lesions throughout skull vault, shafts of long bones and pelvis
- Myeloma ISS stage III
- Frontline therapy
  - Initial treatment with CTD with not much improvement, hence changed to DT-PACE, then PAD, V, R + cyclophosphamide; complicated with infections including ITU admission
  - Paraprotein became <10 g/L in Jul 2014 – Oct 2015
  - Follow-up – all the way through
  - Progression again in Oct 2015

Relapsed/Refractory Setting

- Further therapies
  - 2016: Pom + D
  - 2017: ixazomib + D + cyclo arm – MUK 8 trial
  - 2017 Aug – 2018 Aug: V + panobinostat + D
  - 2019 Apr – 2020 Jun: Pom + D
  - 2020 Sep – Oct 2020: selinexor + V + D × 2
  - 2020 Oct – to date: CTD, currently #9

  - Recent Hb 99, no transfusion required; Ca normal, Cr 86
  - ECOG status 0





Points for Discussion

- Where to go from here?
  - Anti-CD38 antibodies are not accessible at this stage in UK
  - Continue CTD until plateauing or refractory
  - Considering belantamab mafodotin
  - Any good ideas?
- What could have been done better?

Global Multiple Myeloma Academy

Discussion: Case 1

Presenter: Dr Ni Ni Aung

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Relapsed/Refractory Multiple Myeloma Patient Case

Case 2: Plasma Cell Leukemia Relapse

Dr Badr Bennani

Internal Medicine and Onco-Hematology Department

University Hospital Hassan II, Fes, Morocco

APTITUDE HEALTH®

Patient History and Frontline Therapy

- 57-year-old housewife
- Past medical history: diabetes under OAD
- Jun 2018: fatigue, pallor, and weight loss
  - Hb 8.8g/dL, WBC 3.8 × 10^9/L, neut 1.4, plt 82
  - IgA 9.11 g/L, SFLC kappa 647 mg/L, kappa/lambda ratio = 100
  - Normal Ca^{++} and kidney function
  - Urine test: positive kappa LC
  - Bone BMT: 56% plasma cells, CD138+
  - Bone survey: lytic lesions throughout iliac bone and skull
- Risk assessment: albumin 44 g/L, β2m 2.3 mg/L (ISS Stage I)
- Frontline therapy
  - Initial treatment with CTD × 9 + zoledronic acid
  - Treatment outcome: Dec 2019 **complete response** (CR; IgA reduced from 9.11 g/L to 0.82 g/L)
    Bone marrow: 7% plasma cells
  - ASCT delayed: melphalan shortage
  - Maintenance with thalidomide

Relapsed/Refractory Setting

- Progression: Aug 2020 – symptomatic hypercalcemia
- Blood count: **Hb 6.2 g/L**, MCV 91 fl, WBC 3.7 × 10^9/L, neut 0.3, plasma cells 31%, **plt 39**
- IgA increased to 13.8 g/L
- Albumin 34 g/L, β2m 7.1 mg/L (ISS Stage III)

> Second-line therapy

- Treatment choice: VCD (bortezomib, cyclophosphamide, dexamethasone), EPO and transfusion support
- Treatment outcome after VCD first cycle: persistent neutropenia and thrombopenia, absence of blood transfusion effectiveness and growth factor support response
- **Issue**: very low platelets rate » bortezomib CI
- **Decision point:** continue with VCD despite plt rate (bone marrow disinfiltration)
- Second cycle in Dec 2020
- After 14 days, hyperkalemia + kidney failure (creatinine clearance = 6 mL/min)
- Death

Points for Discussion

- Issues
  - Secondary plasma cell leukemia
  - Prolonged refractory cytopenia due to massive marrow infiltration
  - Poor response to treatment

Global Multiple Myeloma Academy

Discussion: Case 2

Presenter: Dr Badr Bennani

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Global Multiple Myeloma Academy

Relapsed/Refractory Multiple Myeloma Patient Case

Case 3

Dr Viktoria Ryabchikova

Municipal Clinical Hospital 31,
St. Petersburg, Russian Federation

APTITUDE HEALTH®

Patient History and Frontline Therapy

- Patient: male, 54 yo
- Initial presentation and diagnosis (22 Feb 2019)
  - Multiple myeloma, kappa, stage IIIB (Durie-Salmon), ISS III, R-ISS III
  - Blood test: Hb 119 g/L, WBC 14 × 10^9/L, ANC 10.4 × 10^9/L, plasma cells 2%, PL 134 × 10^9/L, ESR 84 mm/hr, total protein 53 g/L, albumin 27 g/L**,** creatinine 0.649 mmol/L, CFR 7.6 mL/min, calcium **-4.34 mmol/L (17.39 mg/dL), LDH -247 units/L, beta-2 microglobulin -11.7 mg/L**
  - **Serum protein electrophoresis:** kappa immunoglobulin light chain -3125.0 mg/mL, lambda immunoglobulin light chain -28.16 mg/mL
  - Bone marrow biopsy: total numbers of plasma cells 11.6% (plasmablast -9.6%)
  - Plasmacytoma C7 biopsy: CD138, CD56, CD38. Kappa FLC, **Ki67+ 98%**
  - **Cytogenetic abnormalities:** 45, XY, del(14) T(11;14) (q13;q32), t(17;18) (q10;q10), 18[2]/45, idem, trp (1) (q25;q32) [5]/53, idem, +7, +9, +12, +der(14)t(11,14), +15, t(17,18),+22, +mar [11]/в 35%
  - CT result: plasmacytoma of right supraclavicular region 33 × 65 mm with invasion into the muscles of the neck, destruction of the C7 vertebra. Multiple lytic bone lesions
- Frontline therapy
  - Induction (Feb–May 2019): 1VD + 3VRD
  - Consolidation (5 Aug 2019 and 7 Feb 2020): melphalan 200 mg/m^2 with double autologous hematopoietic cell transplantation
  - Maintenance (April–Nov 2020): lenalidomide 15 mg per day
  - Treatment outcome: CR (PET-, FISH without high-risk chromosomal abnormalities)
  - Progression: Nov 2020 multiple focus of extramedullary plasmacytoma (lung, stomach, pancreas, nodes in the retroperitoneum)

Relapsed/Refractory Setting

> Second-line therapy: Dara-Pom-Dex, 26 Nov 2020 to 29 Apr 2021
  - Treatment outcome: SD (PET-CT; multiple focus of extramedullary plasmacytoma [stomach, pancreas, nodes in the retroperitoneum] completely regressed). Bone lesions with metabolic activity, Deauville 5
  - Progression of disease 06 Apr 2021. MRI – paravertebral plasmacytoma L4–L5 with obstruction of left ureter
  - Hb 87 g/L, WBC 3.77 × 10^9/L, ANC 2.62 × 10^9/L, PL 106 × 10^9/L, ESR 66 mm/hr, creatinine 0.206 mmol/L, calcium -2.36 mmol/L (9.45 mg/dL), LDH -384 units/L

> Third-line therapy: KD-PACE

Relapsed/Refractory Setting

- What is the best choice of third-line therapy in this case?
  - Treatment choice: KD-PACE

- Are the bone plasmacytomas with invasion into nearby tissues and organs determine a high-risk MM?
- What is the best choice of induction therapy for NDMM with extramedullary plasmacytomas; standard or intensified?
- What is the optimal timing of radiation therapy for MM with plasmacytoma?
- What is the best technique for evaluating plasmacytomas - MRI, CT or PET-CT?

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Discussion: Case 3

Presenter: Dr Viktoria Ryabchikova

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Session Close – Audience Response Questions

Rafael Fonseca

APTITUDE HEALTH®

Question 1

What treatment belongs to the T-cell engagers category?

1. Melflufen
2. Belantamab
3. Ide-cel
4. Selinexor
5. Venetoclax

@rfonsi1, fonseca.rafael@mayo.edu

Question 2

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

1. Dara-Pd
2. Elotuzumab-venetoclax and dexamethasone
3. Bortezomib, pomalidomide, and dexamethasone
4. Bortezomib plus daratumumab and dexamethasone
5. Carfilzomib plus lenalidomide and 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 of the above
E. A and C

@rfonsi1, fonseca.rafael@mayo.edu

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 will also receive a certificate of attendance via email by April 30

THANK YOU!

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Emerging and Practical Concepts in Multiple Myeloma

THANK YOU FOR YOUR PARTICIPATION!

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