Global Multiple Myeloma Academy

# Global Multiple Myeloma Academy – Day 2

## Emerging and Practical Concepts in Multiple Myeloma

June 18–19, 2021

AMGEN Pfizer Bristol Myers Squibb™

APTITUDE HEALTH®

Global Multiple Myeloma Academy

# Session Open

Rafael Fonseca, MD

APTITUDE HEALTH®

# Faculty

## Chair

**Rafael Fonseca, MD**
Mayo Clinic Cancer Center, USA

**Irene Ghobrial, MD**
Dana-Farber Cancer Institute, USA

**Vania Hungria, MD, PhD**
São Germano Clinic, Brazil

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

**María-Victoria Mateos, MD, PhD**
University of Salamanca, Spain

**Natalia Schütz, MD, MS**
Instituto Universitario del Hospital Italiano de Buenos Aires, Argentina

**Humberto Martínez Cordero, MD, MSc**
National Cancer Institute, Colombia

**Jorge Vela-Ojeda, MD, PhD**
CMN La Raza, Mexico

# 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

| Time (UTC –3) | Topic | Speaker |
|---|---|---|
| 6.00 PM – 6.10 PM<br>10 min | **Session Open** | Rafael Fonseca, MD |
| 6.10 PM – 6.30 PM<br>20 min | **Identification and Special Considerations for High-Risk Multiple Myeloma**<br>• Risk stratification, prognosis, and treatment choices<br>(15 min; 5-min discussion) | María-Victoria Mateos, MD, PhD |
| 6.30 PM – 6.55 PM<br>25 min | **Management of Early Relapse of Multiple Myeloma**<br>• Definition, prognosis, and treatment choices<br>(15 min; 10-min discussion) | Rafael Fonseca, MD |
| 6.55 PM – 7.20 PM<br>25 min | **Management of Heavily Pretreated Multiple Myeloma**<br>• Optimal use of treatment choices in relapsed/refractory multiple myeloma, excluding T-cell engagers<br>(15 min; 10-min discussion) | Keith Stewart, MBChB, MBA |
| 7.20 PM – 7.30 PM<br>10 min | **Break** | |
| 7.30 PM – 8.20 PM<br>50 min | **New and Future Therapies for Multiple Myeloma**<br>• Promising new developments in relapsed/refractory MM<br>• Latest trial updates and upcoming new strategies; focus on BCMA-directed therapies<br>(35 min; 15-min discussion) | Irene Ghobrial, MD |
| 8.20 PM – 9.15 PM<br>55 min | **Patient Case Discussion: Relapsed/Refractory Multiple Myeloma**<br>• Cases from the region will be discussed with the faculty – “tumor board approach”<br>• Relapsed/refractory MM, treatment challenges in the region – Natalia Schütz (Arg)<br>– Case 1: Cristian Seehaus and Natalia Schütz (Arg)<br>– Case 2: Ana Luiza Miranda Silva Días and Vania Hungria (Bras)<br>– Case 3: Didier Larios Sanjuan and Humberto Martínez-Cordero (Col)<br>– Case 4: Sofía Sánchez and Jorge Vela-Ojeda (Mex) | All faculty |
| 9.15 PM – 9.30 PM<br>15 min | **Session Close**<br>• ARS questions | Rafael Fonseca, MD |

# 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


@rfonsi1, fonseca.rafael@mayo.edu

# Question 3

Which statement(s) 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

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# Identification and Special Considerations for High-Risk Multiple Myeloma

María-Victoria Mateos

APTITUDE HEALTH®

HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

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 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

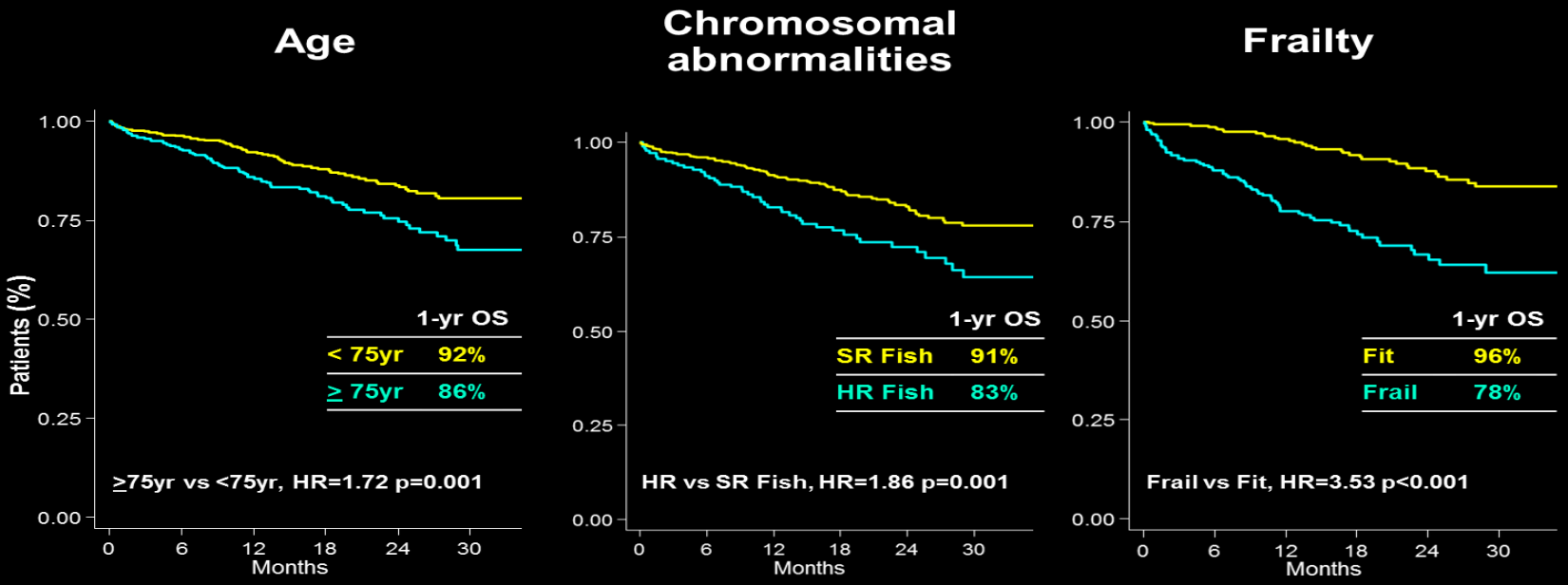
- ISS stage/R-ISS
- Cytogenetic abnormalities
- Extramedullary disease
- Plasma cell leukemia
- Lactate dehydrogenase level

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

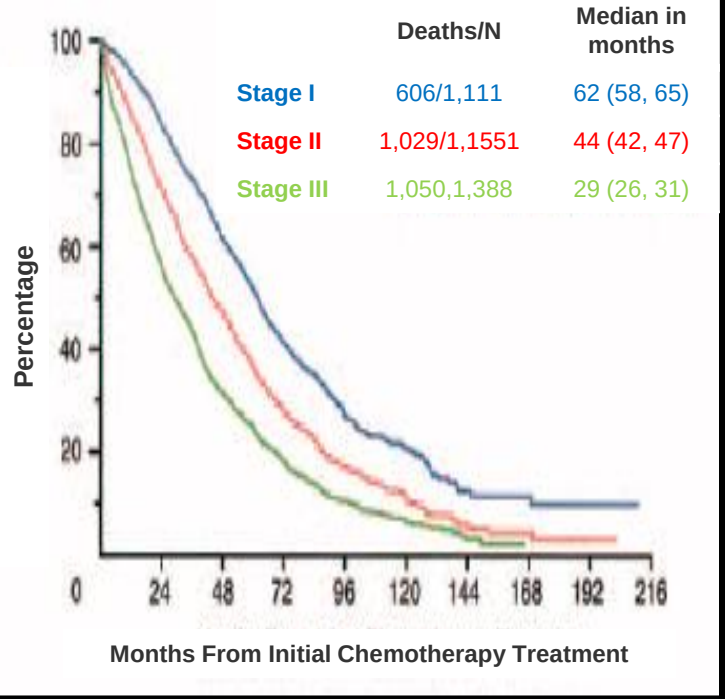
- ISS stage/R-ISS
- Lactate dehydrogenase level
- Cytogenetic abnormalities
- Extramedullary disease
- Plasma cell leukemia
- Response to treatment

# International Staging System for MM

**Table 2.** New International Staging System

| Stage | Criteria | Median Survival (months) |
|---|---|---|
| I | Serum $\beta_2$-microglobulin < 3.5 mg/L<br>Serum albumin ≥ 3.5 g/dL | 62 |
| II | Not stage I or III* | 44 |
| III | Serum $\beta_2$-microglobulin ≥ 5.5 mg/L | 29 |

*There are two categories for stage II: serum $\beta_2$-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum $\beta_2$-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.

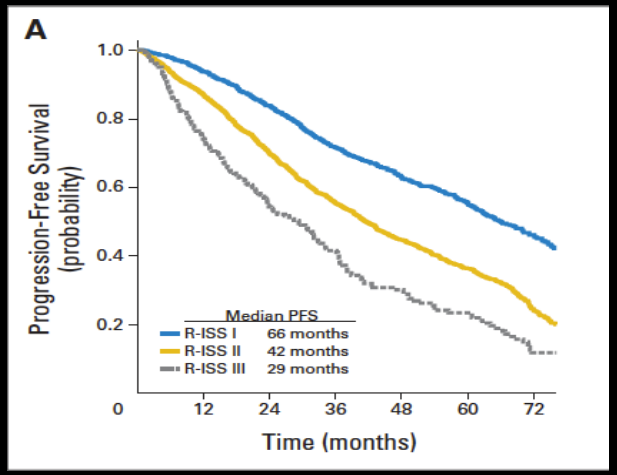
# ISS III, high LDH, and t(4;14) and/or del(17p) as a prognostic index for OS

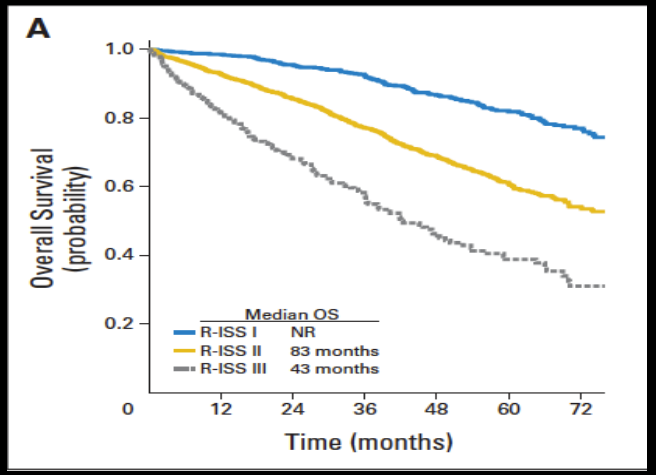
| Score | Definition | Percentage of overall population | Outcome |
|---|---|---|---|
| 0 | **Absence of adverse factors** (neither high LDH, nor ISS III, nor t[4;14] and/or del[17p]) | 57% | 4-year OS: 84% |
| 1 | **Presence of only 1 adverse factor** (either high LDH, or ISS III, or t[4;14] and/or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

# 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]

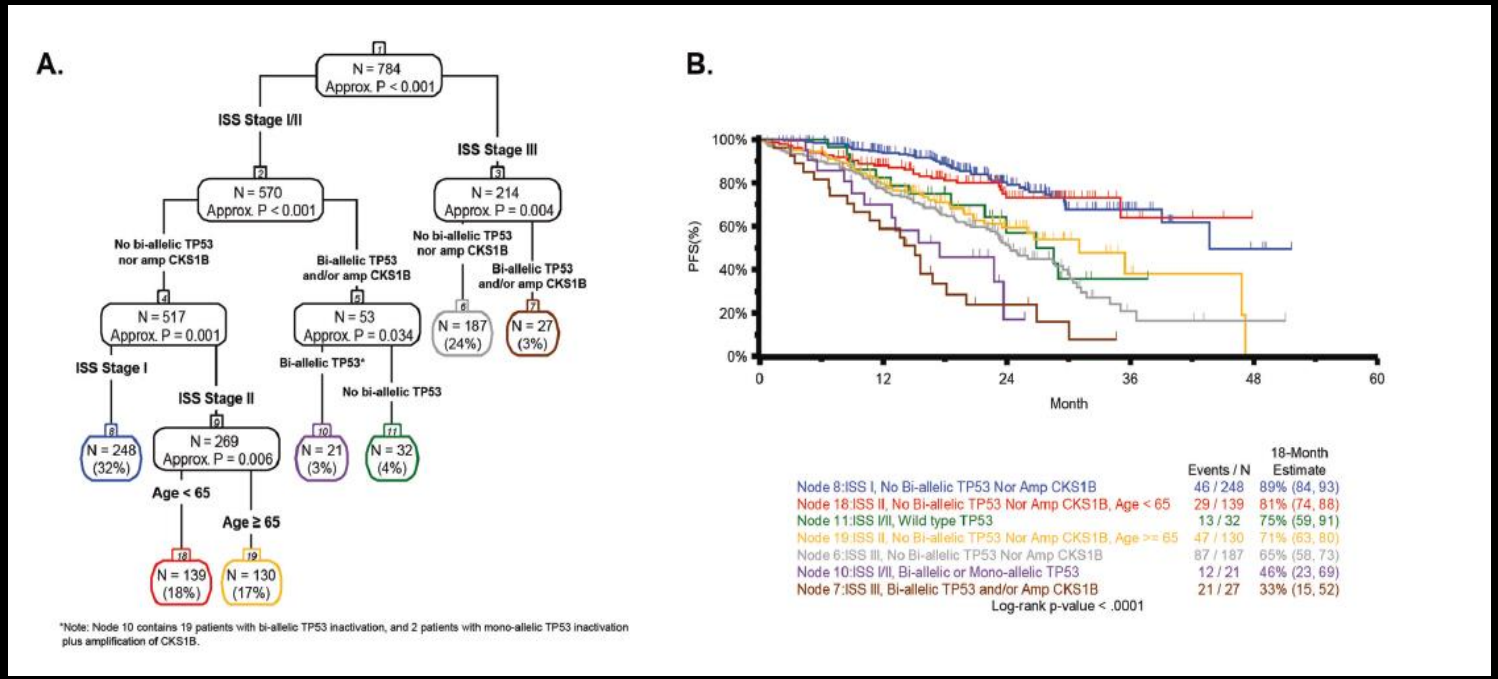
1. Touzeau C, Moreau P. *Blood.* 2016;127(8):971-976; 2. Suska A, et al. *Clin Hematol Int*. 2020;2(4):133-142; 3. Albarracin F, Fonseca R. *Blood Rev.* 2011;25:107-112.

# 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)**

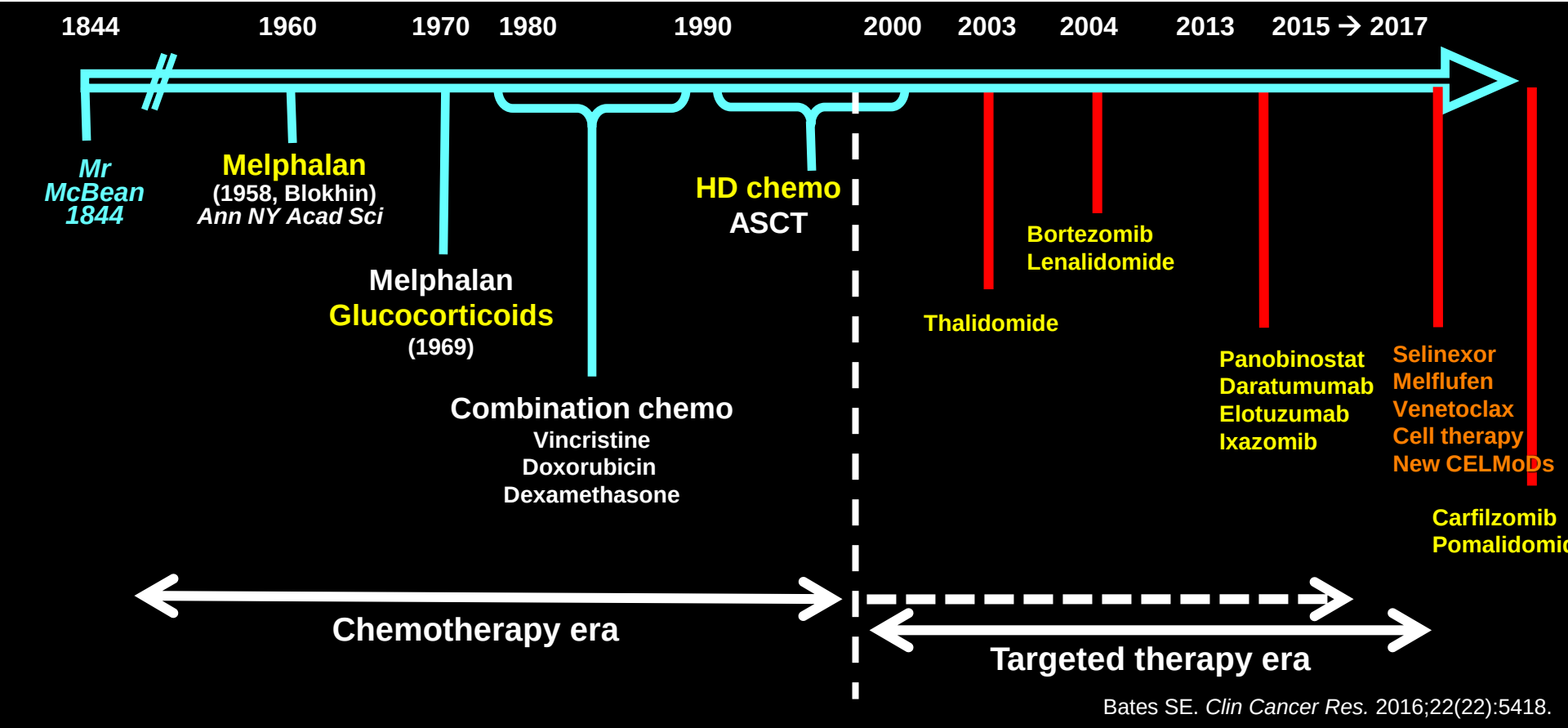
Walker B, et al. *Leukemia.* 2019;33(1):159-170.

# 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?

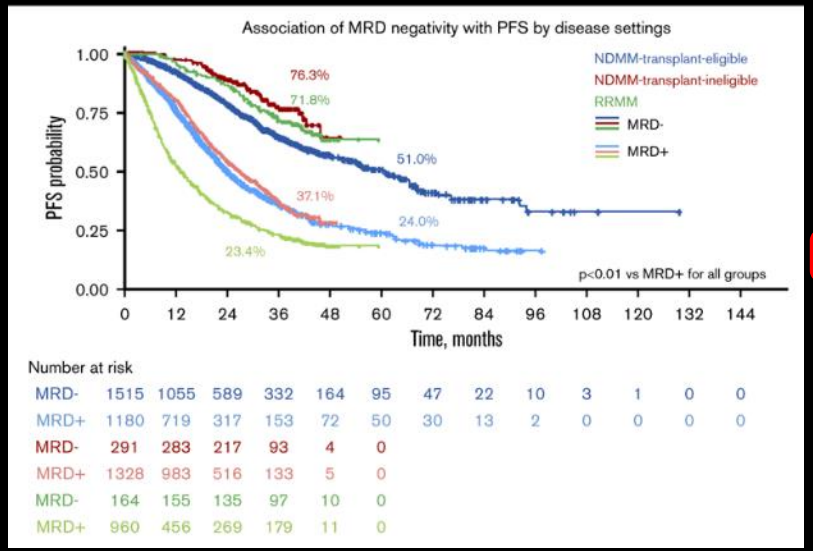
1. To use novel agent-based combinations
2. To try to achieve minimal residual disease negativity
3. To use combinations that are based on alkylators and conventional chemotherapy
4. 1 and 2 are correct

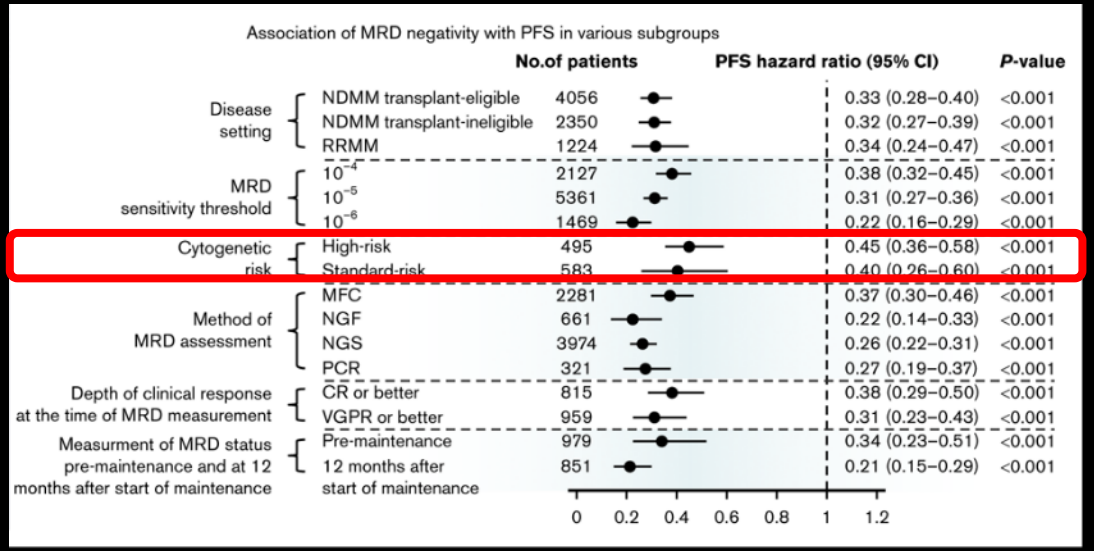
# Treatment of MM




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

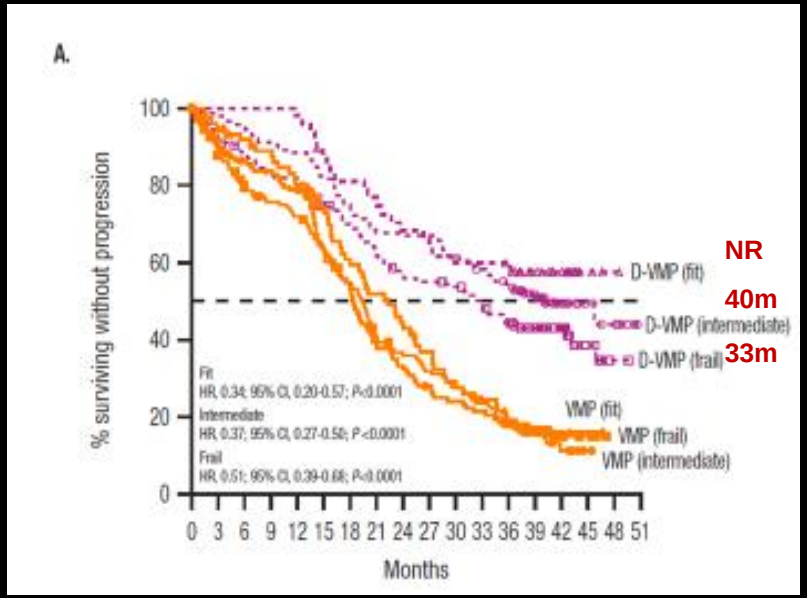
- **Age**
- **Comorbidities**, eg, renal failure, spinal cord compression

## Disease-specific factors

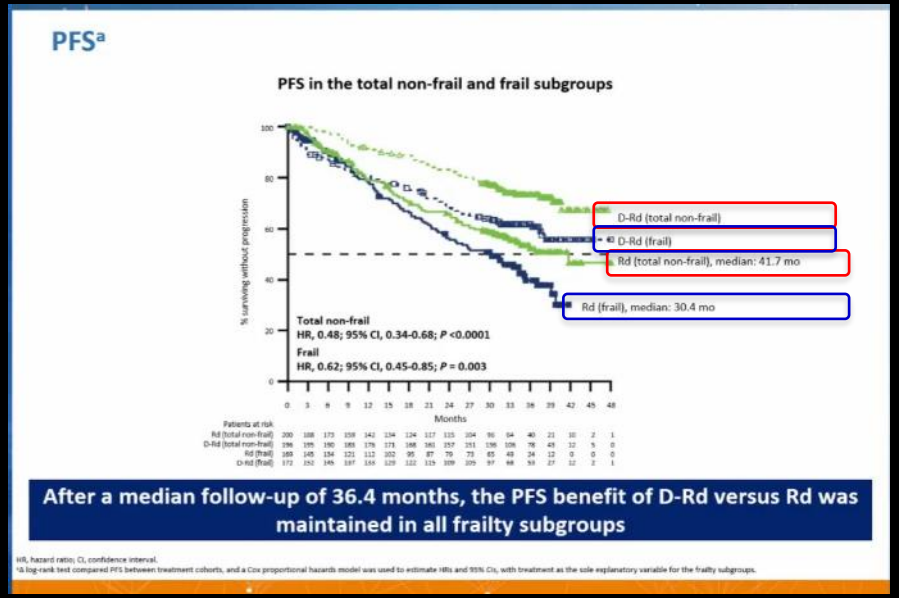
- ISS stage/R-ISS
- Cytogenetic abnormalities
- Extramedullary disease
- Plasma cell leukemia
- Lactate dehydrogenase level

# 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)**



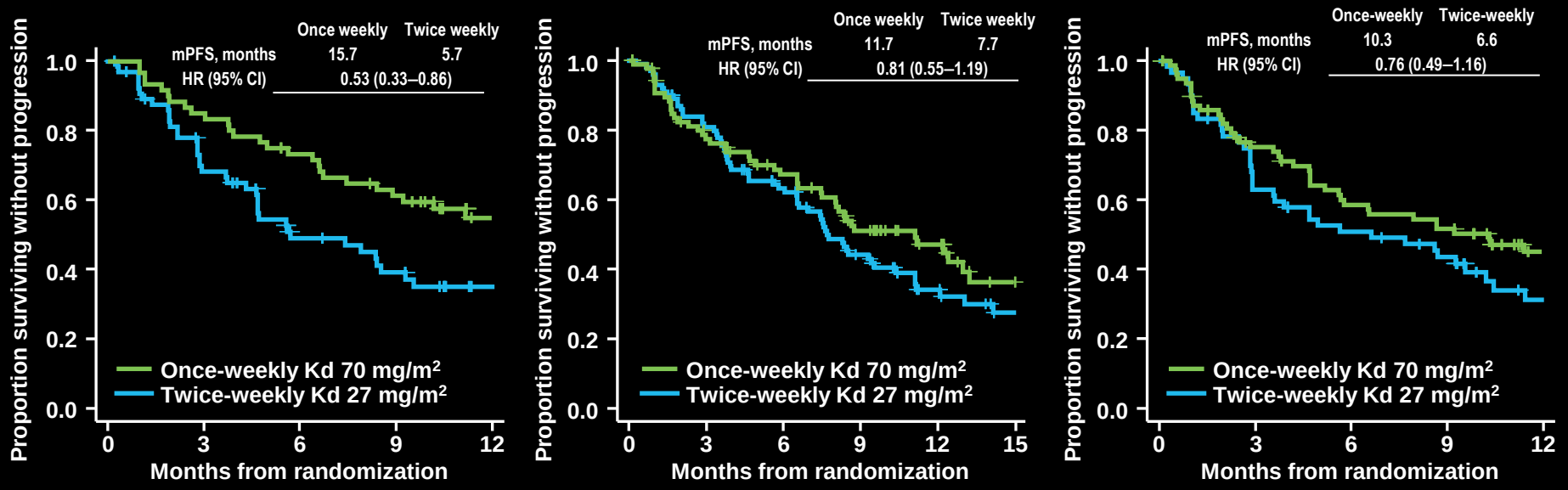

**The addition of daratumumab improved the outcomes of frail patients.**
**Frailty evaluated through the use of chronologic age, ECOG, and Charlson comorbidity index.**

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 |
|---|---|---|

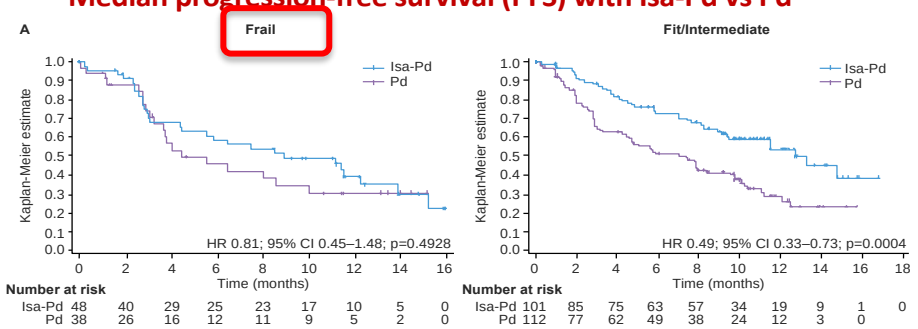



Mateos MV. 17th International Myeloma Workshop. Boston, MA, 2019.

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

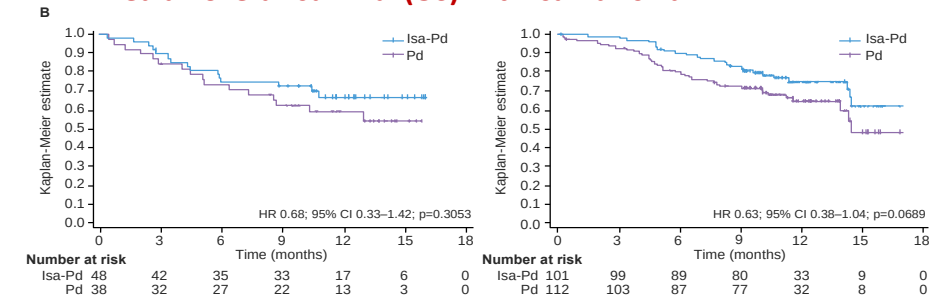
In **ICARIA**, median PFS was 11.5 mo for ISA-Pd vs 6.5 mo for Pd, with HR of 0.59

## 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

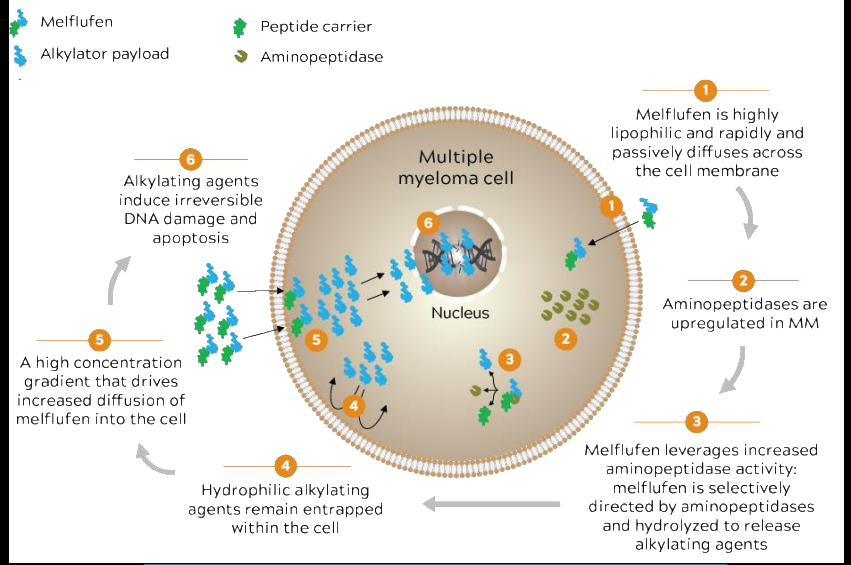
- Age
- Comorbidities, eg, renal failure, spinal cord compression

## 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]

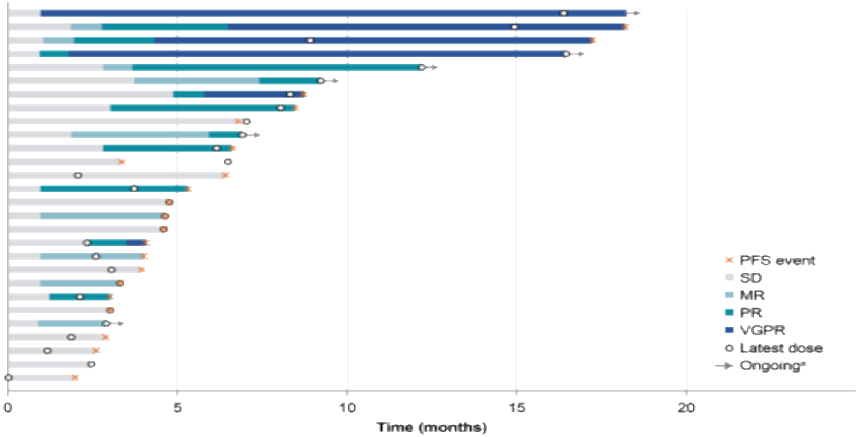



| Outcome[6] | Overall Population (N=157) |
|---|---|
| **ORR (95% CI), %** | **29 (22-37)** |
| **OS, median (95% CI), mo** | **11.6 (9.3-15.4)** |
| **PFS, median (95% CI), mo** | **4.2 (3.4-4.9)** |
| DOR (≥PR), median (95% CI), mo | 5.5 (3.9-7.6) |

**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 is not approved by any regulatory agency.**

[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

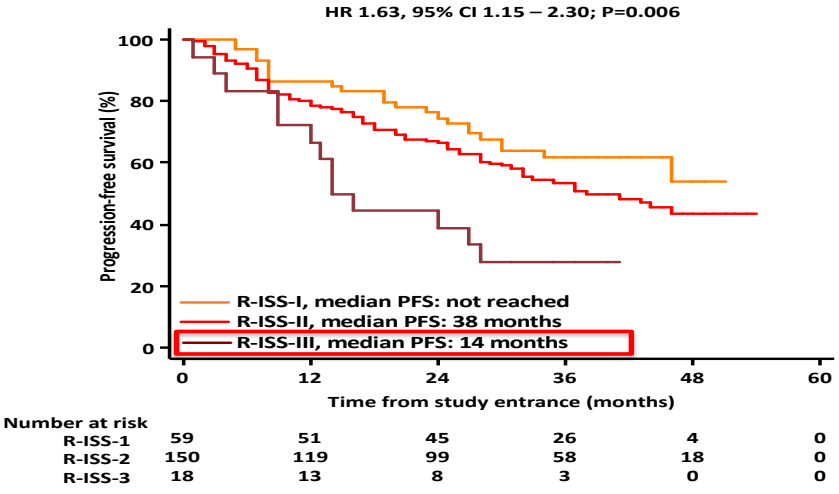
**Response to treatment**

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

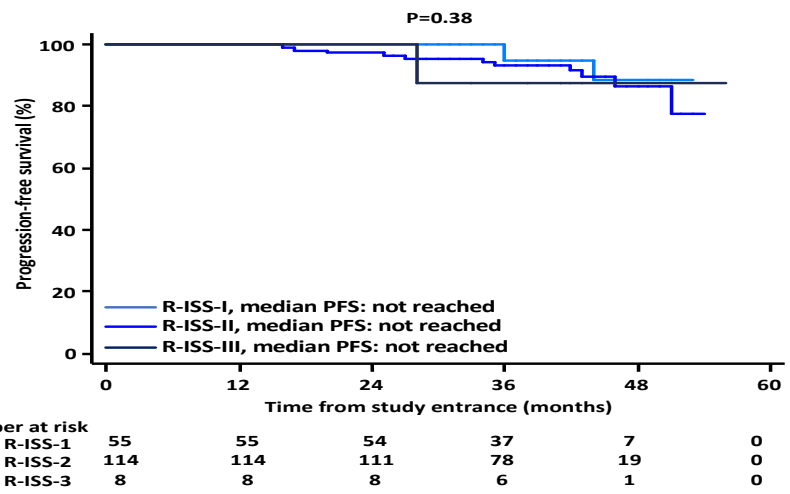
## RVD × 6c → ASCT→ RVD × 2c → Rd +/– ixazomib

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

**MRD-positive**




**MRD-negative**

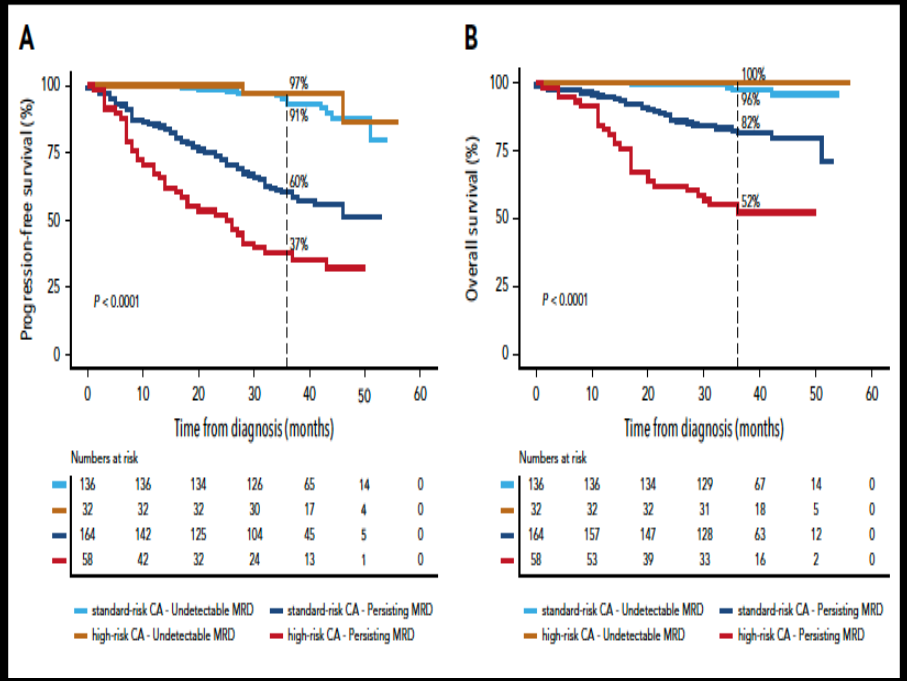


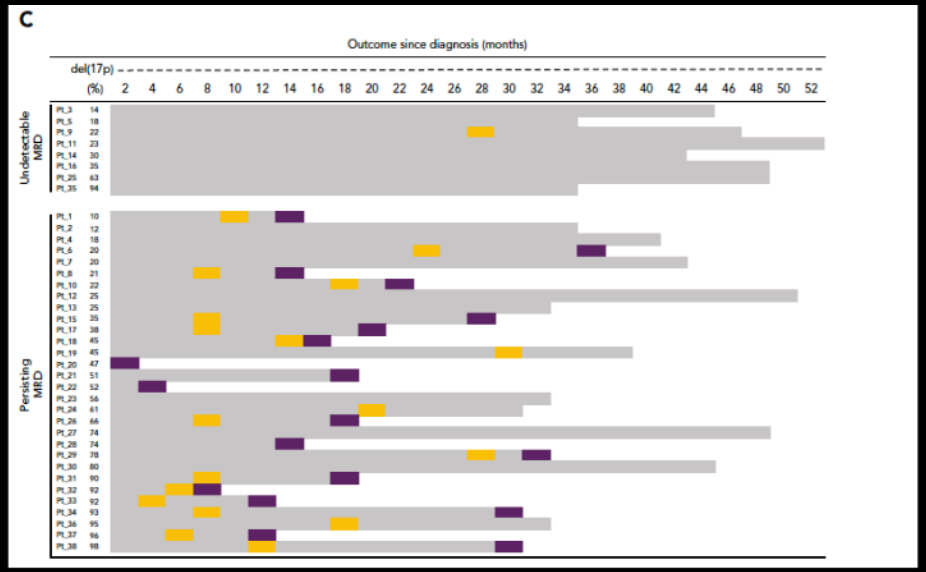

*The best way to overcome high-risk cytogenetics is through the achievement of MRD-negativity*

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

# MRD negativity is able to overcome the poor prognosis defined by the presence of HR CA

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




**Patients with del17p according to the percentage of tumor cells having each CA. OS is represented by gray bars, and progressions are in orange and deaths in purple.**

Goicoechea I, et al. *Blood*. 2021;137:49-60.

# Management of HR 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.

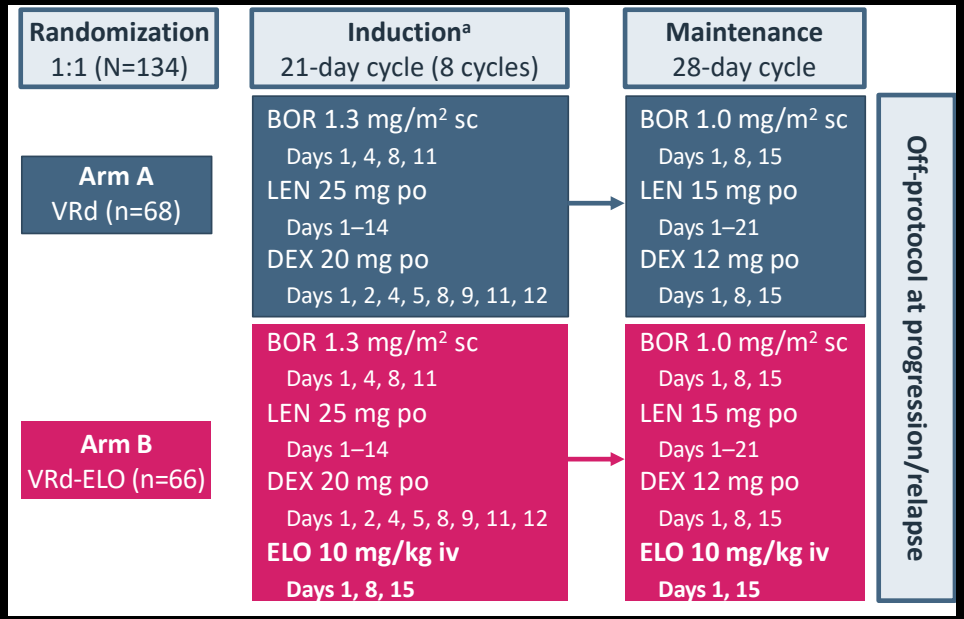
1. Dimopoulos MA, et al. *HemaSphere.* 2021;5(2):e528;
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple myeloma. Version 5.2021. 2021.

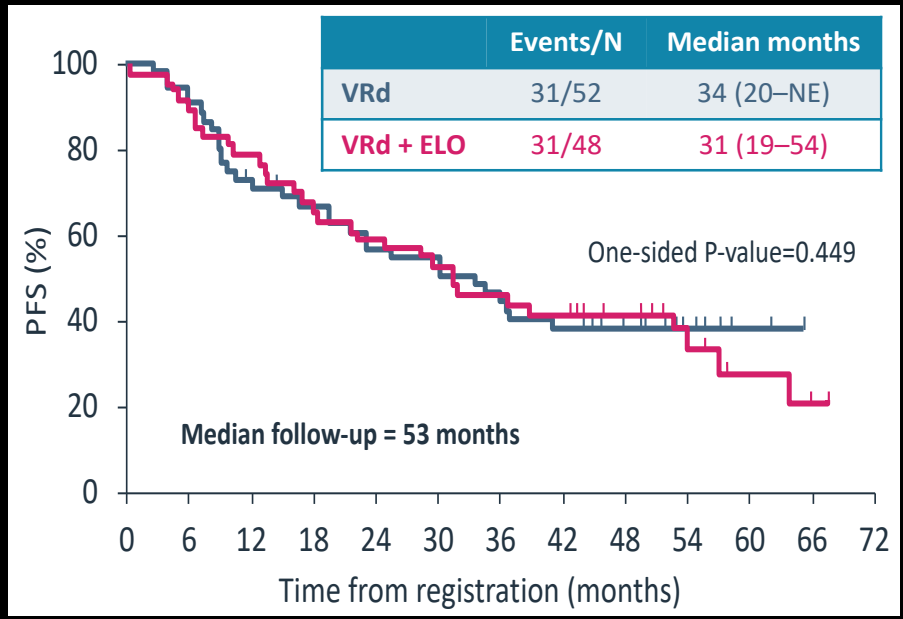
# SWOG-1211: Phase 2 randomized trial of bortezomib, lenalidomide, dexamethasone with/without elotuzumab for newly diagnosed, high-risk multiple myeloma

**Poor-risk score by gene expression profiling**

**≥1 cytogenetic abnormalities: t(14;20)(q32;q12) t(14;16)(q32.3;q23) del(17p),1q21 amplification**

**PPCL or elevated serum LDH 2 × ULN**

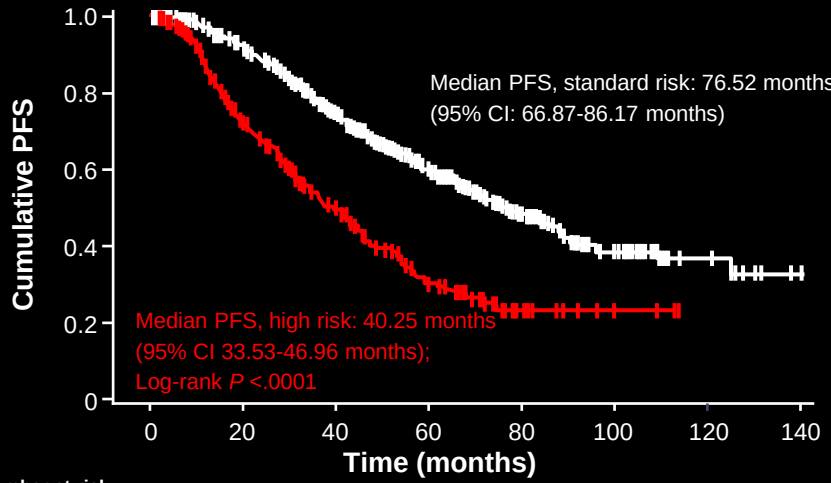



Usmani SZ, et al. *Lancet Haematol.* 2021;8(1):e45-e54.

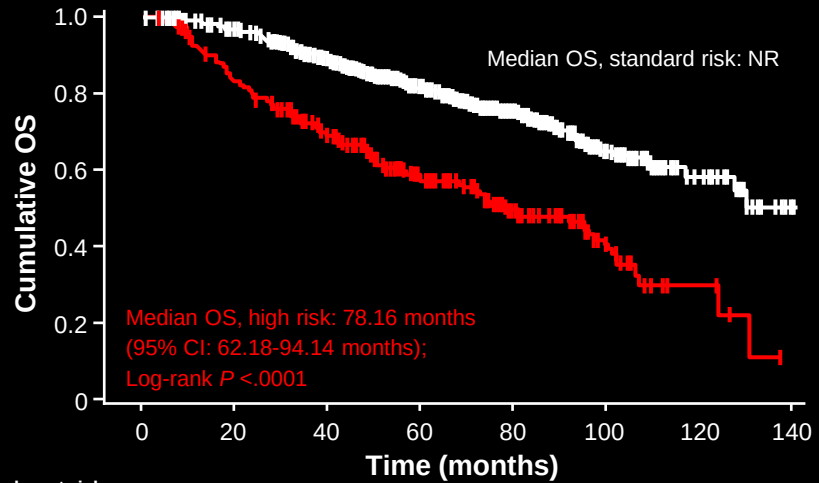
# Real-world outcomes of RVd induction in transplant by standard- and high-risk status

**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 |

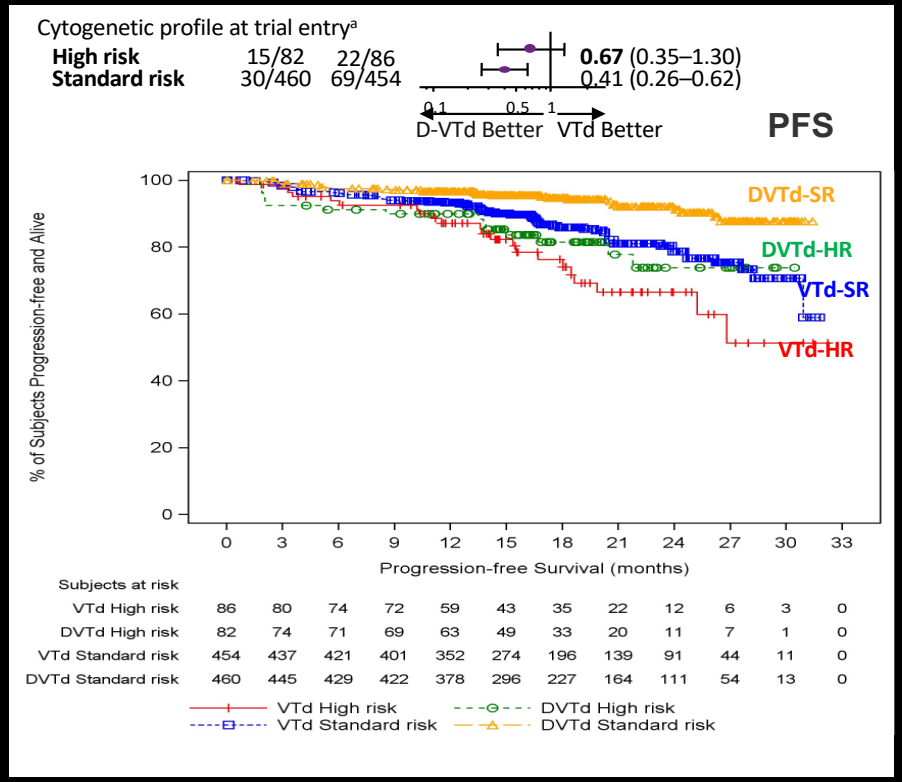
| Patients | Median PFS (months) | Median OS (months) | OS rates (5 years) | OS rates (10 years) |
|---|---|---|---|---|
| High risk | 40.3 | 78.2 | 57% | 29% |
| Standard risk | 76.5 | NR | 81% | 58% |

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

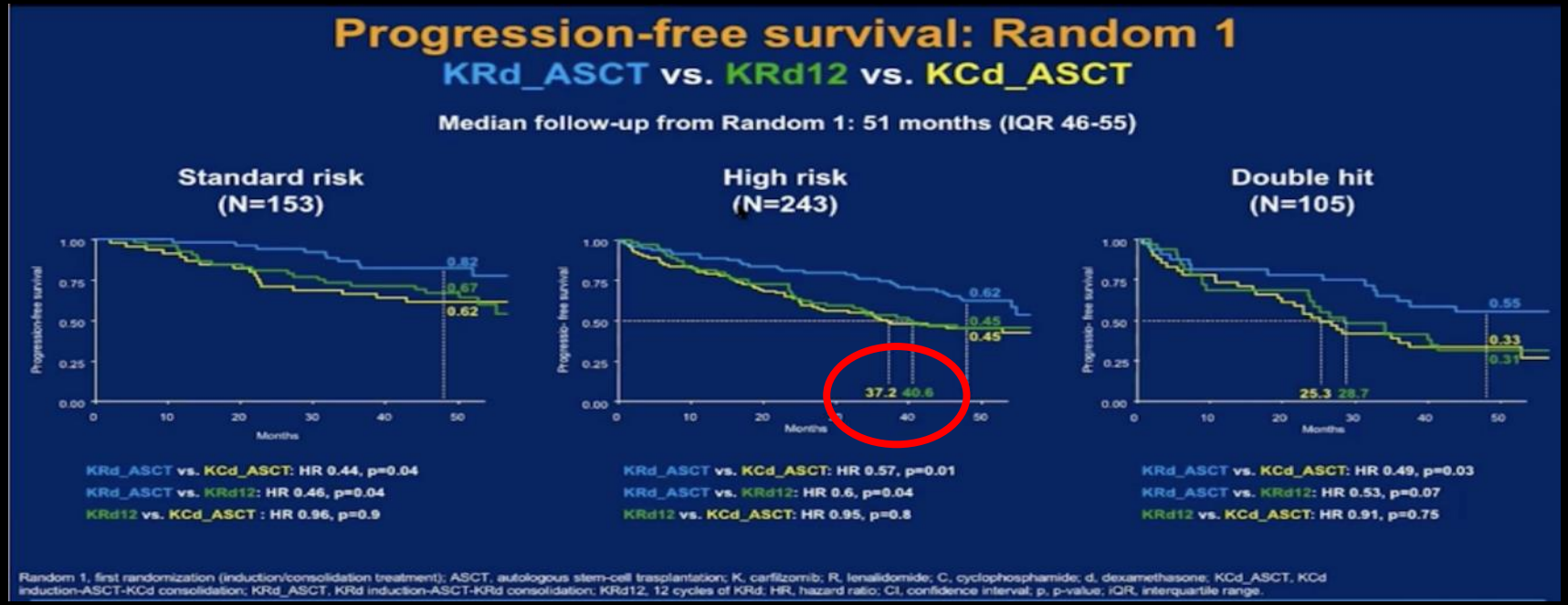
| Subgroup | VTd *minimal residual disease negative, n (%)* | D-VTd | Odds Ratio (95% CI) |
|---|---|---|---|
| **Sex** | | | |
| Male | 131 (41) | 192 (61) | 2.22 (1.62–3.05) |
| Female | 105 (47) | 154 (68) | 2.37 (1.62–3.48) |
| **Age** | | | |
| <50 years | 38 (42) | 56 (68) | 2.84 (1.53–5.28) |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

1 5 10
VTd Better D-VTd Better

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

# Phase 2 FORTE study: KRd-ASCT vs KRd12 vs KCd-ASCT in TE NDMM

**61% vs 56% vs 67% of pts presented HR CA, defined by the presence of t(4;14), t(14;16), gain 1q, amp 1q, del1p**




**KCd-ASCT and KRd12 seem to be non-superior to RVd**

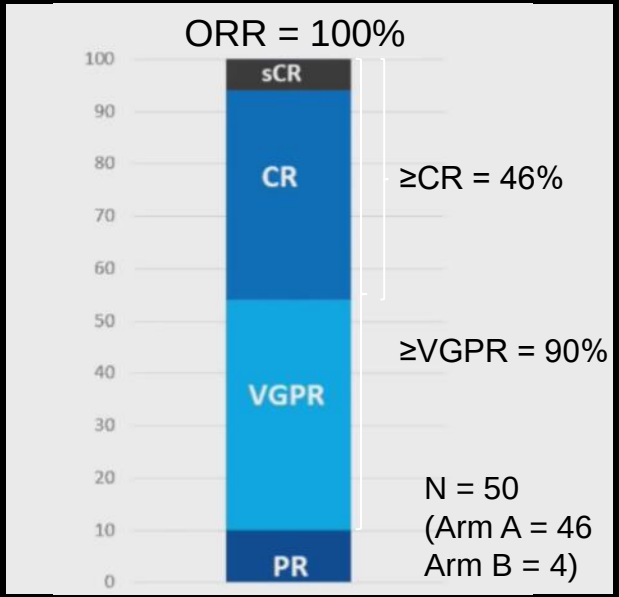
Gay F, et al. ASCO 2021.

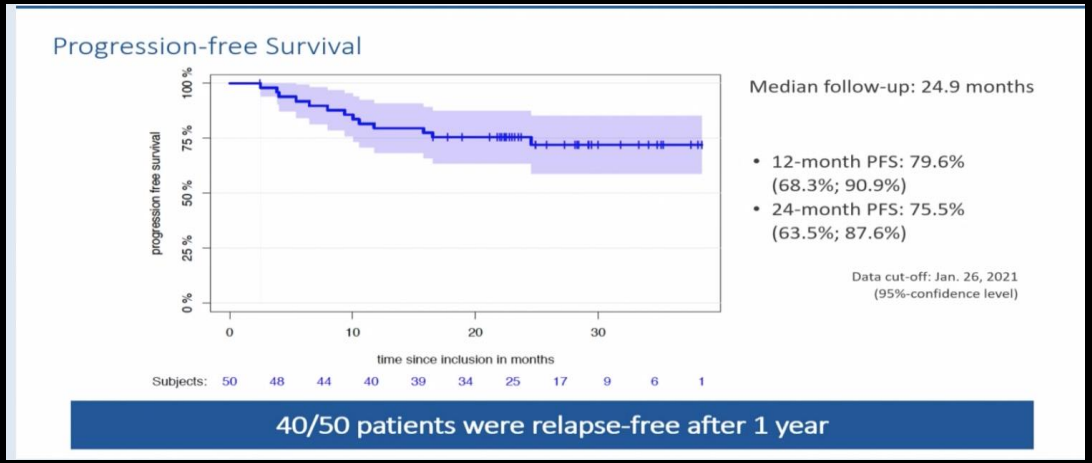
# Phase 2 GMMG-CONCEPT study: Interim analysis of isatuximab + carfilzomib-lenalidomide-dexamethasone in high-risk NDMM

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)**




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

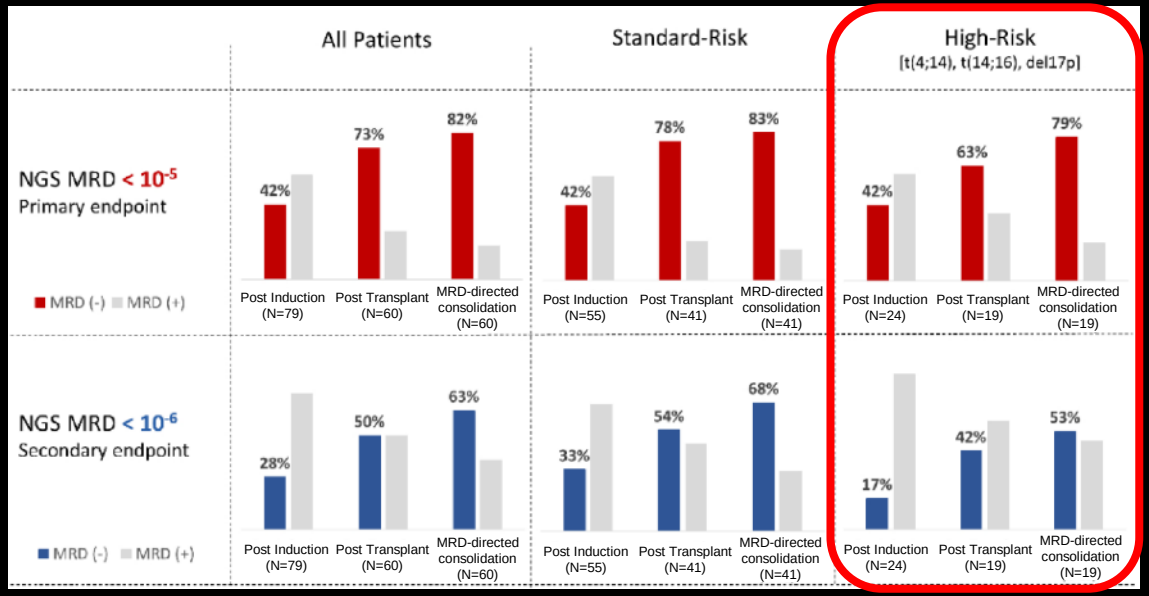
CR, complete response; PR, partial response; sCR, stringent complete response; TEAE, treatment-emergent adverse event; TE, transplant eligible; TNE, transplant non-eligible; URI, upper respiratory tract infection; VGPR, very good partial response.

Weisel K, et al. EHA 2021. Abstract S183.

# 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?

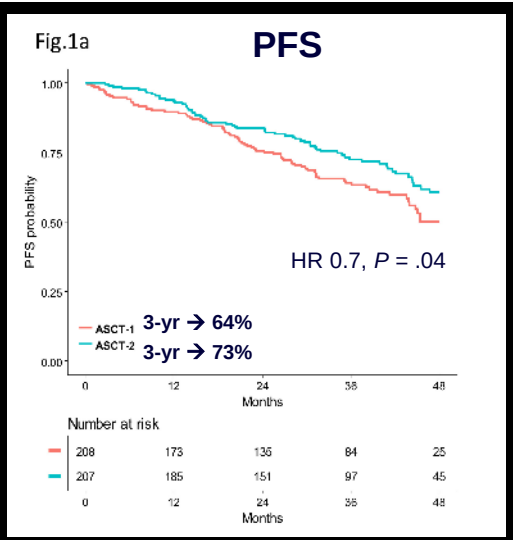
AE, adverse event; MRD, minimal residual disease; NGS, next-generation sequencing.

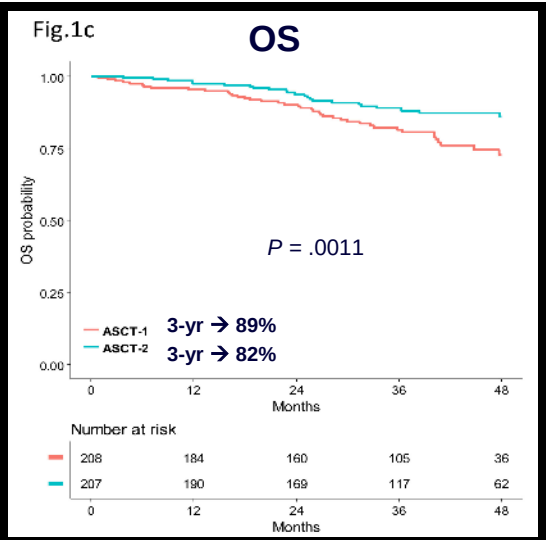
Costa L, et al. EHA 2020. Abstract EP928.

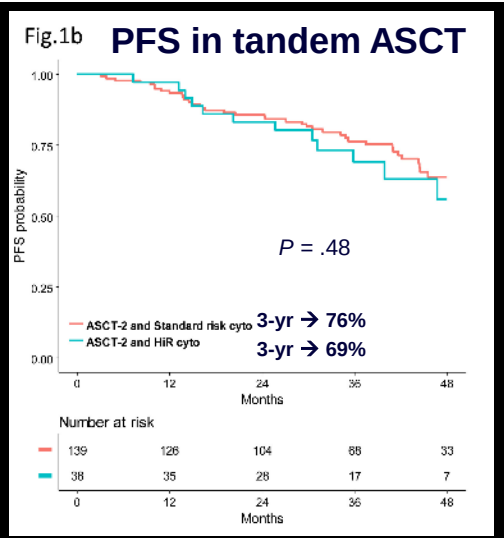
# Tandem ASCT in high-risk NDMM patients

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

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



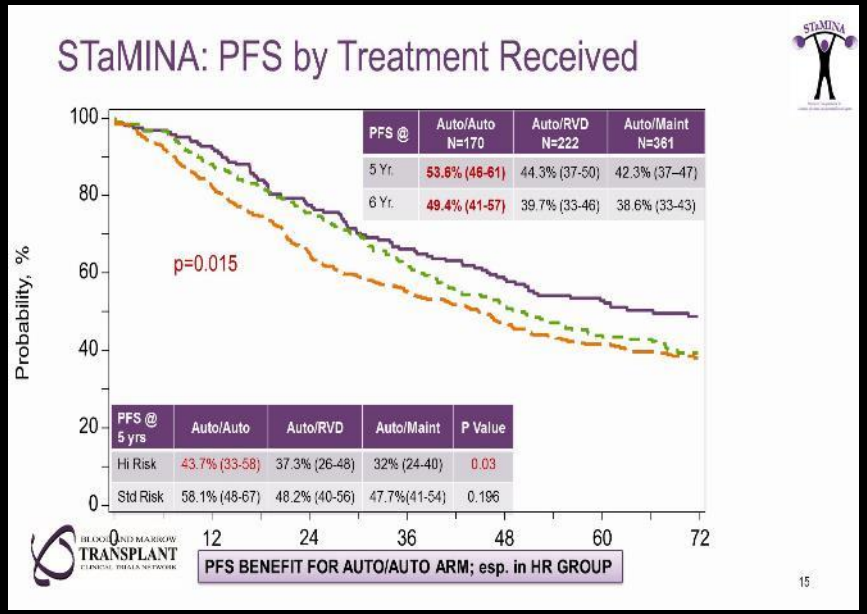

**ASCT-2 was superior to ASCT-1 in terms of prolonged PFS and OS in the overall population and seems to be able to overcome the poor prognosis of patients with advanced R-ISS and HiR CA.**

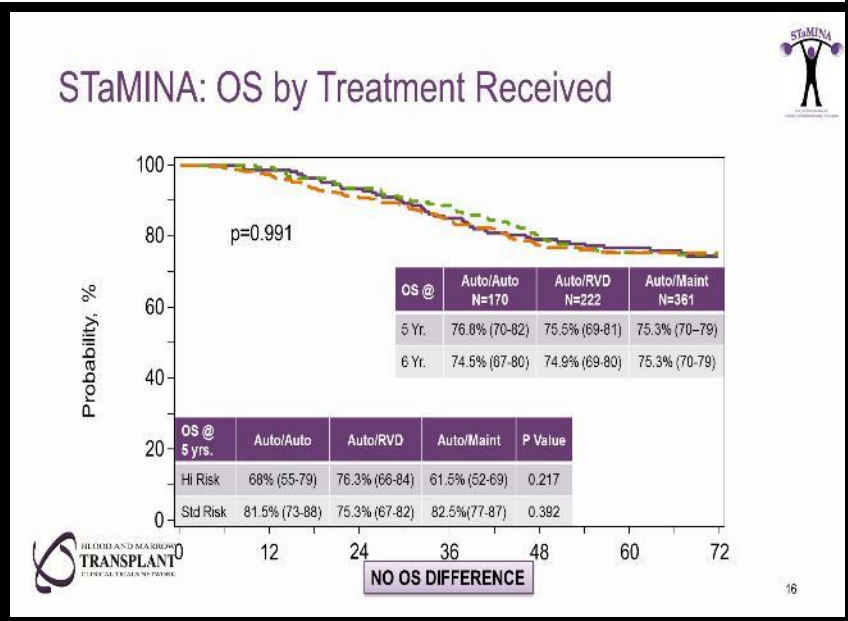
Cavo M, et al. ASH 2017. Oral presentation.

# Tandem ASCT in high-risk NDMM patients

**Induction → HDM 1R**

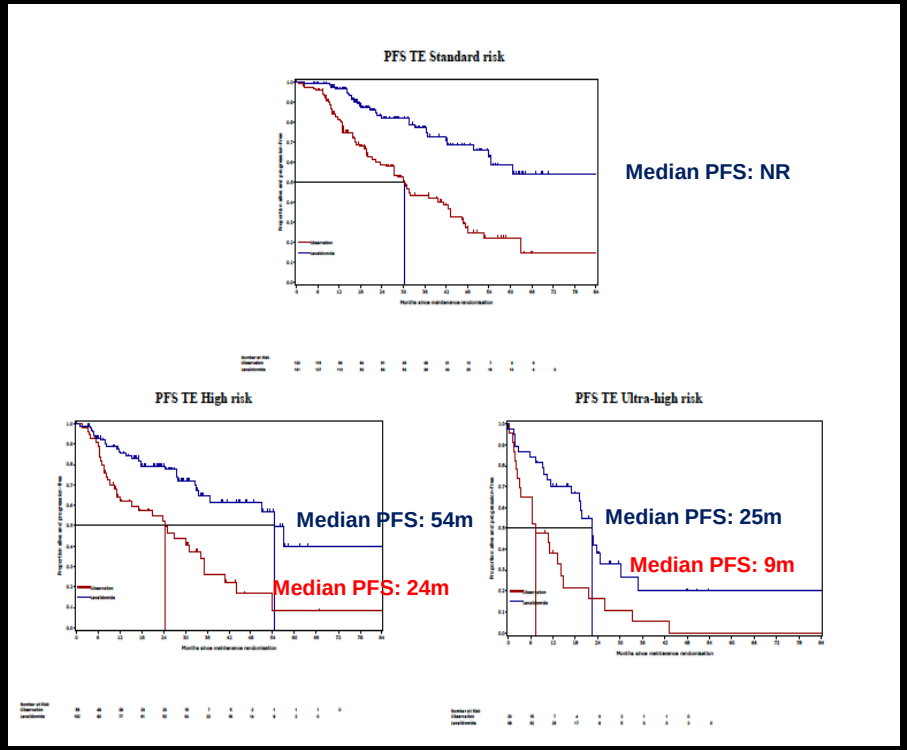
- **No consol → Len maint**
- **RVD × 4c → Len maint**
- **HDM → Len maint**

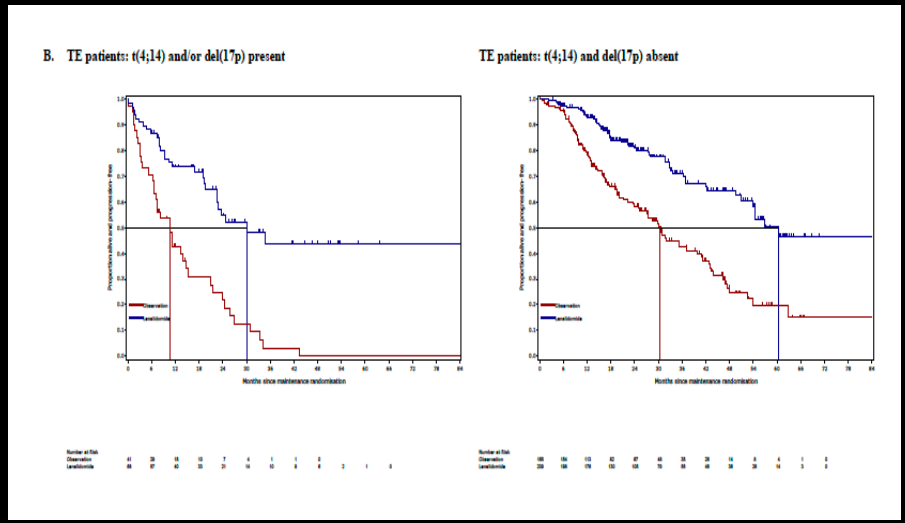



Hari P, et al. ASCO 2020.

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



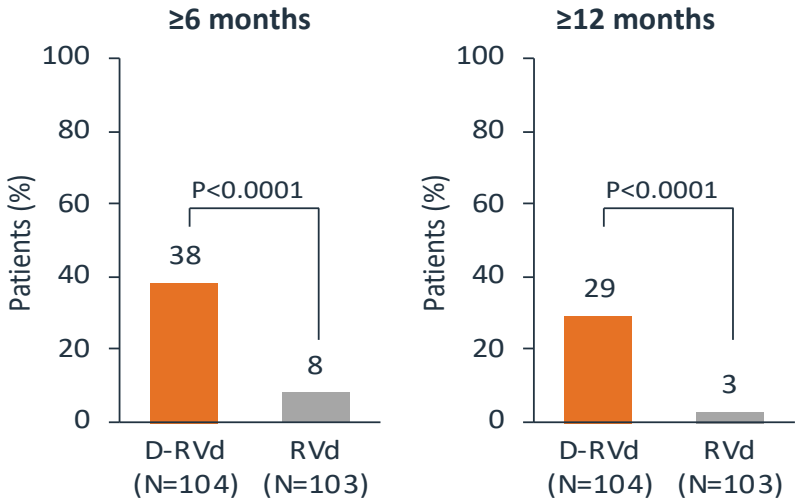

**Lenalidomide improves the outcome of patients with HR or ultra HR, but does not overcome its poor prognosis.**

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

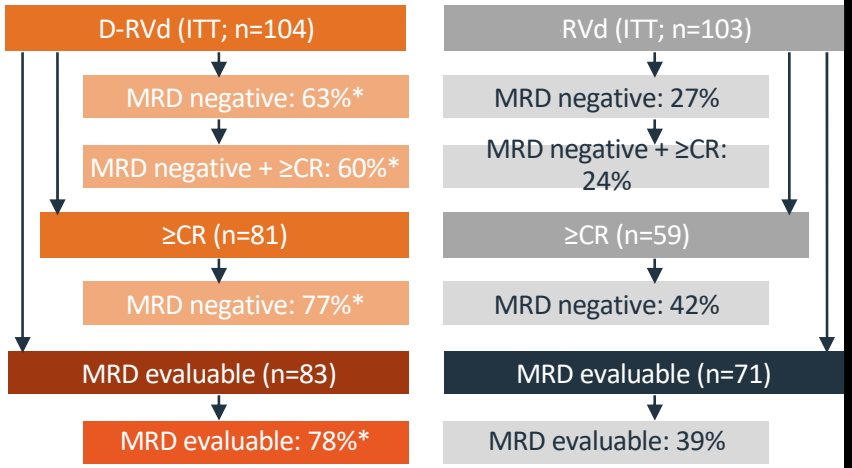
# New options for maintenance in HR-NDMM transplant eligible

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

## MRD negativity at ≥6 and ≥12 months




## MRD negativity at 12-month maintenance cutoff



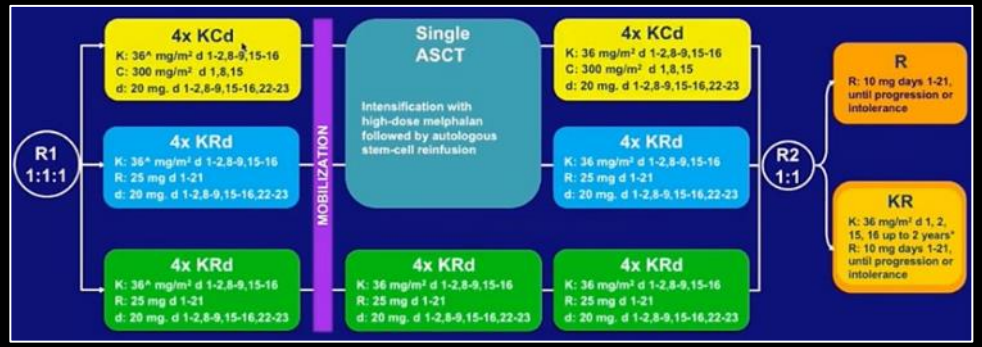

*P<0.0001 for all comparisons

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

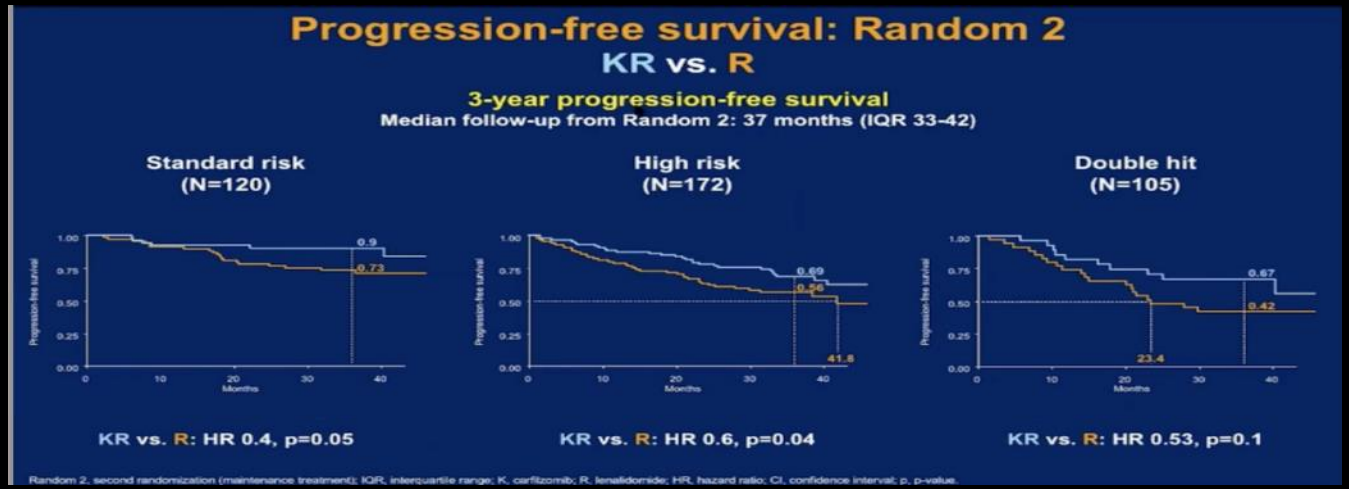
CR, complete response; D-RVd, daratumumab, lenalidomide, bortezomib, dexamethasone; ITT, intention to treat; MRD, minimal residual disease; RVD, lenalidomide, bortezomib, dexamethasone; sCR, stringent CR.

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

# New options for maintenance in HR-NDMM transplant eligible

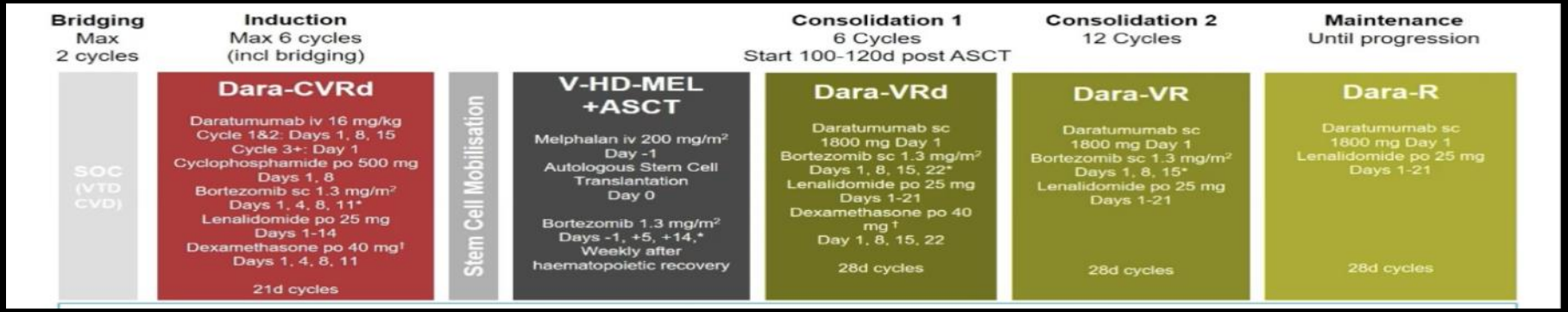



- KR maintenance improves PFS compared with R in all patients
- No significant toxicity signal
- Disadvantages: 4 days of infusion, HR still does worse than SR



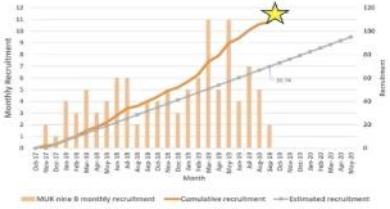

Gay F, et al. ASCO 2021.

# OPTIMUM trial

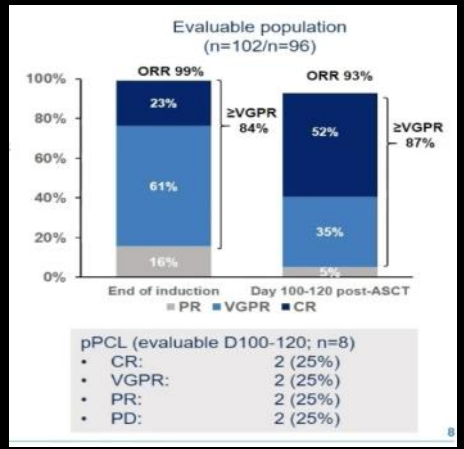


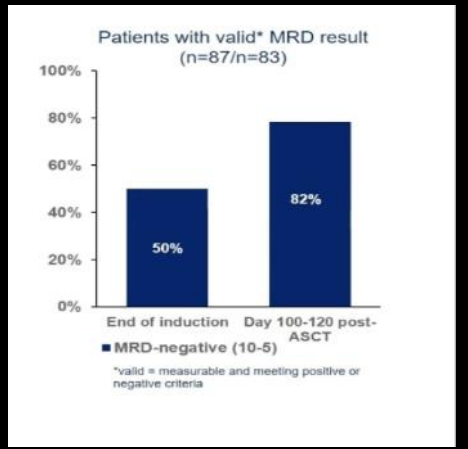

## Trial population

- 472 patients entered OPTIMUM Screen
- Recruitment September 2017 to July 2019
- 39 UK NHS hospitals
- 128 with Ultra High-Risk features
- 10 primary plasma cell leukaemia
- 107 consented and eligible for OPTIMUM Treat



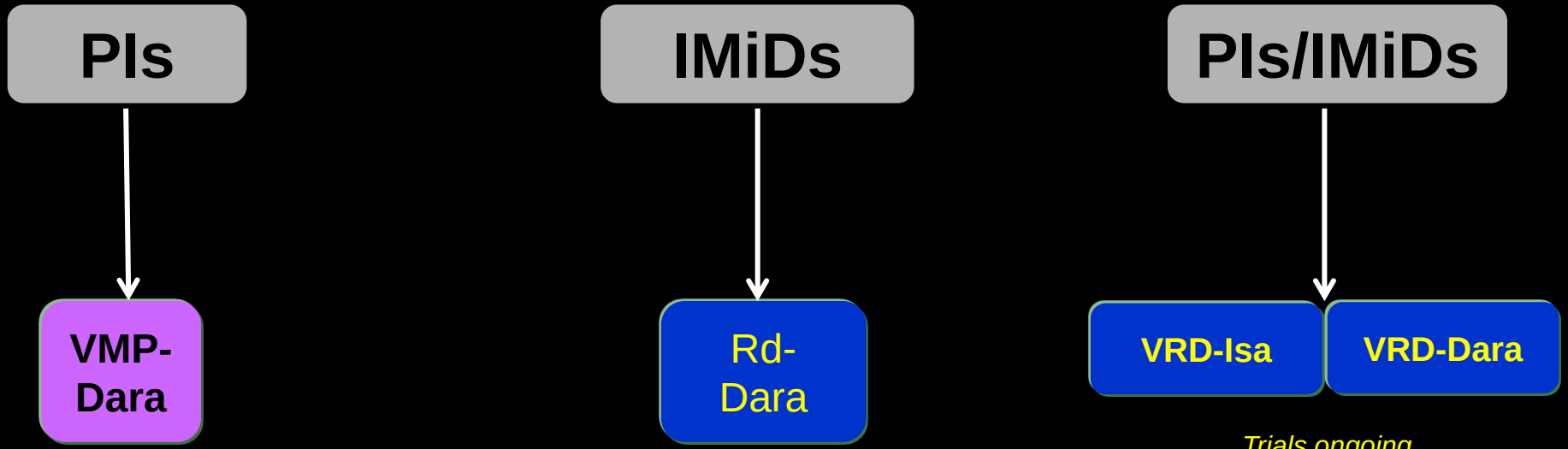

| Patient Characteristics | Safety population (n=107) |
|---|---|
| Median age, yrs (IQR) | 60 (35-78) |
| Male, n (%) | 64 (60%) |
| ISS Stage 1, n (%) | 29 (27%) |
| Stage 2, n (%) | 44 (40%) |
| Stage 3, n (%) | 34 (32%) |
| missing, n (%) | 1 (1%) |
| ECOG Performance Status | |
| 0, n (%) | 51 (48%) |
| 1, n (%) | 42 (39%) |
| 2, n (%) | 10 (9%) |
| missing, n (%) | 4 (4%) |
| Received bridging induction therapy, n (%) | 86 (80%) |
| Double hit genetics, n (%) | 57 (53%) |
| SKY92 risk signature present, n (%) | 83 (77%) |
| Both Double hit and SKY92, n (%) | 33 (31%) |




Kaiser M, et al. ASCO 2021.

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



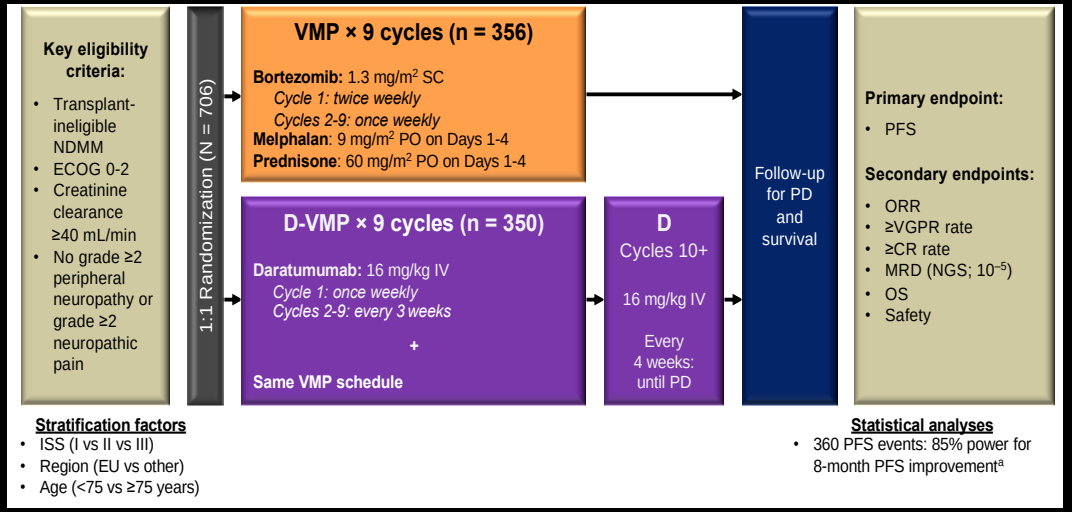

**ALCYONE trial**[1]

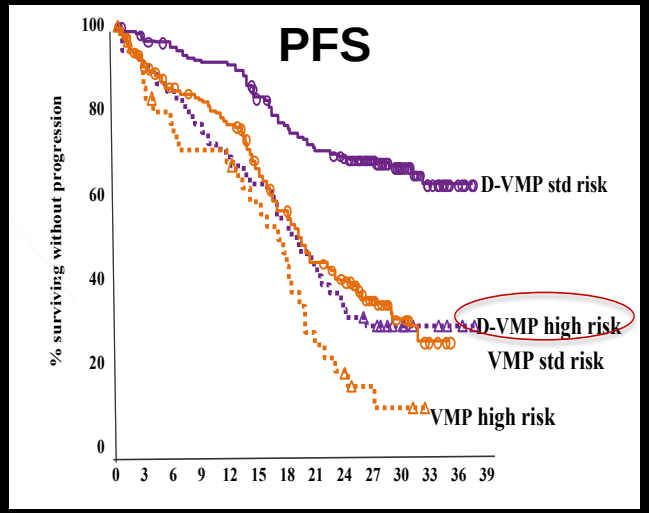
**MAIA trial**[2]

**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

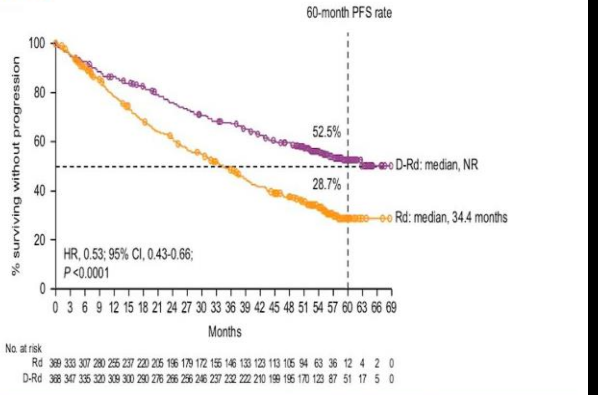
**Rd (n = 369)**
R: 25 mg PO daily on Days 1-21 until PD
d: 40 mg[b] PO or IV weekly until PD

**Primary endpoint:**
- PFS

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

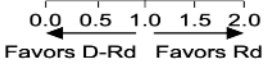
**ORR: 93% vs 81%**
**CR: 48% vs 25%**
**PFS at 28 mo: 71% vs 56%**
**15% with HR CA**

## Updated PFS




- D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd
- These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible

| | 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.

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

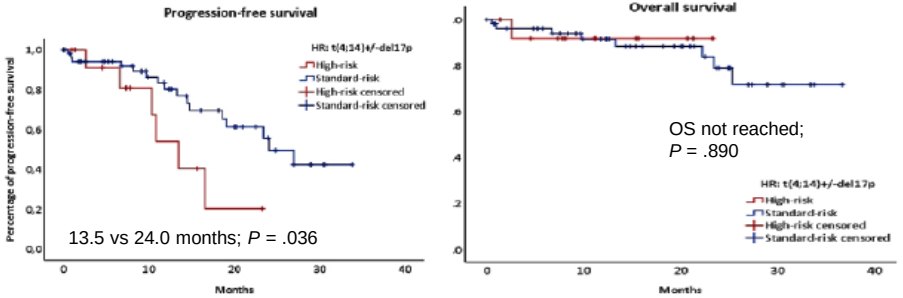
- Median age: 75 years
- Median follow-up: 15.7 months

## Response rate by risk group

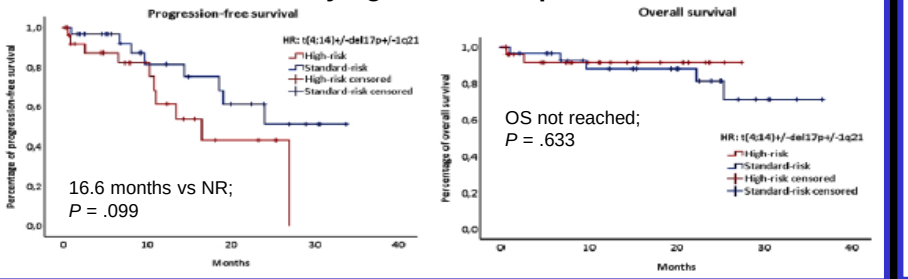
| Response | SR patients without HR (n=49) | HR patients (n=11) | SR patients without HR ± 1q21 (n=29) | HR ± 1q21 (n=20) |
|---|---|---|---|---|
| ORR | 93.9% | 100% | 89.6% | 100% |
| PR | 16.3% | 27.3% | 17.2% | 20.0% |
| VGPR | 38.8% | 36.4% | 48.3% | 25.0% |
| CR | 38.8% | 36.4% | 24.1% | 55.0%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

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

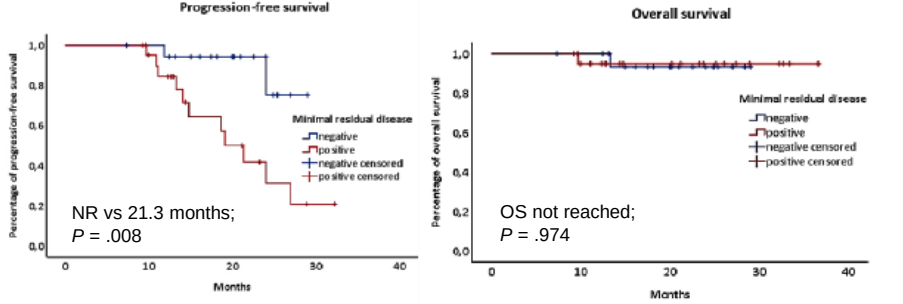
## PFS was shorter in HR patients; no difference in OS was seen




## 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



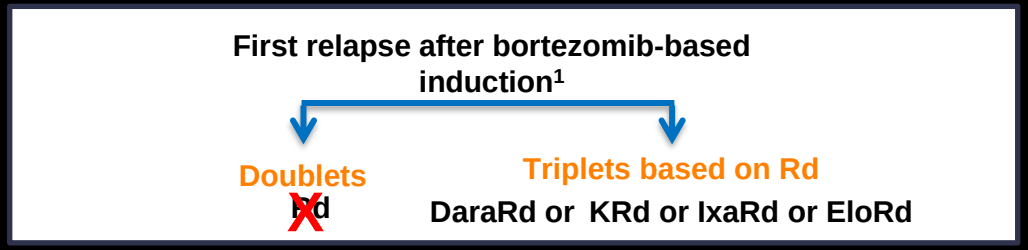

CR, complete response; HR, high risk; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SR, standard risk; VGPR, very good partial response.

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**



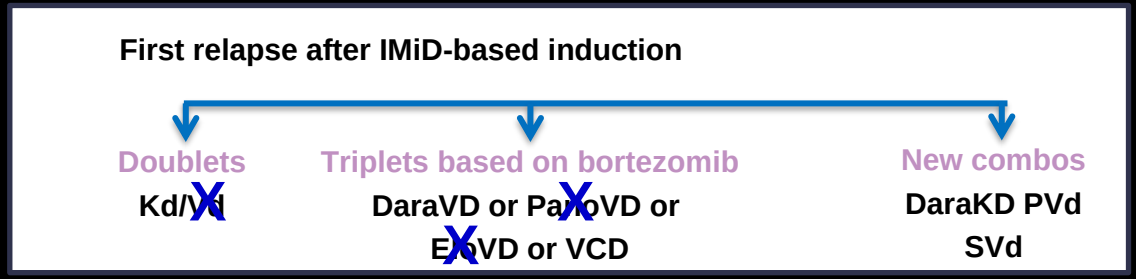

| Efficacy | POLLUX DaraRd vs Rd[2,3] | ASPIRE KRd vs Rd[4,5] | ELOQUENT-2 ERd vs Rd[6] | TOURMALINE-MM1 IRd vs Rd[7] |
|---|---|---|---|---|
| PFS HR (95% CI) | 0.44 (0.35–0.55)<br>44.5 vs 17.5 mo | 0.69 (0.57–0.83)<br>26.3 vs 17.6 mo | 0.71 (0.59–0.86)<br>19.4 vs 14.9 mo | 0.74 (0.59–0.94)<br>20.6 vs 14.7 mo |
| OS HR (95% CI) | 0.63 (0.42–0.95) | 0.79 (0.63–0.99)<br>48 vs 40 mo | 0.78 (0.63–0.96)<br>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**



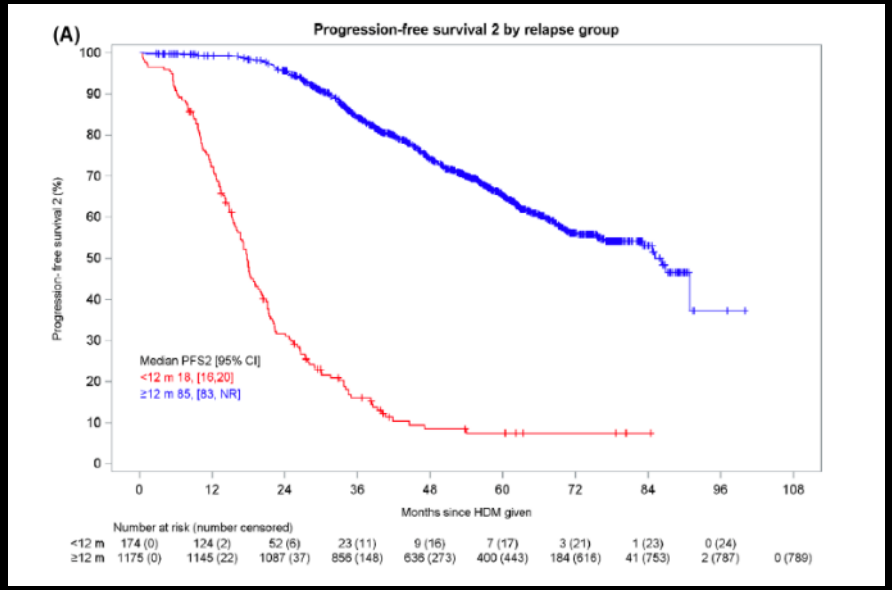

| Efficacy | ENDEAVOR [1] (n = 929) Kd vs Vd | CASTOR [2] (n = 499) DaraVd vs Vd | CANDOR [3] (n = 466) DaraKd vs Kd | OPTIMISMM [4] (n = 559) PVd vs Vd | BOSTON [5] (n = 402) SVd vs Vd |
|---|---|---|---|---|---|
| PFS HR (95% CI) | 0.53 (0.44 – 0.63)<br>18.7 vs 9.4 m | 0.31 (0.25 – 0.40)<br>16.7 vs 7.1 m | 0.59 (0.45–0.78)<br>28.6 vs 15.2 | 0.61 (0.49–0.77)<br>11.2 vs 7.1 | 0.67<br>13.9 vs 9.4 |
| OS HR (95% CI) | 0.79 (0.65–0.96)<br>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]) |

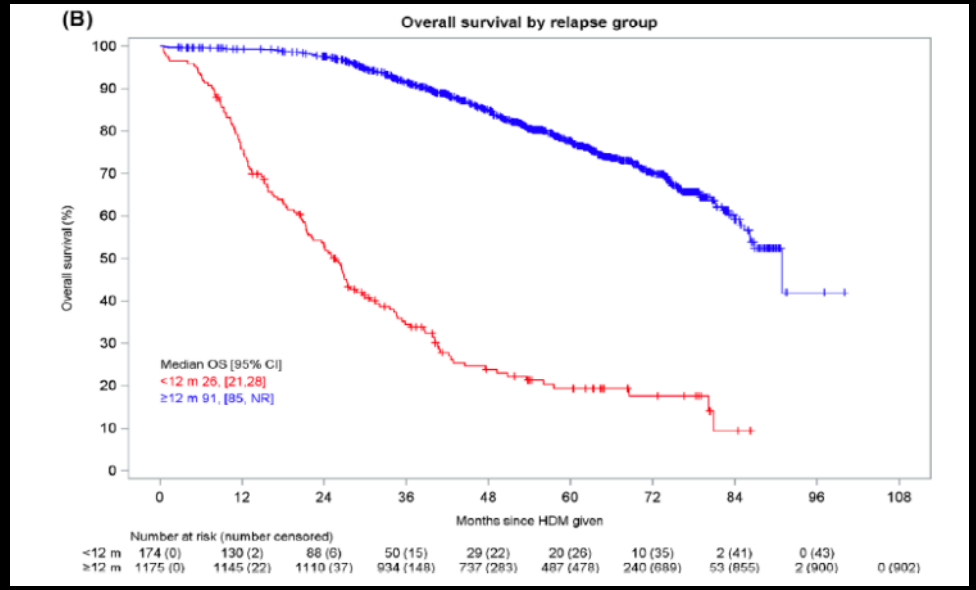
1. Dimopoulos M, et al. *Lancet Oncol.* 2016;17:27-38; 2. Palumbo A, et al. *N Engl J Med.* 2016;375:754-766; 3. Dimopoulos M, et al. *Lancet.* 2020;396:186-197; 4. Richardson PG, et al. *Lancet Oncol.* 2019;20(6):781-794; 5. Grosicki S, et al. *Lancet.* 2020;396:1563-1573.

**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

# Early relapse after HDM-ASCT as predictor of inferior survival and associated with high tumor disease burden and disease of high risk from the cytogenetic point of view



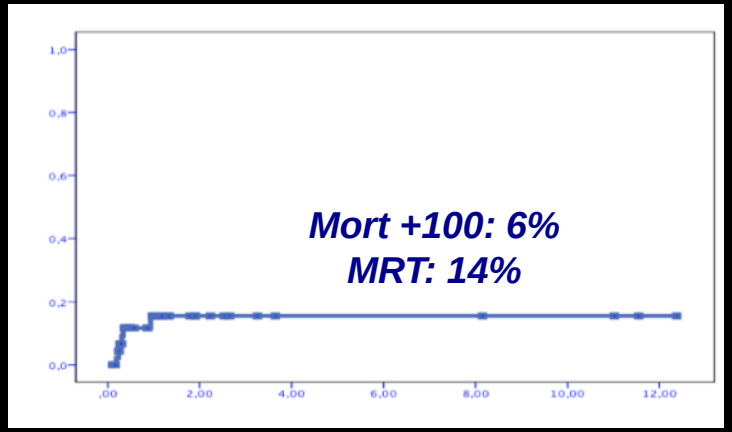

**Early relapsers presented with**

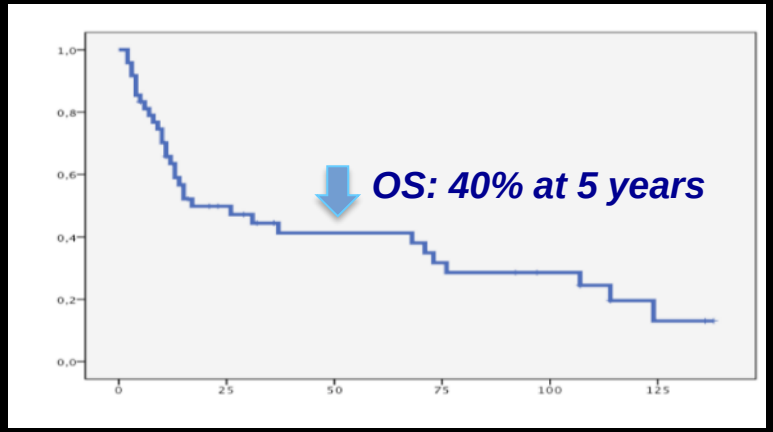
Lower levels of Hb, platelets, higher PBMC infiltration, higher B2M, ISS-3, and HR or ultra-HR CA

Bygrave C, et al. *Br J Haematol.* 2021;193(3):551-555.

# 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**

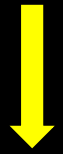
***Allo-transplant can be a therapeutic option in selected patients, but it is key to do immunosuppression manipulation (withdrawal, DLI, . . .) in order to develop graft-versus-myeloma.***

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**



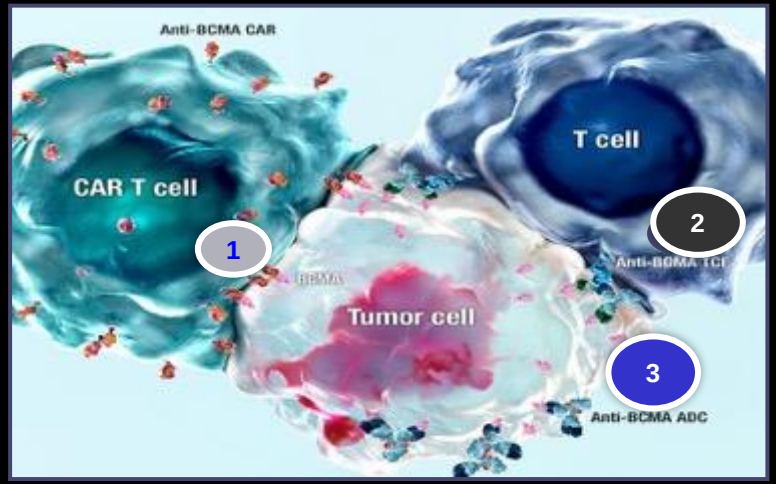
***Modern approach***

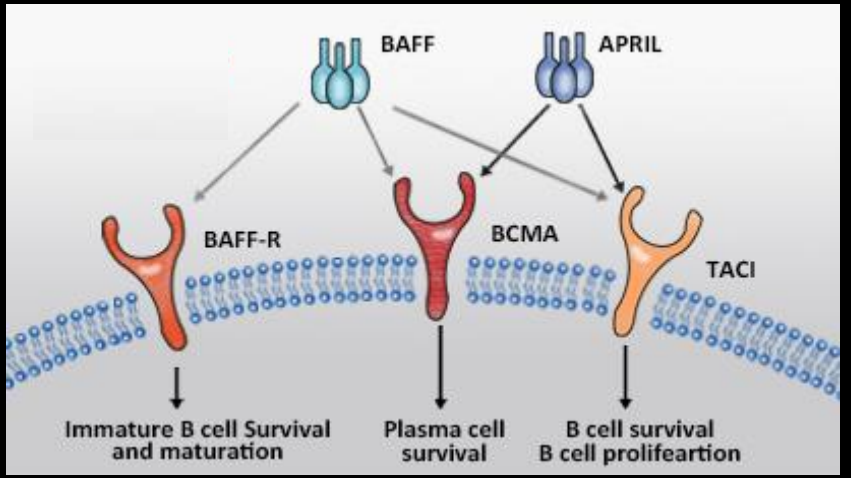
***"Overcome drug resistance"***

**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]**

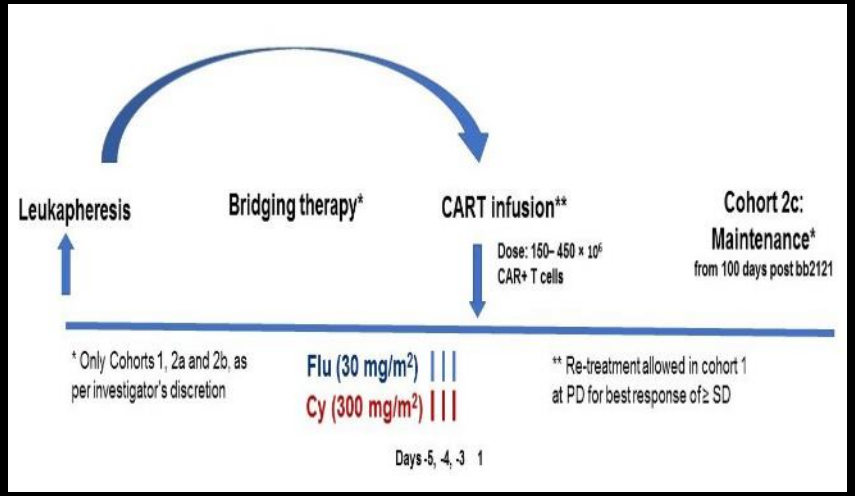
**Belantamab mafodotin monotherapy is an ADC approved for patients with RRMM with ≥4 prior therapies, whose disease is refractory to ≥1 PI, IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy[1]**

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

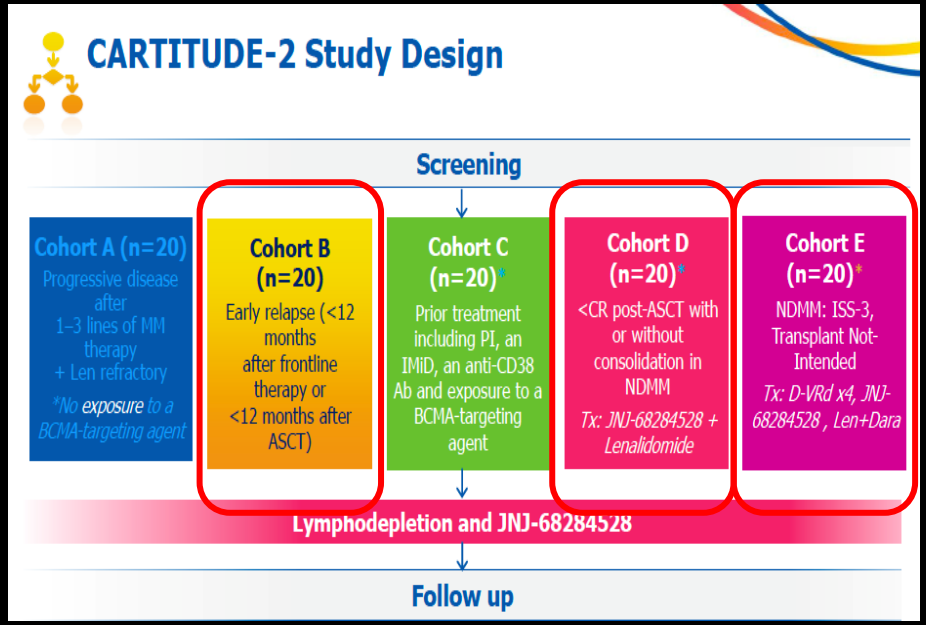
1. https://www.ema.europa.eu/en/documents/product-information/blenrep-epar-product-information_en.pdf;
2. Yu B, et al. *J Hematol Oncol.* 2020;doi:10.1186/s13045-020-00962-7.

# 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.

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

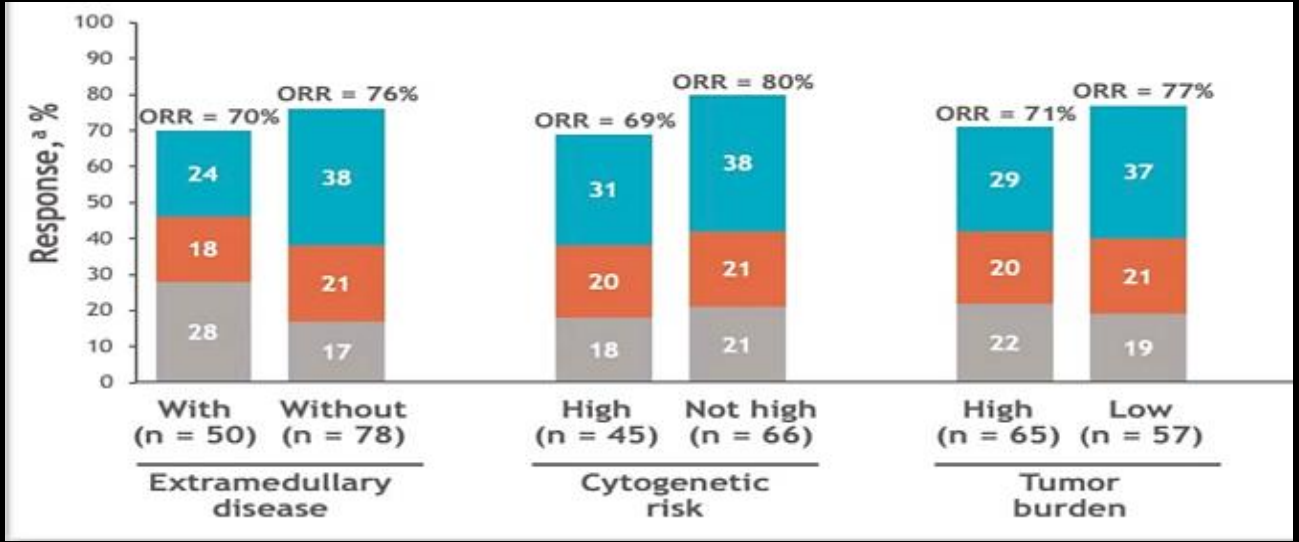
| | Ide-cel[1] (all treated) (N = 128) | Cilta-cel[2] (N = 97) |
|---|---|---|
| Follow-up, median | 13.3 mo (0.2–21) | 12.4 mo (1.5–24.9) |
| Prior lines of therapy, median (range) | 6 (3–16) | 6 (3–18) |
| Triple refractory | 84% | 87% |
| Extramedullary disease (EMD) | 39% | 13% |
| High-risk cytogenetics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

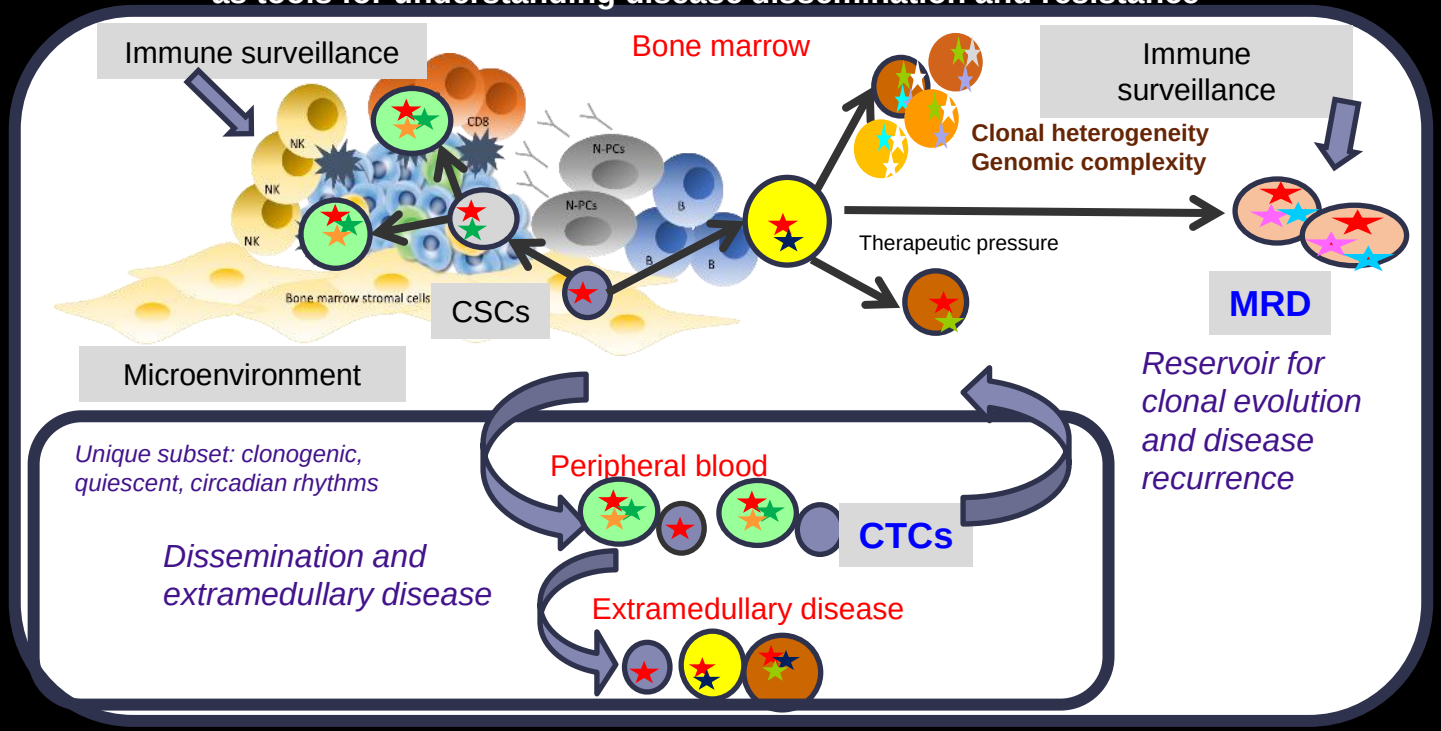
ORR, overall response rate; UK, unknown.

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.

# 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

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# Management of Early Relapse of Multiple Myeloma

Rafael Fonseca, MD

APTITUDE HEALTH®

MAYO CLINIC

# Rafael Fonseca, MD
# Interim Executive Director, Mayo Clinic Cancer Center

## MM Early Relapse – 2021

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

MAYO CLINIC

# 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**

@rfonsi1, fonseca.rafael@mayo.edu

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# PRESENTATION QUESTION

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# Early RR MM Question

- **Which of the following is not true in the treatment of RR MM?**
  - **a) In a direct comparison in RR MM, carfilzomib is superior to bortezomib**
  - **b) The addition of daratumumab to bortezomib and dexamethasone does not improve outcomes**
  - **c) Adding oral proteasome inhibitors can augment the depth of response to lenalidomide and dexamethasone**
  - **d) Cyclophosphamide can be combined effectively with proteasome inhibitors in RR MM**
  - **e) Both lenalidomide and pomalidomide can be combined with daratumumab**

@rfonsi1, fonseca.rafael@mayo.edu

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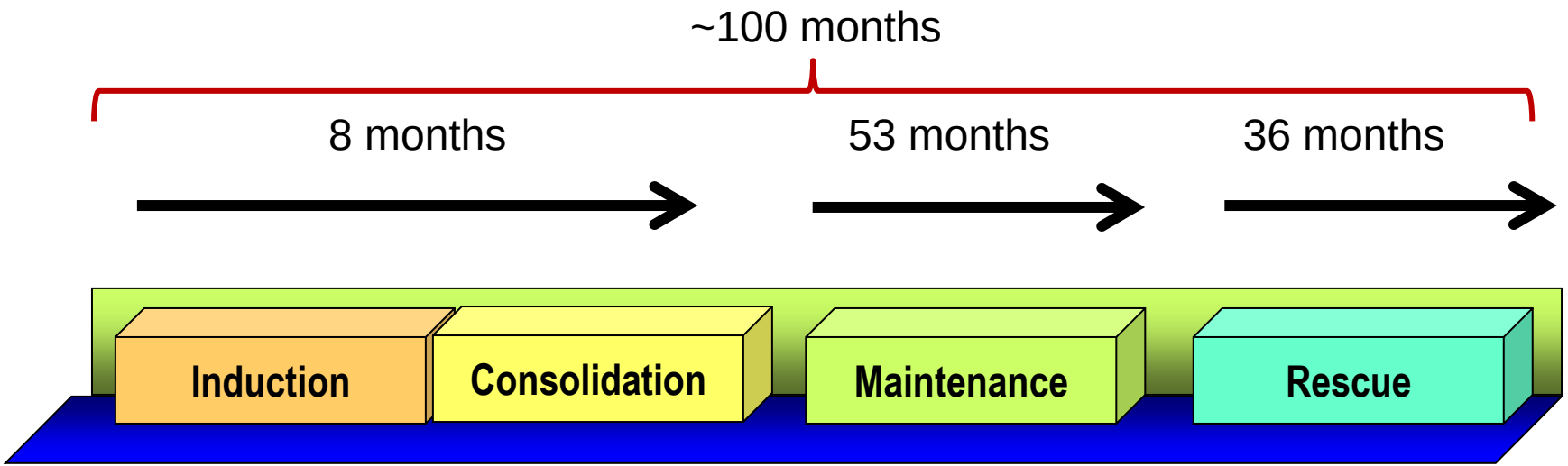
# Multiple Myeloma Treatment Lines 2021




@rfonsi1, fonseca.rafael@mayo.edu

Fonseca R, unpublished.

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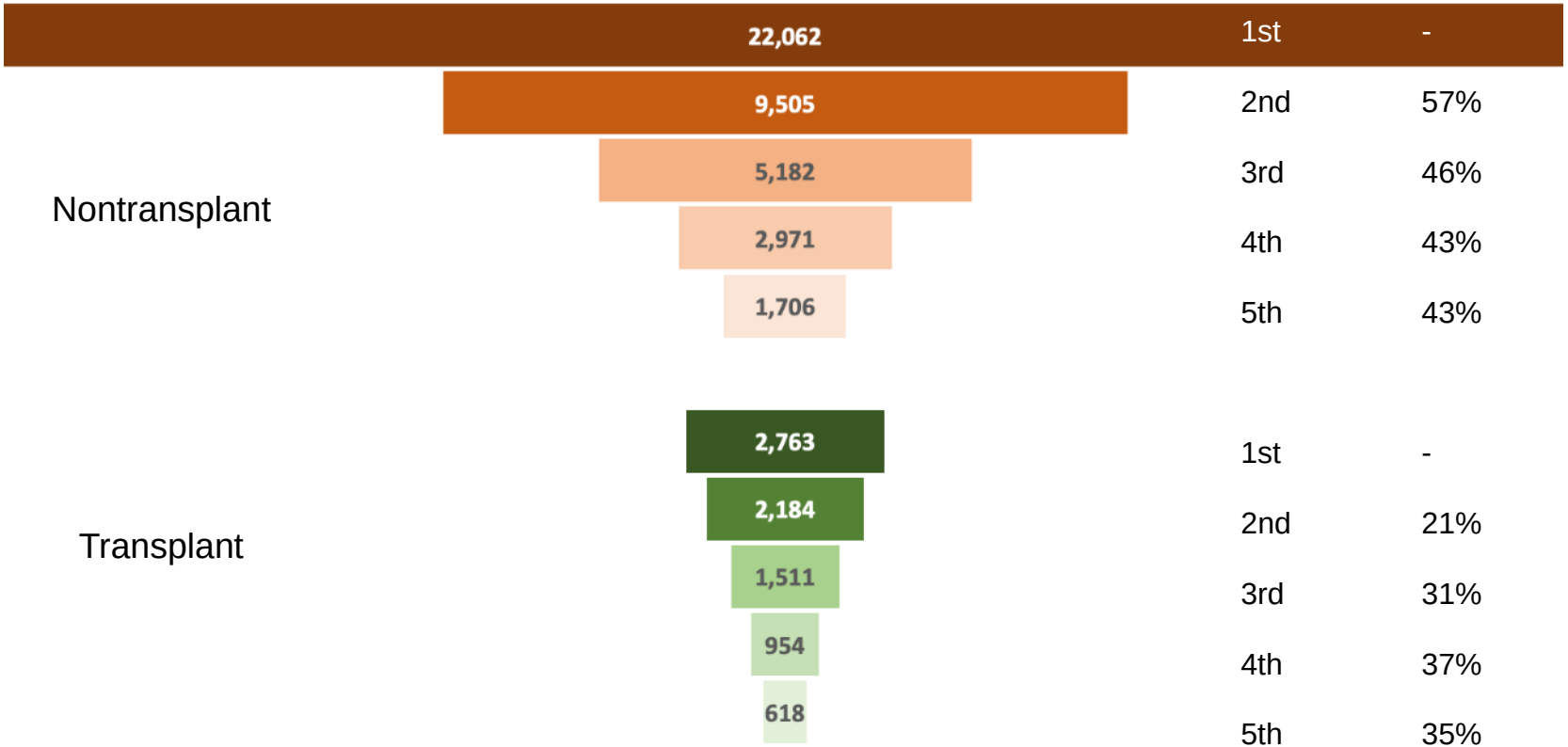
# Attrition With Subsequent Treatment




@rfonsi1, fonseca.rafael@mayo.edu

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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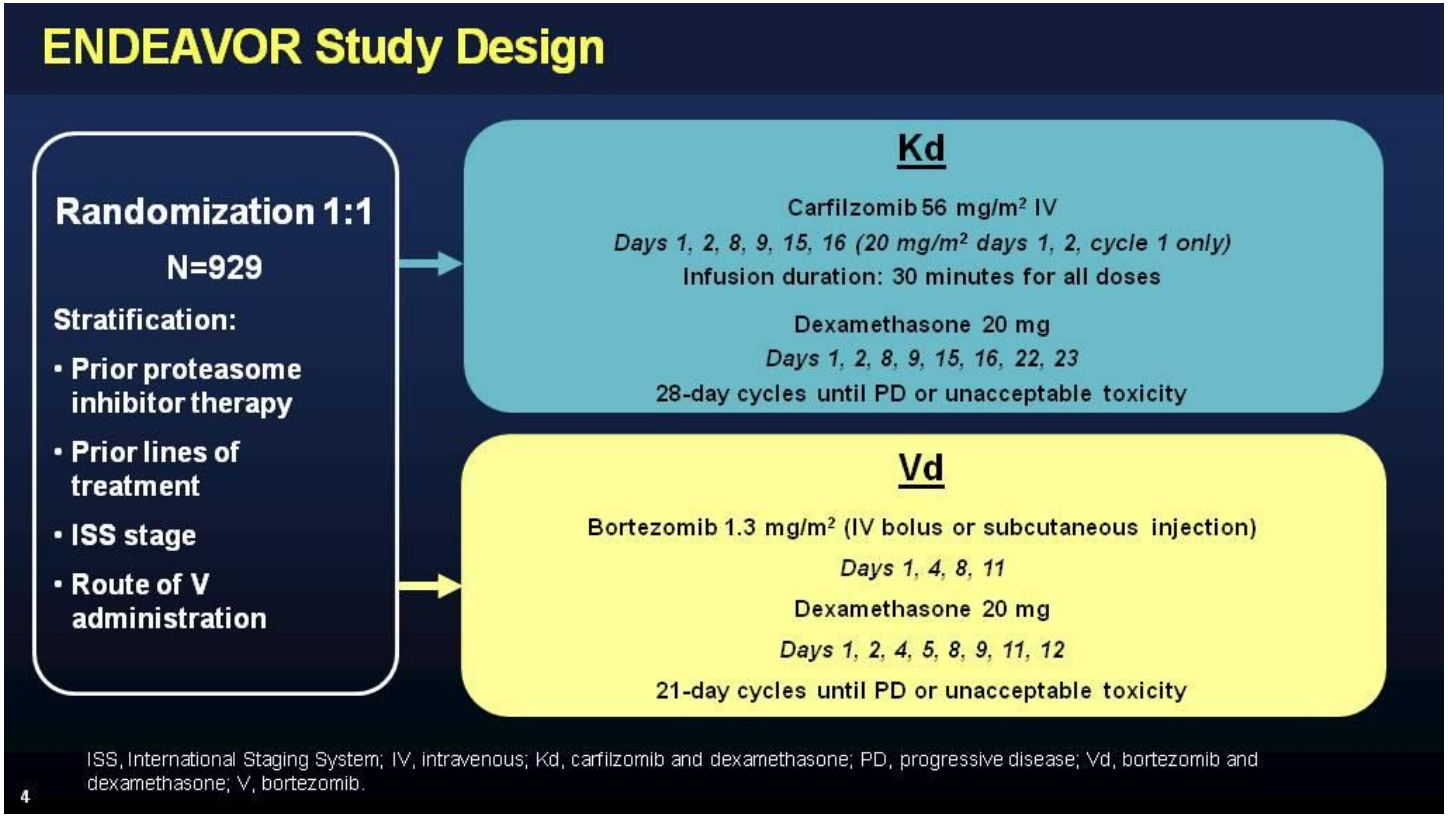
# ENDEAVOR: Kd vs Vd




@rfonsi1, fonseca.rafael@mayo.edu

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

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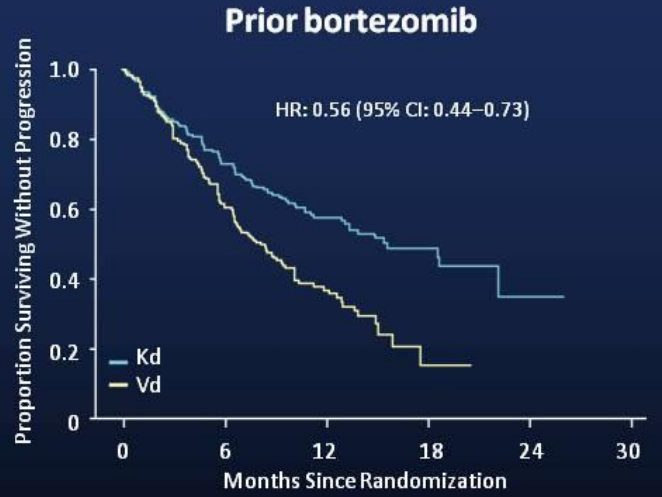
# ENDEAVOR: Kd vs Vd

## 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.

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@rfonsi1, fonseca.rafael@mayo.edu

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

@rfonsi1, fonseca.rafael@mayo.edu

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

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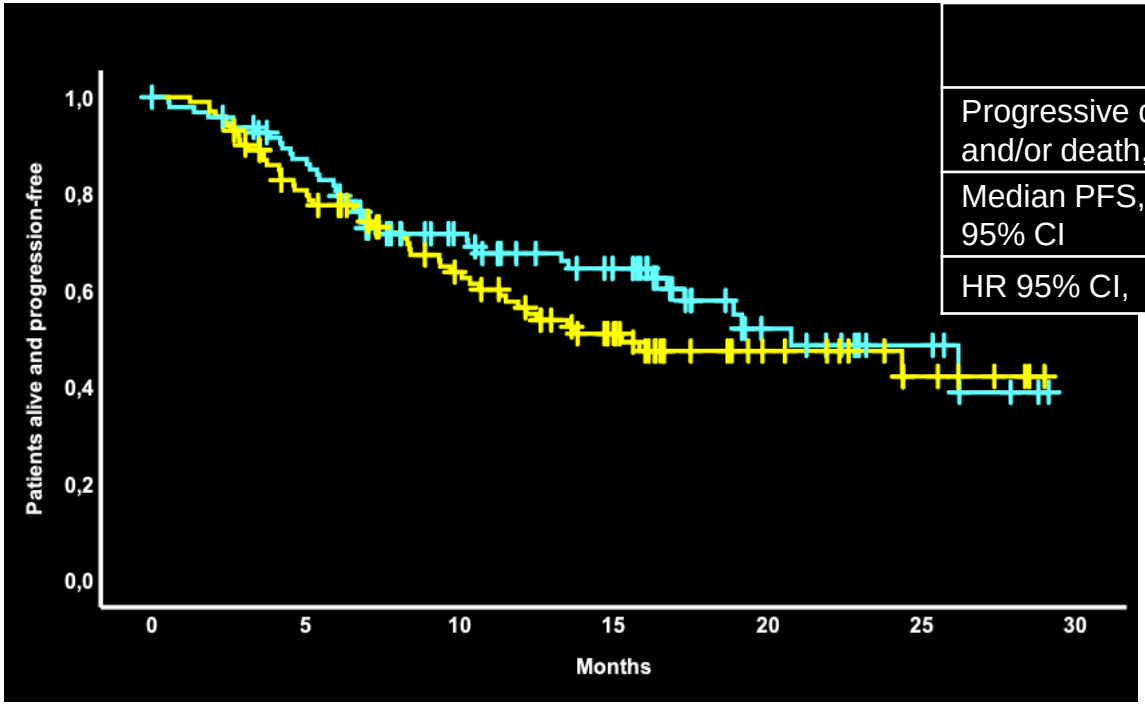
# GEM-KyCydex: PFS

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 | |

@rfonsi1, fonseca.rafael@mayo.edu

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

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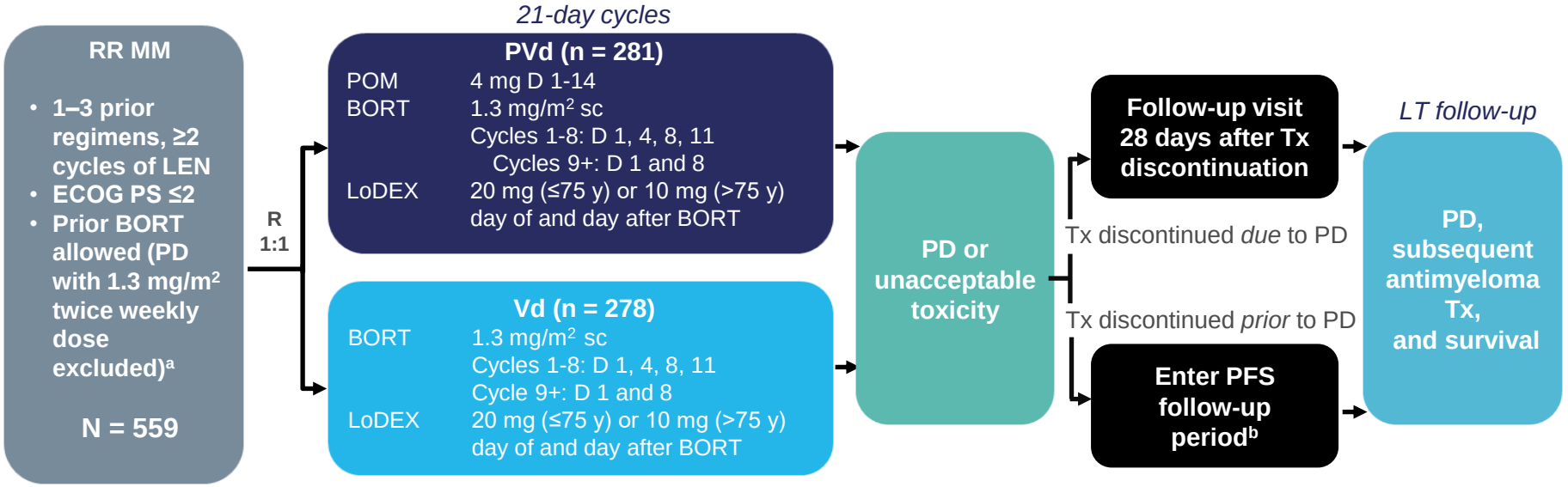
# Phase III OPTIMISMM Study Design




- **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**

@rfonsi1, fonseca.rafael@mayo.edu

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

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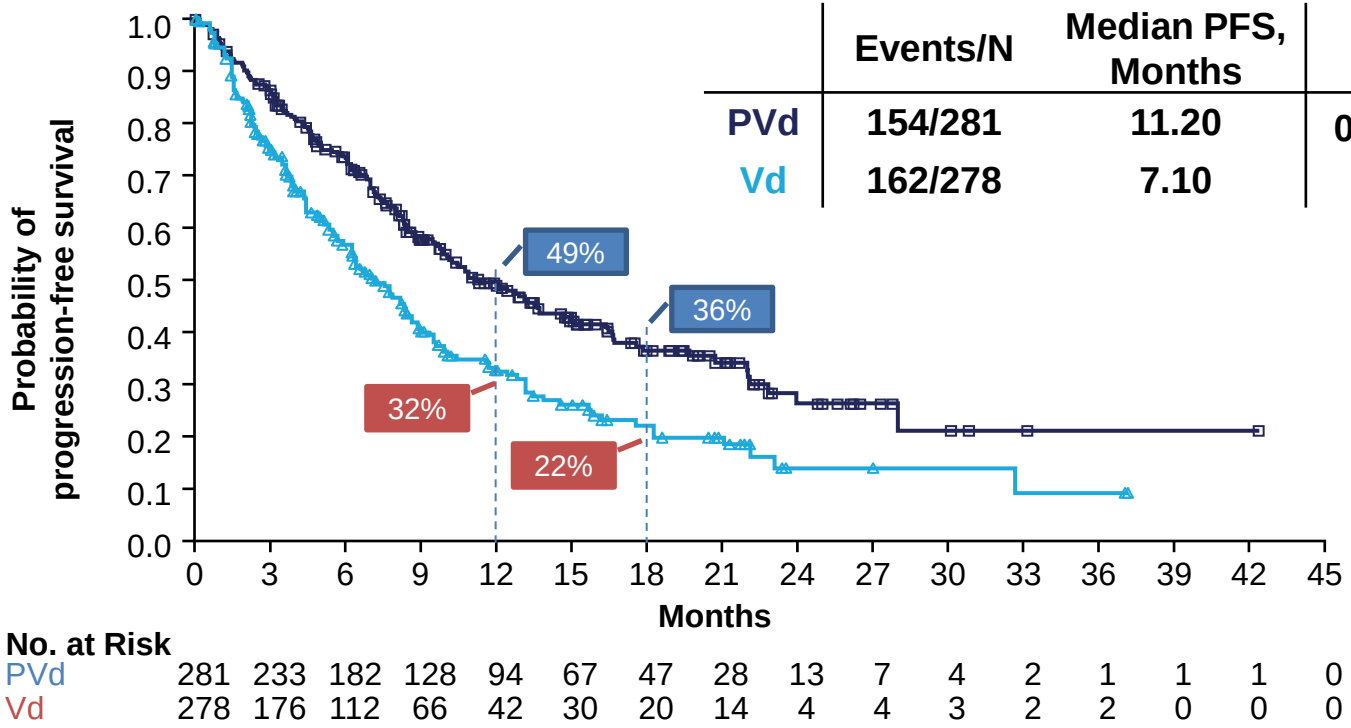
# Progression-Free Survival (ITT)




| | 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**

@rfonsi1, fonseca.rafael@mayo.edu

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

MAYO CLINIC

# TOURMALINE-MM1: Len-Dex ± Ixazomib

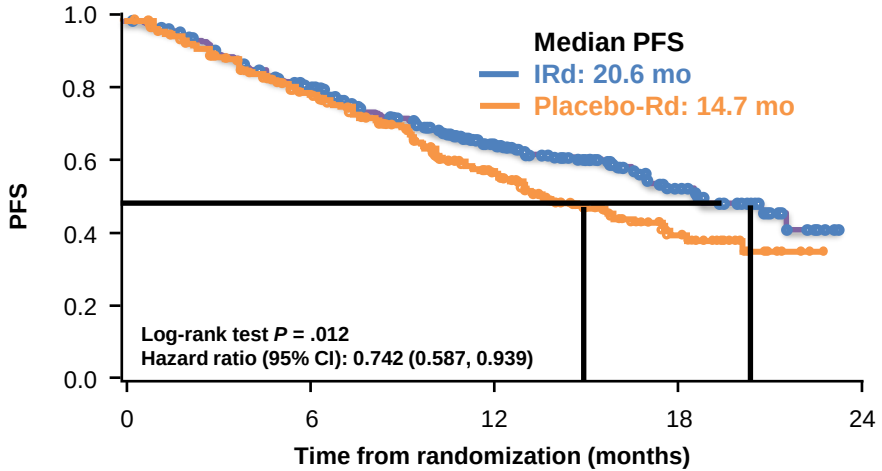
**Ixazomib** 40 mg d1, 8, 15
**Lenalidomide** 25 mg d1-21
**Dexamethasone** d1, 8, 15, 22

**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 |

@rfonsi1, fonseca.rafael@mayo.edu

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

MAYO CLINIC

# ASPIRE: Len-Dex ± Carfilzomib

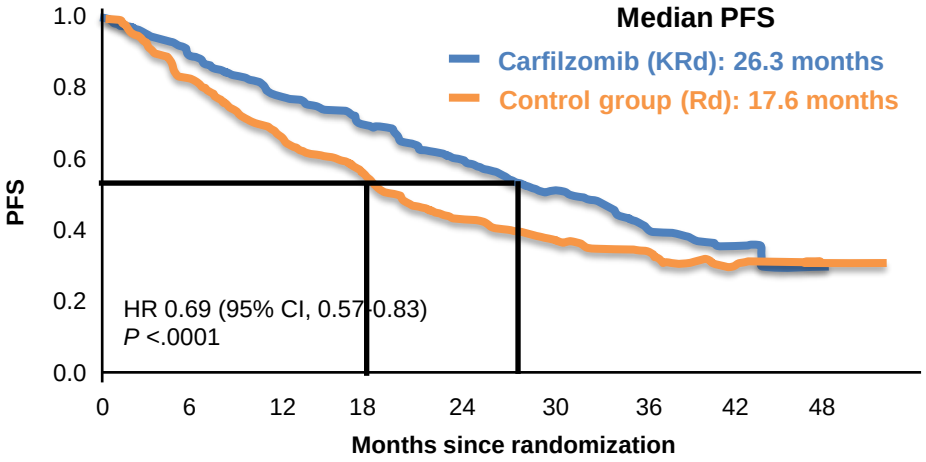
- **Carfilzomib 20 mg/m² (27 mg/m²)**
  - Cycle 1-12: d 1, 2, 8, 9, 15, 16
  - Cycles 13-18: d 1, 2, 15
- **Lenalidomide 25 mg** d1-21
- **Dexamethasone 40 mg** d1, 8, 15, 22

- **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 |

@rfonsi1, fonseca.rafael@mayo.edu

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*

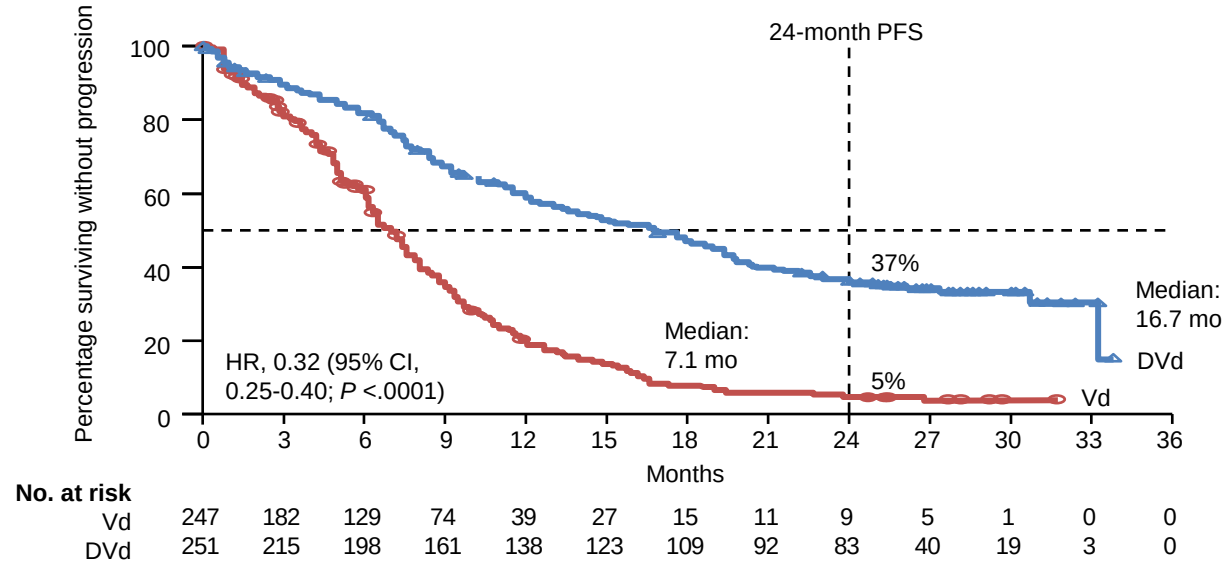


Palumbo A, et al. *N Engl J Med*. 2016;375:754-766.

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.

@rfonsi1, fonseca.rafael@mayo.edu

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

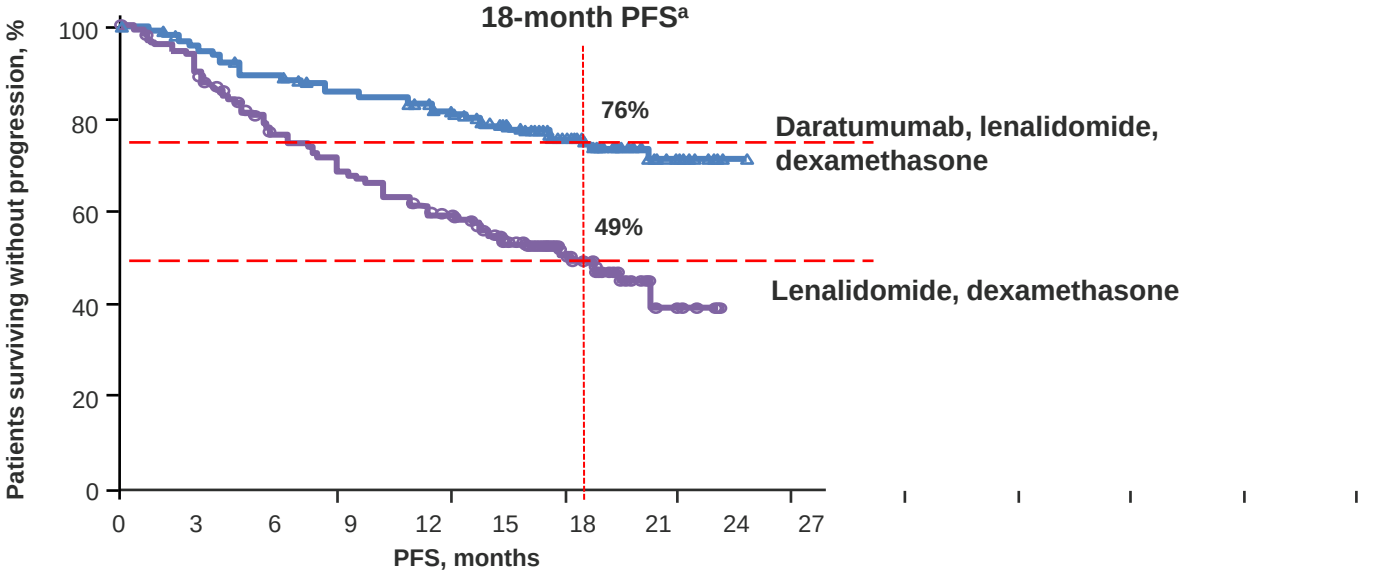
M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau,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

@rfonsi1, fonseca.rafael@mayo.edu

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)**

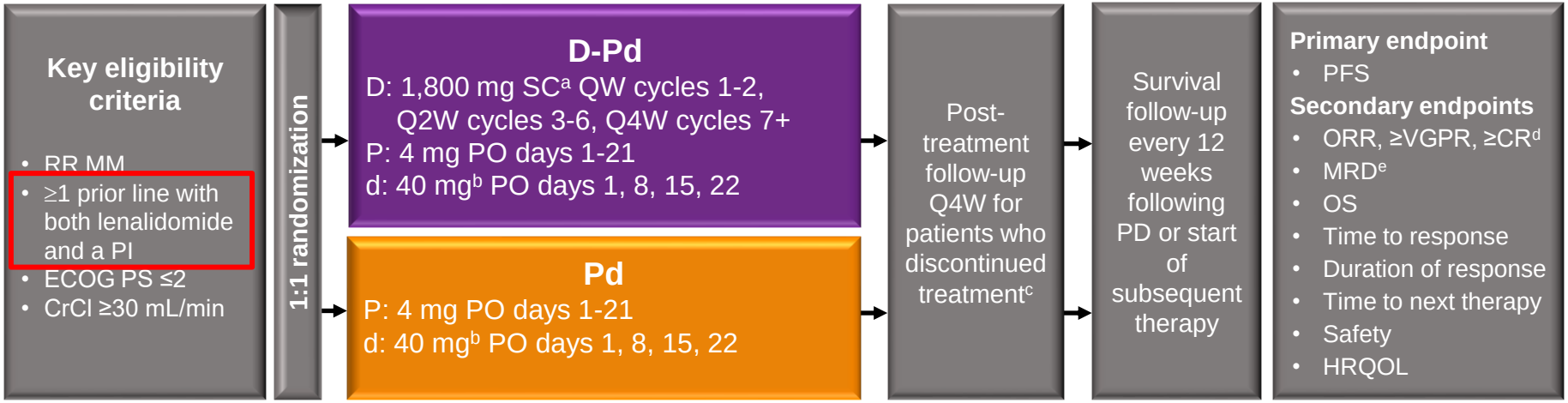
HR, hazard ratio.
[a]Kaplan-Meier estimates.
Clinical cutoff: June 30, 2016.

@rfonsi1, fonseca.rafael@mayo.edu

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)

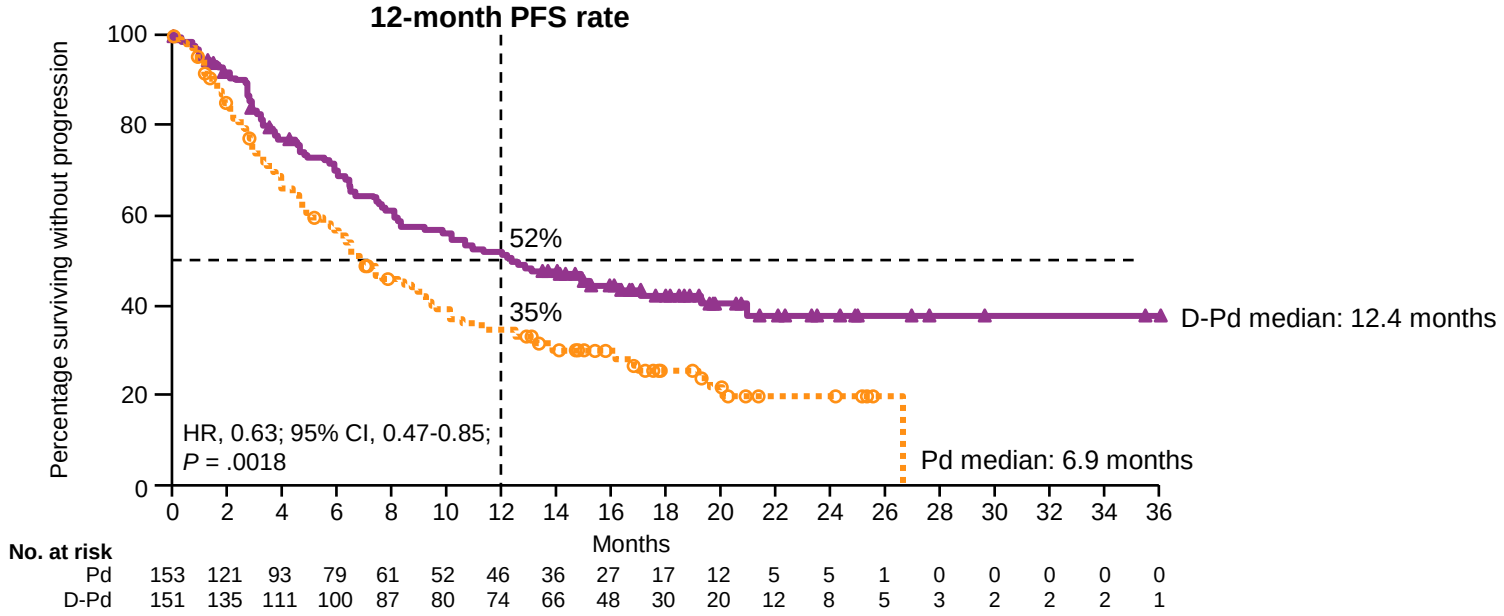
**Cycle duration: 28 days**
**Treatment until PD or unacceptable toxicity**

@rfonsi1, fonseca.rafael@mayo.edu

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

MAYO CLINIC

# APOLLO PFS (FU 16.9 mo)



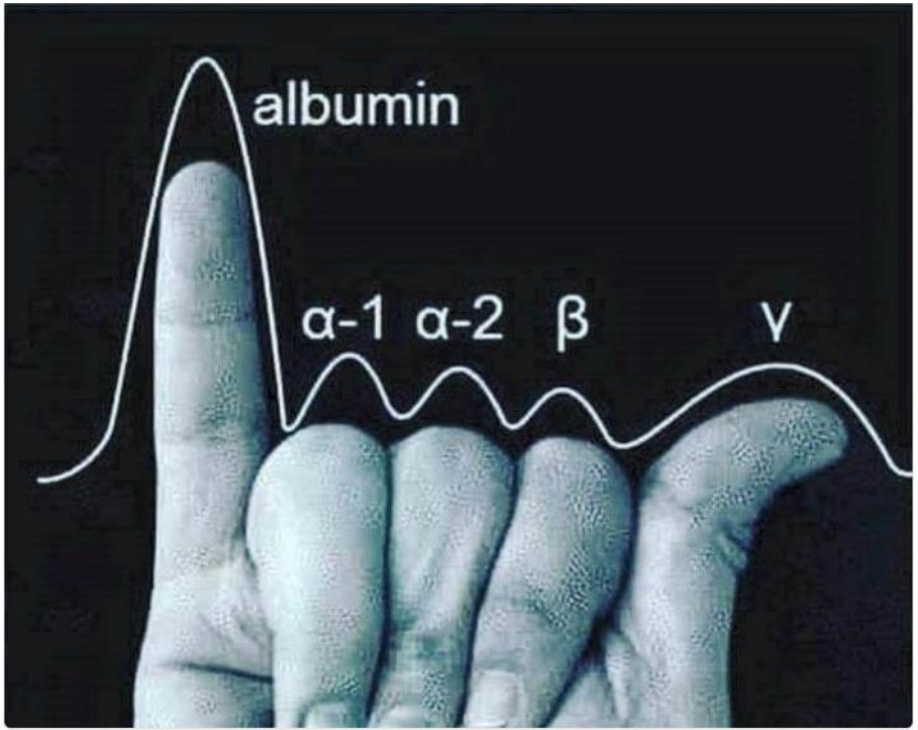

- Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

@rfonsi1, fonseca.rafael@mayo.edu

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

MAYO CLINIC

# Thank you!




@rfonsi1, fonseca.rafael@mayo.edu

Global Multiple Myeloma Academy

# Discussion

APTITUDE HEALTH®

Global Multiple Myeloma Academy

# Management of Heavily Pretreated Multiple Myeloma

Keith Stewart, MBChB, MBA

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?

a) 90%

b) 80%

c) 65%

d) 50%

e) 40%

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

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

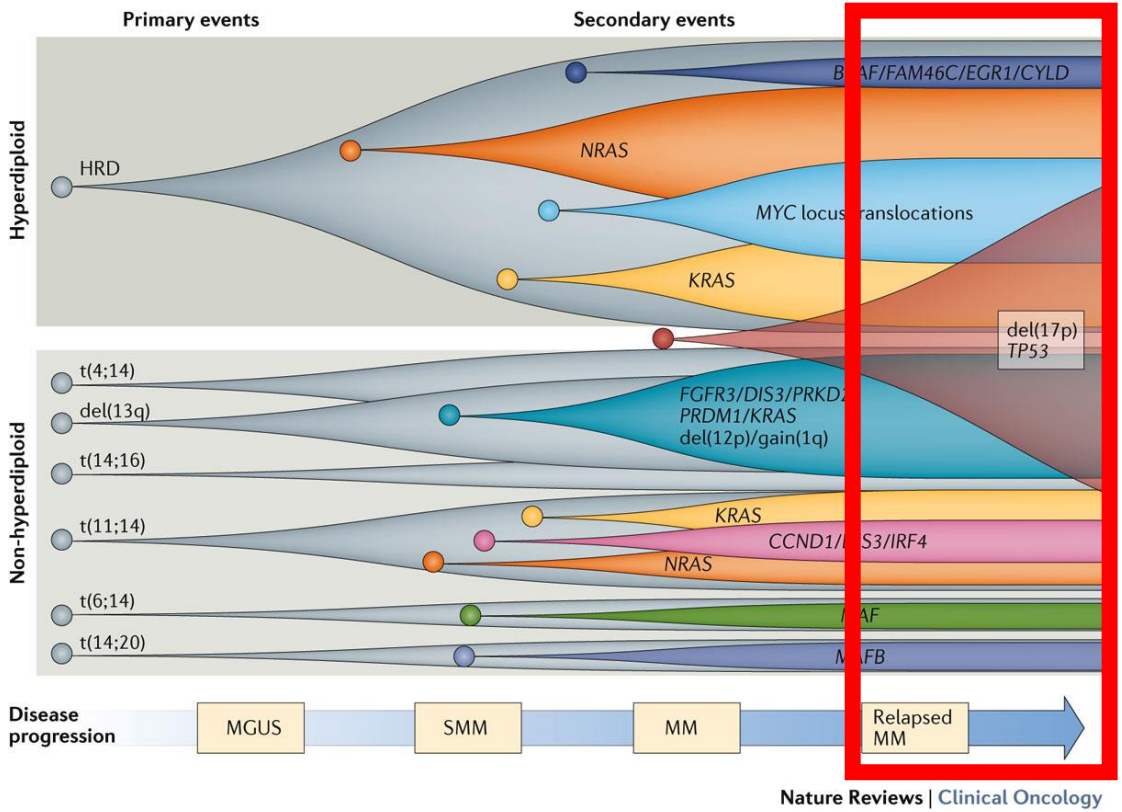
b) A less common but significant toxicity is early onset cytokine release syndrome

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

d) The response rate in first relapse is 72%

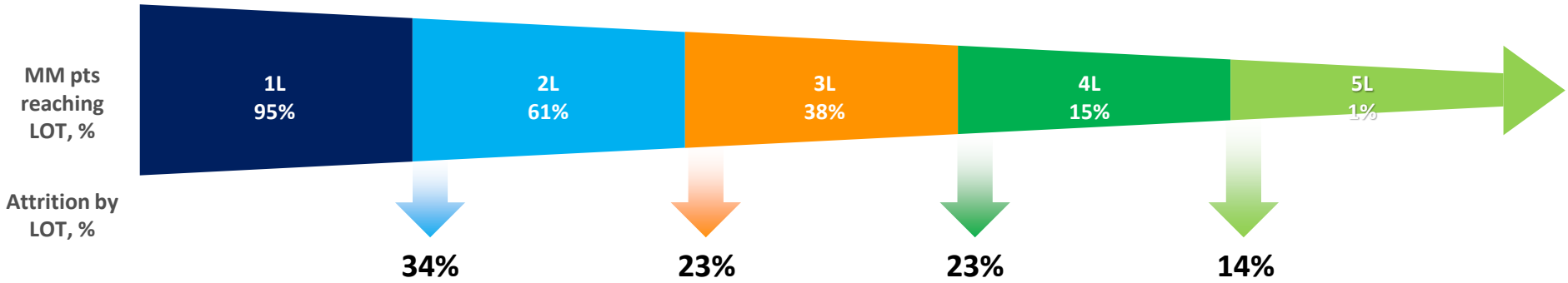
e) Ocular toxicity is manageable with steroid eye drops

# Relapsed MM Is a Biologically and Genetically Heterogeneous Disease




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

# Only a Few MM Patients Reach Later Lines of Therapy



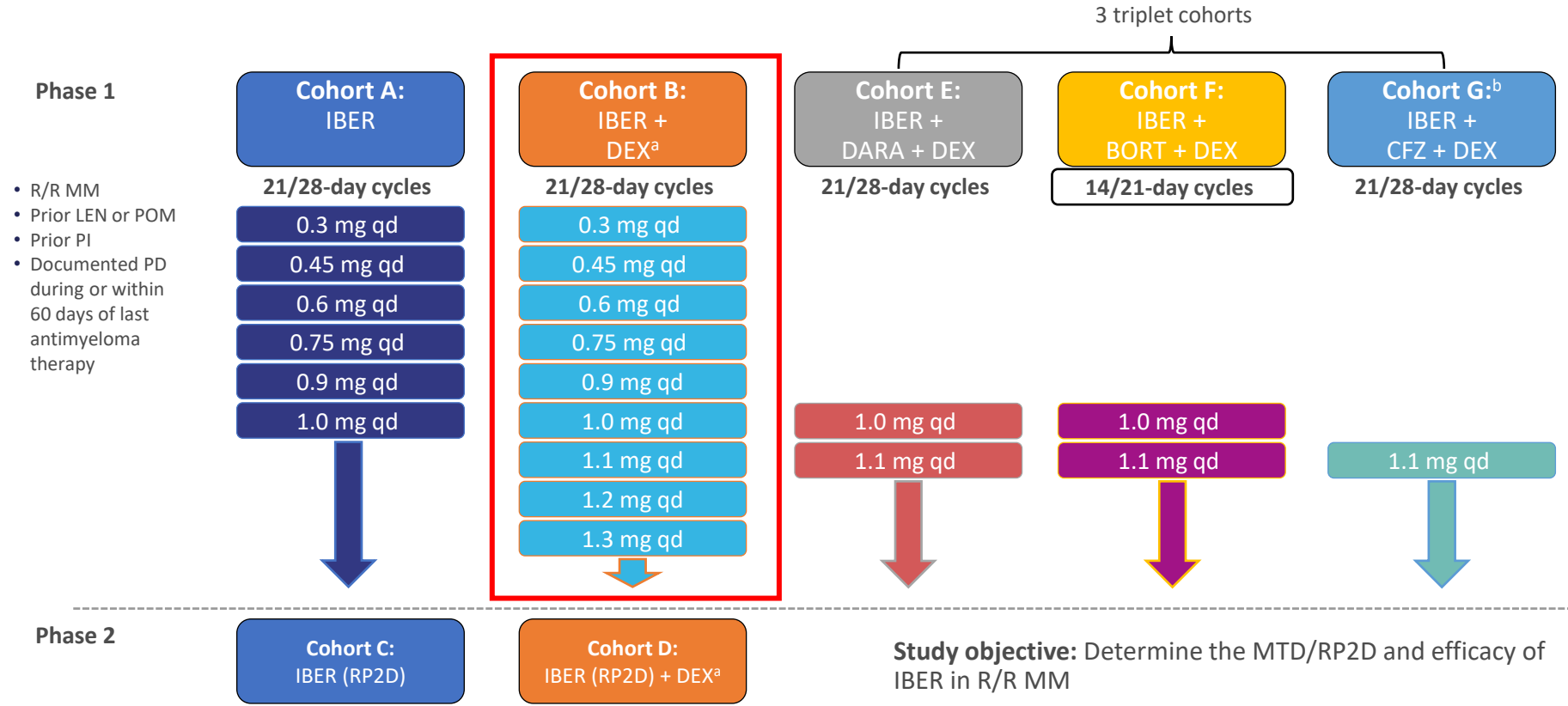

**In every new LOT, ~15%–35% of patients are lost**

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

What to Do After Lenalidomide and Pomalidomide?

# IMIDS

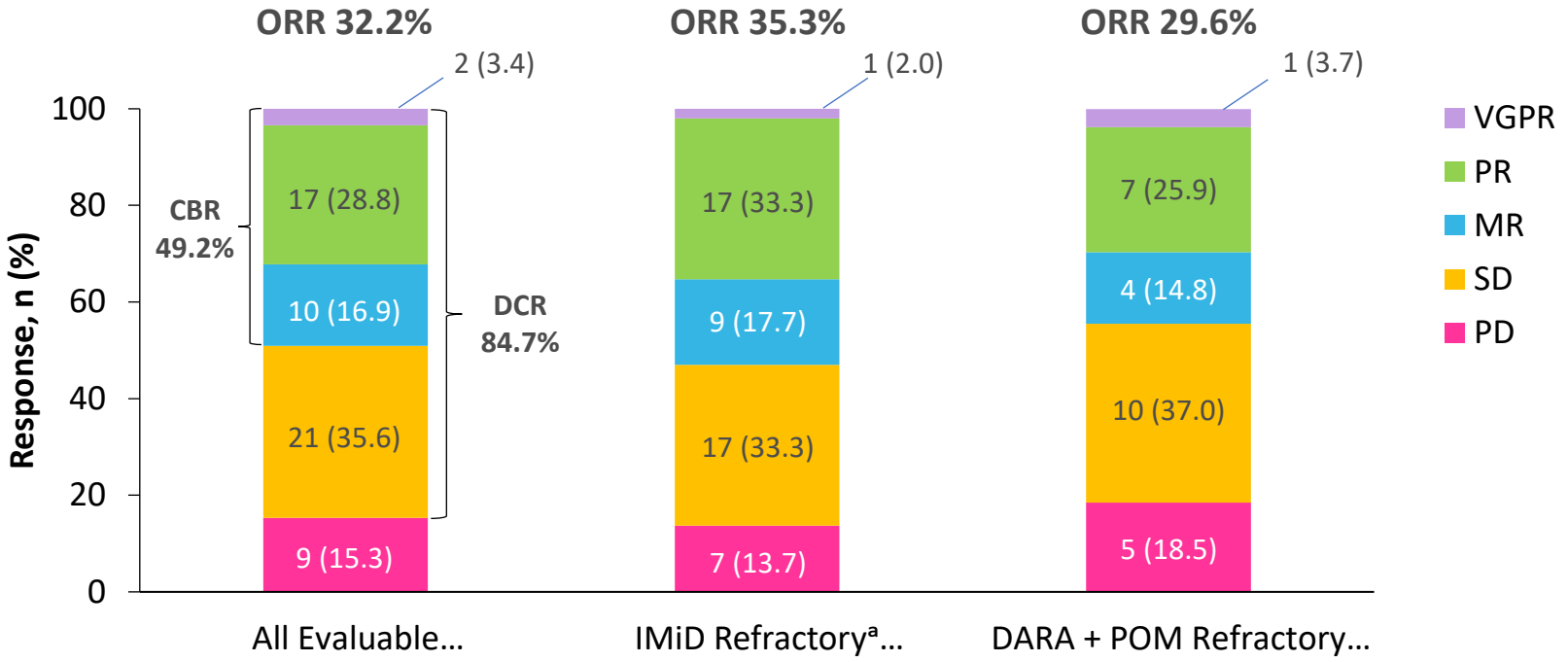
# Iberdomide MM-001 Phase 1b/2a Trial: Study Design




[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.

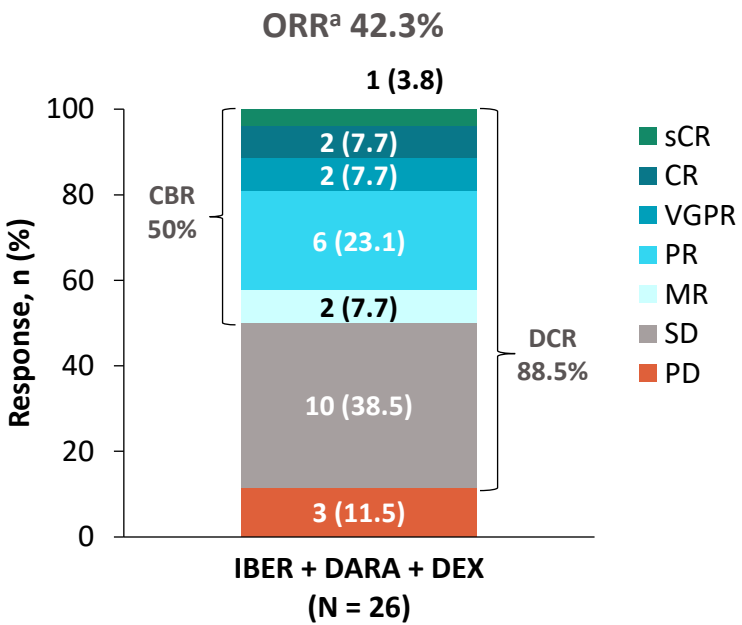
Lonial S, et al. ASCO 2019. Abstract 8006.

# Response

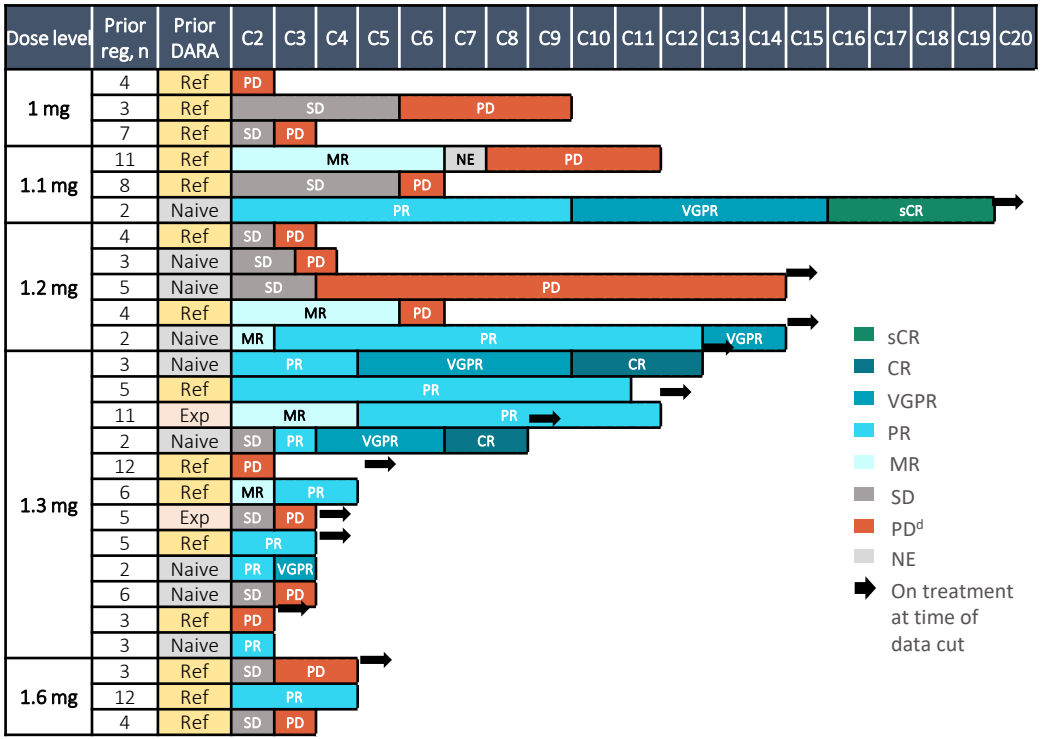



Evaluable patients include those who have received ≥1 dose of IBER, had measurable disease at baseline, and ≥1 postbaseline response assessment.
[a]Includes LEN and POM.
CBR, clinical benefit rate; DCR, disease control rate; MR, minimal response; ORR, overall response rate; PR, partial response; SD, 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]



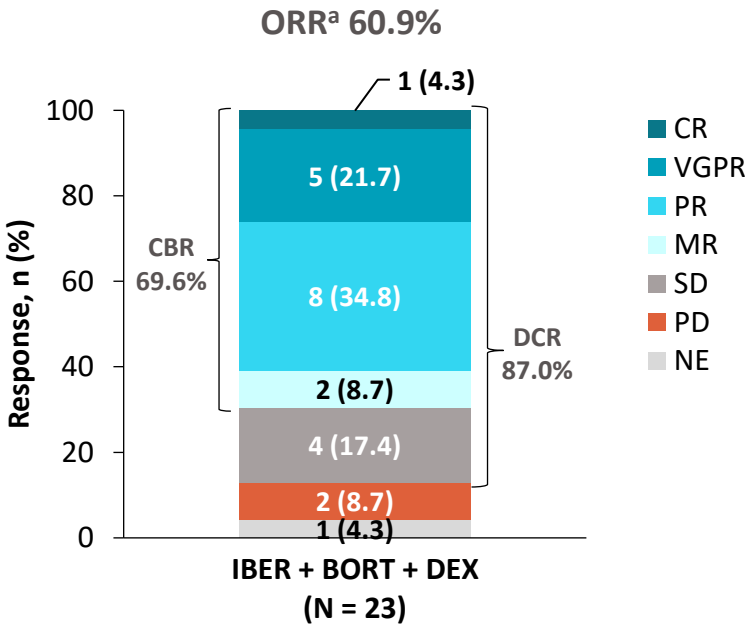

- Median time to response was 4.1 (range 4.0–12.0) weeks

[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.

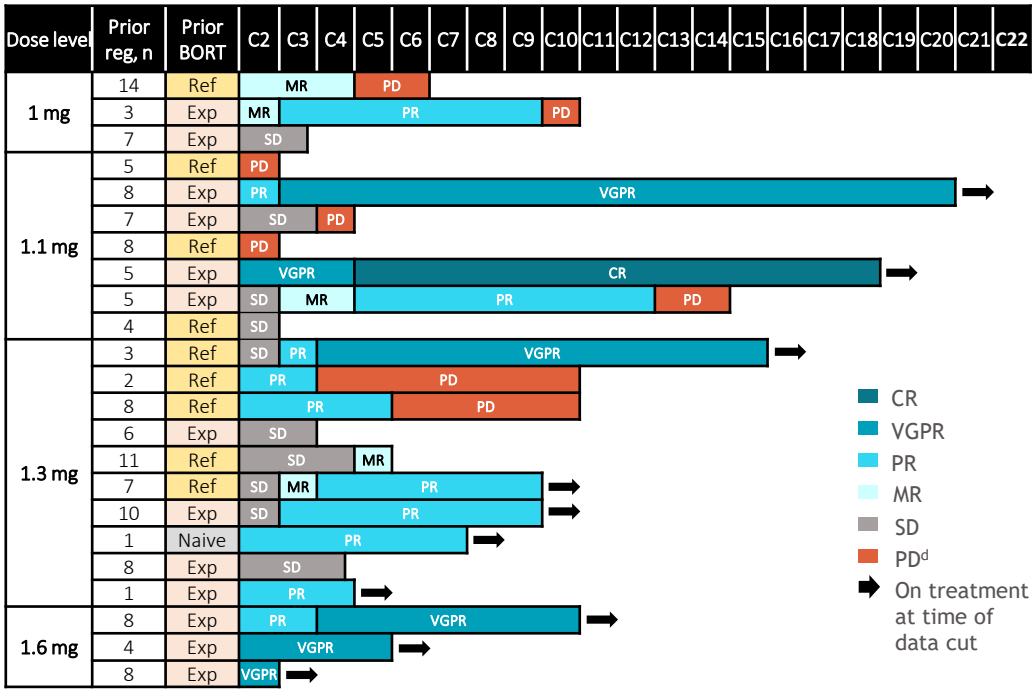
CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; Exp, exposed; MR, minimal response; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; Ref, refractory; reg, regimen; sCR, stringent complete response;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

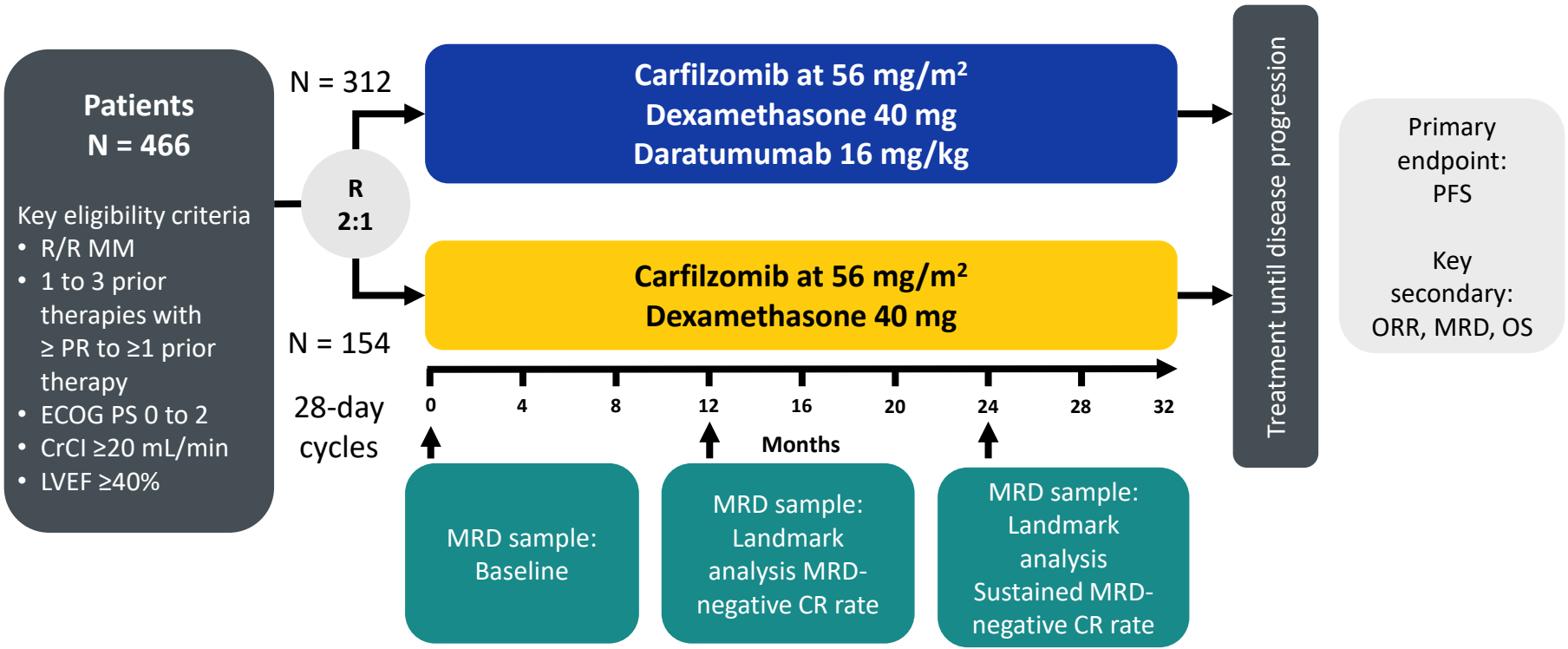



- Median time to response was 3.6 (range 3.0–13.1) weeks

[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.

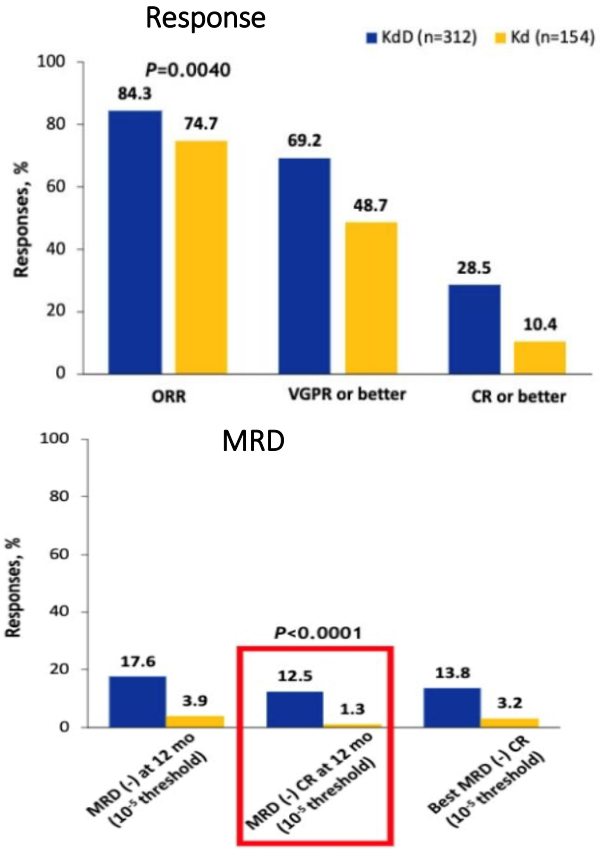
# NOVEL COMBINATIONS?

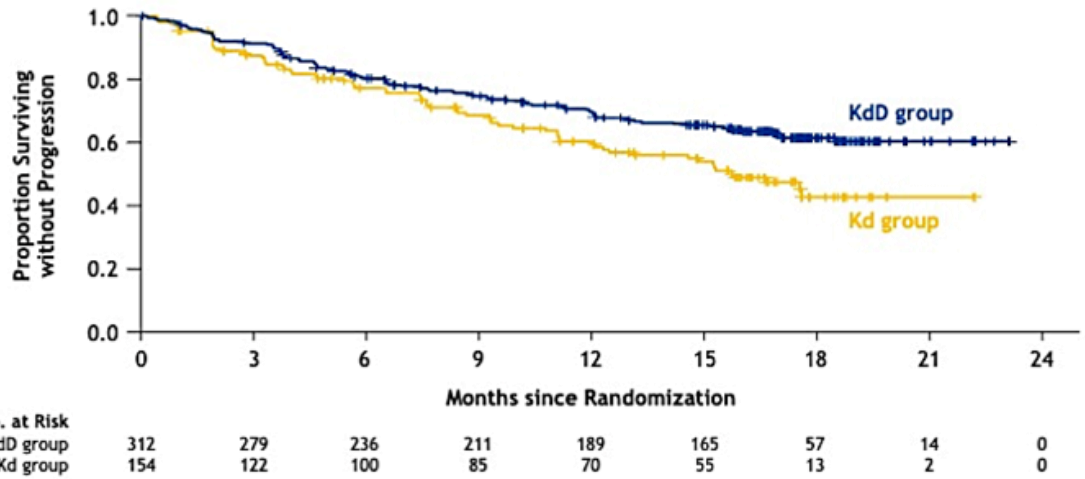
# CANDOR: CAR-DARA-DEX vs CAR-DEX




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 | |

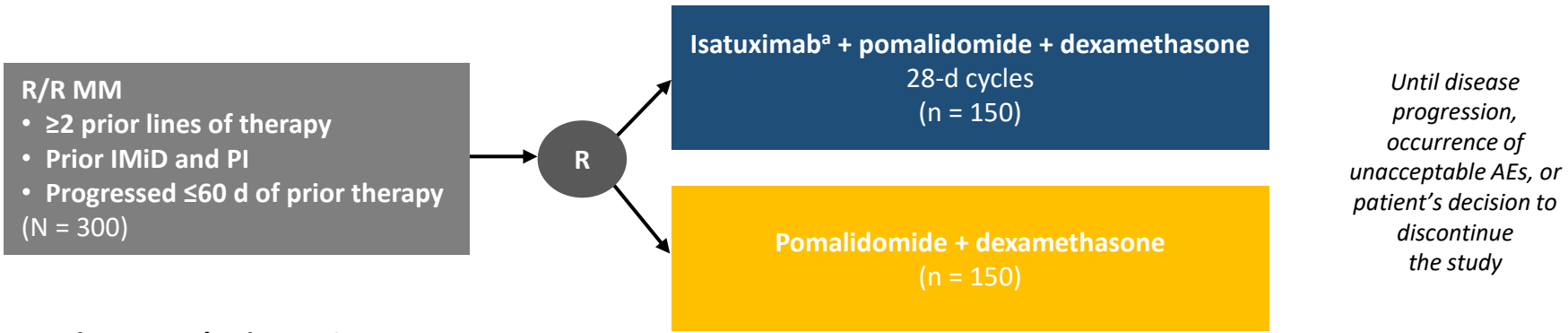
Usmani SZ, et al. ASH 2019. Abstract LBA6.

# 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]

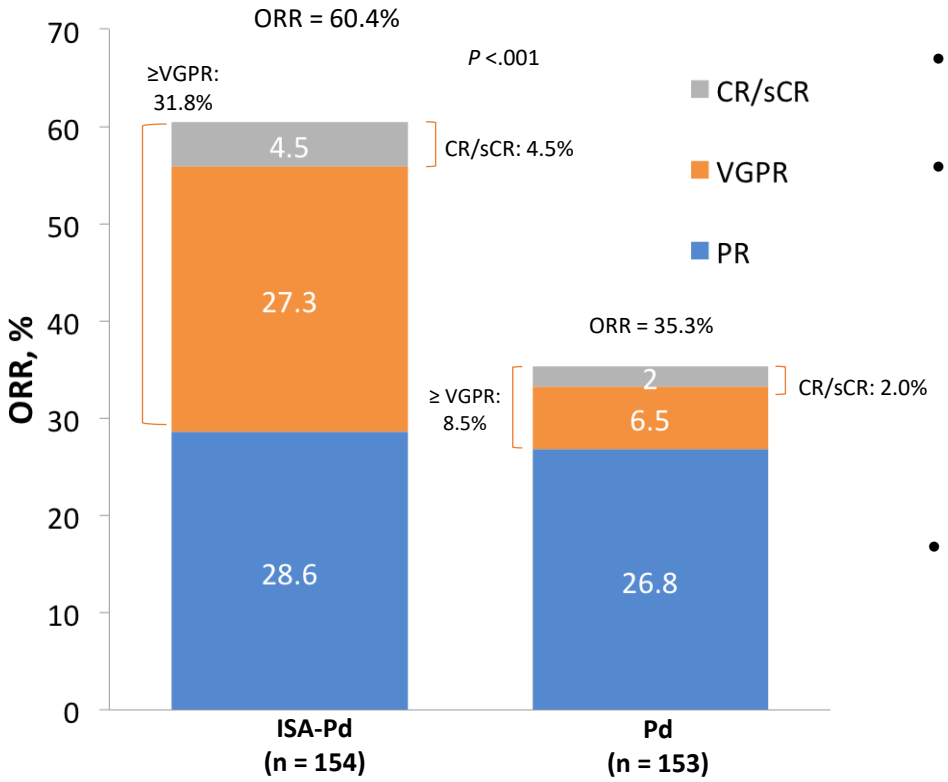



- **Primary endpoint:** PFS
- **Key secondary endpoints:** ORR, OS, safety

[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



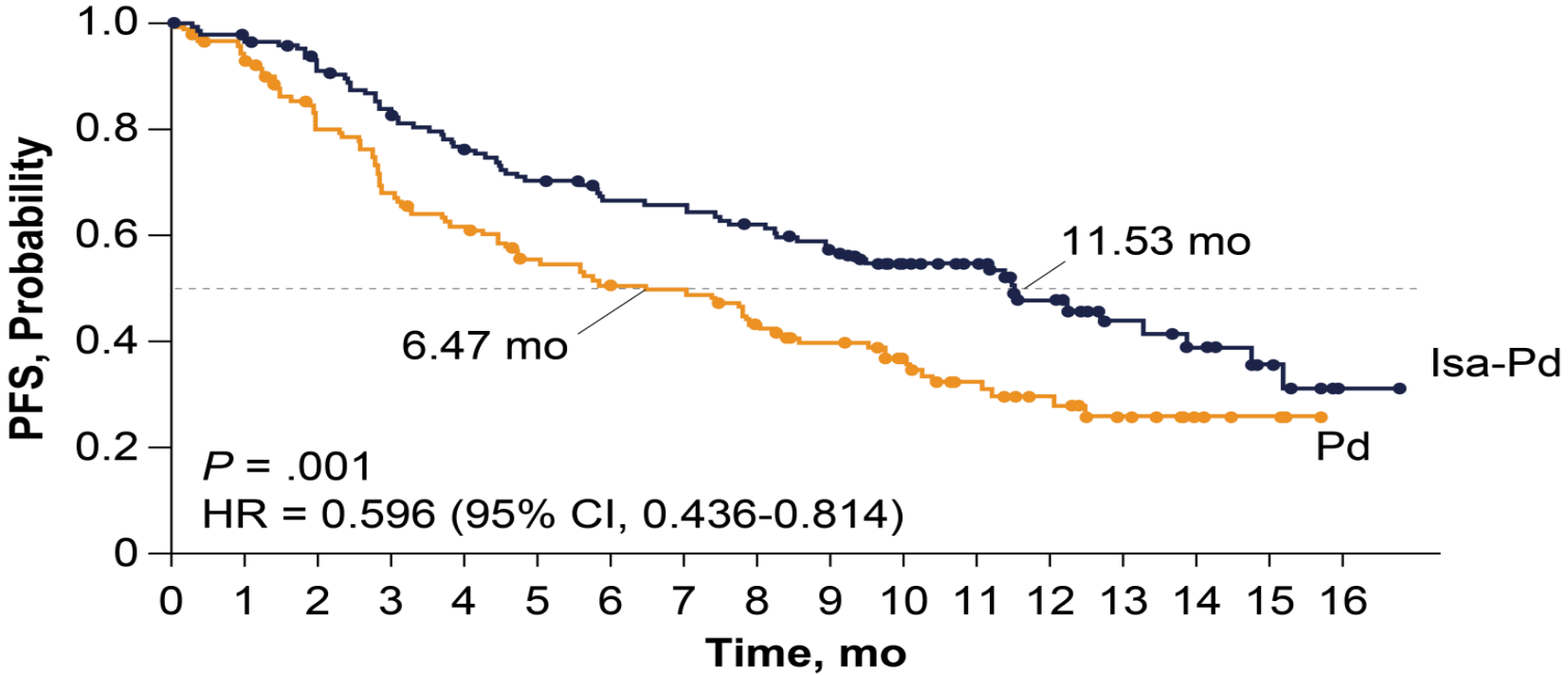

- Median time to first response: ISA-Pd = 35 days vs Pd = 58 days
- True CR rate in ISA-Pd underestimated because of ISA interference with M-protein measurement

| | 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**

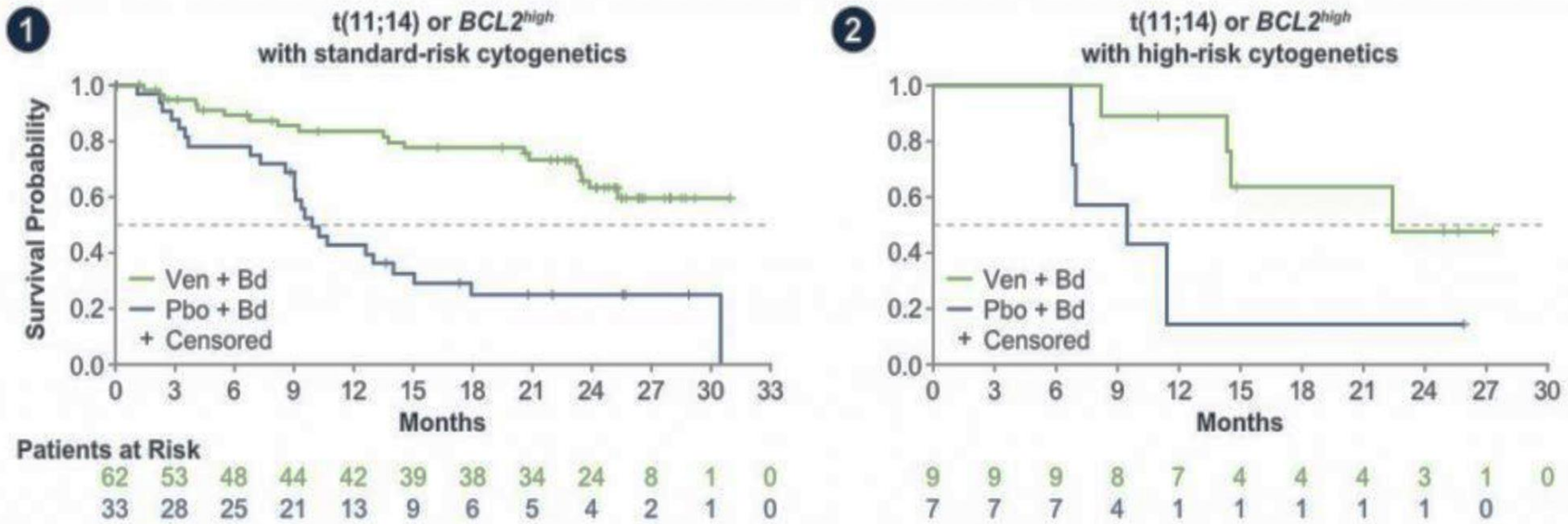
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Isa-Pd | 154 | 129 | 106 | 89 | 81 | 52 | 30 | 14 | 1 |
| Pd | 153 | 105 | 80 | 63 | 51 | 33 | 17 | 5 | 0 |

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

# NEW SMALL MOLECULES

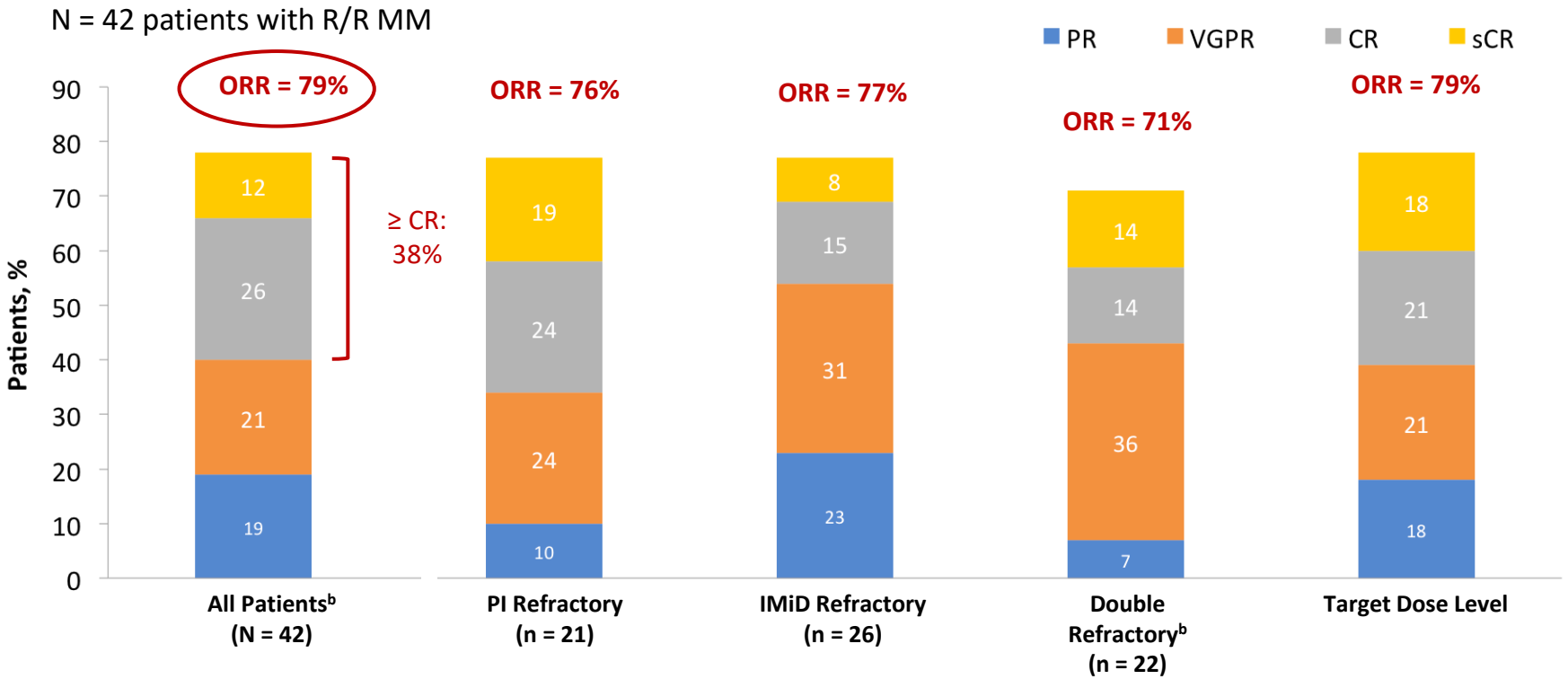
# Venetoclax-Bortezomib-DEX Highly Active in t(11;14) or High BCL-2

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




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

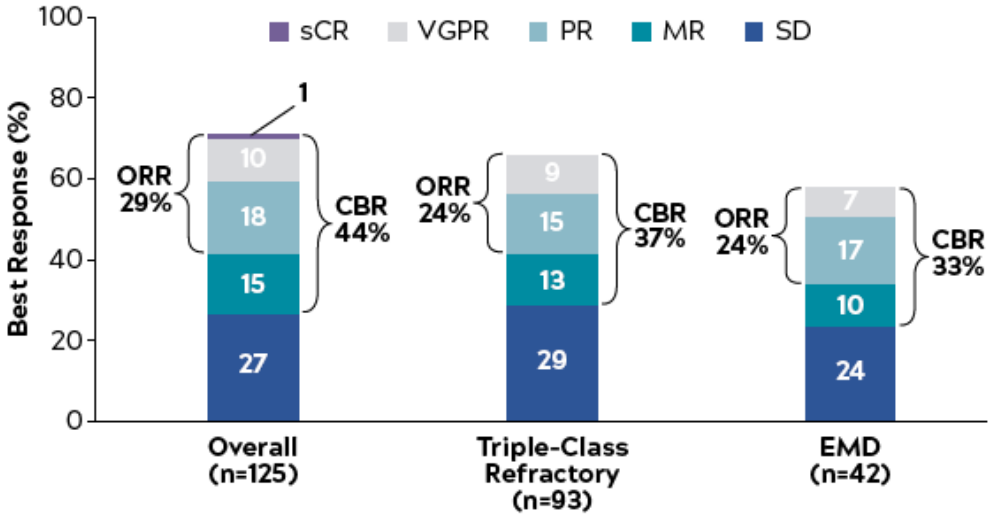
# . . . And With Carfilzomib-Dexamethasone[a]




[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.

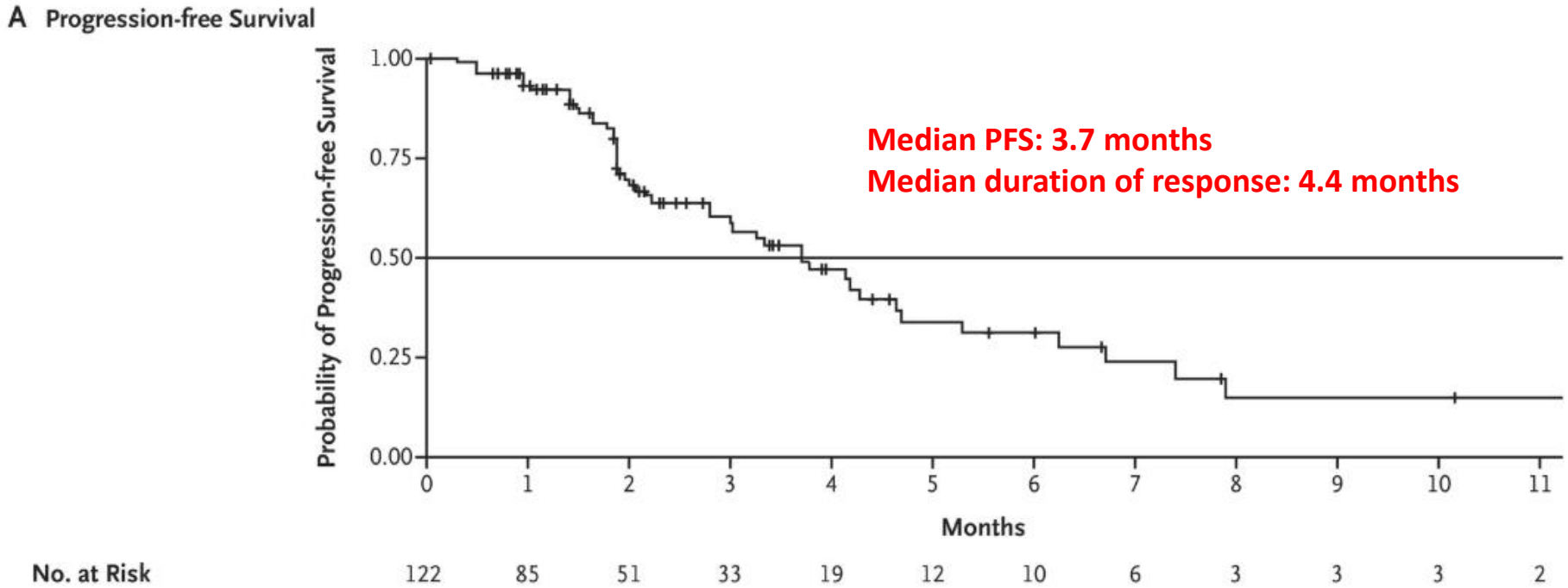
# Phase 2 STORM Trial: Response Assessment

| 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**

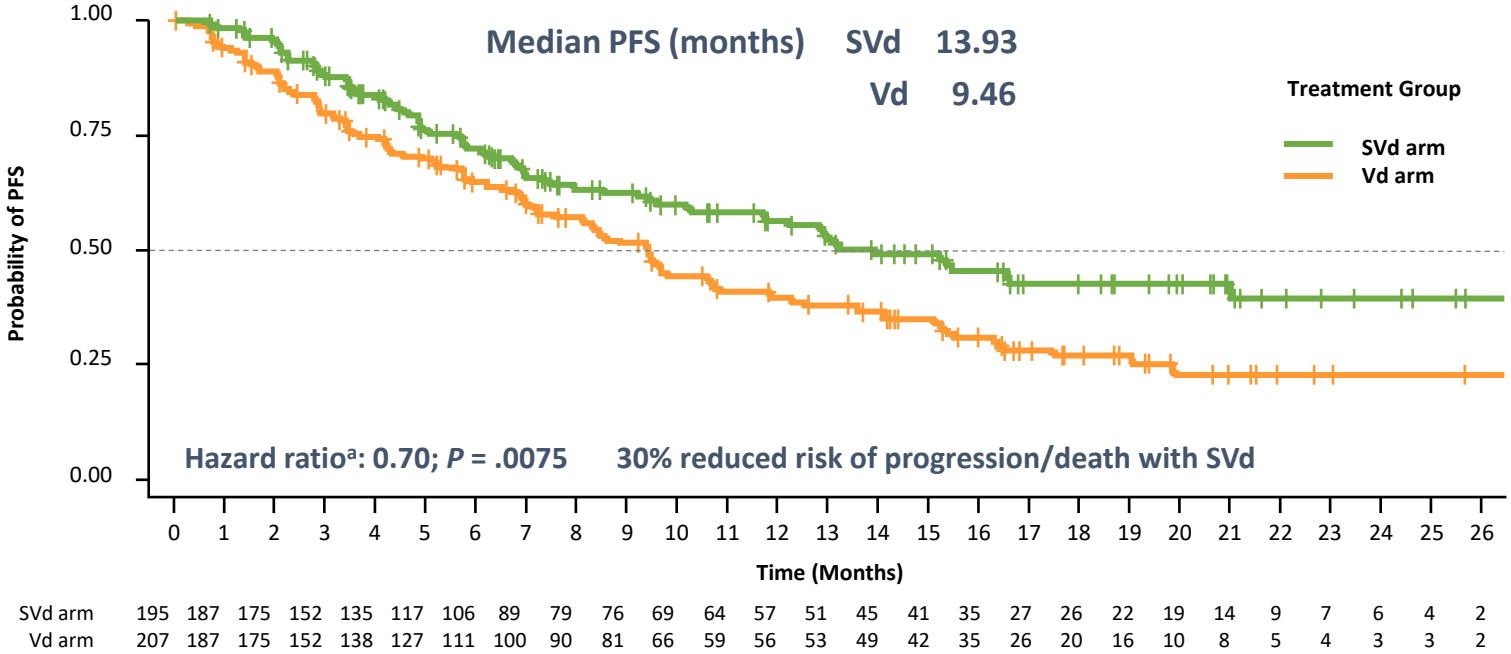
- Hematologic, GI related, constitutional symptoms, and hyponatremia
- Typically responsive to dose modification and standard supportive care agents

**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*

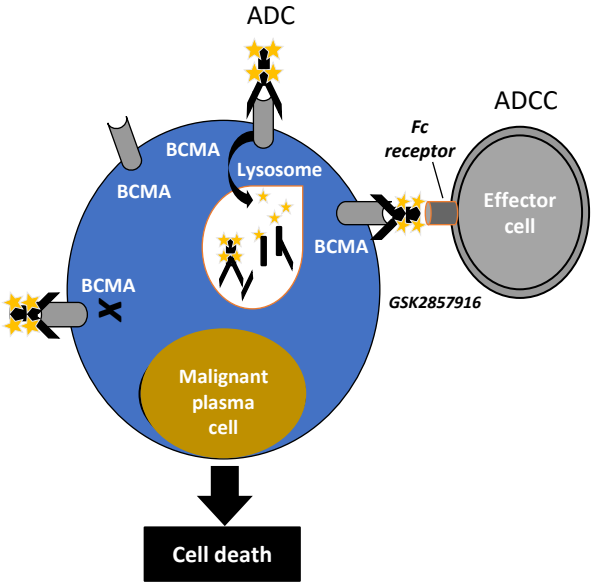
| | SVd (n=195) | | Vd (n=204) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| **Non-hematological (%)** | | | | |
| Nausea | 50.3 | 7.7 | 9.8 | 0 |
| Fatigue | 42.1 | 13.3 | 18.1 | 1.0 |
| Decreased Appetite | 35.4 | 3.6 | 5.4 | 0 |
| Diarrhea | 32.3 | 6.2 | 25.0 | 0.5 |
| 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<br>• 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?

[repeated question]

a) 90%

b) 80%

c) 65%

d) 50%

e) 40%

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

[repeated question]

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

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

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

d) The response rate in first relapse is 72%

e) Ocular toxicity is manageable with steroid eye drops

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# Discussion

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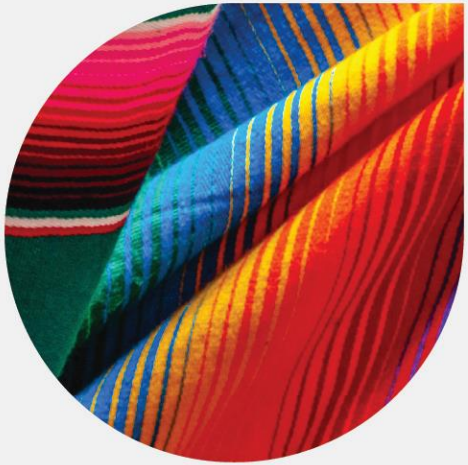

# Break

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# New and Future Therapies for Multiple Myeloma

Irene Ghobrial, MD

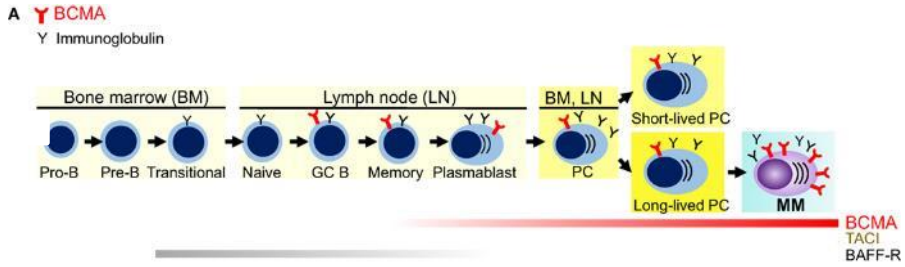
APTITUDE HEALTH®

# Promising New Developments in Relapsed MM: Recent Clinical Updates

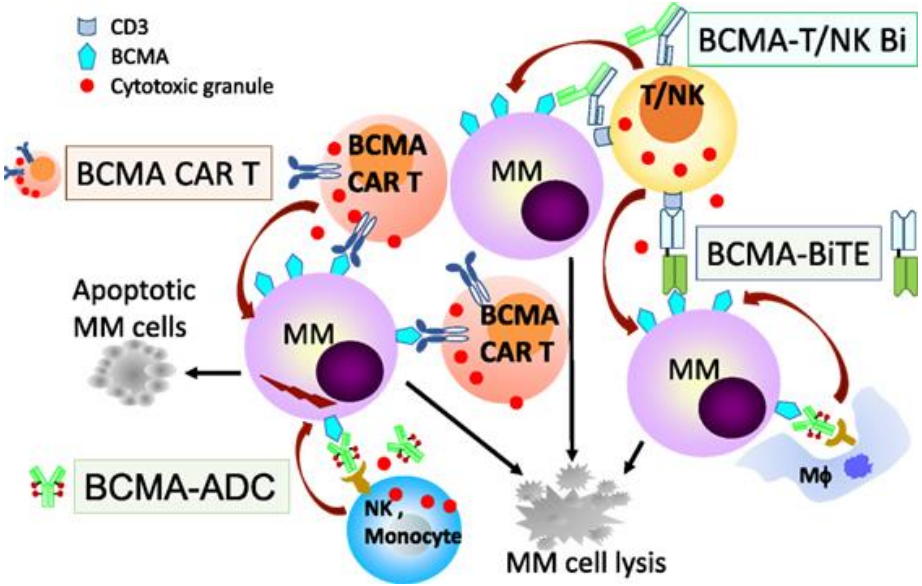
**Irene Ghobrial, MD**
Lavine Family Chair of Preventative Cancer Therapy
Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, MA

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



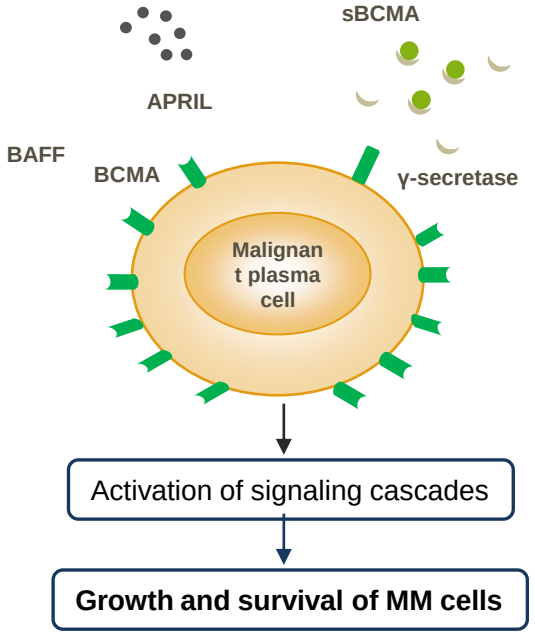
# Rationale for Targeting BCMA

**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]**

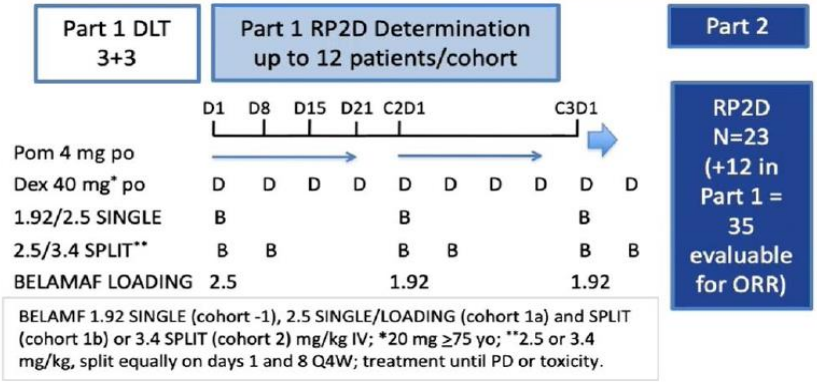



1. Tai YT, et al. *Immunotherapy*. 2015;7(11):1187-1199; 2. Ryan MC, et al. *Mol Cancer Ther*. 2007;6(11):3009-3018;
3. Cho SF, et al. *Front Immunol*. 2018;9:1821; 4. Novak AJ, et al. *Blood*. 2004;103(2):689-694; 5. Tai YT, et al. *Blood*. 2014;123(20):3128-3138.

# Comparing Options

| | CAR T | Bispecifics | ADCs |
|---|---|---|---|
| **Treatment logistics** | Specialized center; need to wait for production | TBA, likely community friendly, off-the-shelf<br>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 | ?<br>But have to consider length of treatment | $24K/month |

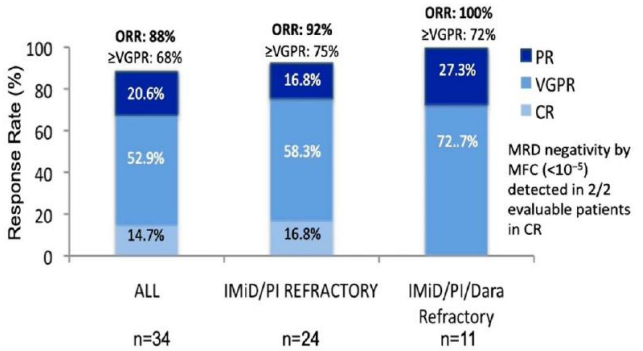
# Belantamab Mafodotin in Combination With Pomalidomide and Dexamethasone for RR MM: Dose-Finding Study (Part 1)




| 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<br>LEN refractory | 37 (100%)<br>33 (89.2%) |
| PI exposed<br>Bortezomib<br>Carfilzomib<br>PI refractory | 37 (100%)<br>36 (97.3%)<br>13 (35.1%)<br>30 (81.1%) |
| DARA exposed<br>DARA refractory | 16 (43.2%)<br>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

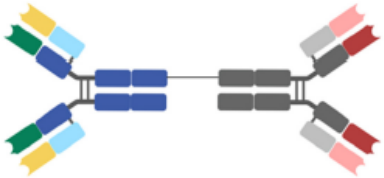



| Outcome (median) | All | IMiD/PI Refractory | IMiD/PI/Dara Refractory |
|---|---|---|---|
| Follow-up, months (range) | 7.8 (1.9, 20.3) | 7.8 (1.9, 18.9) | 7.4 (2.1, 16.1) |
| PFS, months (95% CI) | NR (10.8, -) | NR (10.8, NR) | 11.1 (4.9, NR) |

# Bispecific Antibodies: Many Different Platforms

Bispecific T-cell Engager or BiTE (Amgen)

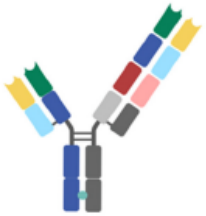
Dual Affinity Re-Targeting or DART (Janssen, MacroGenics)



Tandem diabodies or TandAb (Affimed)

BsAb armed activated T cells or BAT (mostly academic)

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



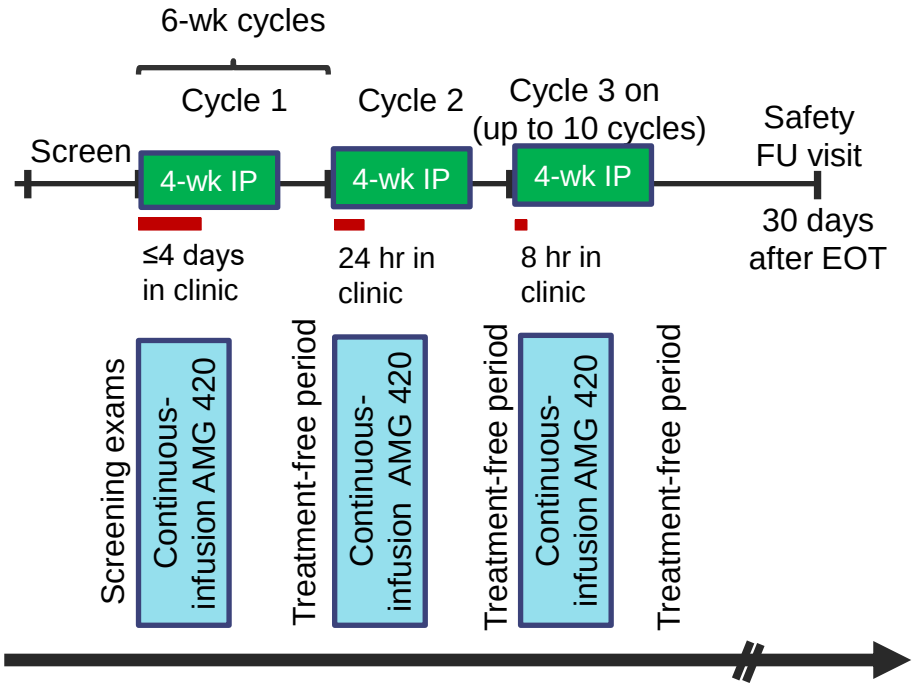
CrossMAb (Celgene, Roche)

Duobody (Genmab)

Trifunctional Antibody or TriFAb

# 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

# TECLISTAMAB, A B-CELL MATURATION ANTIGEN × CD3 BISPECIFIC ANTIBODY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED RESULTS OF A PHASE 1, FIRST-IN-HUMAN STUDY

Niels WCJ van de Donk[1,*], Alfred L Garfall[2], Maria-Victoria Mateos[3], Amrita Y Krishnan[4], Hareth Nahi[5], Jesús F San-Miguel[6], Albert Oriol[7], Laura Rosiñol[8], Ajai Chari[9], Manisha Bhutani[10], Lionel Karlin[11], Lotfi Benboubker[12], Lixia Pei[13], Raluca Verona[13], Suzette Girgis[13], Tara Stephenson[13], Jenna D Goldberg[14], Arnob Banerjee[13], Saad Zafar Usmani[10]

[1]Amsterdam University Medical Center, VU University Medical Center, Amsterdam, Netherlands; [2]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]Hospital Clínico Universitario de Salamanca, Salamanca, Spain; [4]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [5]Karolinska University Hospital at Huddinge, Stockholm, Sweden; [6]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; [7]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [8]Institute of Hematology and Oncology, IDIBAPS Hospital Clínic University of Barcelona, Barcelona, Spain; [9]Mount Sinai School of Medicine, New York, NY, USA; [10]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [11]Service d'Hématologie Clinique, Centre Hospitalier Lyon Sud, Pierre-Bénite, France; [12]Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire, Tours, France; [13]Janssen Research & Development, Spring House, PA, USA; [14]Janssen Research & Development, Raritan, NJ, USA

TECLISTAMAB

# Patient Demographics and Disease Characteristics

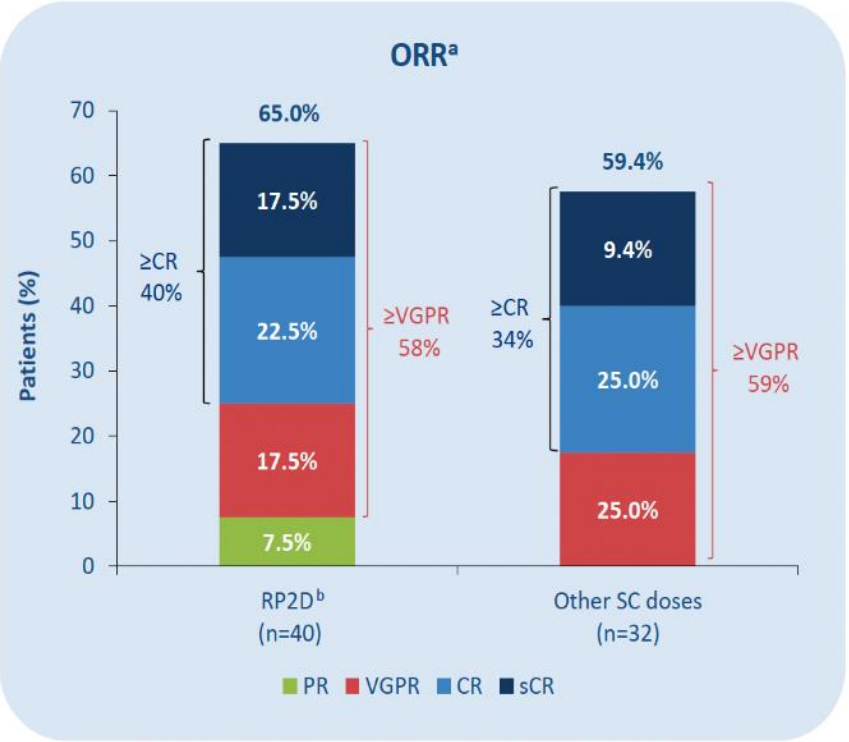
| Characteristic | SC Total n=73 | RP2D (1500 µg/kg SC QW)[a] n=40 |
|---|---|---|
| Age, years, median (range) | 64.0 (39–84) | 62.5 (39–84) |
| Aged ≥70 years, n (%) | 18 (25) | 9 (23) |
| Sex, n (%) | | |
| Male | 43 (59) | 26 (65) |
| Female | 30 (41) | 14 (35) |
| Time since diagnosis, years, median (range) | 5.9 (0.8–23.5) | 5.7 (0.8–17.4) |
| Extramedullary soft tissue plasmacytomas ≥1, n (%)[b] | 11 (15) | 8 (20) |
| Bone marrow plasma cells ≥60%, n (%)[c] | 12 (18) | 3 (8) |
| High-risk cytogenetics, n (%)[d] | 16 (30) | 10 (37) |
| ISS stage, n (%)[e] | | |
| I | 36 (50) | 24 (62) |
| II | 25 (35) | 11 (28) |
| III | 11 (15) | 4 (10) |

| Characteristic | SC Total n=73 | RP2D (1500 µg/kg SC QW)[a] n=40 |
|---|---|---|
| Prior number of lines of therapy, median (range) | 5.0 (2–14) | 5.0 (2–11) |
| Prior transplantation, n (%) | 63 (86) | 34 (85) |
| Exposure status, n (%) | | |
| Triple-class[f] | 71 (97) | 40 (100) |
| Penta-drug[g] | 50 (68) | 26 (65) |
| Refractory status, n (%) | | |
| PI[h] | 65 (89) | 35 (88) |
| Carfilzomib | 49 (67) | 27 (68) |
| IMiD[i] | 70 (96) | 38 (95) |
| Pomalidomide | 55 (75) | 28 (70) |
| Anti-CD38 mAb[j] | 68 (93) | 39 (98) |
| Triple-class[f] | 58 (79) | 33 (83) |
| Penta-drug[g] | 28 (38) | 15 (38) |
| Refractory to last line of therapy | 64 (88) | 33 (83) |

[a]Step-up doses of 60 µg/kg and 300 µg/kg; [b]Soft-tissue component of a bone-based plasmacytoma not included; [c]Percentages calculated from n=66 for SC total and n=36 at RP2D; [d]del(17p), t(4:14), and/or t(14;16); percentages calculated from n=53 for SC total and n=27 at RP2D; [e]At baseline; percentages calculated from n=72 for SC total and n=39 at RP2D; [f]≥1 PI, ≥1 IMiD, and 1 anti-CD38 mAb; [g]≥2 PI, ≥2 IMiD, and 1 anti-CD38 mAb; [h]Bortezomib, carfilzomib, and/or ixazomib; [i]Thalidomide, lenalidomide, and/or pomalidomide; [j]Daratumumab and/or isatuximab. IMiD, immunomodulatory drug; ISS, international Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; QW, once weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

TECLISTAMAB

# Overall Response Rate




- The RP2D of 1500 µg/kg SC QW has been administered to 40 patients with a median duration of follow-up of 6.1 months (range: 1.2–12.2)
  - ORR was 65%, with 58% of patients achieving ≥VGPR and 40% achieving ≥CR
  - Median time to first confirmed response was 1.0 month (range: 0.2–3.1)
  - ORR in 33 triple-class refractory patients was 61%
- Of 6 evaluable patients in RP2D cohorts as of the data cut-off date, all achieved MRD-negative CR/sCR at $10^{-6}$ (n=5) or $10^{-5}$ (n=1)
  - Across IV and SC cohorts, 18/26 evaluable patients (69%) had MRD-negative CR/sCR at $10^{-6}$ (n=16) or $10^{-5}$ (n=2)
  - 2 evaluable patients with CR >12 months had sustained MRD negativity

Van De Donk N, et al. EHA 2021. Abstract S193.

# UPDATED RESULTS OF A PHASE 1, FIRST-IN-HUMAN STUDY OF TALQUETAMAB, A GPRC5D × CD3 BISPECIFIC ANTIBODY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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

[1]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [2]City of Hope, Duarte, CA, USA; [3]Institut Català d'Oncologia and Institut Josep Carreras; Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [4]Amsterdam University Medical Center, VU University Medical Center, Amsterdam, Netherlands; [5]Clínica Universidad de Navarra, Navarra, Spain; [6]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [7]Hospital Clínico Universitario de Salamanca, Salamanca, Spain; [8]University Medical Center Utrecht, Utrecht, Netherlands; [9]University of Alabama at Birmingham, Birmingham, AL, USA; [10]Janssen R&D, Spring House, PA, USA; [11]Janssen R&D, Raritan, NJ, USA; [12]Mount Sinai School of Medicine, New York, NY, USA

TALQUETAMAB

# Patient Demographics and Disease Characteristics

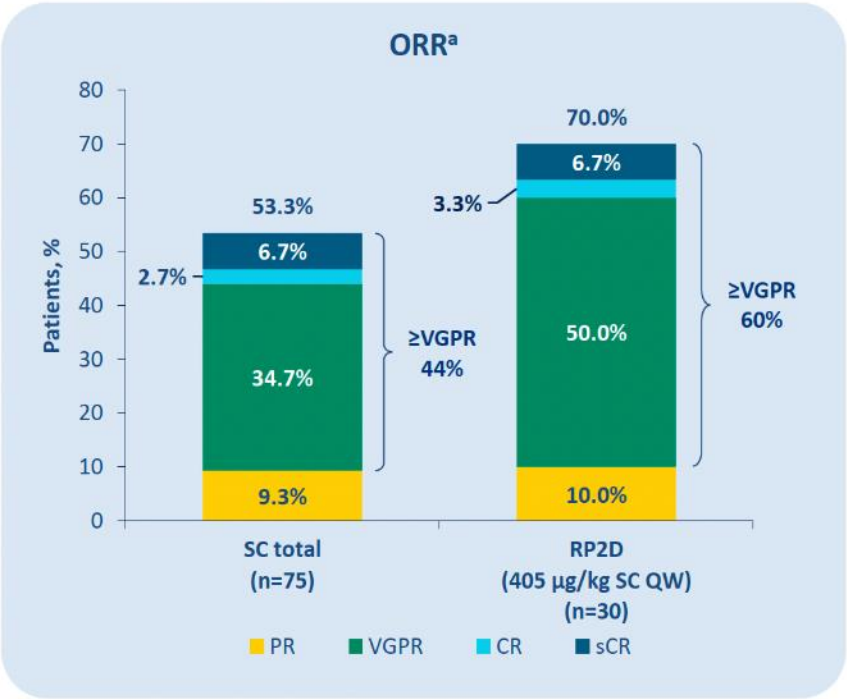
| Characteristic | SC Total n=82 | RP2D (405 µg/kg SC QW)[a] n=30 |
|---|---|---|
| Age, years, median (range) | 63.0 (42–80) | 61.5 (46–80) |
| Age ≥70 years, n (%) | 22 (27) | 7 (23) |
| Sex, n (%) | | |
| Male | 47 (57) | 19 (63) |
| Female | 35 (43) | 11 (37) |
| Years since diagnosis, median (range) | 5.9 (1–20) | 5.6 (2–20) |
| Extramedullary plasmacytomas ≥1, n (%)[b] | 27 (33) | 10 (33) |
| Bone marrow plasma cells ≥60%, n (%)[c] | 13 (17) | 6 (21) |
| ISS stage, n (%)[d] | | |
| I | 26 (32) | 12 (40) |
| II | 36 (44) | 13 (43) |
| III | 13 (16) | 3 (10) |
| Prior transplantation, n (%) | 71 (87) | 27 (90) |

| Characteristic | SC Total n=82 | RP2D (405 µg/kg SC QW)[a] n=30 |
|---|---|---|
| Prior lines of therapy, n, median (range) | 6.0 (2–17) | 6.0 (2–14) |
| Exposure status, n (%) | | |
| Prior BCMA therapy[e] | 20 (24) | 8 (27) |
| Triple-class[f] | 81 (99) | 30 (100) |
| Penta-drug[g] | 64 (78) | 24 (80) |
| Refractory status, n (%) | | |
| PI[h] | 69 (84) | 25 (83) |
| Carfilzomib | 54 (66) | 19 (63) |
| IMiD[i] | 76 (93) | 28 (93) |
| Pomalidomide | 67 (82) | 26 (87) |
| Anti-CD38 mAb[j] | 77 (94) | 30 (100) |
| BCMA[e] | 14 (17) | 5 (16) |
| Triple-class[f] | 62 (76) | 23 (77) |
| Penta-drug[g] | 23 (28) | 6 (20) |
| To last line of therapy | 69 (84) | 26 (87) |

[a]Step-up doses of 10 µg/kg and 60 µg/kg; [b]Soft-tissue component of a bone-based plasmacytoma not included; [c]Percentages calculated from n=76 for SC total and n=29 at RP2D; [d]Percentages calculated from n=66 for SC total and n=27 at RP2D; [e]BCMA CAR-T therapy or BCMA non–CAR-T therapy; [f]≥1 PI, ≥1 IMiD, and 1 anti-CD38 mAb; [g]≥2 PI, ≥2 IMiD, and 1 anti-CD38 mAb; [h]Bortezomib, carfilzomib, and/or ixazomib; [i]Thalidomide, lenalidomide, and/or pomalidomide; [j]Daratumumab and/or isatuximab.
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; QW, once weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

TALQUETAMAB

# Overall Response Rate



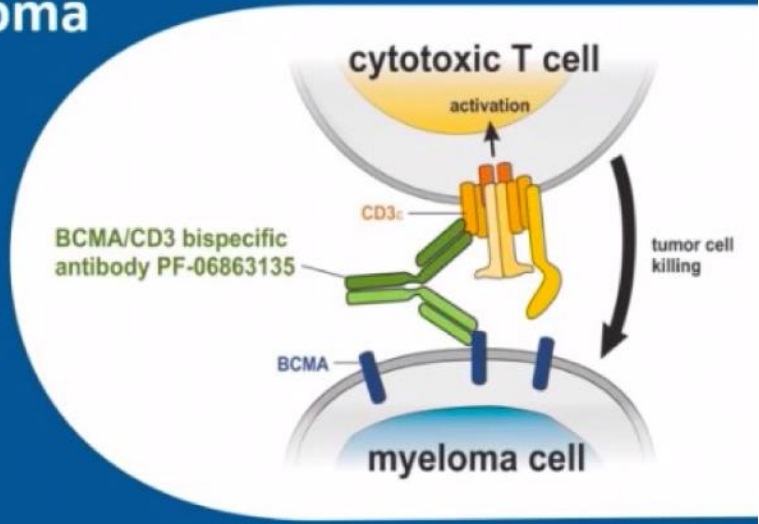

- The RP2D of 405 µg/kg SC QW has been administered to 30 patients with a median follow-up of 6.3 months (range: 1.4–12.0) for responders
- At the RP2D:
  - 70.0% ORR (21/30)
  - Median time to first confirmed response was 1 month (range: 0.2–3.8)
  - 65.2% (15/23) of triple-refractory patients responded
  - 83.3% (5/6) of penta-refractory patients responded
- Of 6 evaluable patients across IV and SC cohorts, 4 had MRD-negative CR/sCR at $10^{-6}$, including 1 patient in RP2D cohort
  - MRD negativity was sustained 7 months post CR in 1 evaluable patient

[a]Investigator assessment of evaluable patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation per 2011 International Myeloma Working Group response criteria; includes unconfirmed response.
CR, complete response; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; QW, once weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

# MagnetisMM-1: Phase 1 Study of Elranatamab (PF-06863135), a B-Cell Maturation Antigen Targeted CD3-Engaging Bispecific Antibody, for Patients With Relapsed or Refractory Multiple Myeloma

**Caitlin L Costello, MD**
Moores Cancer Center
University of California San Diego
La Jolla, CA, USA

**June 11, 2021**



# Patient and Disease Characteristics

- 30 patients had received elranatamab SC by the data cutoff
  - 80 (n=6), 130 (n=4), 215 (n=4), 360 (n=4), 600 (n=6), and 1000 (n=6) µg/kg weekly

| Characteristics | SC dosing total (N=30) |
|---|---|
| Gender, n (%) | |
| Female | 17 (56.7) |
| Median age, y (range) | 63.0 (46–80) |
| ≥65 y, n (%) | 12 (40.0) |
| R-ISS stage at initial diagnosis, n (%) | |
| Stage I | 6 (20.0) |
| Stage II | 12 (40.0) |
| Stage III | 7 (23.3) |
| Not reported | 5 (16.7) |
| Cytogenetic risk | |
| High | 7 (23.3) |
| Standard | 19 (63.3) |
| Unknown | 4 (13.3) |

Data cutoff was February 4, 2021.
R-ISS=Revised International Staging System; SC=subcutaneous
Definition of high cytogenetic risk includes t(4;14), t(14;16), del(17p), and del(13q).

# Treatment-Emergent Adverse Events (All Causality) Occurring in ≥20% of Patients

| Adverse event, n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total (N=30) |
|---|---|---|---|---|---|
| **Hematological** | | | | | |
| Lymphopenia | 0 | 0 | 6 (20.0) | 19 (63.3) | 25 (83.3) |
| Anemia | 0 | 3 (10.0) | 15 (50.0) | 0 | 18 (60.0) |
| Neutropenia | 0 | 0 | 7 (23.3) | 9 (30.0) | 16 (53.3) |
| Thrombocytopenia | 3 (10.0) | 2 (6.7) | 5 (16.7) | 6 (20.0) | 16 (53.3) |
| Leukopenia | 1 (3.3) | 3 (10.0) | 7 (23.3) | 1 (3.3) | 12 (40.0) |
| **Non-hematological** | | | | | |
| CRS | 17 (56.7) | 5 (16.7) | 0 | 0 | 22 (73.3) |
| Injection site reaction | 13 (43.3) | 2 (6.7) | 0 | 0 | 15 (50.0) |
| Nausea | 5 (16.7) | 5 (16.7) | 1 (3.3) | 0 | 11 (36.7) |
| Increased AST | 5 (16.7) | 2 (6.7) | 3 (10.0) | 0 | 10 (33.3) |
| Increased ALT | 5 (16.7) | 1 (3.3) | 3 (10.0) | 0 | 9 (30.0) |
| Diarrhea | 6 (20.0) | 2 (6.7) | 1 (3.3) | 0 | 9 (30.0) |
| Vomiting | 7 (23.3) | 1 (3.3) | 0 | 0 | 8 (26.7) |
| Decreased appetite | 5 (16.7) | 2 (6.7) | 0 | 0 | 7 (23.3) |
| Dry skin | 5 (16.7) | 2 (6.7) | 0 | 0 | 7 (23.3) |
| Hypokalemia | 1 (3.3) | 5 (16.7) | 1 (3.3) | 0 | 7 (23.3) |
| Arthralgia | 3 (10.0) | 2 (6.7) | 1 (3.3) | 0 | 6 (20.0) |
| ICANS | 3 (10.0) | 3 (10.0) | 0 | 0 | 6 (20.0) |
| Pyrexia | 5 (16.7) | 1 (3.3) | 0 | 0 | 6 (20.0) |

- No DLT was observed

Data cutoff was February 4, 2021. Reporting of TEAEs based on CTCAE version 4.03, except for CRS (Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625).
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; DLT=dose-limiting toxicity; ICANS=immune effector cell-associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event

# Investigator IMWG Response

- Responses were observed beginning at 215 µg/kg
- At doses ≥215 µg/kg (n=20), confirmed ORR was 70% and CR/sCR rate was 30%
- At the RP2D of 1000 µg/kg (n=6), confirmed ORR was 83.3%
- Median duration of follow-up for patients treated at doses ≥215 µg/kg (n=20) was 7.7 months
- Median (range) time to response in the 14 responders was 22 (21–50) days

| IMWG response, n (%) | 215 µg/kg (n=4) | 360 µg/kg (n=4) | 600 µg/kg (n=6) | 1000 µg/kg (n=6) | Total ≥215 µg/kg (n=20) |
|---|---|---|---|---|---|
| sCR | 2 (50.0) | 1 (25.0) | 2 (33.3) | 0 | 5 (**25.0**) |
| CR | 0 | 0 | 0 | 1 (16.7) | 1 (**5.0**) |
| VGPR | 0 | 2 (50.0) | 2 (33.3) | 3 (50.0) | 7 (35.0) |
| PR | 0 | 0 | 0 | 1 (16.7) | 1 (5.0) |
| MR | 0 | 0 | 0 | 0 | 0 |
| SD | 2 (50.0) | 0 | 1 (16.7) | 0 | 3 (15.0) |
| PD | 0 | 1 (25.0) | 1 (16.7) | 1 (16.7) | 3 (15.0) |
| Confirmed ORR | 2 (50.0) | 3 (75.0) | 4 (66.7) | 5 (**83.3**) | 14 (**70.0**) |

CR=complete response; IMWG=International Myeloma Working Group; MR=minimal response; ORR=objective response rate; PD=progressive disease; PR=partial response; RP2D=recommended phase 2 dose; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

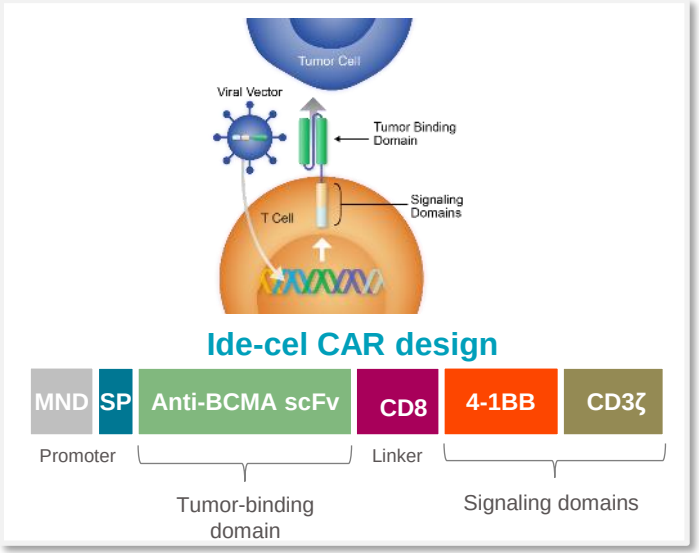
# Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Raje, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., Michel Delforge, M.D., Michele Cavo, M.D., Hermann Einsele, M.D., Hartmut Goldschmidt, M.D., Katja Weisel, M.D., Alessandro Rambaldi, M.D., Donna Reece, M.D., Fabio Petrocca, M.D., Monica Massaro, M.P.H., Jamie N. Connarn, Ph.D., Shari Kaiser, Ph.D., Payal Patel, Ph.D., Liping Huang, Ph.D., Timothy B. Campbell, M.D., Ph.D., Kristen Hege, M.D., and Jesús San-Miguel, M.D., Ph.D.

# 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**

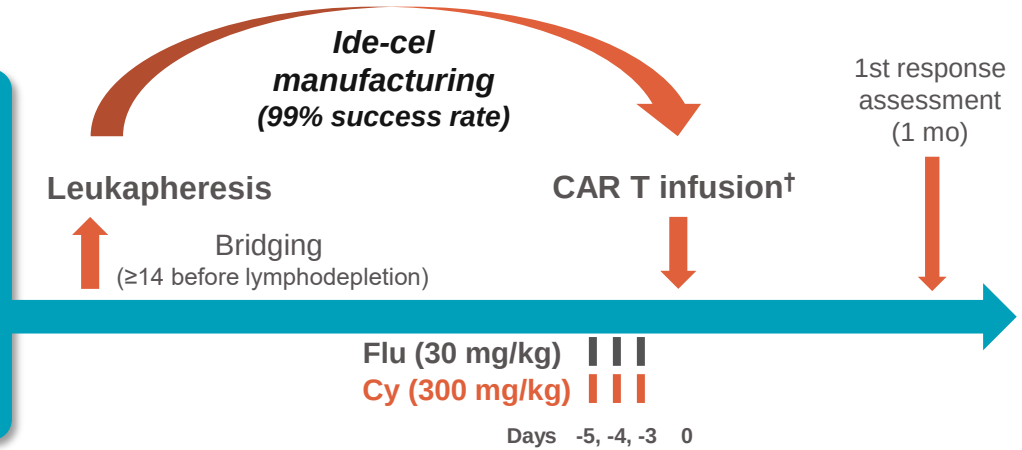
- **Autologous** T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- Targeting domain: **anti-BCMA**
- Co-stimulatory domain: **4-1BB**
- T-cell activation domain: **CD3ζ**

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)

| | |
|---|---|
| $150 \times 10^6$ | n = 4 |
| $300 \times 10^6$ | n = 70 |
| $450 \times 10^6$ | n = 54 |

Median Follow-up (mo)

| | |
|---|---|
| $150 \times 10^6$ | 18.0 |
| $300 \times 10^6$ | 15.8 |
| $450 \times 10^6$ | 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.

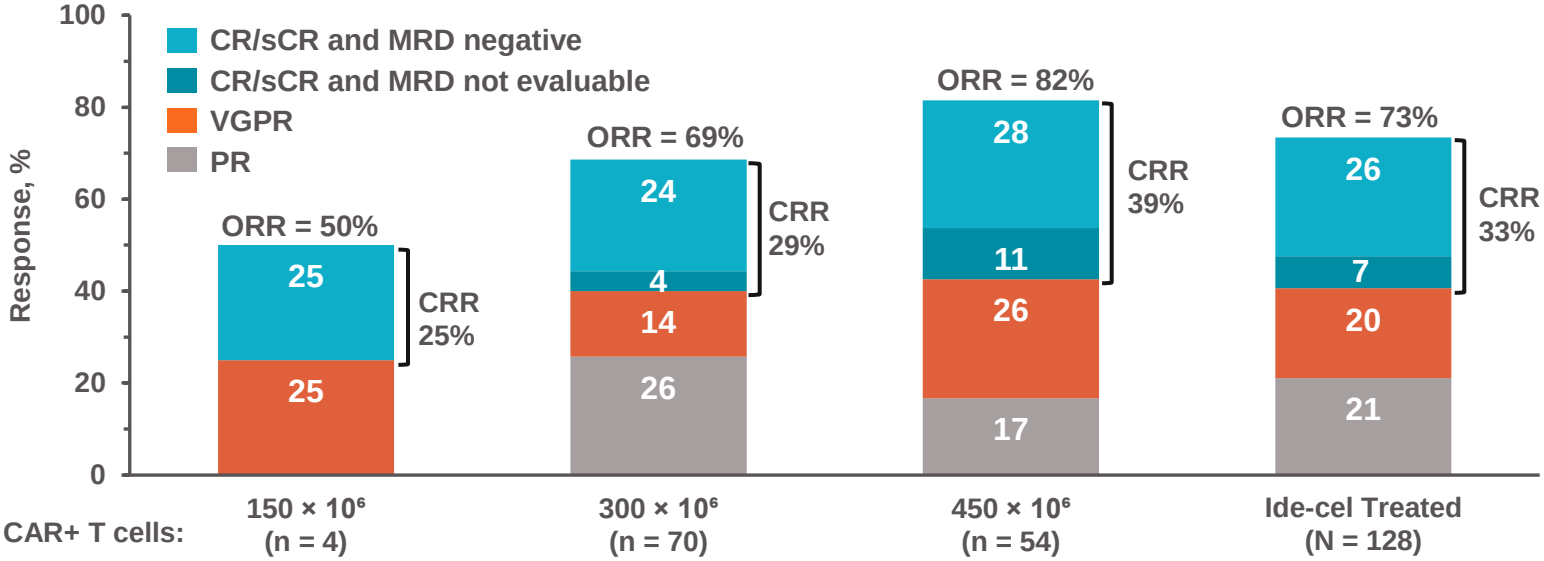
# Baseline Demographics and Clinical Characteristics

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

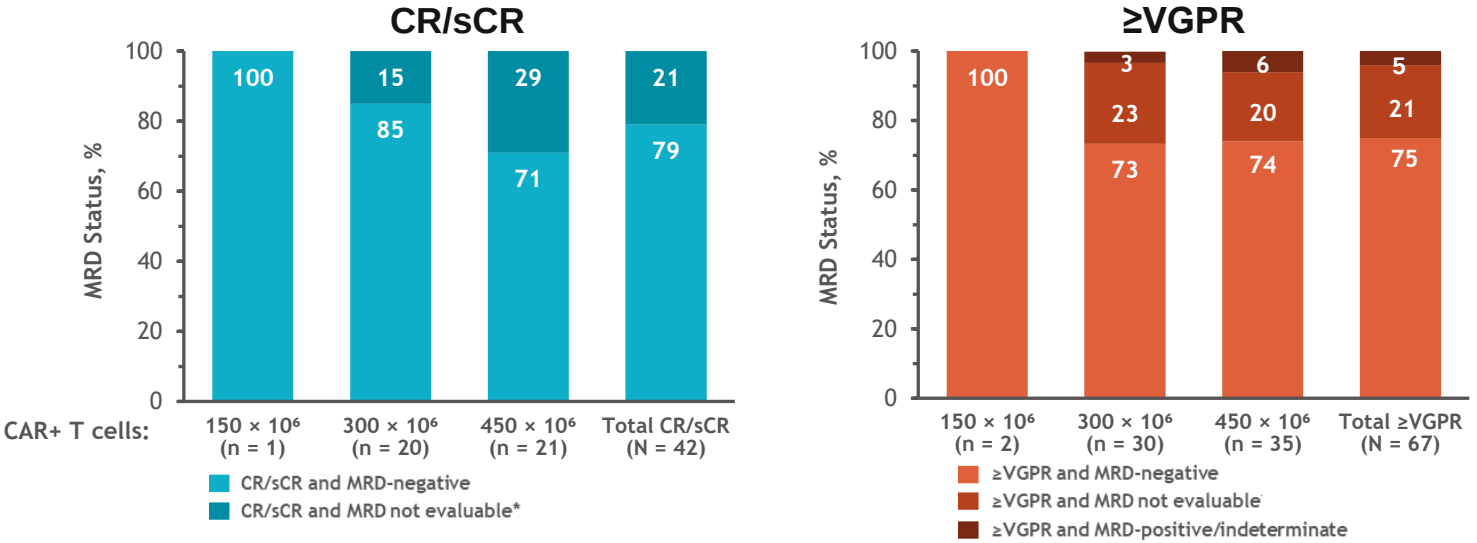



- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel–treated population
  - *ORR of 73% (95% CI, 65.8−81.1; P <.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7−40.9; P <.0001)*
- Median time to first response of 1.0 mo (range, 0.5−8.8); median time to CR of 2.8 mo (range, 1.0−11.8)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

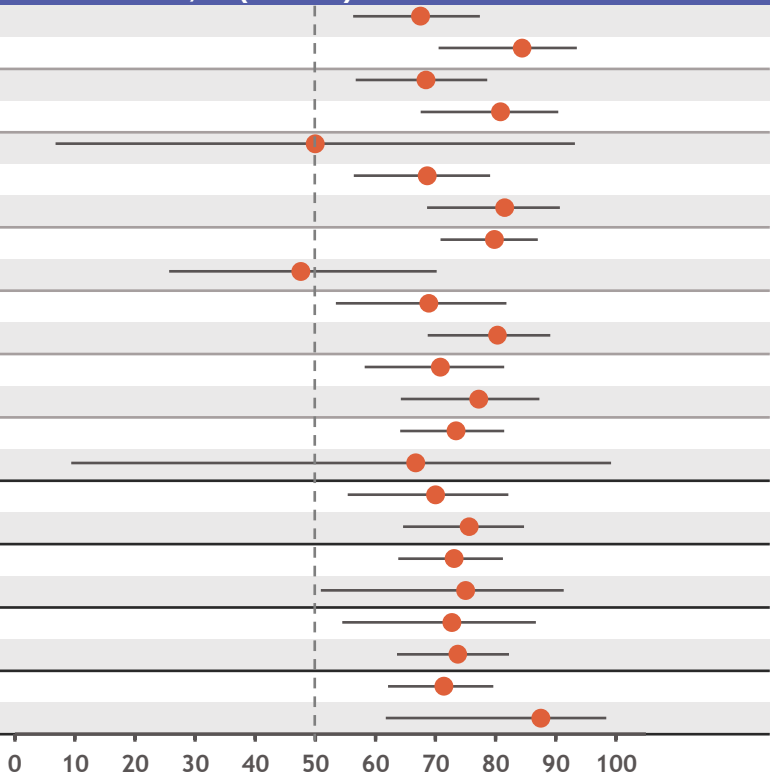
| Target dose, CAR+ T cells | 150 × $10^6$ | 300 × $10^6$ | 450 × $10^6$ | Total |
|---|---|---|---|---|
| All ide-cel treated | n = 4 | n = 70 | n = 54 | n = 128 |
| MRD negative and ≥CR, n (%) [95% CI] | **1 (25)** [0.6–80.6] | **17 (24)** [14.8–36.0] | **15 (28)** [16.5–41.6] | **33 (26)** [18.5–34.3] |
| 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

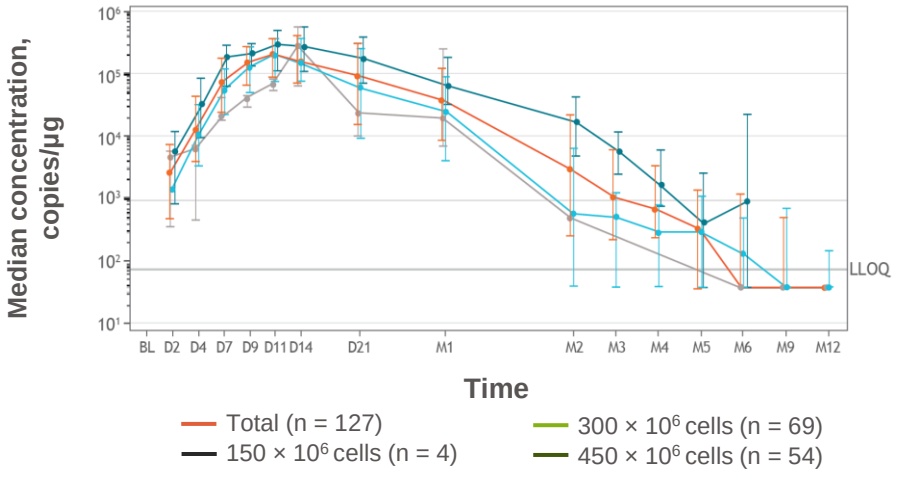
| Subgroup | | N | ORR, % (95% CI) |
|---|---|---|---|
| **Age group, years** | <65 | 83 | |
| | ≥65 | 45 | |
| **Sex** | Male | 76 | |
| | Female | 52 | |
| **Ide-cel target dose level, CAR+ T cells** | 150 × $10^6$ | 4 | |
| | 300 × $10^6$ | 70 | |
| | 450 × $10^6$ | 54 | |
| **R-ISS stage at enrollment** | 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.

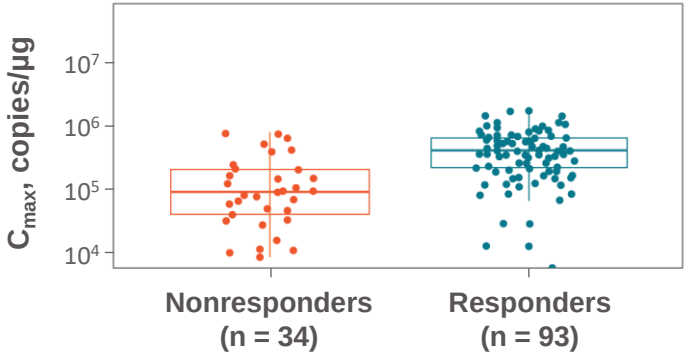
# CAR+ T-Cell Expansion, Persistence, and Peak Exposure

## 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) |

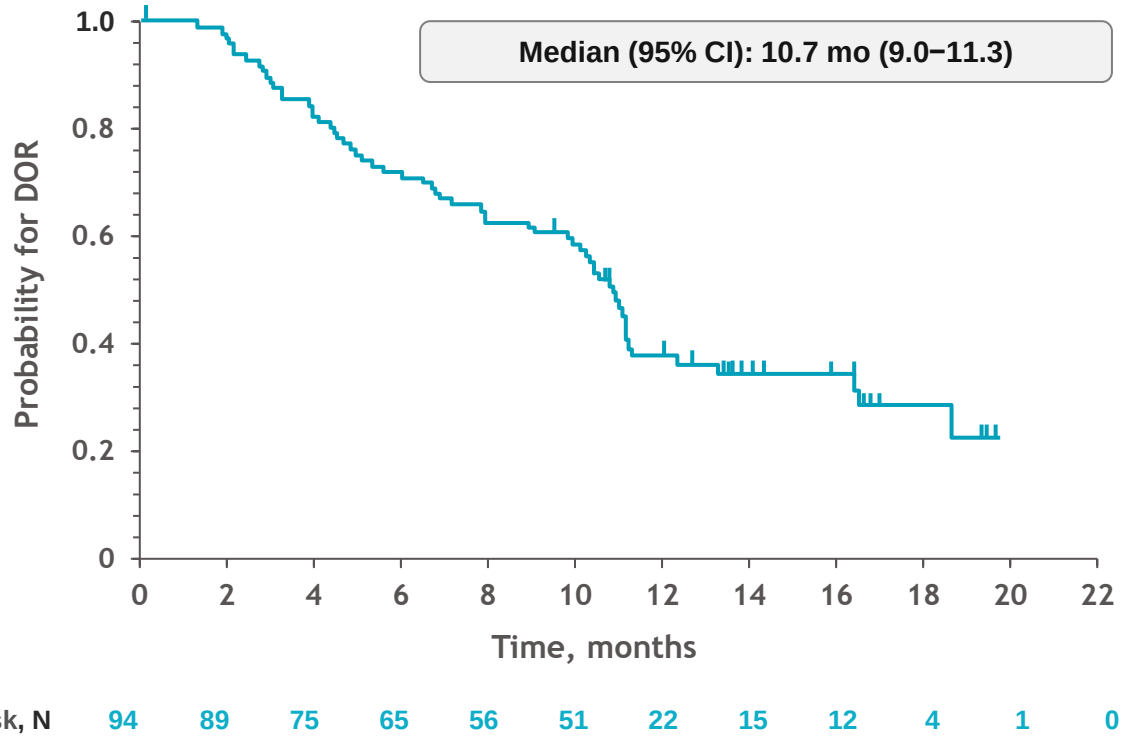
## Peak Vector Copies in Responders (≥PR) vs Nonresponders (<PR)




- 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.

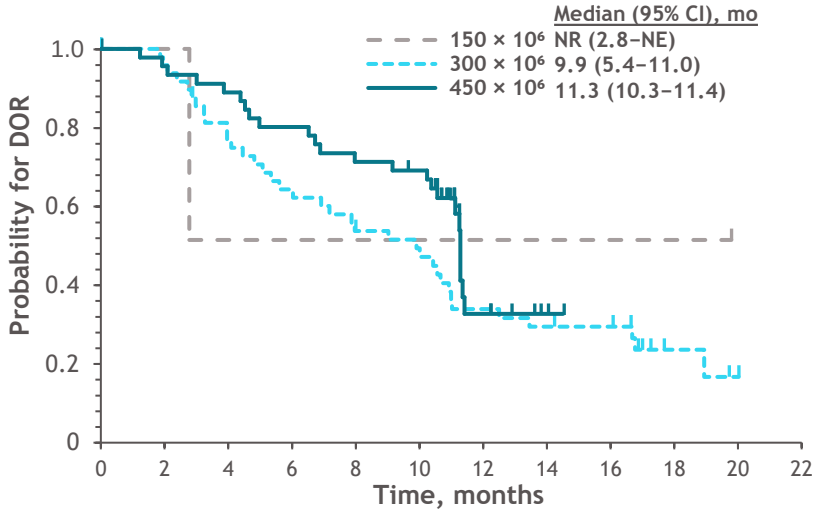
# Duration of Response




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

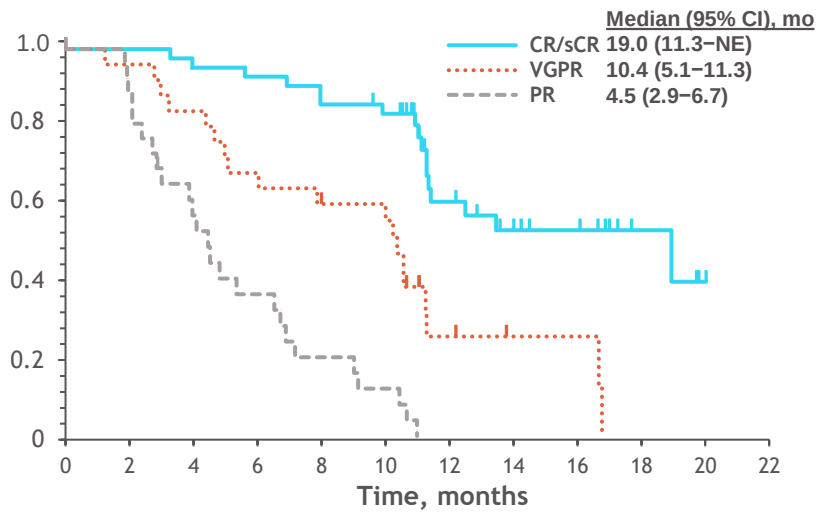
# Duration of Response by Target Dose and Best Response

## 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

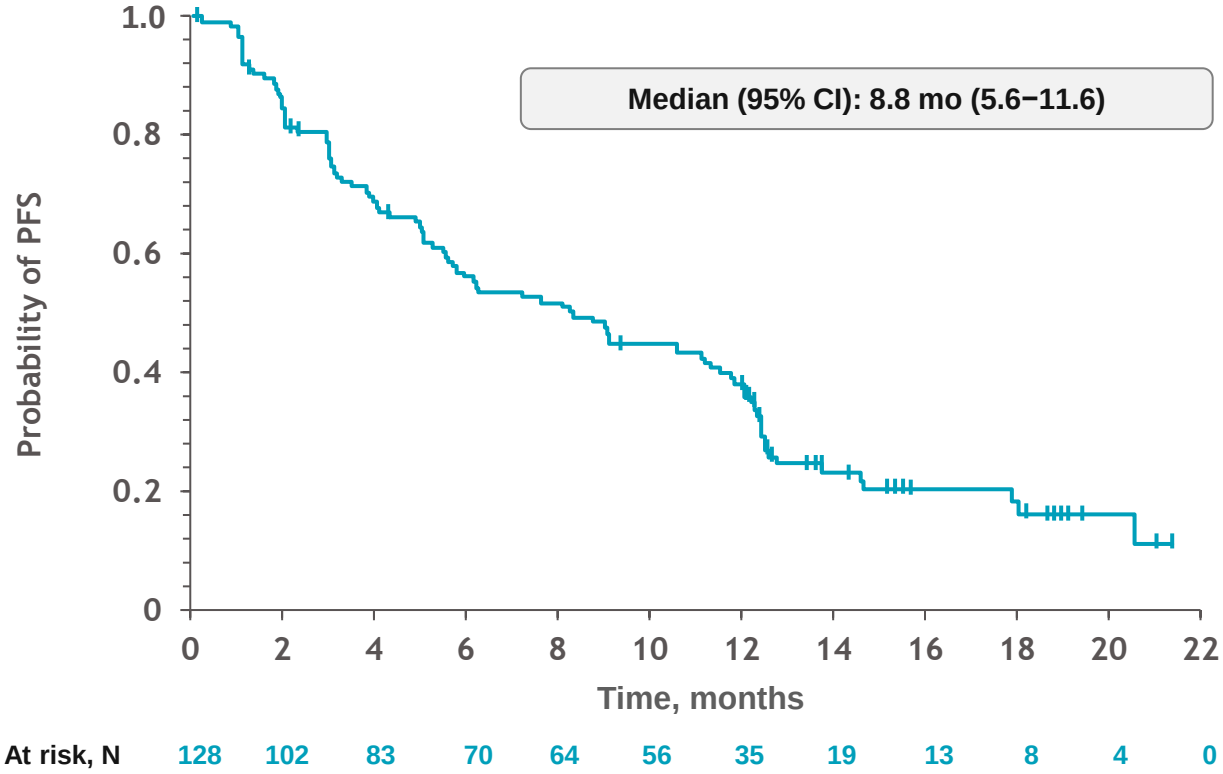



| At risk, n | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CR/sCR | 42 | 42 | 40 | 39 | 36 | 34 | 18 | 13 | 10 | 4 | 1 | 0 |
| VGPR | 25 | 24 | 21 | 17 | 15 | 14 | 4 | 2 | 2 | 0 | 0 | |
| PR | 27 | 23 | 14 | 9 | 5 | 3 | 0 | 0 | 0 | 0 | 0 | |

- 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.

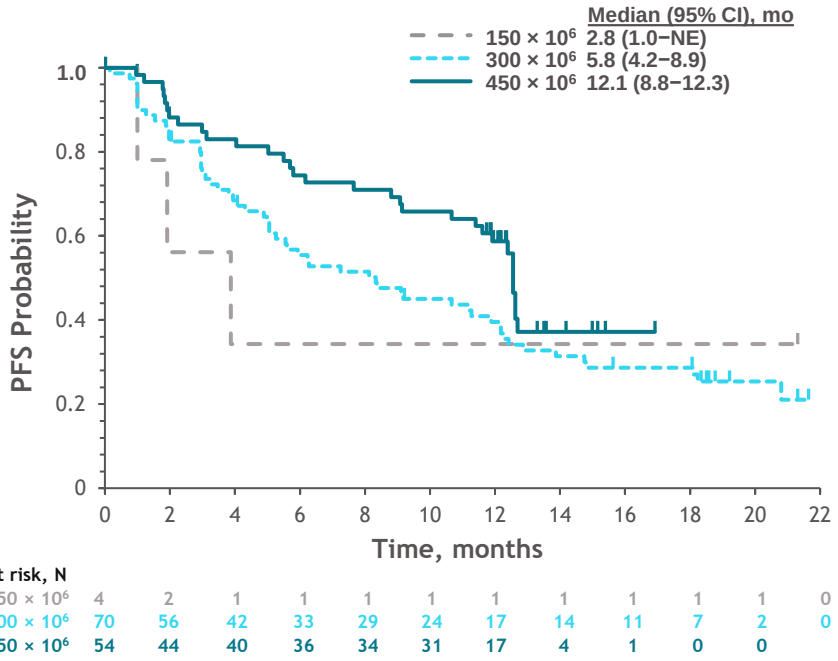
# Progression-Free Survival




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

# Progression-Free Survival

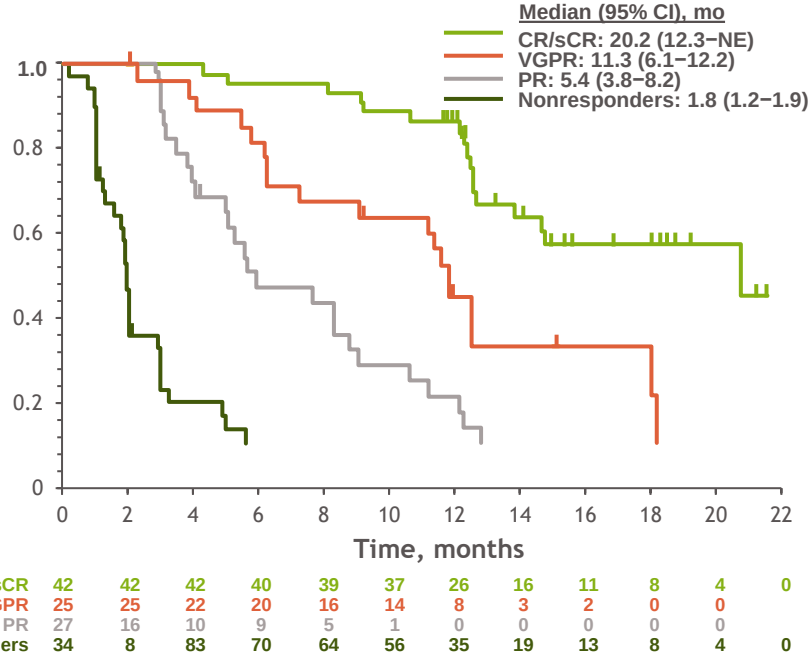
## PFS by Target Dose




| 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

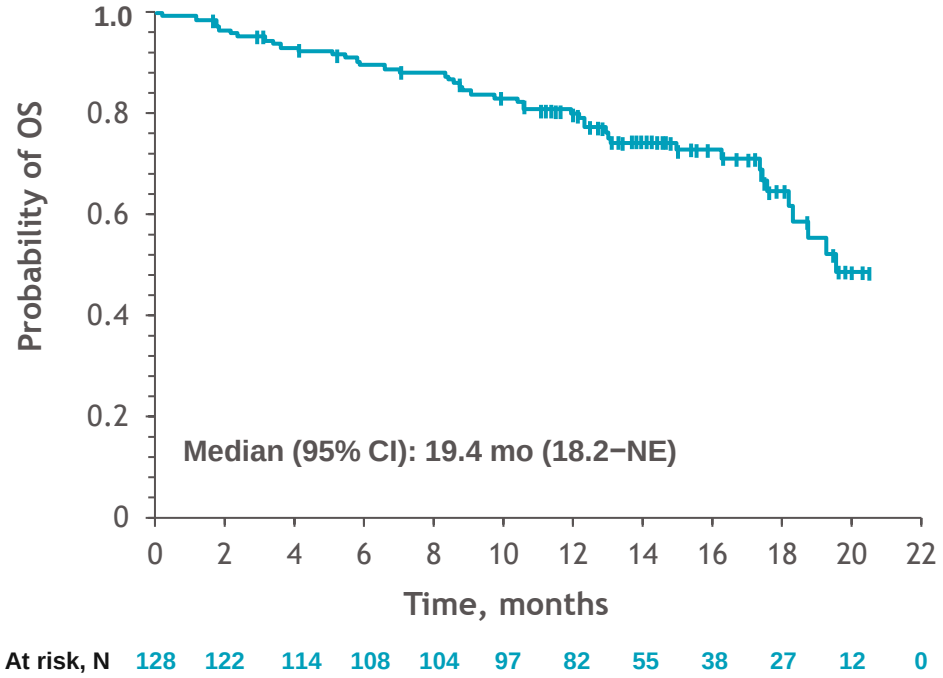



| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CR/sCR | 42 | 42 | 42 | 40 | 39 | 37 | 26 | 16 | 11 | 8 | 4 | 0 |
| VGPR | 25 | 25 | 22 | 20 | 16 | 14 | 8 | 3 | 2 | 0 | 0 | |
| PR | 27 | 16 | 10 | 9 | 5 | 1 | 0 | 0 | 0 | 0 | 0 | |
| Nonresponders | 34 | 8 | 83 | 70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

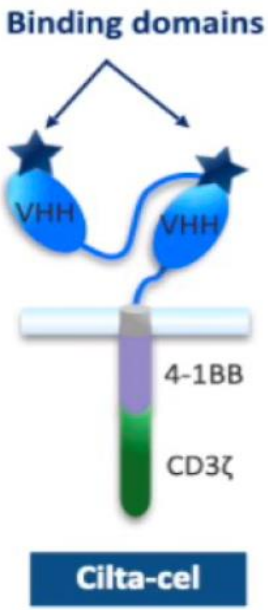
# EFFICACY AND SAFETY OF THE BCMA-DIRECTED CAR T-CELL THERAPY, CILTACABTAGENE AUTOLEUCEL, IN PATIENTS WITH PROGRESSIVE MULTIPLE MYELOMA AFTER 1–3 PRIOR LINES OF THERAPY: INITIAL RESULTS FROM CARTITUDE-2

**Mounzer Agha[1,*], Adam Cohen[2], Deepu Madduri[3], Yael C Cohen[4], Michel Delforge[5], Jens Hillengass[6], Hartmut Goldschmidt[7], Katja Weisel[8], Marc-Steffen Raab[9,10], Christoph Scheid[11], Jordan M Schecter[12], Kevin C De Braganca[12], Helen Varsos[12], Liwei Wang[12], Martin Vogel[13], Marlene J Carrasco-Alfonso[14], Muhammad Akram[14], Xiaoling Wu[14], Tonia Nesheiwat[14], Hermann Einsele[15]**

[1]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [5]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]University Hospital Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany; [8]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [9]University Hospital Heidelberg, Heidelberg, Germany; [10]Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center, Heidelberg, Germany; [11]University of Cologne, Cologne, Germany; [12]Janssen R&D, Raritan, NJ, USA; [13]Janssen Global Services, LLC, Raritan, NJ, USA; [14]Legend Biotech USA, Inc, Piscataway, NJ, USA; [15]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany

# CARTITUDE-2: Introduction

- Treatment options are limited for patients who have progressive MM after 1–3 lines of treatment and are refractory to lenalidomide and/or proteasome inhibitors[1,2]
  - A recent study with daratumumab + Pd and Pd group alone in lenalidomide exposed patients (lenalidomide refractory: 80%) reported a reduced risk in disease progression with a median PFS of 12.4 and 6.9 months, respectively[3]
  - There is an unmet need for novel and durable treatment options in this patient population
- Cilta-cel is a CAR T-cell therapy expressing 2 BCMA-targeting, single-domain antibodies designed to confer avidity
- In CARTITUDE-2, a multicohort phase 2 study, cilta-cel is being evaluated in patients with MM in earlier-line settings than in CARTITUDE-1[4]
- Here, we present initial results from patients (n=20) in Cohort A of CARTITUDE-2 who had progressive MM after 1–3 prior lines of therapy and were refractory to lenalidomide (median follow-up: 5.8 months)

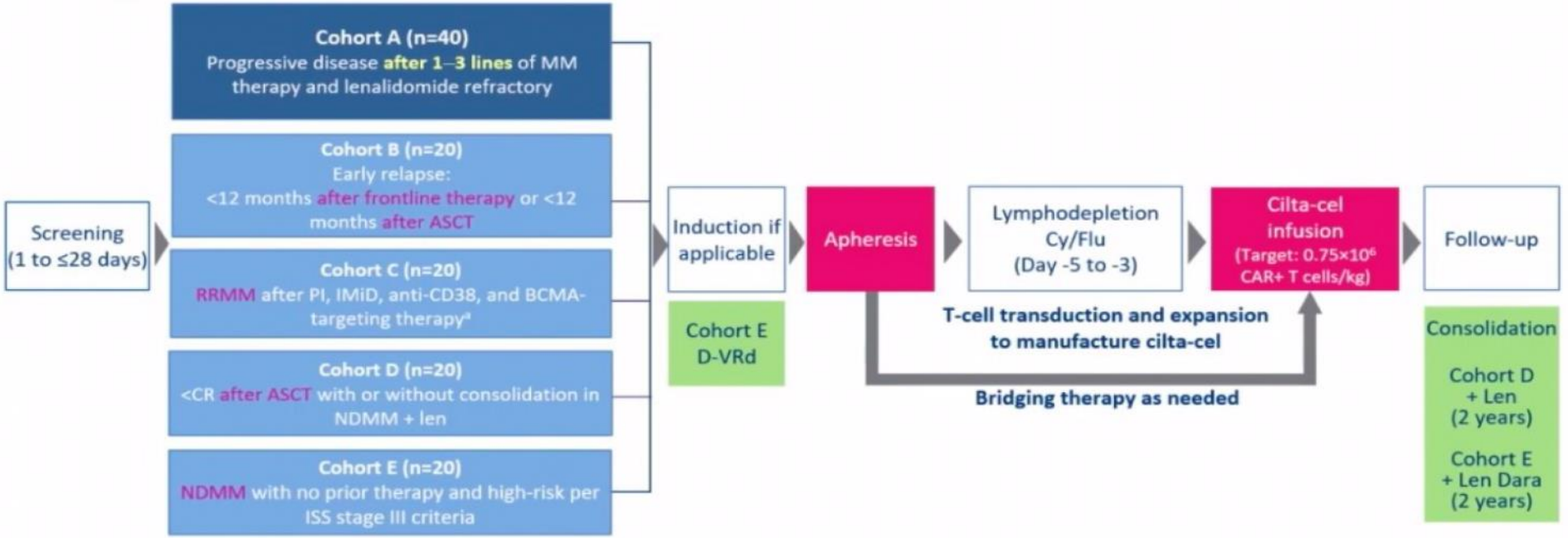



Abstract EP972

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; MM, multiple myeloma; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; VHH, variable heavy chain.

1. Richardson PG, et al. *Lancet Oncol* 2019;20:781-94. 2. Moreau P, et al. *Leukemia* 2017;31:115-22. 3. Dimopoulos M, et al. *Blood* 2020;136(Suppl 1):5-6. 4. CARTITUDE-1 phase 1b/2 efficacy and safety results will be presented at EHA Virtual Congress 2021 (Abstract EP972 available by scanning the QR code on this slide).

# CARTITUDE-2: Phase 2 Multi-Cohort Study in Various MM Settings




[a]Excluding prior BCMA-targeting cellular therapy.

ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; Cy, cyclophosphamide; Dara, daratumumab; D-VRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ISS, International Staging System; Len, lenalidomide; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.



Agha M, et al. EHA 2021. Abstract S190.

# CARTITUDE-2 Cohort A: Study Design

## Primary Objectives

- MRD $10^{-5}$ negativity as assessed by next-generation sequencing[a]

## Secondary Objectives

- ORR; per IMWG response criteria
- Duration of response
- Time and duration of MRD negativity
- Incidence and severity of AEs[b,c]

## Key Eligibility Criteria

- Progressive MM after 1–3 prior lines of therapy
  - Including a PI and an IMiD
- Lenalidomide refractory
- No prior exposure to BCMA-targeting agents


[a]ClonoSEQ, Adaptive Biotechnologies. [b]Assessed according to the Common Terminology Criteria for AEs version 5.0. [c]CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy criteria.
AE, adverse event; BCMA, B-cell maturation antigen; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; Cy, cyclophosphamide; Flu, fludarabine; ICANS, immune effector cell–associated neurotoxicity; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; MM, multiple myeloma; ORR, overall response rate; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics.



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# CARTITUDE-2: Baseline Characteristics

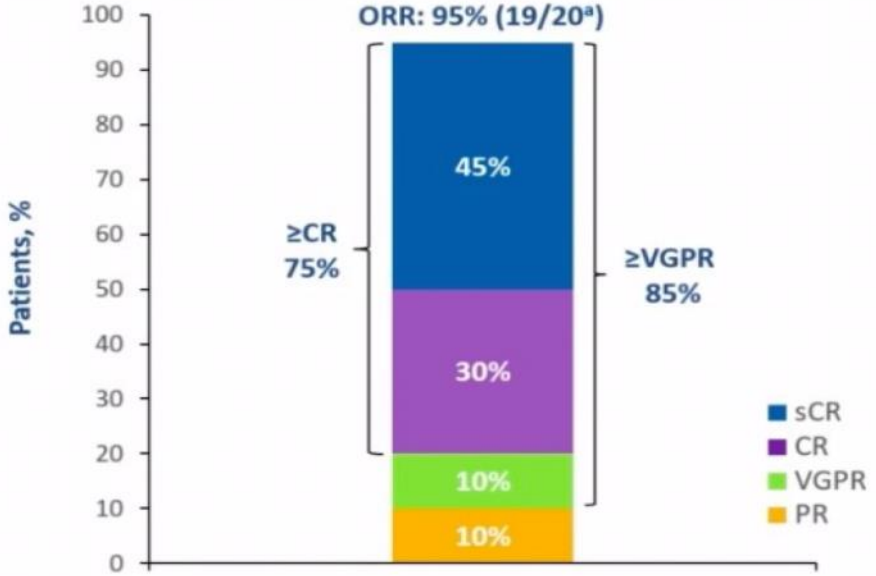
| Characteristic | N=20 |
|---|---|
| Male, n (%) | 13 (65) |
| Years since diagnosis, median (range) | 3.5 (0.7–8.0) |
| Age, years, median (range) | 60 (38–75) |
| Extramedullary plasmacytomas ≥1, n (%) | 3 (15) |
| Bone-marrow plasma cells[a] ≥60%, n (%) | 3 (15) |
| Prior lines of therapy, median (range) | 2 (1–3) |
| Number of prior lines of therapy, n (%) | |
| <3 prior lines | 12 (60) |
| 3 prior lines | 8 (40) |
| High-risk cytogenetic profile, n (%) | 7 (35)[b] |
| del17p | 3 (15) |
| t(14;16) | 5 (25) |
| t(4;14) | 0 |

| Characteristic | N=20 |
|---|---|
| Previous stem-cell transplantation, n (%) | |
| Autologous | 17 (85) |
| Allogeneic | 0 |
| Triple-class exposed,[c] n (%) | 13 (65) |
| Triple-class refractory,[c] n (%) | 8 (40) |
| Penta-drug exposed,[d] n (%) | 4 (20) |
| Penta-drug refractory,[d] n (%) | 1 (5) |
| Refractory status, n (%) | |
| Bortezomib | 8 (40) |
| Carfilzomib | 2 (10) |
| Pomalidomide | 7 (35) |
| Daratumumab | 12 (60) |
| Refractory to last line of therapy, n (%) | 19 (95) |

- All patients were refractory to lenalidomide
- All patients were exposed to a PI, an IMiD, and dexamethasone
- 95% were exposed to alkylating agents and 65% to daratumumab

[a]Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available. [b]One patient had both del17p and t(14;16).
[c]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [d]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody.
IMiD, immunomodulatory drug; PI, proteasome inhibitor.

# CARTITUDE-2: Overall Response Rate and MRD Negativity




- Median time to first response: 1.0 month (range, 0.7–3.3)
- Median time to CR or better: 1.9 months (range, 0.9–5.1)
- All patients (n=4) with MRD-evaluable[b] samples at the $10^{-5}$ threshold were MRD negative at data cut-off

Data cut-off date: Jan 2021. [a]Patient who did not respond had stable disease. [b]MRD was assessed in evaluable samples (ie, patients with identifiable clone at baseline and sufficient cells for testing at $10^{-5}$ threshold in post treatment samples) by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients.
CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.



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# CARTITUDE-2: Safety

| Nonhaematologic AEs ≥20%, n (%) | N=20 | |
|---|---|---|
| | Any grade | Grade 3/4 |
| Metabolism and nutrition disorders | | |
| Hypokalaemia | 8 (40) | 0 |
| Hypocalcaemia | 7 (35) | 3 (15) |
| Hypophosphataemia | 7 (35) | 3 (15) |
| Hypomagnesaemia | 6 (30) | 0 |
| Decreased appetite | 5 (25) | 3 (15) |
| Gastrointestinal | | |
| Diarrhoea | 9 (45) | 3 (15) |
| Nausea | 5 (25) | 0 |
| Constipation | 4 (20) | 0 |
| Vomiting | 4 (20) | 0 |
| Other | | |
| Fatigue | 9 (45) | 1 (5) |
| Back pain | 5 (25) | 2 (10) |
| Pyrexia | 5 (25) | 0 |
| Arthralgia | 4 (20) | 0 |
| Renal impairment | 4 (20) | 0 |

| Haematologic AEs ≥20%, n (%) | N=20 | |
|---|---|---|
| | Any grade | Grade 3/4 |
| Neutropaenia | 19 (95) | 18 (90) |
| Thrombocytopaenia | 16 (80) | 7 (35) |
| Anaemia | 13 (65) | 8 (40) |
| Lymphopaenia | 12 (60) | 11 (55) |
| Leukopaenia | 11 (55) | 11 (55) |

- Incidence of prolonged Grade 3/4 cytopaenias beyond Day 60:
  - Neutropaenia: 25%
  - Thrombocytopaenia: 0%
  - Lymphopaenia: 45%

AE, adverse event.



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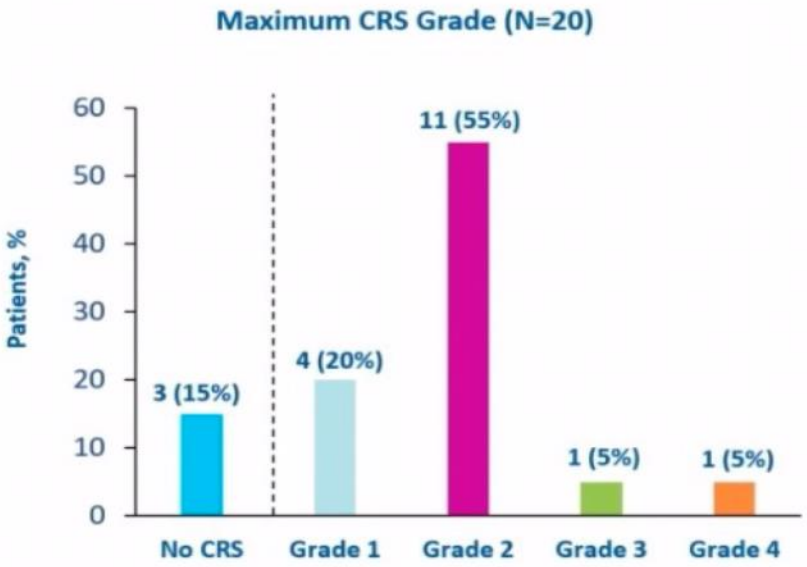
# CARTITUDE-2: Safety

| CRS | N=20 |
|---|---|
| Patients with a CRS event, n (%) | 17 (85) |
| Time to onset, days, median (range) | 7 (5–9) |
| Duration, days, median (range) | 3.5 (2–11) |
| Supportive measures,[a] n (%) | |
| Tocilizumab | 14 (70) |
| Corticosteroids | 6 (30) |
| IV fluids | 6 (30) |
| Oxygen | 4 (20) |
| Anakinra | 1 (5) |
| Vasopressor | 1 (5) |
| **CRS resolved or recovered in 94% of patients at the time of data cut-off** | |

| Neurotoxicity | N=20 |
|---|---|
| ICANS, n (%) | 3 (15) |
| Median time to onset, days (range) | 8 (7–11) |
| Median duration, days (range) | 2 (1–2) |
| **All ICANS were grades 1/2** | |
| **No cases of movement and neurocognitive TEAEs** | |




- 1 death occurred on Day 100 after infusion due to COVID-19, and was assessed as treatment-related by the investigator

[a]Includes supportive measures to treat CRS events and symptoms. Data cut-off date: Jan 2021

AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity; IV, intravenous; TEAE, treatment-emergent adverse event.



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# 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)
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 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: Newly Diagnosed and Relapsed/Refractory Multiple Myeloma

All Faculty

APTITUDE HEALTH®

# LATAM Faculty

**Jorge Vela-Ojeda, MD, PhD**
CMN La Raza, Mexico

**Humberto Martinez Cordero, MD, MSc**
National Cancer Institute,
Colombia

**Vania Hungria, MD, PhD**
São Germano Clinic,
Brazil

**Natalia Schütz, MD, MS**
Instituto Universitario del Hospital
Italiano de Buenos Aires, Argentina

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# Treatment Challenges in Relapsed/Refractory MM in the Region

Natalia Schütz, MD, MS

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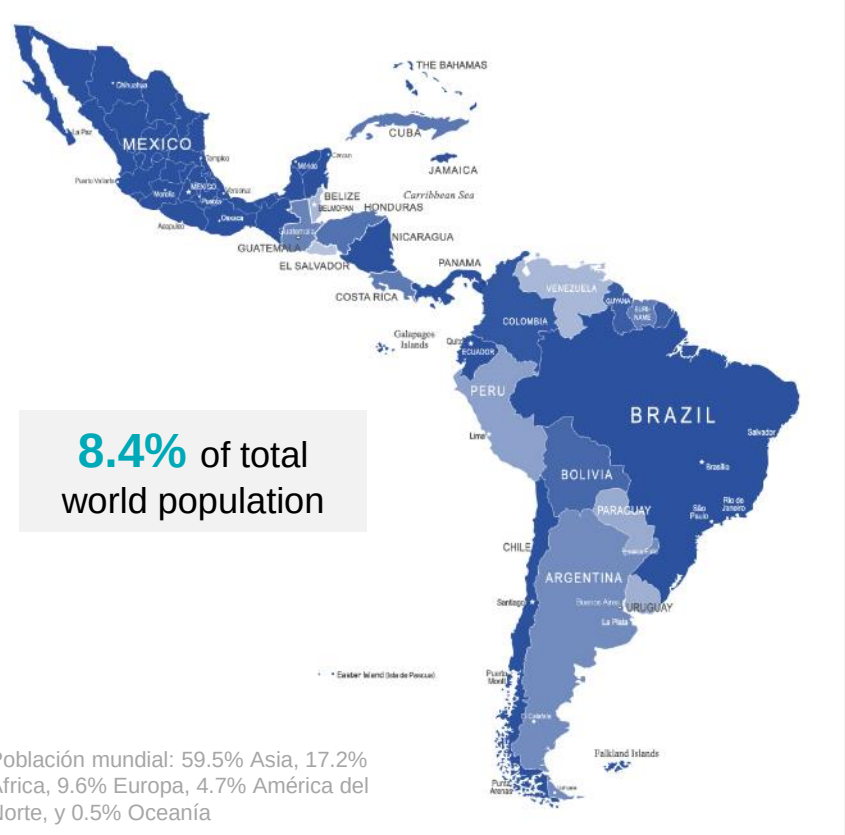
# Latin America in Numbers




**8.4%** of total world population

Población mundial: 59.5% Asia, 17.2% Africa, 9.6% Europa, 4.7% América del Norte, y 0.5% Oceanía

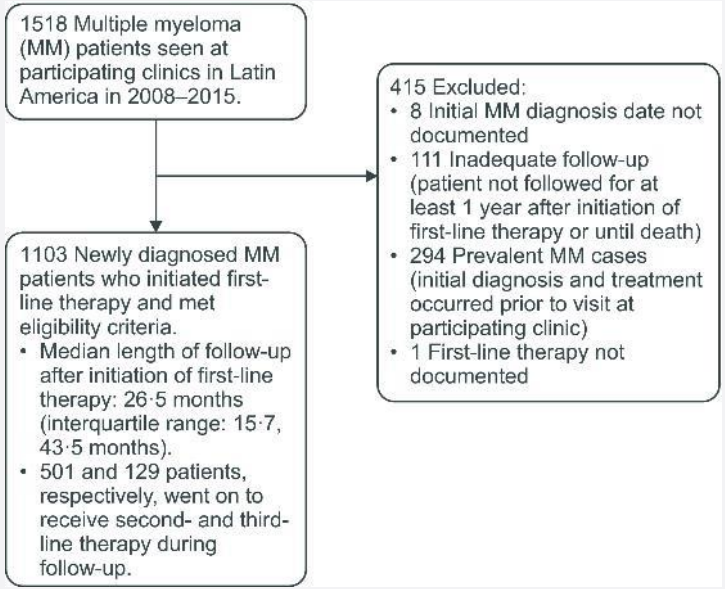
| | |
|---|---|
| Area | 19,197,000 km$^2$ (7,412,000 sq mi) |
| Population | 646,421,670 (2020) |
| Countries | 20 |
| Languages | **Mainly:** Spanish and Portuguese |

~12,000 new MM cases per year (Underdiagnosed)

Sources: Worldometer 2020; GLOBOCAN 2020.

# RWE LATAM: HOLA Study

## Epidemiologic Data



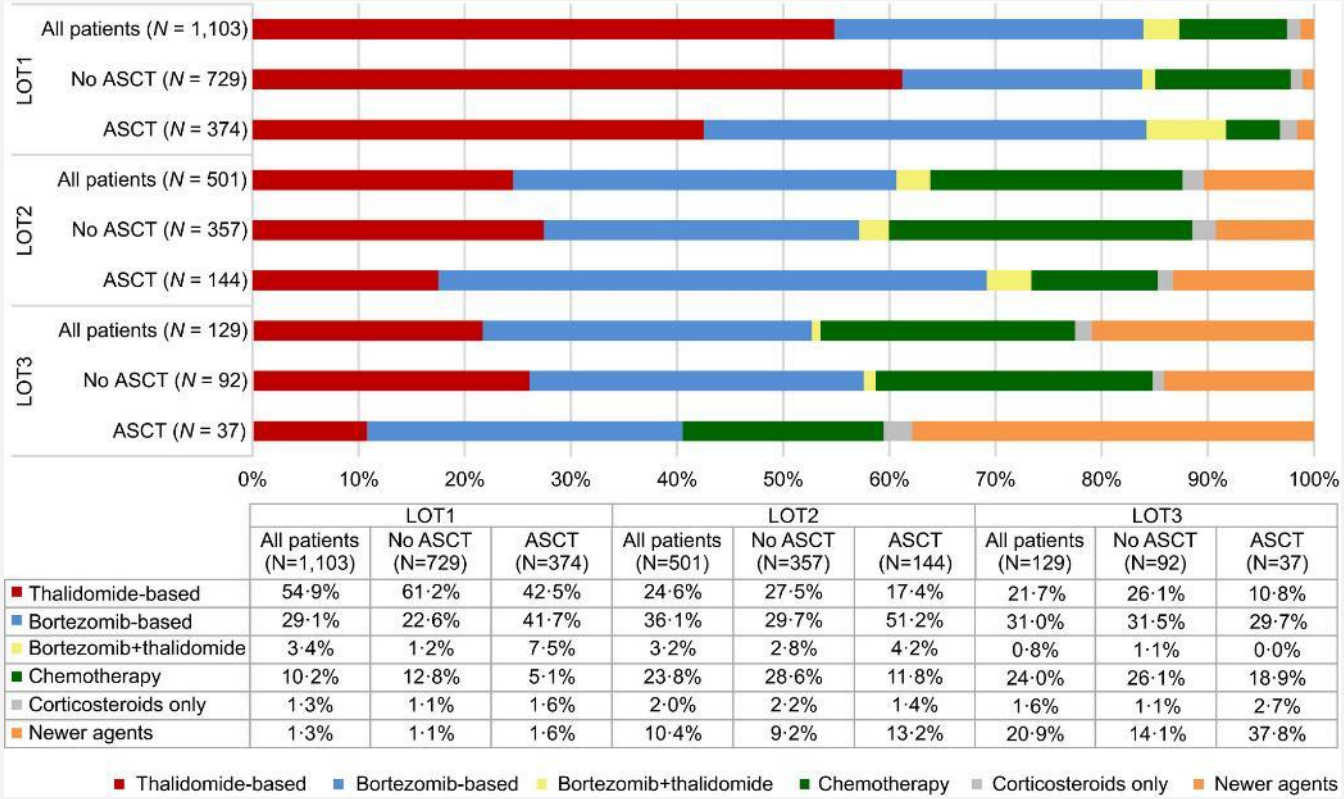

- The study cohort included 1103 eligible patients with NDMM from 2008 to 2015, and longitudinal follow-up ≥1 year or until death
- Median age at diagnosis was 61 years (IQR 53–69)
- ISS staging
  - 15.4% stage I
  - 21.2% stage II
  - 31.5% stage III
  - 31.9% Not documented
- CRAB at diagnosis
  - Bone disease 78.5%
  - Anemia 72.7%
  - Renal disease 27%
  - Hypercalcemia 16.7%
- For most patients (80%), cytogenetic testing was unavailable
- Among the 221 patients with cytogenetic test results
  - 34 (15.4%) have high-risk cytogenetics (del[17p], t[4; 14], or t[14; 16])



Tietsche de Moraes Hungria V, et al. *Br J Haematol*. 2020;188:383-393.

# RWE LATAM: HOLA Study

## Treatment Patterns




| | LOT1 | | | LOT2 | | | LOT3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | All patients (N=1,103) | No ASCT (N=729) | ASCT (N=374) | All patients (N=501) | No ASCT (N=357) | ASCT (N=144) | All patients (N=129) | No ASCT (N=92) | ASCT (N=37) |
| Thalidomide-based | 54·9% | 61·2% | 42·5% | 24·6% | 27·5% | 17·4% | 21·7% | 26·1% | 10·8% |
| Bortezomib-based | 29·1% | 22·6% | 41·7% | 36·1% | 29·7% | 51·2% | 31·0% | 31·5% | 29·7% |
| Bortezomib+thalidomide | 3·4% | 1·2% | 7·5% | 3·2% | 2·8% | 4·2% | 0·8% | 1·1% | 0·0% |
| Chemotherapy | 10·2% | 12·8% | 5·1% | 23·8% | 28·6% | 11·8% | 24·0% | 26·1% | 18·9% |
| Corticosteroids only | 1·3% | 1·1% | 1·6% | 2·0% | 2·2% | 1·4% | 1·6% | 1·1% | 2·7% |
| Newer agents | 1·3% | 1·1% | 1·6% | 10·4% | 9·2% | 13·2% | 20·9% | 14·1% | 37·8% |

Only 29% of patients received bortezomib in first line.

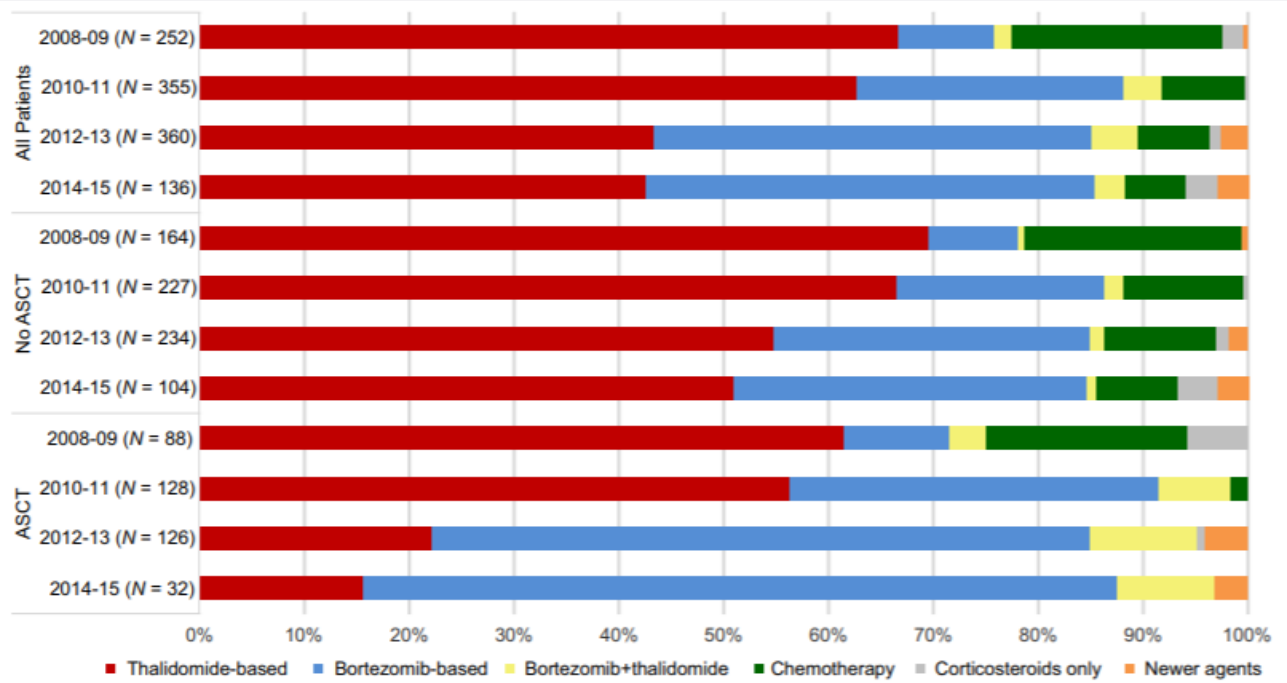
Only 33.9% underwent ASCT.

Newer agents: lenalidomide and carfilzomib.

Tietsche de Moraes Hungria V, et al. *Br J Haematol*. 2020;188:383-393.

# RWE LATAM: HOLA Study

## Time Trends




Over the course of the study period, it was shown that use of bortezomib in LOT1 increased markedly in recent years (2014–2015)

Newer agents: lenalidomide and carfilzomib.

Tietsche de Moraes Hungria V, et al. *Br J Haematol*. 2020;188:383-393.

# GELAMM Study

## Access to Tests and Treatments in LATAM

> Survey sent to 185 hematologists from 15 Latin American countries (2018)

**Table 4** First-line treatment choice for non-transplant-eligible MM patients

| First option | Public system | Private system |
|---|---|---|
| Standard risk patients | (*n* = 66) | (*n* = 83) |
| VTD | 15.1% (10) | 12.65% (11) |
| CTD | 34.8% (23) | 2.53% (3) |
| CYBORD | 21.2% (14) | 36.70% (30) |
| TD | 1.51% (1) | 1.26% (1) |
| RVd | 0 | 2.52% (2) |
| Rd | 8.06% (5) | 22.78% (18) |
| MPT | 15.1% (10) | 8.86% (7) |
| MP | 1.51% (2) | 3.79% (4) |
| VMP | 1.51% (1) | 8.86% (7) |
| High-risk patients | (*n* = 62) | (*n* = 84) |
| VTD | 17.7% (11) | 15.4% (13) |
| CTD | 25.8% (16) | 1.2% (1) |
| CYBORD | 25.8% (16) | 39.2% (33) |
| TD | 0 | 2.4% (2) |
| RVd | 4.8% (3) | 17.8% (15) |
| Rd | 1.6% (1) | 7.14% (6) |
| VAD | 3.2% (2) | 0 |
| KRd | 0 | 1.2% (1) |
| MPT | 4.8% (3) | 1.2% (1) |
| VMP | 16.1% (10) | 14.2% (12) |

**Table 3** First-line treatment choice for transplant-eligible MM patients

| First option | Public system (*n* = 67) | Private system (*n* = 85) |
|---|---|---|
| Standard risk patients | | |
| VTD | 26.8% (18) | 37.6% (32) |
| CyBorD | 23.8% (16) | 44.7% (38) |
| RVd | 0 | 4.7% (4) |
| KRD | 0 | 0 |
| VCTD | 1.5% (1) | 0 |
| CTD | 39% (26) | 13% (11) |
| TD | 7.46% (5) | 0 |
| High-risk patients | | |
| VTD | 31.3% (21) | 24.7% (21) |
| CyBorD | 36% (24) | 42.3% (36) |
| RVd | 4.4% (3) | 26% (22) |
| KRD | 0 | 1.1% (1) |
| VCTD | 1.5% (1) | 0 |
| CTD | 21% (14) | 0 |
| TD | 1 | 0 |
| VDT-PACE | 1.5% (1) | 0 |
| VAD | 1.5% (1) | 0 |

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Riva E, et al. *Ann Hematol*. 2020;99:1025-1030.

# Relapsed/Refractory MM

## Access to Combination Treatment in LATAM

| | ARGENTINA | | BRAZIL | | COLOMBIA | | MEXICO | |
|---|---|---|---|---|---|---|---|---|
| | Private | Public | Private | Public | Private | Public | Private | Public |
| DRd | | | | | | | | |
| KRd | | | | | | | | |
| IRd | | | | | | | | |
| ERd | | | | | | | | |
| DKd | | | | | | | | |
| DVd | | | | | | | | |
| DPd | | | | | | | | |
| Kd* | | | | | | | | |

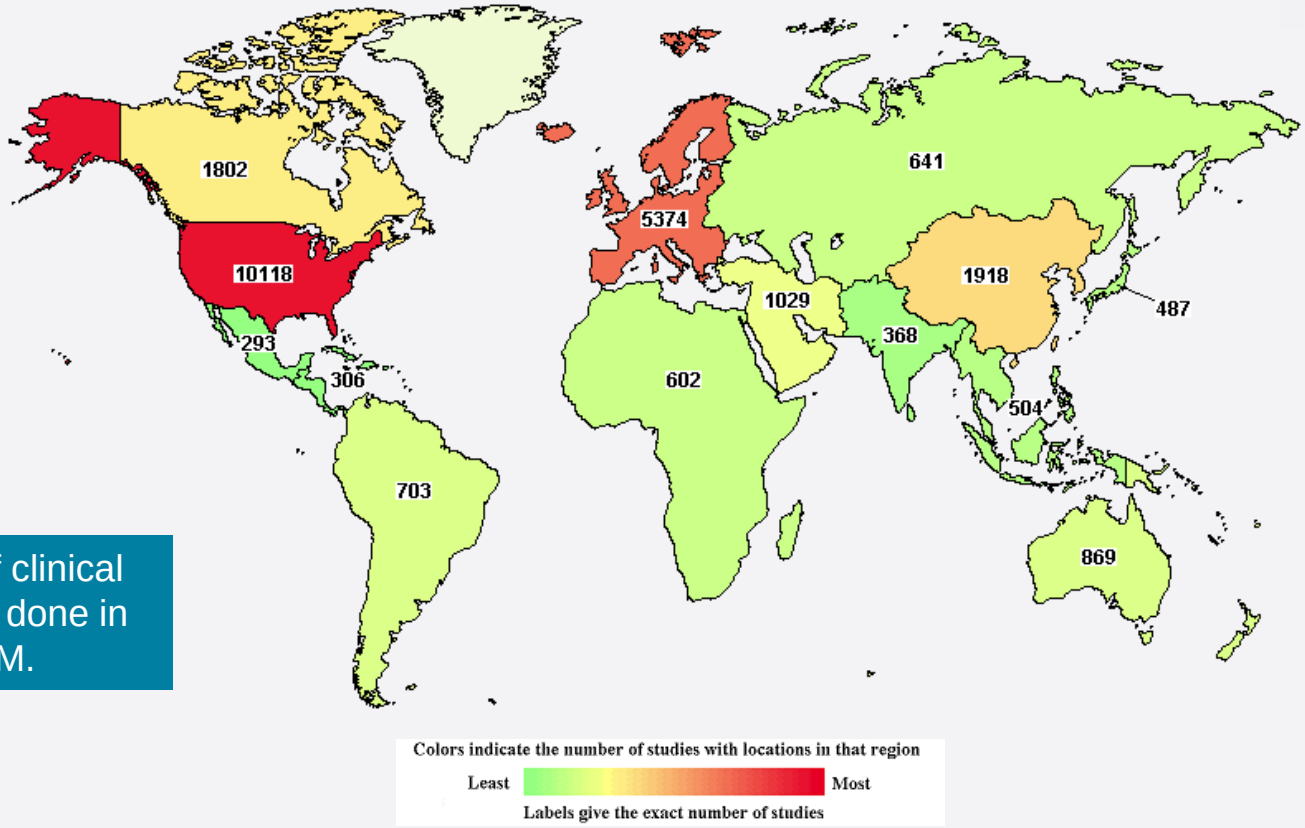
Even when new drugs are approved in most countries, access to combination therapy is limited, especially in the public setting.

*Kd: Reimbursement based on dose.

Based on preliminary data from American Health Foundation. Publication in process.

# Clinical Research in LATAM

## MAP of Hematology Registered Studies

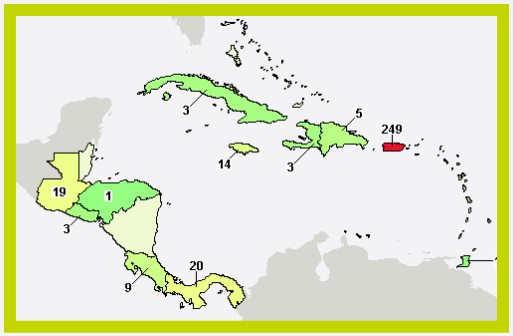


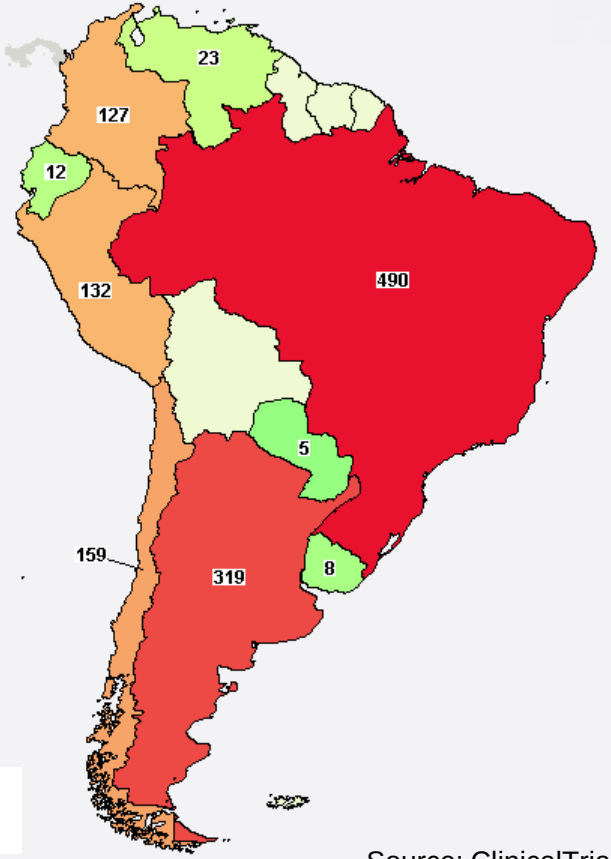

Only 2% of clinical research is done in LATAM.

Source: ClinicalTrials.gov 2018.

# Clinical Research in LATAM

## MAP of Hematology Registered Studies




Most RCTs in LATAM are conducted in Brazil, Mexico, and Argentina.

Colors indicate the number of studies with locations in that region

Least — Most

Labels give the exact number of studies

Source: ClinicalTrials.gov 2018.

# Treatment Challenges in the Region

## Healthcare Policy

- Healthcare system
- National guidelines
- Regulatory approvals
- Reimbursement

## Access to Innovation

- Clinical research
- Education
- Health technology assessment agencies
- Healthcare policies

CHALLENGES

## Medical Education

- Physicians
- Healthcare providers
- Patients
- Diagnosis and awareness

## Clinical Research

- Clinical trials
- RWE data


Source: Author opinion – Natalia Schütz.

Global Multiple Myeloma Academy

# Short Discussion

All Faculty

APTITUDE HEALTH

Global Multiple Myeloma Academy

# Case 1: Patient with HRMM and early relapse after ASCT

Cristian M. Seehaus, MD

Hospital Italiano de Buenos Aires,

Buenos Aires, Argentina

HOSPITAL ITALIANO de Buenos Aires

Instituto Universitario Hospital Italiano

G.A.M.M. Grupo Argentino de Mieloma Múltiple

APTITUDE HEALTH

# Patient History and Frontline Therapy

## > Patient characteristics

- 46-year-old male patient
- No past medical history
- ECOG performance status: 1

## > Initial presentation and diagnosis

JAN 2019

- Symptoms: tumor in the left rib, asthenia, and weight loss

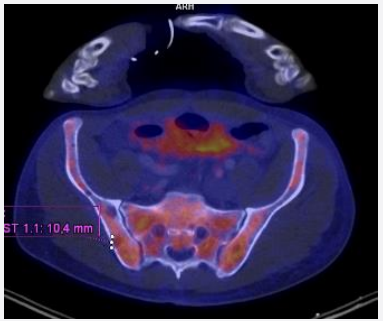
| CBC and chemistry | |
|---|---|
| Hemoglobin | **7.9 g/dL** |
| WBC | 5.152/mm$^3$ |
| Platelets | **65.100/mm$^3$** |
| Creatinine | 1.09 mg/dL |
| Calcium | 10.5 mg/dL |
| Liver panel | Normal |

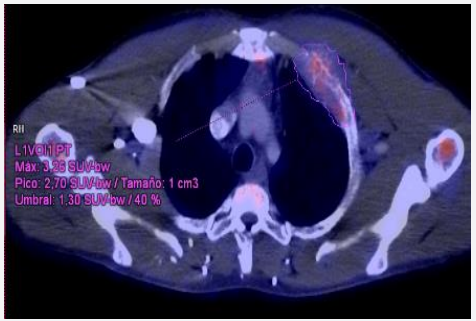
| Protein test | |
|---|---|
| Serum immunofixation | **IgA lambda** |
| M-spike | **8.38 g/dL** |
| IgA/IgG/IgM levels | **8.800/260/5 mg/dL** |
| FLC kappa/lambda | **840/4.5 mg/dL (ratio 194)** |
| Albumin/B2 microglobulin | 2.6 g/dL/8.7 mg/L |
| LDH UI/L | Normal |

| Urine analysis | |
|---|---|
| 24-hour protein excretion | 0.45 g/day |
| Creatinine clearance | 75 mL/min |
| Urine immunofixation | **IgA lambda with glomerular proteinuria** |
| Urine LC | 36.9 mg/dL |
| Urine M-spike | Not available |

# Patient History and Frontline Therapy

- Bone marrow biopsy: 90% clonal plasma cells
- Cytogenetics: 48.XY.+add(1)(p13)×2.der(1;6)(p10;p10).+3.-8.-12.r(13)(p11.2q?).+15.+18.-20.-22.+mar1.+mar2[6]/46.XY[14]
- Imaging: PET/CT SCAN




- Hypermetabolic lytic lesions in the right and left acetabulum (SUV 12.8 and 4.2)
- Bone lesion with soft tissue infiltration in the second left rib (SUV 3.3)

> Risk assessment

- ISS 3; R-ISS 2
- Amplification of *CKS1B* gene at chromosome region 1q21 (1q+) in 21% of BM cells by FISH (PCs sorting was not performed)

HRMM IgA lambda (ISS 3; R-ISS 2 with 1q+)
Myeloma-defining events: anemia and lytic lesions

# Patient History and Frontline Therapy

> Frontline therapy

**JAN 2019**

- Induction: patient received VRD. He achieved VGPR after 4 cycles
- Patient presented with AE: G3 PNP
- He underwent a tandem ASCT. He achieved sCR
- Maintenance: IRD (ixazomib 3 mg, lenalidomide 10 mg)

**JAN 2020**

- Relapse from CR: in a follow-up visit (2 months after starting maintenance), sIFx results tested positive

**JUN 2020**

- Progressive disease: serum protein electrophoresis showed an M-spike >0.5 g/dL

Biochemical relapse was confirmed, with progressive increase in M-spike

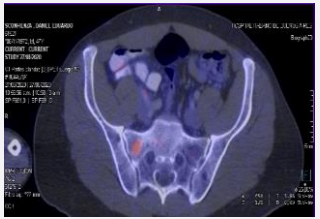


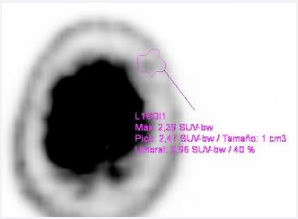
AE, adverse event; IRD, ixazomib, lenalidomide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone.

# Relapsed/Refractory Setting

AUG 2020

- Bone marrow biopsy: 35% clonal plasma cells
- Cytogenetics: 47.XY.+1.add(1)(q21).-2.+3.add(5)(q22).add(6)(q23).-8.+9.-13.+15.-16.-20.[2]/46.XY[18]
- FISH t(4;14), t(14;16), del(17p): negative
- Imaging: PET/CT SCAN. New bone lesions (2)





| Blood test | |
|---|---|
| Hemoglobin | 12.3 g/dL |
| Creatinine | 0.98 mg/dL |
| Calcium | 8.9 mg/dL |
| M-spike | **1.98 g/dL** |
| IgA level | **1.320 mg/dL** |
| FLC kappa/lambda | **332/5 mg/dL (ratio 59)** |

Clinical relapse was confirmed

The patient had an early relapse (it occurred within 18 months of starting initial therapy and within 12 months from ASCT)

# Audience ARS Question

> In your daily clinical practice, how do you treat patients with HRMM relapsed/refractory to lenalidomide?

a) Pomalidomide-based treatment regimens (PCD, PVD)
b) Daratumumab-based treatment regimens (DVD, DPD, DD)
c) Intensive chemotherapy regimens (PACE, DCEP, etc)
d) Carfilzomib-based regimens (KCD, KD)
e) Other regimens (re-exposure to the same induction regimen, CD, etc)

# Relapsed/Refractory Setting

> Second-line therapy

SEP 2020

- DPD was started as second line
- He achieved partial response after 2 cycles
- He presented progressive disease with M-spike of 2.01 after 4 cycles

> Further therapies

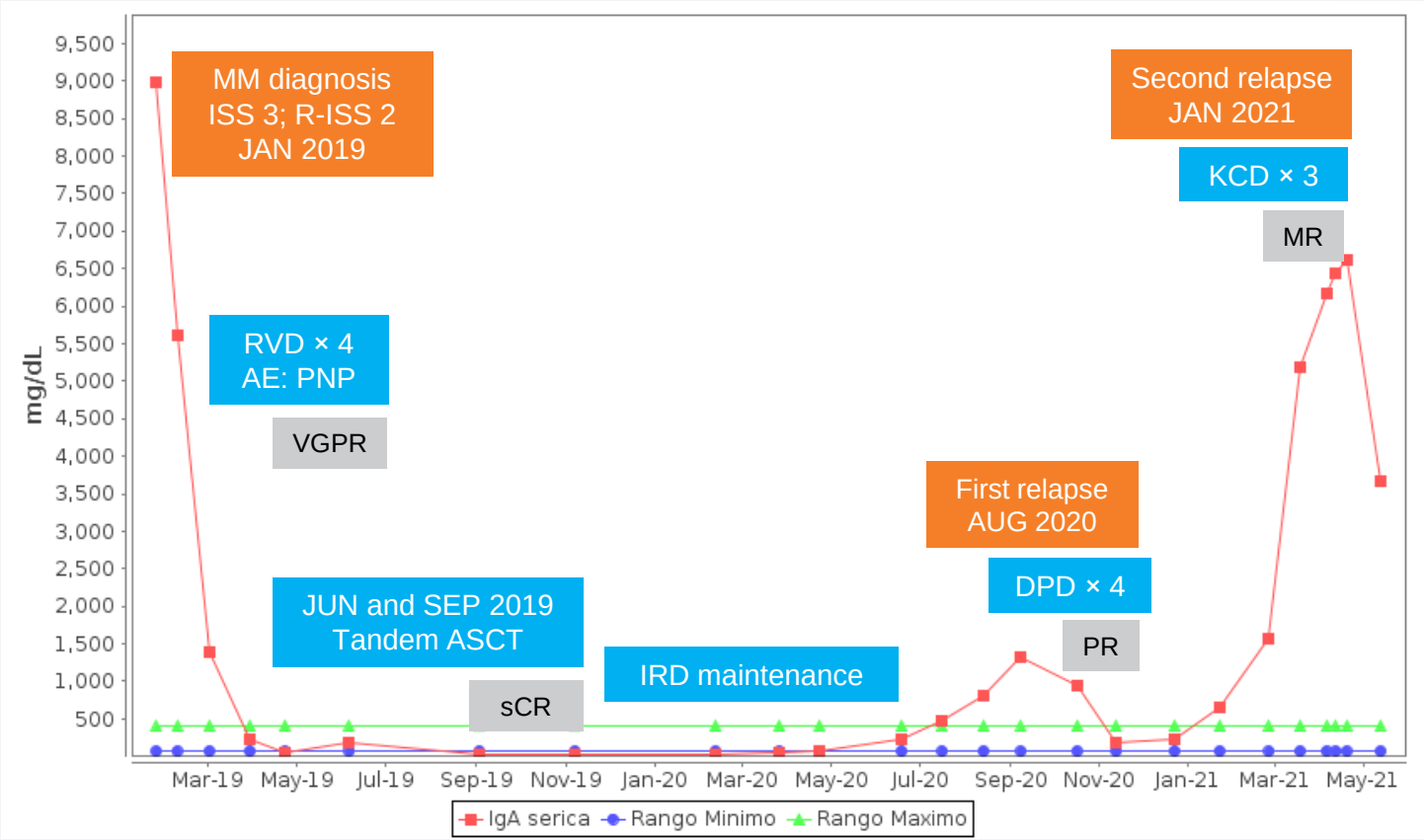
MAR 2021

- He presented on PET/CT with positive uptake in second left rib with lytic lesion and M-spike of 4.98 g/dL
- He started a third line with KCD (20/36 mg/m$^2$, 300 mg/m$^2$, and 20 mg, respectively)
- He presented a 25% reduction in M-spike after 2 cycles (minimal response)



DPD, daratumumab, pomalidomide, dexamethasone; KCD, carfilzomib, cyclophosphamide, dexamethasone.

# Resume


MM diagnosis
ISS 3; R-ISS 2
JAN 2019
RVD × 4
AE: PNP
VGPR
JUN and SEP 2019
Tandem ASCT
sCR
IRD maintenance
First relapse
AUG 2020
DPD × 4
PR
Second relapse
JAN 2021
KCD × 3
MR
mg/dL
9,500
9,000
8,500
8,000
7,500
7,000
6,500
6,000
5,500
5,000
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
Mar-19
May-19
Jul-19
Sep-19
Nov-19
Jan-20
Mar-20
May-20
Jul-20
Sep-20
Nov-20
Jan-21
Mar-21
May-21
IgA serica
Rango Minimo
Rango Maximo

# Audience ARS Question

> In your daily clinical practice, how do you treat patients with penta-refractory MM?

a) Anti-BCMA therapy (BiTEs, CAR T cells, belantamab mafodotin)
b) Intensive chemotherapy regimens (PACE, DCEP, etc)
c) Selinexor-based treatment regimens
d) Other regimens
e) Palliative care

Global Multiple Myeloma Academy

# Discussion: Case 1

Case Discussants: Cristian M. Seehaus, MD + Natalia Schütz, MD, MS

Moderator: Rafael Fonseca, MD

APTITUDE HEALTH

# Case 2: High-Risk MM Patient

Ana Luiza Miranda Silva Dias, MD
São Germano Clinic
São Paulo, Brazil

# Clinical Case Study

***58-year-old man referred to his orthopedist for back pain (March 2020)***

| Lab tests | BM biopsy | FISH test | Imaging |
|---|---|---|---|
| **Hb: 7.7 g/dL**<br>**Creatinine: 1.79 mg/dL**<br>**Calcium: 9.5 mg/dL**<br>**M-spike: 7.0 g/dL**<br>**IgA Kappa**<br>**IgA: 7,414 mg/dL**<br>**B2 m: 6.5 mg/dL**<br>**Albumin: 2.5 g/dL**<br>**LDH 147 IU/L**<br>**sFLC (k/l): 571** | **90% k-restricted clonal CD 138 plasma cells** | **FISH CD 138 isolated plasma cells**<br>**t(4;14), 1q+ (63%), 17 del (25%)** | **Whole-body low-dose CT scan showed multiple lytic lesions and vertebral fractures (T7, T8, T9, L2, L3 and L4)** |

Personal data: Dra Ana Luiza Miranda.

# Clinical Case Study

- 58-year-old man
- No comorbidities
- Multiple myeloma IgA-kappa
- ISS 3
- R-ISS 3
- Fit

Personal data: Dra Ana Luiza Miranda.

## Clinical Case Treatment Proposal

- Induction regimen Dara-VTd followed by ASCT

## Clinical Case Treatment Performed

- 6 cycles of Dara-VTD since 26/Mar 2020 to 28/Oct 2020 (delayed because of COVID-19 pandemic)
- After induction: VGPR

Personal data: Dra Ana Luiza Miranda.

# Clinical Case Study

- In your clinical practice, which do you perform for high-risk transplant-eligible MM patients?

A) Single ASCT

B) Double ASCT

# Clinical Case Study

***After double transplant, he achieved stringent complete response, MRD negativity***

| Lab tests (after 2nd SCT) | BM biopsy + MCF (after 2nd SCT) | FISH test (after 2nd SCT) | PET CT (after 2nd SCT) |
|---|---|---|---|
| Hb: 12.4 g/dL<br>Creatinine: 0.82 mg/dL<br>Calcium: 10.5 mg/dL<br>M-spike: absent<br>IF negative<br>IgA: 222 mg/dL<br>B2 m: 2.5 mg/dL<br>Albumin: 4.5 g/dL<br>LDH 180 IU/L<br>sFLC (k/l): 1.20 | Clonal CD 138 plasma cells: negative<br><br>MRD negative (MCF $10^{-6}$) | FISH CD 138 isolated plasma cells: negative | Negative |

Personal data: Dra Ana Luiza Miranda.

# Clinical Case Outcome

- After induction → VGPR

- After double transplant → sCR, MRD negative and PET CT negative

Personal data: Dra Ana Luiza Miranda.

# Clinical Case Study

- In your opinion, what is the best choice for this patient after the double ASCT?

A) 2 cycles of D-VTd follow by daratumumab until progression or toxicity

B) 2 cycles of D-VTd follow by daratumumab plus lenalidomide until progression or toxicity

C) 2 cycles of D-VTd follow by PI plus lenalidomide until progression or toxicity

D) Daratumumab, PI plus lenalidomide until progression or toxicity

E) Carfilzomib plus lenalidomide until progression or toxicity

F) Ixazomib plus lenalidomide until progression or toxicity

Personal data: Dra Ana Luiza Miranda.

# THANK YOU!!!

GBRAM
GRUPO BRASILEIRO DE MIELOMA

São Germano
Oncologia

Global Multiple Myeloma Academy

# Discussion: Case 2

Case Discussants: Ana Luiza Miranda Silva Dias, MD + Vania Hungria, MD, PhD

Moderator: Rafael Fonseca, MD

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# Case 3: Newly Diagnosed + R/R MM Patient

Didier Larios Sanjuan, MD

National Cancer Institute of Colombia

Bogotá, Colombia

Instituto Nacional de Cancerología-ESE
Colombia
Por el control del cáncer

APTITUDE HEALTH®

# Patient History and Frontline Therapy

- Sociodemographic data
  - Woman
  - 54 years old
  - Born: Bogotá
  - Resident: Bogotá
  - Occupation: Bacteriologist
  - Civil status: Single
  - Evaluation date: September 2016

# Patient History and Frontline Therapy

- Clinical data
  - 54-year-old woman with diagnosis of IgG kappa ISS III multiple myeloma in September 2016
  - She presented with sternal chest pain of moderate intensity, not irradiated, of 1 year of evolution, receiving stepped analgesic treatment without clinical improvement
  - CRAB component (without hypercalcemia, without renal involvement, without anemia but with generalized lytic lesions on PET CT)

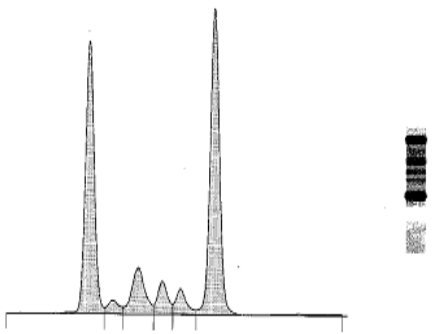
# Patient History and Frontline Therapy

- Clinical data
  - Important personal history: right nephrectomy in 2015 due to renal cell carcinoma, papillary variant type 2, unifocal, without vascular invasion. Hysterectomy for uterine myomatosis in 2012. Nontoxic and non-exposure history
  - Family history: mother died of colon carcinoma at 62 years of age
  - System review: no relevant data
  - Physical examination: in general, acceptable condition, with no pathologic findings during evaluation

# Patient History and Frontline Therapy

| PARACLINICS | |
|---|---|
| | |
| Blood count (Sept 10, 2016) | Hb 12.90 g/dL, Hto 39%, MCV 89 fL, leukocytes 6560 × $mm^3$, neutrophils 3660 × $mm^3$, lymphocytes 2010 × $mm^3$, platelets 232,000 × $mm^3$ |
| | |
| Kidney function tests (Sept 10, 2016) | Creatinine 0.8 mg/dL<br>Ureic nitrogen 12 mg/dL |
| | |
| Liver function (Sept 10, 2016) | SGPT 19 U/L, SGOT 19.5 U/L, total bilirubin 0.2 mg/dL, alkaline phosphatase 80 U/L |
| | |
| Electrolytes (Sept 10, 2016) | Sodium 135 mmol/L, potassium 4.2 mmol/L, chlorine 101 mmol/L, calcium 10.99 mg/dL |

# Patient History and Frontline Therapy



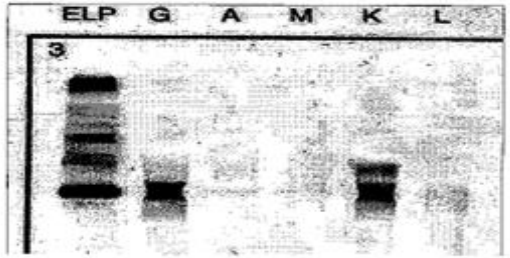
*Serum protein electrophoresis*

| Fractions | % | | Ref. % | Conc. | Ref. Conc. | | |
|---|---|---|---|---|---|---|---|
| Albumina | 37.9 | < | 59.4 - 73.9 | 4.3 | 3.7 - 6.1 | T. P.: 11.3 | g/dL |
| Alfa 1 | 2.2 | | 1.2 - 3.1 | 0.2 | 0.1 - 0.3 | | |
| Alfa 2 | 9.1 | | 7.0 - 12.2 | 1.0 | 0.4 - 1.0 | | |
| Beta 1 | 4.9 | | 4.9 - 9.4 | 0.6 | 0.3 - 0.8 | | |
| Beta 2 | 4.0 | | 1.6 - 5.6 | 0.5 | 0.1 - 0.5 | | |
| Gamma | 41.9 | > | 6.9 - 14.7 | 4.7 | 0.4 - 1.2 | | |

A/G Ratio: **0.61**

Serum beta-2 microglobulin: 7.9 mg/L
LDH 220 U/L

***Immunofixation Serum***




**Comment:**

**Monoclonal component of the IgG kappa type is observed**

September 21, 2016

# Patient History and Frontline Therapy

Serum immunoglobulin levels: IgA 30 mg/dL, IgM 17 mg/d, IgG 5191 mg/dL

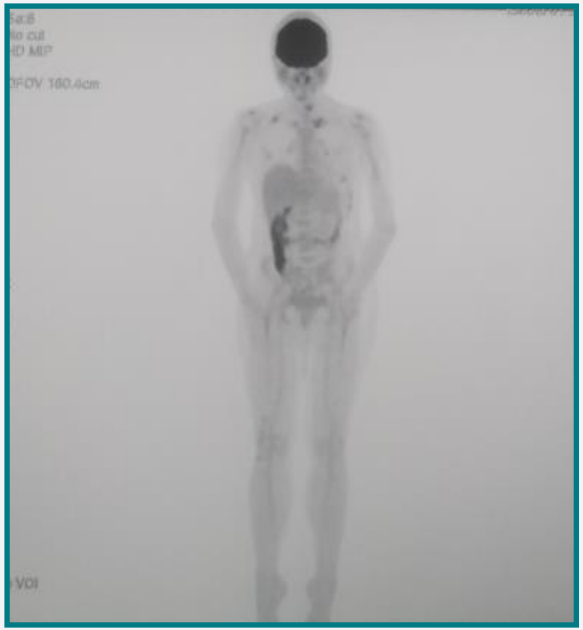
Quantification of free light chains in serum
Kappa: 6277 mg/L
Lambda: 5.70 mg/L
Kappa/Lambda ratio: 1101

September 21, 2016

# Patient History and Frontline Therapy

## IMAGING STUDIES

### POSITRON EMISSION TOMOGRAPHY (PET SCAN)



- Lytic hypermetabolic involvement in the sternal manubrium with SUV 8.0 with adjacent soft tissue component
- Hypermetabolism in the third right anterior costal arch with irregular trabeculation, metabolic increase SUV 5.0 in the tenth left lateral costal arch

# Patient History and Frontline Therapy

| BONE MARROW STUDIES |
| --- |
| **HISTOPATHOLOGY** |
| Bone marrow with a cellularity variable between 30 and 60%, with interstitial and nodular infiltration (70%) by a neoplasm made up of plasma cells with a high nucleus-cytoplasm radius, some with prominent nucleoli of immature appearance; the findings are interpreted as infiltration by a plasma cell neoplasm |
| **IMMUNOHISTOCHEMISTRY** |
| Positivity CD38, CD138, MUM1, CD79a, CD56 with marked kappa predominance. Negative cytokeratin cocktail AE1–AE3, ACL–CD3, CD20, CD10, PAX8, lambda |
| **FLOW CYTOMETRY** |
| 9.4% of abnormal plasma cells with expression of CD38, CD138, CD56, CD19 negative, CD45 negative, and monoclonality of cytoplasmic kappa light chains are detected |

# Patient History and Frontline Therapy

| BONE MARROW STUDIES |
| --- |
| **KARYOTYPE** |
| 46, XX. In 30 metaphases analyzed |
| **FISH** |
| - Negative FISH for t(14;16), trisomy of the 14q32 region suggesting rearrangements of the IGH gene<br>- FISH negative for deletion or loss of p53 (17p)<br>- Positive FISH for t(4;14) translocation, fusion of the FGFR31-IGH genes with an atypical pattern<br>- Positive FISH for rearrangements involving the IGH gene (14q32) with an atypical pattern<br>- FISH positive for deletion of 13q<br>- FISH negative for t(11;14) |

# QUESTION

- What would be the ideal treatment in this case?

A. VTd
B. VRd
C. VCD
D. Daratumumab + VRd
E. Daratumumab + VTd

# Patient History and Frontline Therapy

ISS III (beta-2 microglobulin 7.9 mg/L)

First-line treatment:
VRd (bortezomib, lenalidomide, dexamethasone): October 2016 to February 2017
Zoledronic acid
Levofloxacin prophylaxis ~3 months
Four cycles

Response after the second cycle: partial response
Post-fourth cycle response: very good partial response

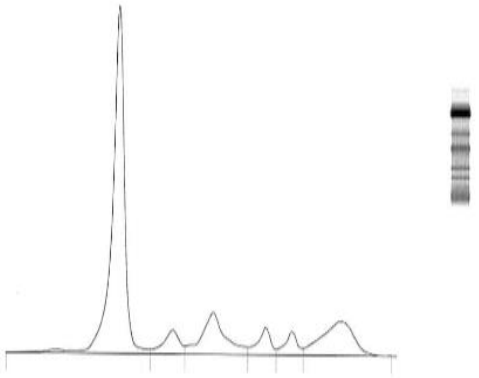
# Patient History and Frontline Therapy

Consolidation with autologous hematopoietic transplantation (April 2017)
Response at day 100 post-HPT: very good partial response

Post-autologous hematopoietic transplant maintenance: lenalidomide (2 years: June 2017–**May 2019**)

Response in May 2019: stringent complete response and complete immunophenotypic response (no NGS or NGF available)

# Patient History and Frontline Therapy



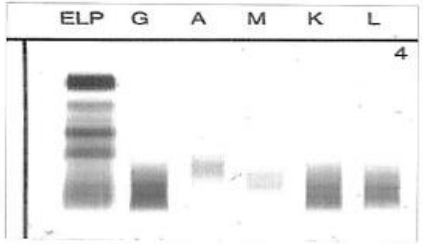
*Serum protein electrophoresis*

| Fractions | % | | Ref. % | Conc. | Ref. Conc. |
|---|---|---|---|---|---|
| Albumin | 57.8 | | 55.8 - 66.1 | 4.0 | 4.0 - 4.8 |
| Alfa 1 | 5.2 | > | 2.9 - 4.9 | 0.4 | 0.2 - 0.4 |
| Alfa 2 | 13.3 | > | 7.1 - 11.8 | 0.9 | 0.5 - 0.9 |
| Beta 1 | 4.8 | | 4.7 - 7.2 | 0.3 | 0.3 - 0.5 |
| Beta 2 | 4.0 | | 3.2 - 6.5 | 0.3 | 0.2 - 0.5 |
| Gamma | 14.9 | | 11.1 - 18.8 | 1.0 | 0.8 - 1.4 |

T. P.: 7 g/dl

A/G Ratio: 1.37

*Immunofixation Serum*




Comment:

Negative for monoclonal component

Studies in bone marrow without neoplastic involvement by plasma cells

May 2019 – stringent complete response

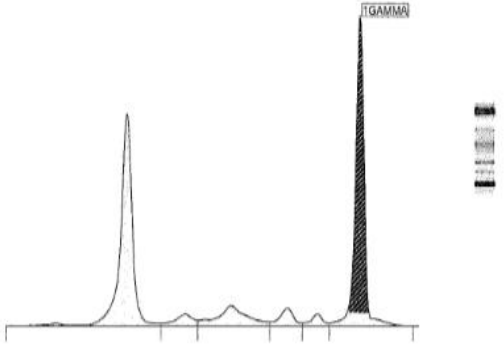
# Should maintenance be stopped?

A. Yes
B. No

# Relapsed/Refractory Setting

Biochemical relapse (November 2020) 18 months after discontinuation of maintenance

# Relapsed/Refractory Setting




*Serum protein electrophoresis*

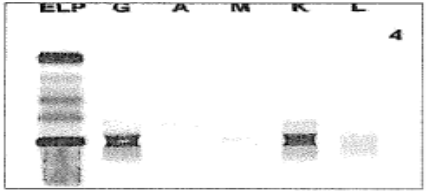
| Fractions | % | | Ref. % | Conc. | Ref. Conc. |
|---|---|---|---|---|---|
| Albumin | 39.1 | < | 55.8 - 66.1 | 4.2 | 4.0 - 4.8 |
| Alfa 1 | 3.1 | | 2.9 - 4.9 | 0.3 | 0.2 - 0.4 |
| Alfa 2 | 8.9 | | 7.1 - 11.8 | 1.0 | 0.5 - 0.9 |
| Beta 1 | 3.7 | < | 4.7 - 7.2 | 0.4 | 0.3 - 0.5 |
| Beta 2 | 2.1 | < | 3.2 - 6.5 | 0.2 | 0.2 - 0.5 |
| Gamma | 43.1 | > | 11.1 - 18.8 | 4.6 | 0.8 - 1.4 |

T. P.: **10.7** g/dl

| Peak | % | g/dl |
|---|---|---|
| 1GAMMA | 36.3 | 3.9 |

A/G Ratio: **0.64**

*Immunofixation Serum*




**Comment:**

**Monoclonal component of the IgG Kappa type is observed**

IgG: 6192 mg/dL
Kappa free light chains: 537.96
Lambda free light chains: 5.19
Ratio: 103.65

Relapse: November 2020

# Relapsed/Refractory Setting

| BONE MARROW STUDIES |
| --- |
| **HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY** |
| Interstitial and small group (30%) infiltration by plasma cells, immunohistochemistry with positive plasma cells with CD38, CD138, and CD56, with kappa monotypicity, few lambda-positive cells |
| **MYELOGRAM** |
| Plasma cell neoplasia (19% of plasma cells) |
| **BONE MARROW FLOW CYTOMETRY** |
| 4.2% of mature T-lymphocyte population and 0.33% of mature polyclonal B-lymphocyte population are observed; 7.2% of abnormal plasma cells are detected with expression of CD38, CD138, CD56, beta-2 microglobulin, cytoplasmic kappa light chain monoclonality, negative CD19, and negative CD45. There is 67.6% of mature myeloid population and 2.7% of monocytic population |
| **NO CRAB** |

# What would be the best salvage treatment?

A. Daratumumab, lenalidomide, and dexamethasone
B. Daratumumab, pomalidomide, and dexamethasone because lenalidomide-refractory disease
C. Daratumumab, bortezomib, and dexamethasone because t(4;14) and bortezomib sensitive at the start of the disease
D. Carfilzomib, daratumumab, pomalidomide, and dexamethasone

# Relapsed/Refractory Setting

Current treatment

CASTOR protocol: daratumumab, bortezomib, dexamethasone **(available)**
Currently the fourth cycle will begin
Waiting for response measurement after 4 cycles

# Points for Discussion

- After 2 years of maintenance, would you be aligned with the need to assess MRD negativity to stop treatment?
- Proposal of ideal treatment lines in this case (not in Latin America)?
- Do you suggest other complementary studies for the monitoring and definition of the therapeutic line?
- What would be the best treatment if this patient is refractory to the current treatment?
- Considering the duration of remission in the first transplant, could the second transplant be an option?

Global Multiple Myeloma Academy

# Discussion: Case 3

Case Discussants: Didier Larios San Juan, MD + Humberto Martinez Cordero, MD, MSc

Moderator: Rafael Fonseca, MD

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# Case 4: Relapsed/Refractory MM Patient

Sofía Sánchez, MD

La Raza Medical Center, IMSS,

Mexico City, Mexico

APTITUDE HEALTH®

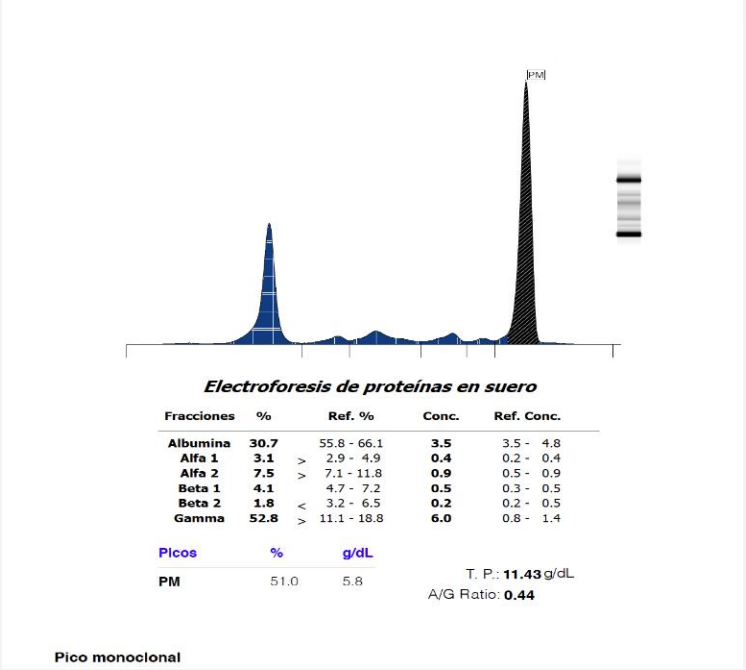
# Patient History and Frontline Therapy

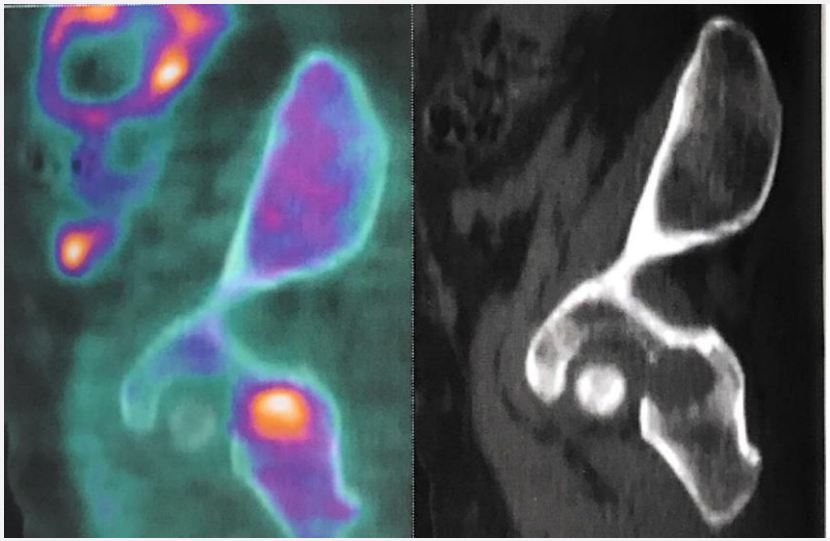
## 56 years old, female

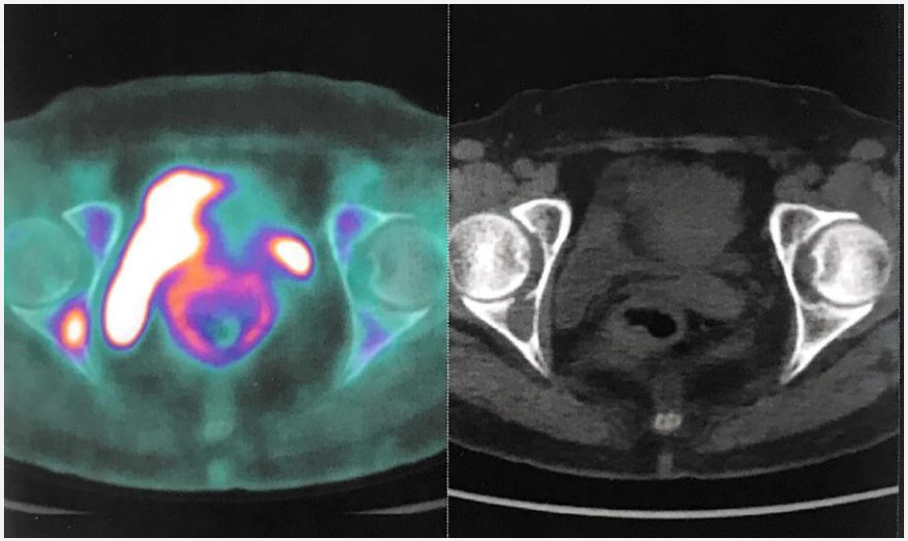
| Blood test | |
|---|---|
| Hemoglobin | 6.4 g/dL |
| **Creatinine** | 3.42/1.42 mg/dL |
| **Albumin** | 3.01 g/dL |
| **IgG** | 6 g/L |
| **LDH** | 131 UI/L (max 250) |
| **B2-micro** | 5.3 mg/L |

## Multiple myeloma IgG/kappa, R-ISS II

- M: 5 g/dL
- K/L: 457
- **FISH: gain of 9, 11, 15/hyperdiploidy (the test was performed on selected clonal plasma cells (CD138+, CD38+, CD19+, CD56+)**







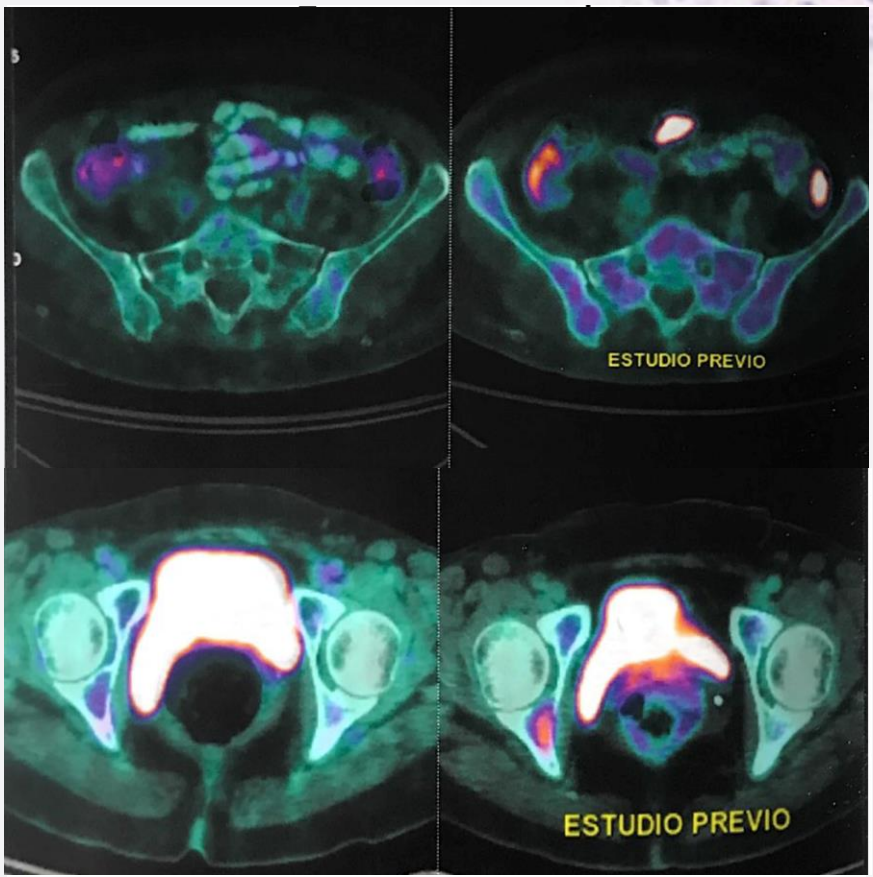
# Frontline Therapy

- D-VTD 4 cycles: VGPR
- ASCT-D/VTD (2)
  - CR, (FLC K/L: 1.05)
  - MRD– (NGF, $10^7$) and PET-CT negative
- Maintenance: lenalidomide

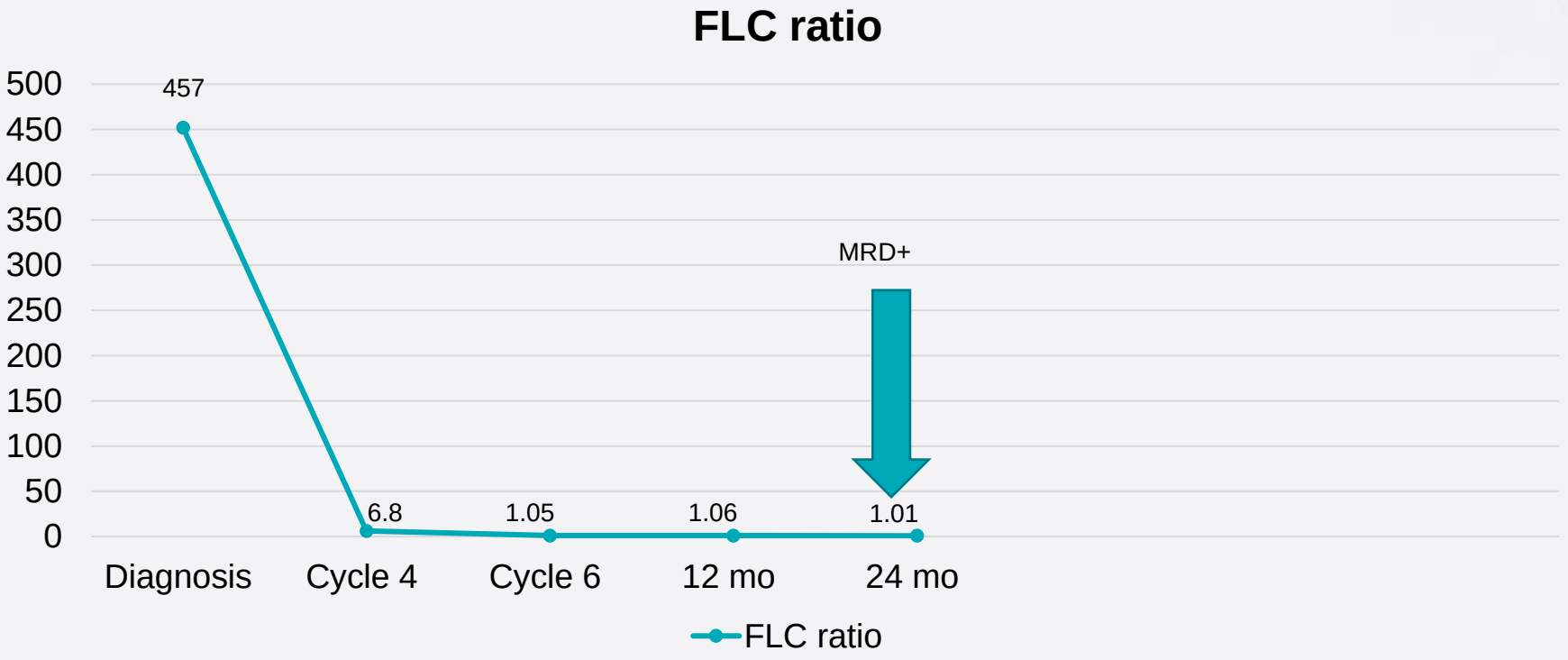
**CD45-,CD38+,CD138+/-heterogéneo,CD56+,CD19-,Beta2 microglobulina+,Kappa+,Lambda-,CD28-,CD81-,CD27+,CD117-**

**INTERPRETACIÓN**
**El presente inmunofenotipo es compatible con Enfermedad mínima residual NO DETECTABLE ( 0.00%) (Sensibilidad 10 - 7 )**

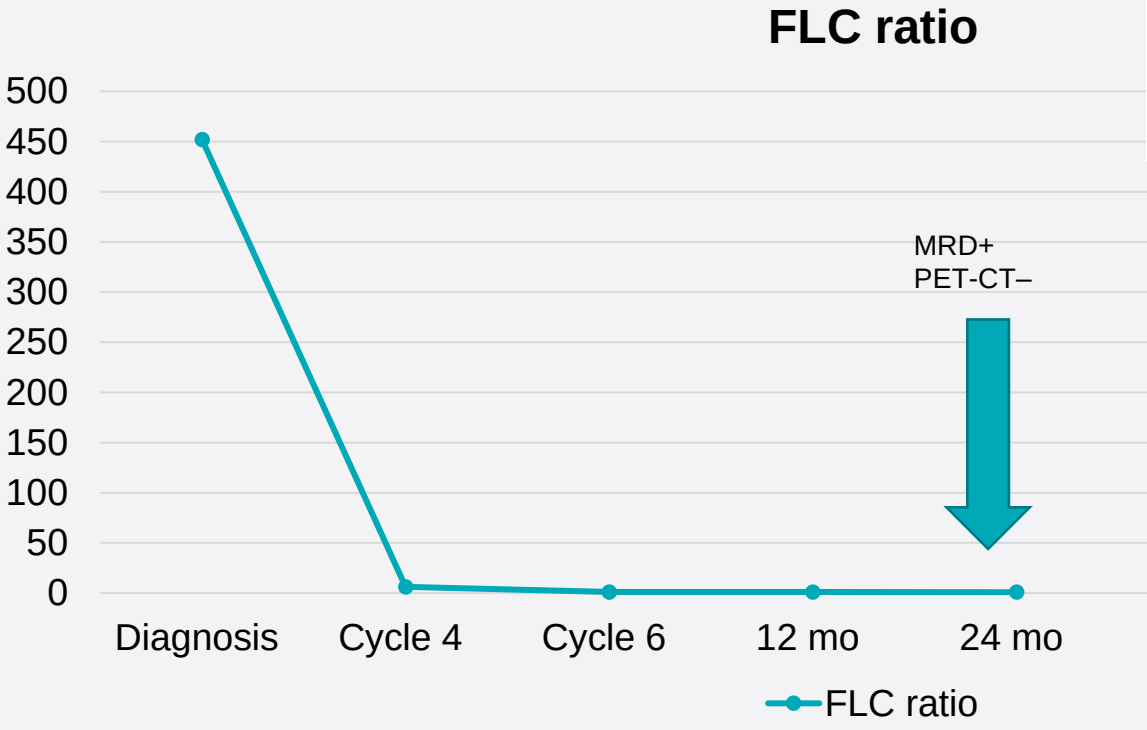
| Población | Eventos | % Parcial | % Visibilidad |
|---|---|---|---|
| EVENTOS | 14,203,229 | NA | 100.00 |
| CÉLULAS PLASMÁTICAS | 0 | 0.00 | NA |



# Evolution


FLC ratio
500
450
400
350
300
250
200
150
100
50
0
457
6.8
1.05
1.06
1.01
MRD+
Diagnosis
Cycle 4
Cycle 6
12 mo
24 mo
FLC ratio

# Evolution




**INFORME DE ANÁLISIS**

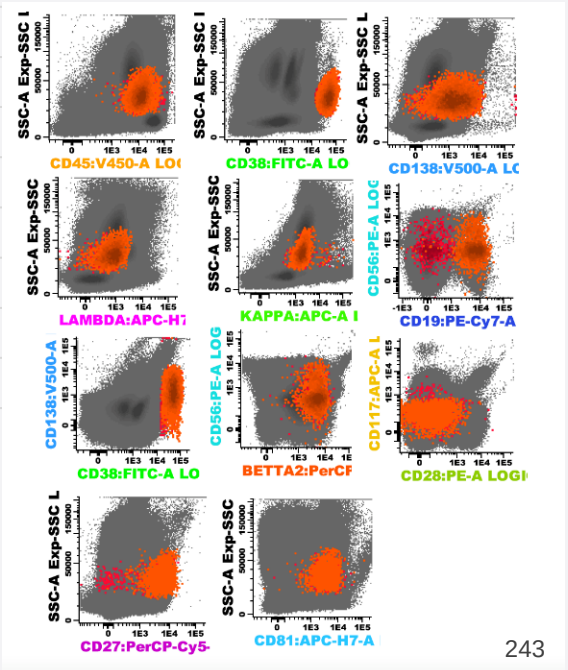
**Siguiendo el protocolo de Euroflow para EMR de alta sensibilidad en Mieloma, se realiza el panel de discrasias de células plasmáticas obteniendo 10,537,725 eventos, identificando una población de 0.07%(6,410)de células plasmáticas de las cuales un 0.02% (1,473) con fenotipo anormal similar al inicial: CD45+débil,CD38+,CD138+/-heterogéneo,CD56+/-heterogéneo, CD19-,Beta2microglobulina+,Kappa+, Lambda-,CD28-,CD81+,CD27+,CD117-**

**INTERPRETACIÓN**

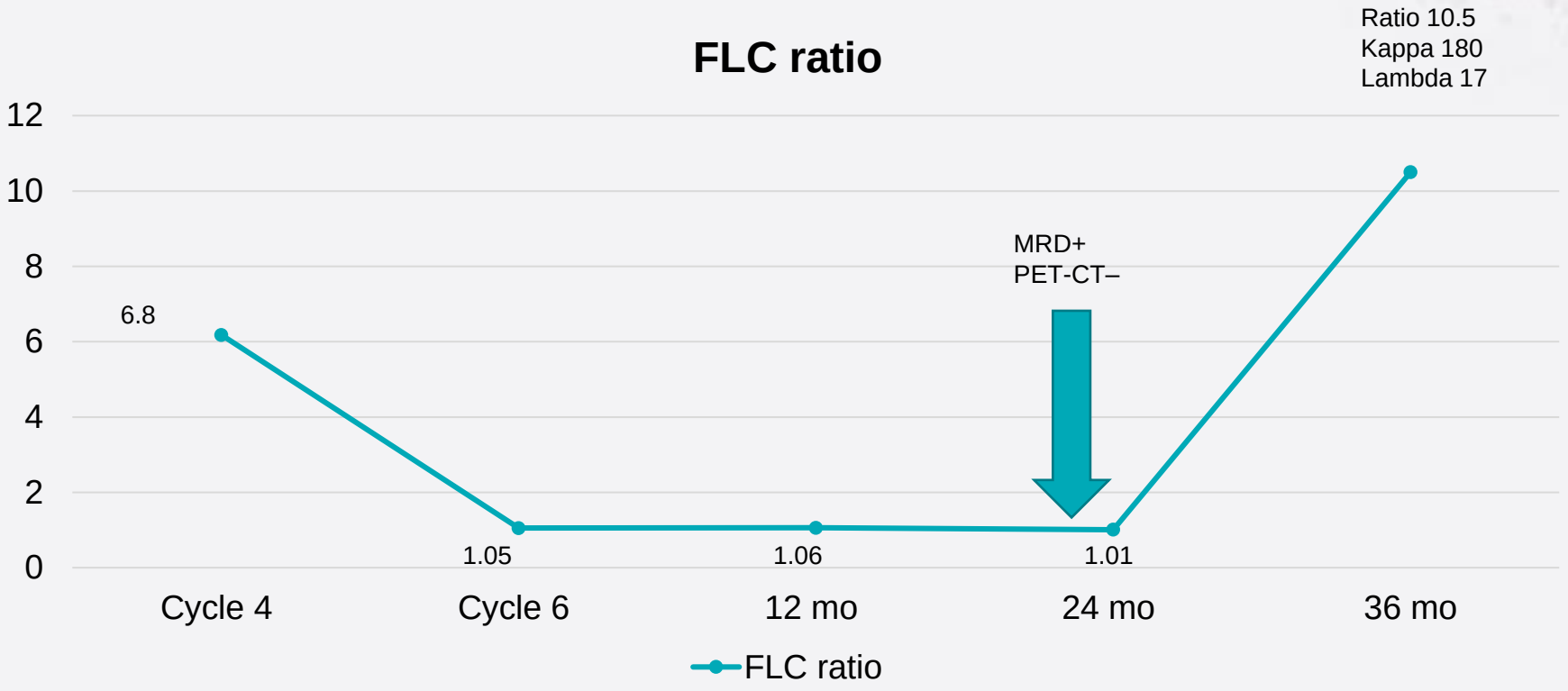
**El presente Inmunofenotipo es compatible con Enfermedad mínima residual DETECTABLE (0.02%) (Sensibilidad 10 - 7) Se sugiere correlación citogenética.**

**Punto de corte para EMR de alta sensibilidad en MM: 0.001%**

| Población | Eventos | % Parcial | % Visibilidad |
|---|---|---|---|
| EVENTOS | 10537725 | NA | 100.00 |
| CÉLULAS PLASMÁTICAS | 6410 | 100.00 | 0.07 |
| CÉLULAS PLASMÁTICAS ANORMALES | 1473 | 22.98 | 0.02 |
| ERITROBLASTOS | 0 | 0.00 | NA |



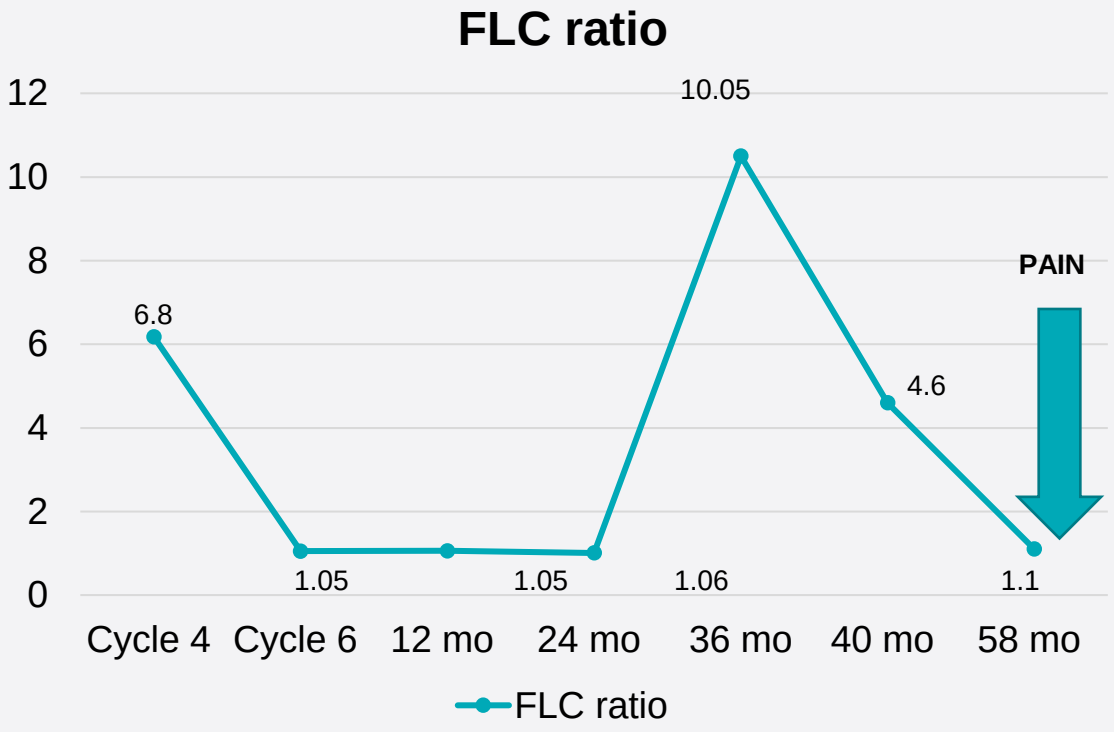
# Evolution

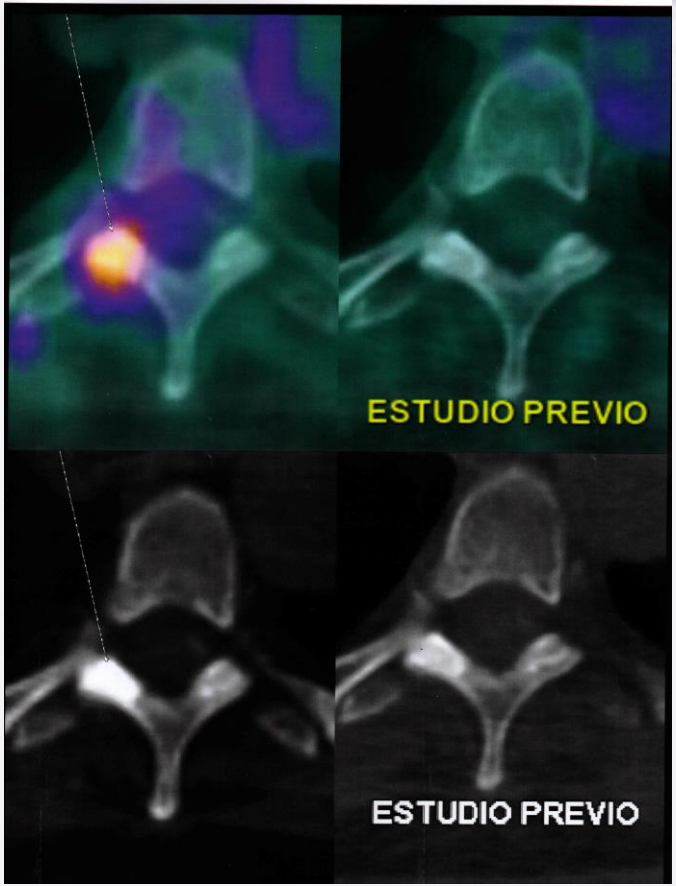

FLC ratio
Ratio 10.5
Kappa 180
Lambda 17
12
10
8
6
4
2
0
MRD+
PET-CT–
6.8
1.05
1.06
1.01
Cycle 4
Cycle 6
12 mo
24 mo
36 mo
FLC ratio

# First Relapse

- KRD
  - 4 cycles: PR
  - Toxicity: PE, grade 3 HAS, grade 1 neuropathy, grade 1 PHTN
- Isatuximab-pomalidomide-dexamethasone (EAP)
  - sRC at cycle 4
  - FLC ratio 1.1
  - MRD– at cycle 8
- Cycle 18
  - FLC ratio 1.16
  - Dorsal bone pain

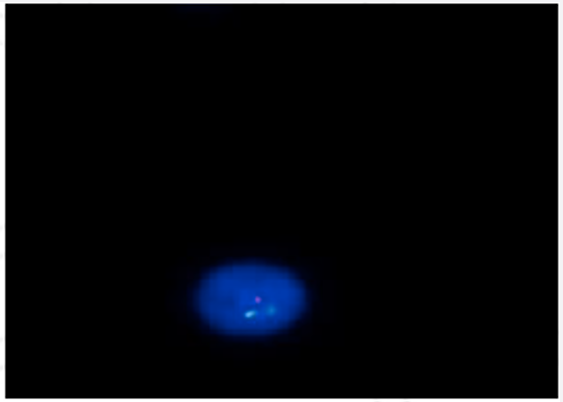
# Evolution


FLC ratio
12
10
8
6
4
2
0
6.8
1.05
1.05
10.05
1.06
4.6
1.1
PAIN
Cycle 4
Cycle 6
12 mo
24 mo
36 mo
40 mo
58 mo
FLC ratio

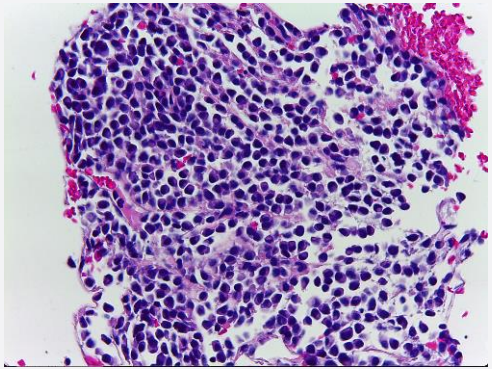

ESTUDIO PREVIO
ESTUDIO PREVIO

# Relapsed/Refractory

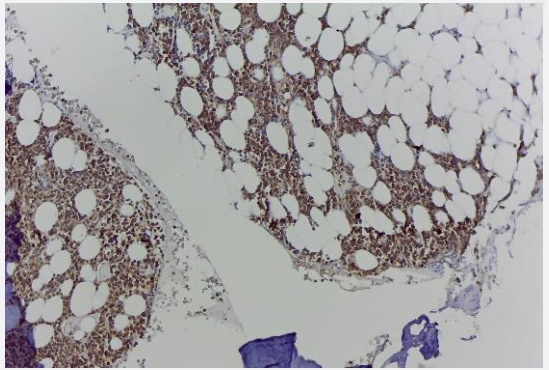
- FISH: 70% PC with *TP53*
  - Nuc ish (*TP53* × 2) (15/50)
  - Nuc ush (*TP53* × 1) (35/50)
  - The test was performed on selected clonal plasma cells (CD138+, CD38+, CD19+, CD56+)

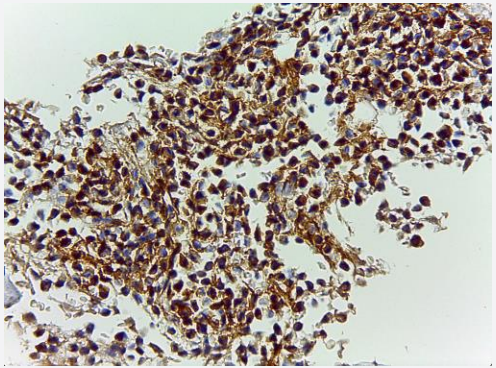


## T5 biopsy

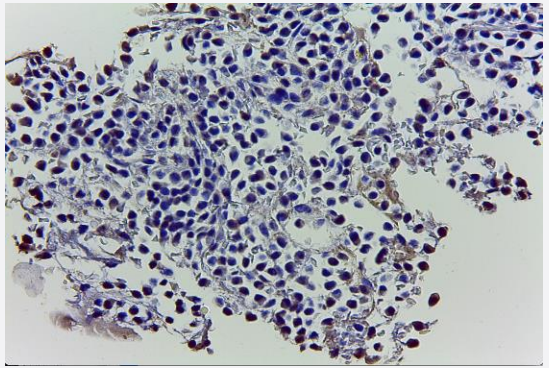


CD38+





Kappa



Lambda

# Relapsed/Refractory

OS: 58 mo

ECOG 1 (just pain)

Previous treatment

- Daratumumab
- Bortezomib
- Thalidomide
- Carfilzomib
- Lenalidomide
- Isatuximab
- Pomalidomide

# Points for Discussion

> What is the best treatment in this case?

A. Include in clinical trial
B. Belantamab mafodotin
C. Selinexor-bortezomib-dexamethasone
D. Bispecific antibody
E. Allo-SCT (61 years old)
F. CAR T-cell therapy

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# Discussion: Case 4

Case Discussants: Sofía Sánchez, MD + Jorge Vela-Ojeda, MD, PhD

Moderator: Rafael Fonseca, MD

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# Session Close – Audience Response Questions

Rafael Fonseca

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# Question 1

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

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? **[repeated question]**

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


@rfonsi1, fonseca.rafael@mayo.edu

# Question 3

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

A. There is a high rate of attrition (loss)
B. Several drug trials show that 2 drugs can be as good as 3 in terms of efficacy
C. Myeloma is a heterogeneous disease with increased rates of *p53* abnormalities with progression
D. All 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 June 30

THANK YOU!

Global Multiple Myeloma Academy

# Global Multiple Myeloma Academy

## Emerging and Practical Concepts in Multiple Myeloma

## THANK YOU FOR YOUR PARTICIPATION!

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