Breakfast with the Investigators: New Advances in Multiple Myeloma

Sunday, June 2, 2024
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD

Moderator

Elizabeth O'Donnell, MD

RTP RESEARCH TO PRACTICE

Faculty

Rafael Fonseca, MD
Chief Innovation Officer
Getz Family Professor of Cancer
Distinguished Mayo Investigator
Mayo Clinic in Arizona
Phoenix, Arizona

María-Victoria Mateos, MD, PhD
Consultant Physician in the Haematology Department
Associate Professor of Medicine
Director of the Myeloma Program
Clinical Trials Unit
University Hospital of Salamanca
Salamanca, Spain

Moderator

Elizabeth O'Donnell, MD
Director of Early Detection and Prevention
Dana-Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

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Dr Fonseca — Disclosures
Faculty

Board of Directors	Antengene
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Scientific Advisory Board	Caris Life Sciences
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Dr Mateos — Disclosures
Faculty

No relevant conflicts of interest to disclose.

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Dr O’Donnell — Disclosures
Moderator

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Dr Love — Disclosures

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Commercial Support

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Friday May 31	**Hepatobiliary Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer with an EGFR Mutation 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday June 1	**Antibody-Drug Conjugates in the Treatment of Lung Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 2	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 3	**Colorectal Cancer (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 4	**Bispecific Antibodies in the Management of Lymphoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

Multiple Myeloma

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD
Elizabeth O'Donnell, MD

LIVE WEBCAST

Colorectal Cancer

Monday, June 3, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Scott Kopetz, MD, PhD
John Strickler, MD

Ovarian and Endometrial Cancer

Sunday, June 2, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Angeles Alvarez Secord, MD, MHSc
Brian M Slomovitz, MD

Metastatic Breast Cancer

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Aditya Bardia, MD, MPH
Harold J Burstein, MD, PhD
Professor Giuseppe Curigliano, MD, PhD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

LIVE WEBCAST

Bispecific Antibodies in Lymphoma

Tuesday, June 4, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

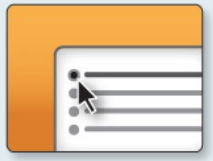
Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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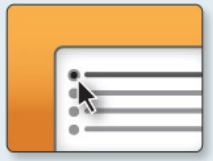
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Moderator

Elizabeth O'Donnell, MD

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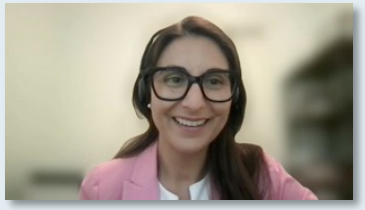
Consulting Oncologists

Neil Love, MD
Research To Practice
Miami, Florida



Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky

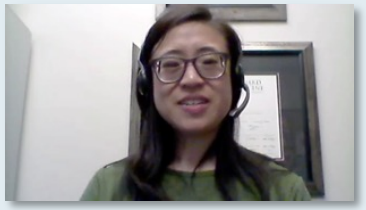
Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Gigi Chen, MD
John Muir Health
Pleasant Hill, California

Sunil Gandhi, MD
Florida Cancer Specialists
& Research Institute
Lecanto, Florida

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
& Research Institute
Lake Worth, Florida



Kimberly Ku, MD
Bloomington, Illinois

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Estelamari Rodriguez, MD, MPH
Sylvester Comprehensive Cancer Center
Miami, Florida

Erik Rupard, MD
Intermountain Health
St George, Utah

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Agenda

Module 1: Treatment Approaches for Newly Diagnosed Multiple Myeloma (MM) — Dr Fonseca

Module 2: Role of Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies in the Care of Patients with MM — Dr Mateos

Module 3: Incorporation of Other Novel Agents and Strategies into the Management of Relapsed/Refractory MM — Dr O'Donnell

Agenda

Module 1: Treatment Approaches for Newly Diagnosed Multiple Myeloma (MM) — Dr Fonseca

Module 2: Role of Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies in the Care of Patients with MM — Dr Mateos

Module 3: Incorporation of Other Novel Agents and Strategies into the Management of Relapsed/Refractory MM — Dr O'Donnell

Consulting Faculty Comments

Approach to first-line therapy for transplant-eligible patients with MM; potential role of minimal residual disease assay results in clinical decision-making

Dr Shaachi Gupta (Lake Worth, Florida)

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QUESTIONS FOR THE FACULTY

In which situations are you currently employing daratumumab as a component of up-front therapy for your transplant-eligible patients with MM?

What about for your transplant-ineligible patients?

QUESTIONS FOR THE FACULTY

What is your approach to maintenance therapy for patients who have received daratumumab-based induction therapy?

Should all patients who receive daratumumab up front also continue it as maintenance?

Consulting Faculty Comments

Effectiveness of single-agent daratumumab in older patients with MM; sequencing of daratumumab and isatuximab

Dr Erik Rupard (St George, Utah)

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QUESTIONS FOR THE FACULTY

Do you consider isatuximab and daratumumab to be essentially equivalent therapeutic options for patients with MM?

Outside of a clinical trial, are there any circumstances in which you would try to access isatuximab for a patient with newly diagnosed disease?

QUESTIONS FOR THE FACULTY

In which line of therapy are you generally recommending an isatuximab-based regimen for your patients with relapsed/refractory MM?

Would you employ isatuximab for a patient who has previously experienced disease progression on daratumumab or vice versa?

MAYO CLINIC

Rafael Fonseca, M.D.
Chief Innovation Officer

Mayo Clinic in Arizona
Multiple Myeloma – RTP ASCO 2024

Phoenix, Arizona

Rochester, Minnesota

Jacksonville, Florida

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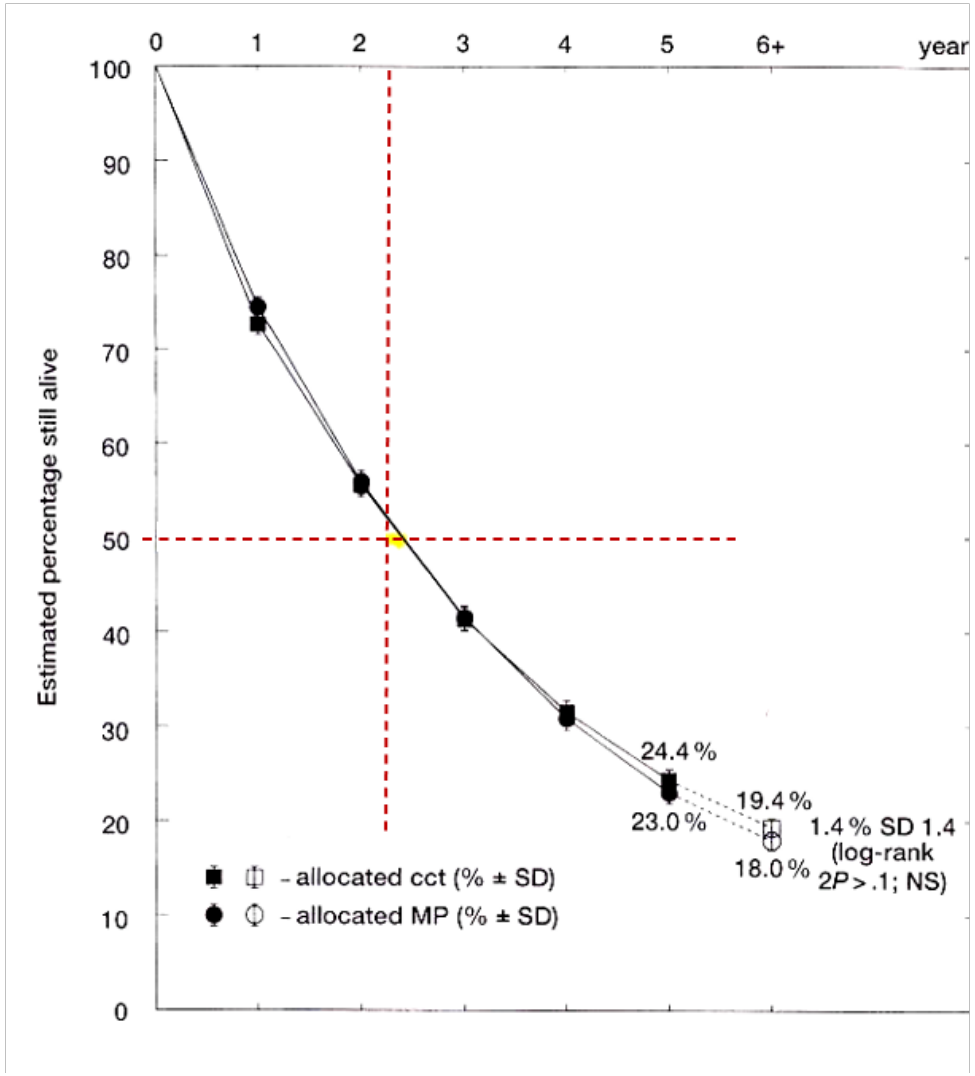
Old survival



New Survival

Series	Treatment	Overall survival	
Emory University (n= 1000)	RVD-SCT-risk adjusted maintenance	156 mos 96 mos	SR HR
MDACC (n= 1,167)	SCT and len maintenance	111 mos	
Canada (n= 2,061)	CyBORD-SCT-len maintenance	159 mos	

MTCG. J Clin Oncol 1998; 16:3832
Joseph, N et al, JCO 2020
Pasvolsky at el Am J Hematol April 2023
Cote el al Blood C J Sep 2023

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How I treat MM in 2024

STEP 1 All MM patients should be treated with Dara-Rd	Regardless of age, PS, or TE
STEP 2 Should this patient undergo SCT?	Today longest survival times include SCT But MAIA provides great survival in elderly pts If yes, the answer to step 3 is yes
STEP 3 Should this transplant ineligible patient get a PI?	• PIs improve response depth and PFS. But at what toxicity cost? Bortezomib PN • Carfilzomib CV toxicity

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Fonseca, R Personal opinion

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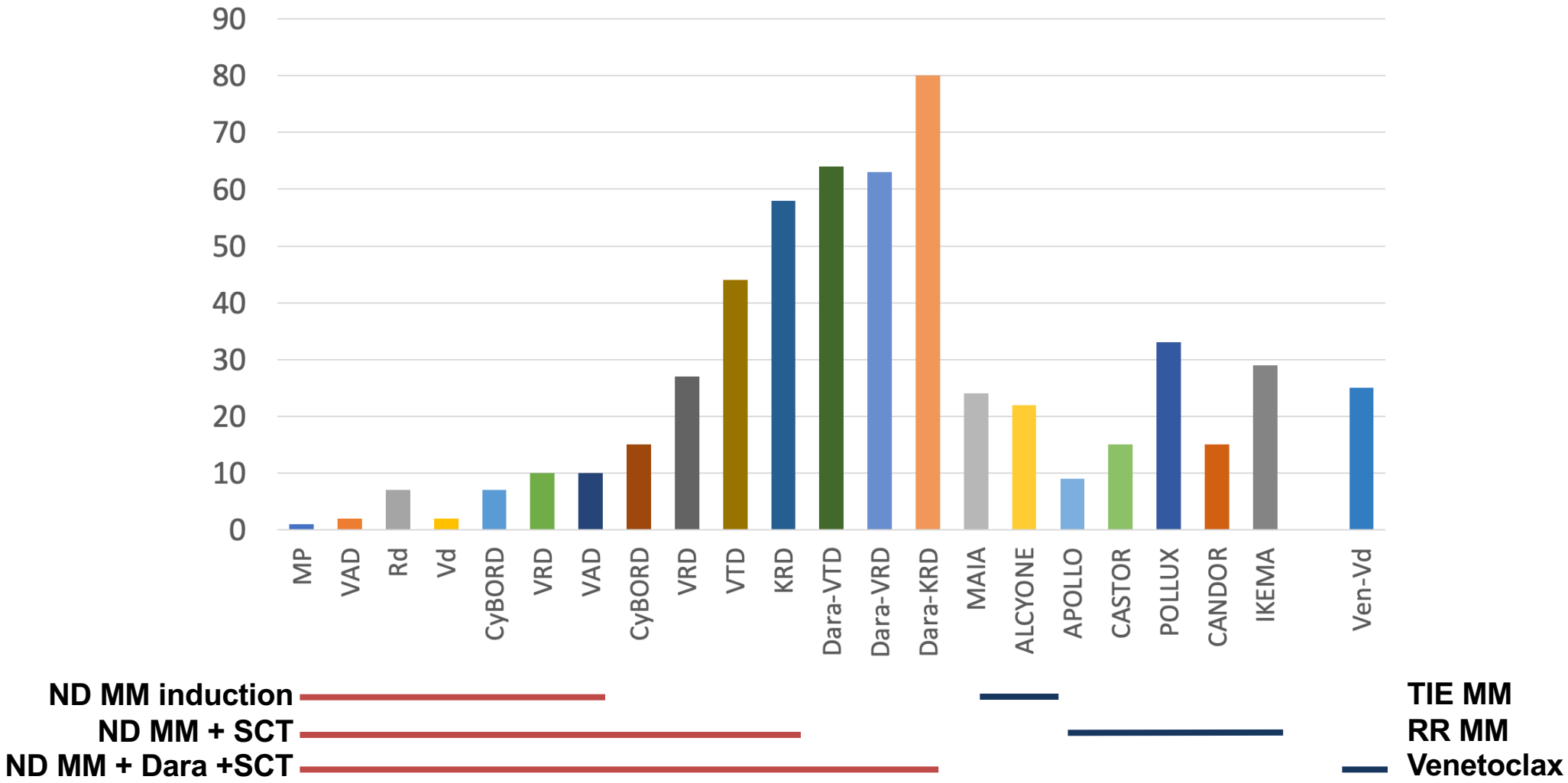
The Progression of MRD (10^{-5}) Negativity



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Fonseca, R Personal opinion

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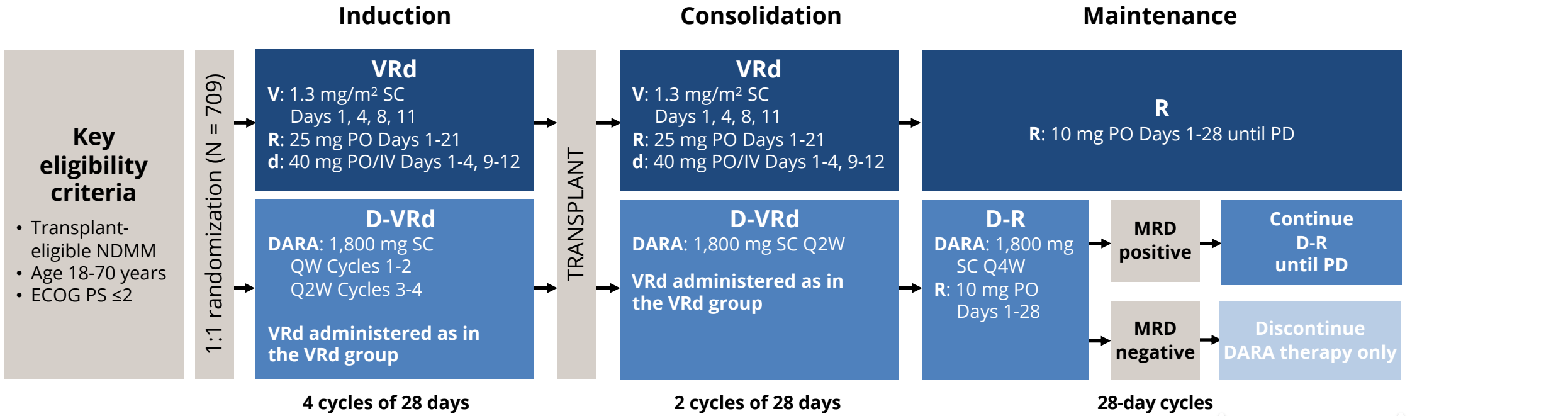
PERSEUS: Study Design



Primary endpoint: PFS

Key secondary endpoints: Overall ≥CR rate, overall MRD-negativity rate, OS

Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

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Sonneveld NEJM Dec 2023
Sonneveld, P. et al. ASH 2023

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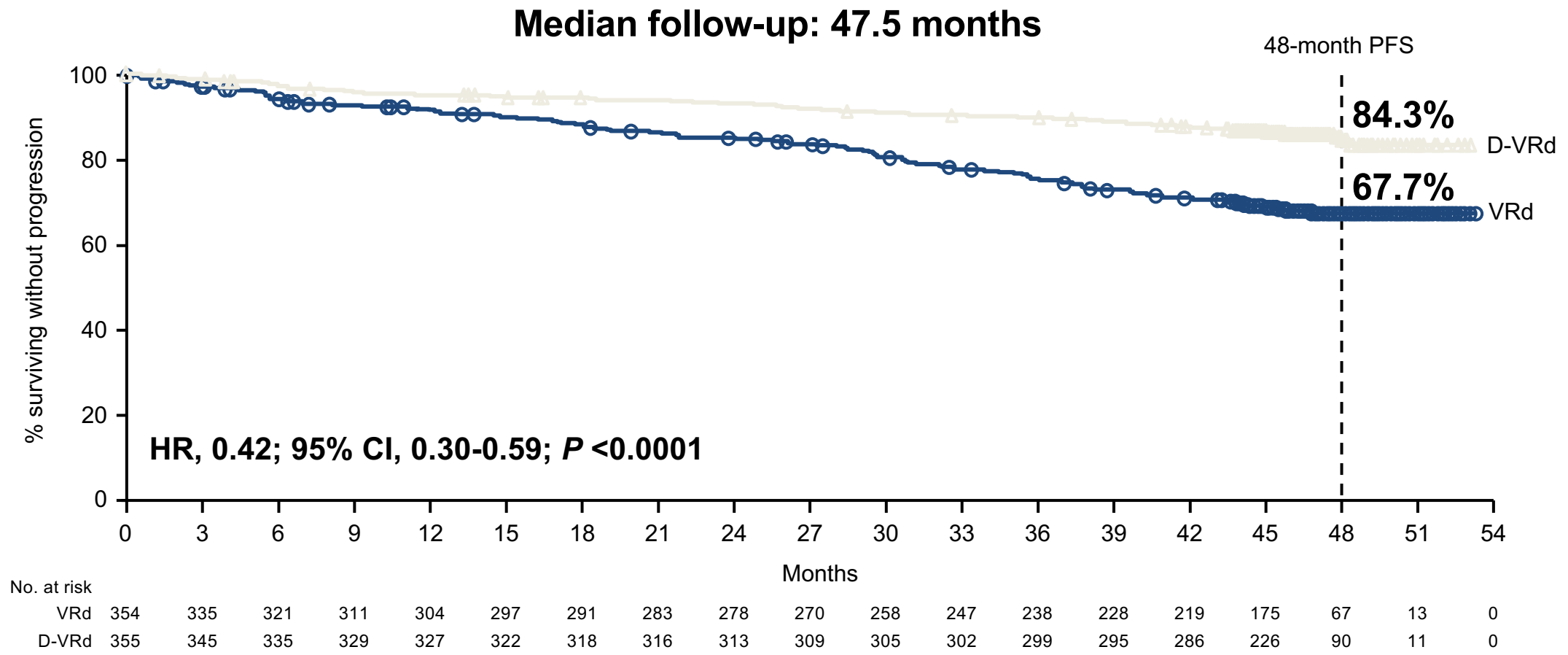
PERSEUS: Progression-free Survival



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Sonneveld NEJM Dec 2023
Sonneveld, P. et al. ASH 2023

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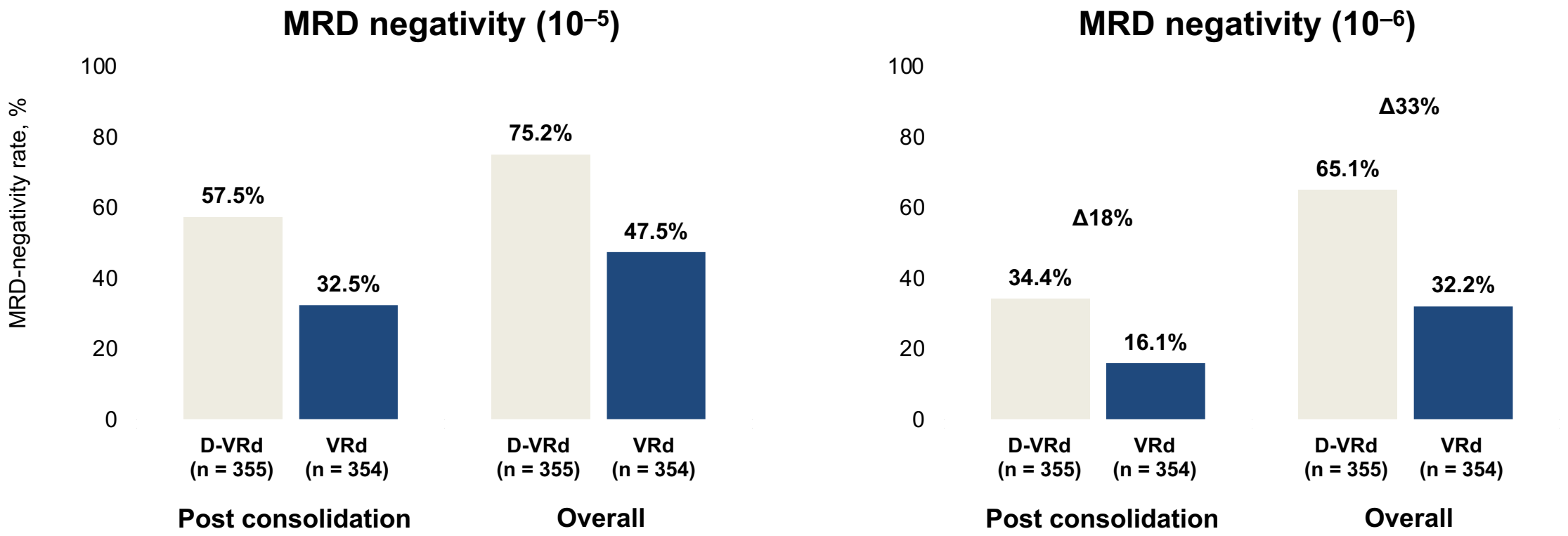
PERSEUS: MRD-negativity Rates Over Time



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Sonneveld NEJM Dec 2023
Sonneveld, P. et al. ASH 2023

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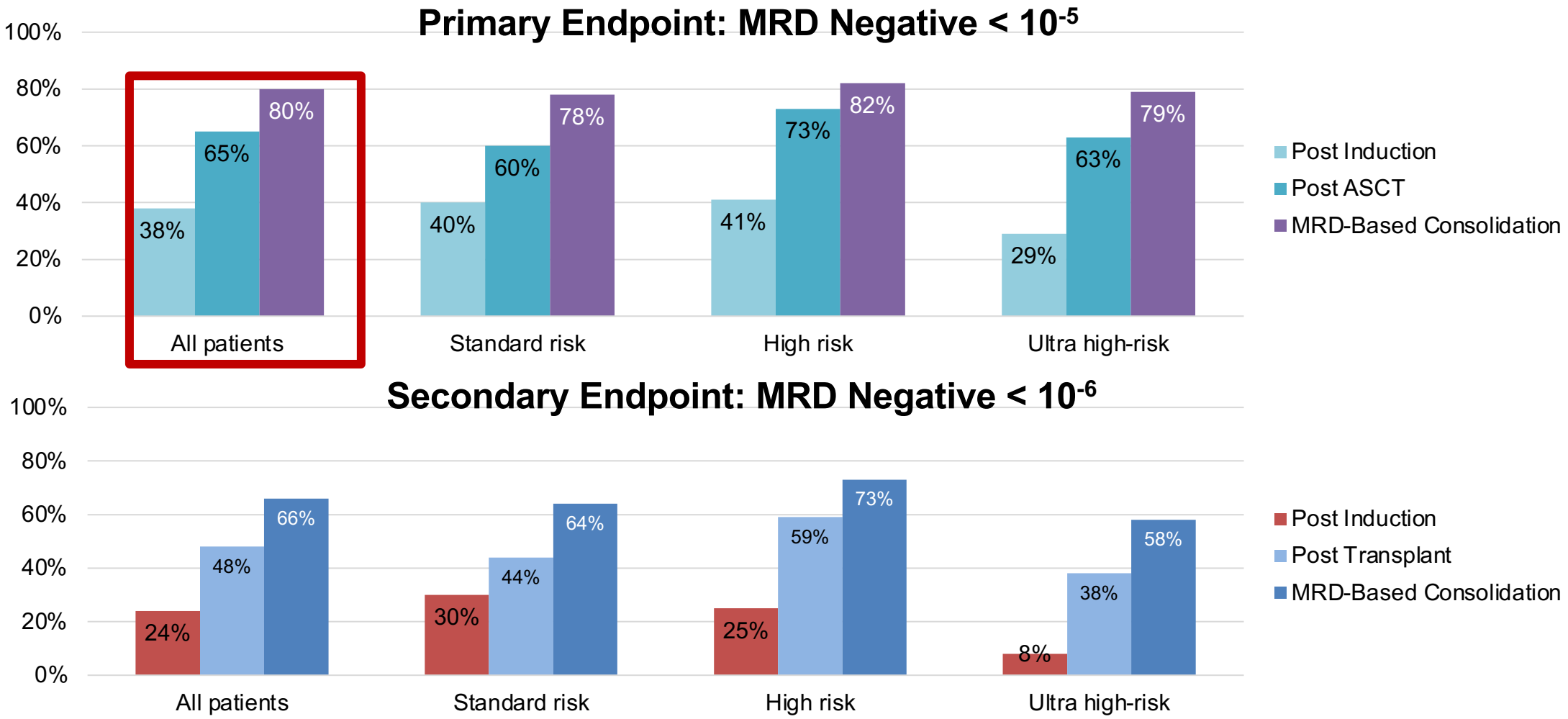
MASTER: best MRD response by phase of therapy



Costa LJ, et al. *J Clin Oncol.* 2021

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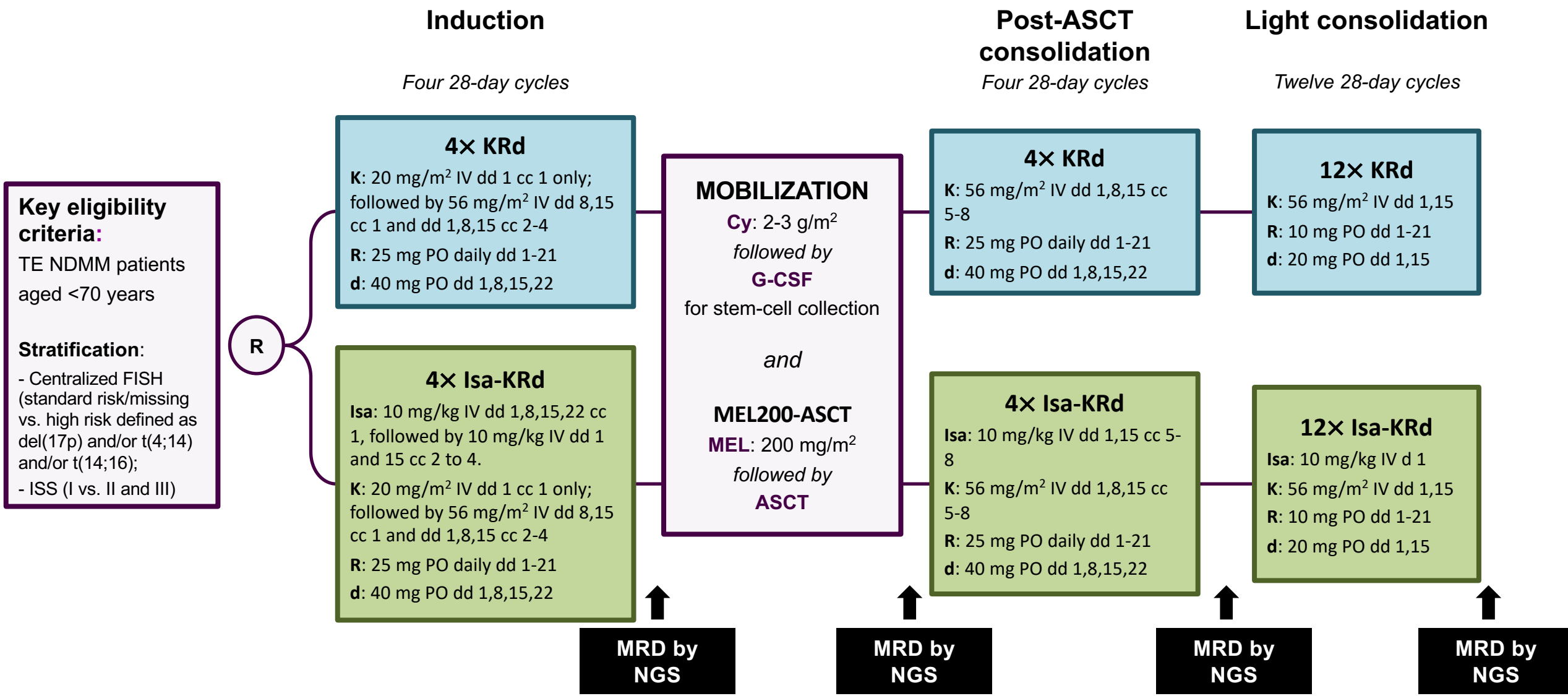
IsKia EMN24 Study Design



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Gay, F. et al. ASH 2023

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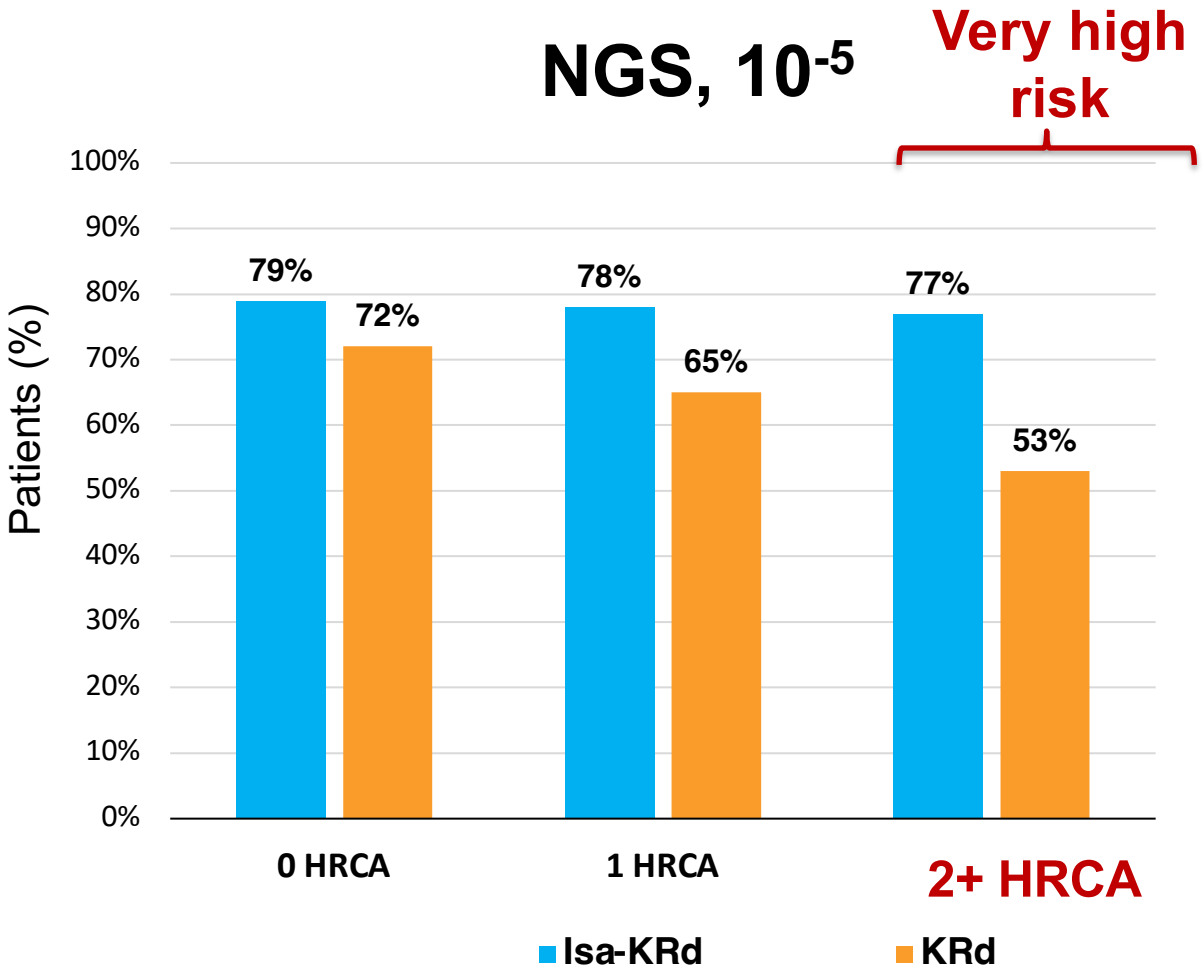
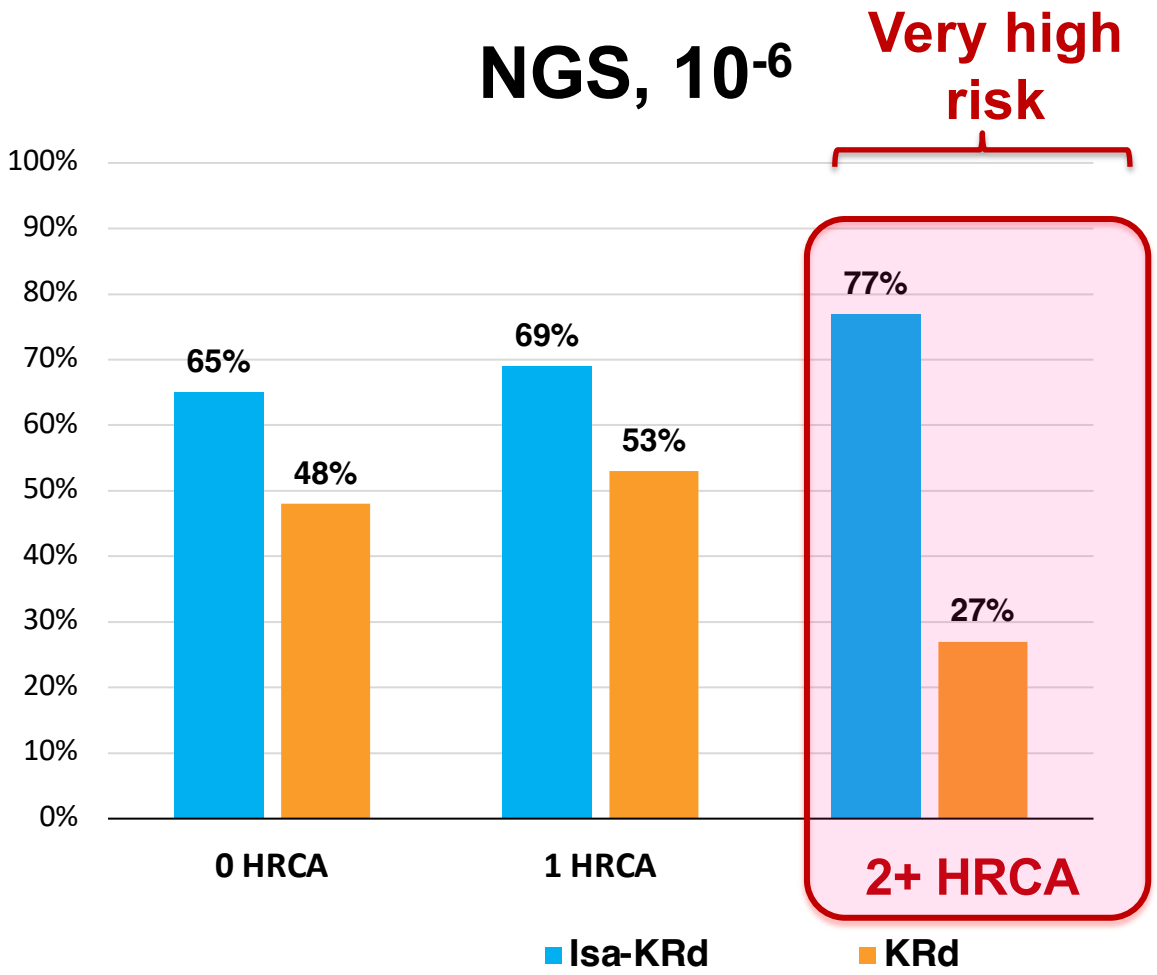
Post-consolidation MRD negativity by NGS





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Gay, F. et al. ASH 2023

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Phase 3 Isa + RVd vs RVd

GMMG GERMAN-SPEAKING MYELOMA MULTICENTER GROUP HD7

NDMM
N=662

Key eligibility criteria[1]:
- ✓ Age 18–70 years
- ✓ NDMM and eligible for HDT and ASCT

Induction phase (3 x 6-week cycles)

Randomization 1:1

- Isa + RVd
- RVd

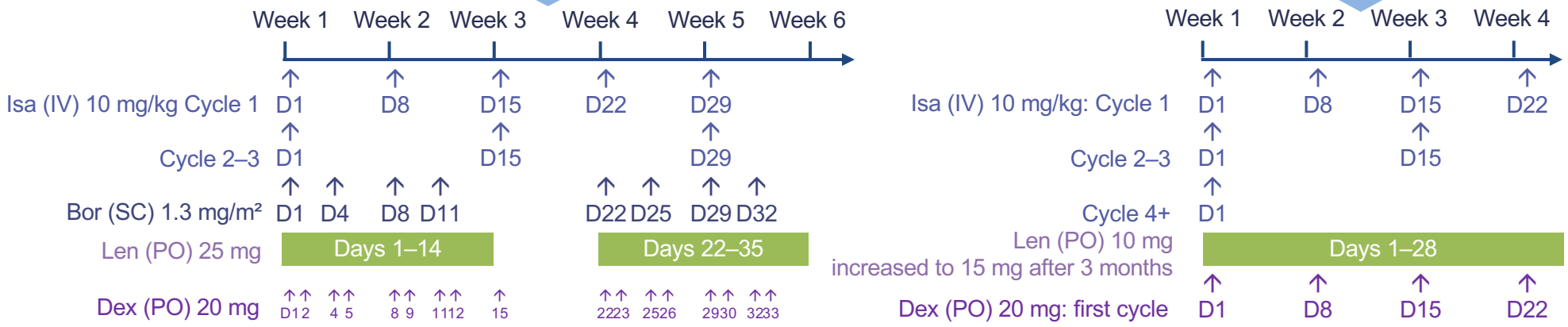
HDT + ASCT

Maintenance phase (4-week cycles)

Randomization

- Isa + R
- R

3 years or PD



ASCT, autologous stem cell transplant; D, day; d/Dex, dexamethasone; HDT, high-dose therapy; Isa, isatuximab; IV, intravenous; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PO, oral; R/Len, lenalidomide; SC, subcutaneous; Te, transplant eligible; V/Bor, bortezomib; RVd is off label use in some countries according to the lenalidomide summary of product characteristics.

1. ClinicalTrials.gov: NCT03617731

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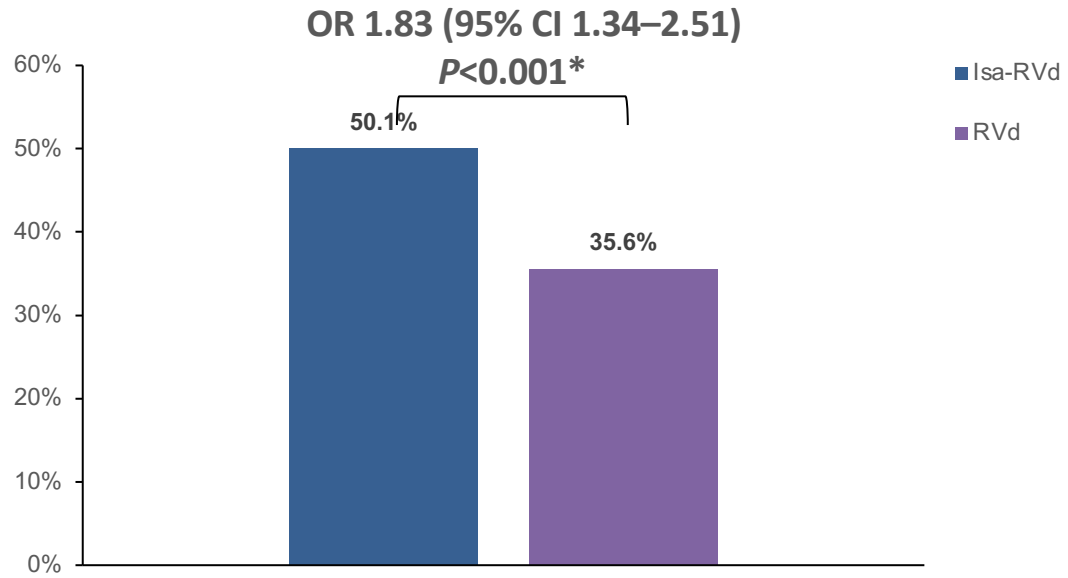
First primary endpoint, end of induction MRD negativity by NGF (10^{-5}), was met in ITT analysis

GM MG GERMAN-SPEAKING MYELOMA MULTICENTER GROUP HD7

Patients with MRD negativity at the end of induction therapy



Low number of not assessable/missing† MRD status: Isa-RVd (10.6%) and RVd (15.2%)

Isa-RVd is the first regimen to demonstrate a rapid and statistically significant benefit from treatment by reaching a MRD negativity of 50.1% at the end of induction and to show superiority vs. RVd in a Phase 3 trial

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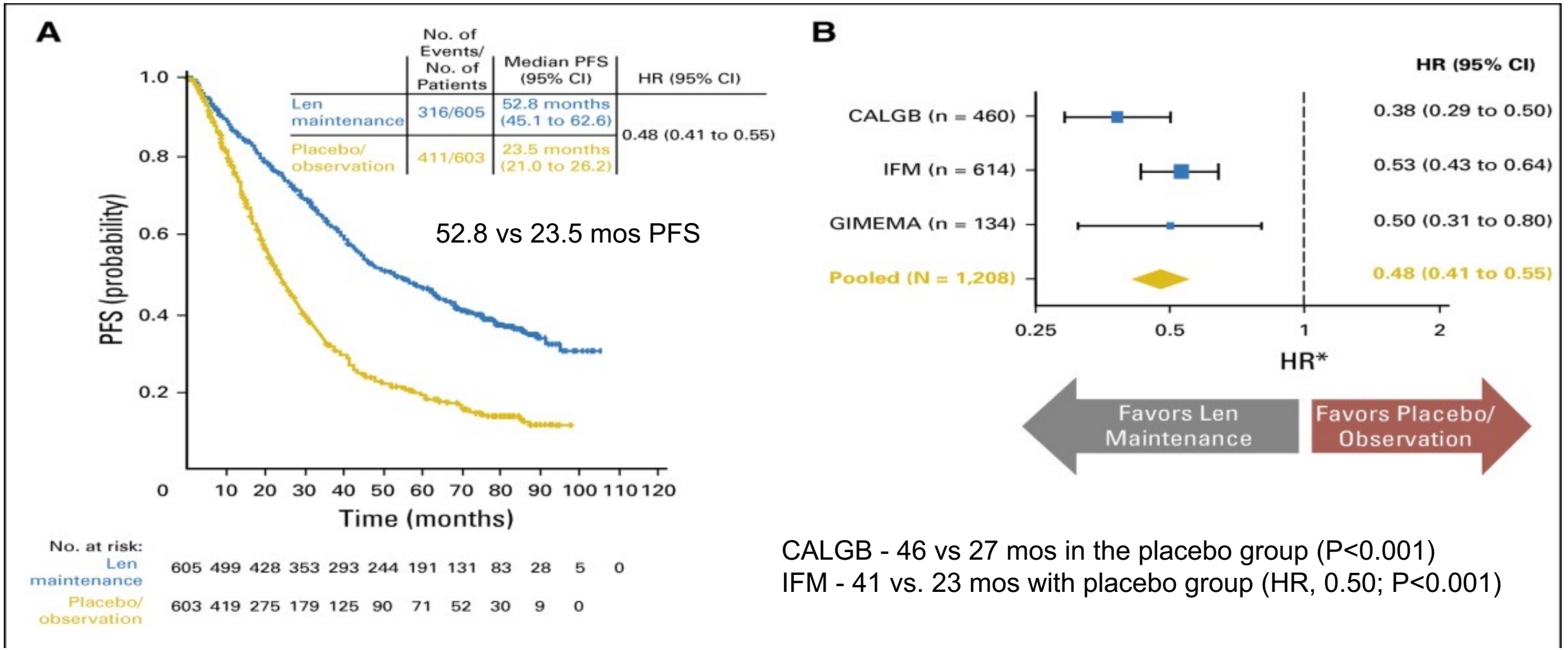
Meta-analysis for Len Maintenance



CALGB - 46 vs 27 mos in the placebo group (P<0.001)
IFM - 41 vs. 23 mos with placebo group (HR, 0.50; P<0.001)

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McCarthy et al JCO 35:1 2017

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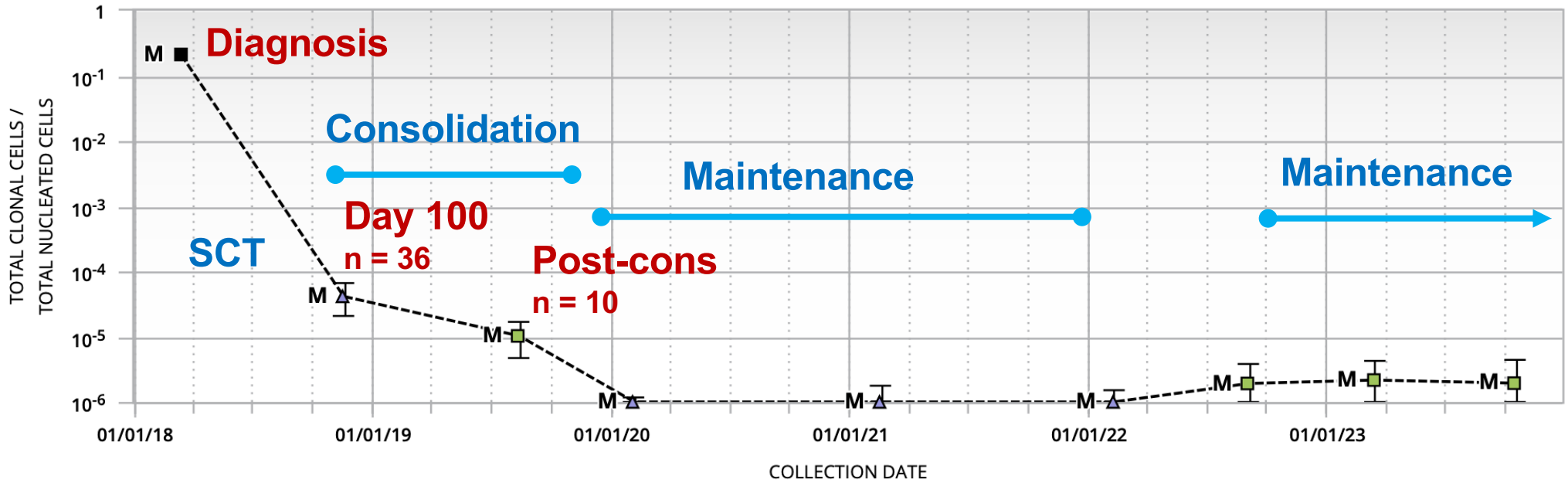
Drive to MRD negative

- 58 yo, ND MM
- Induction with KRD > SCT> Dara-Rd>R maintenance



Maint	Maint	Maint	Off	Maint	Maint
n = 0	n = 0	n = 0	n = 2	n = 2	n = 2

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Fonseca, Personal

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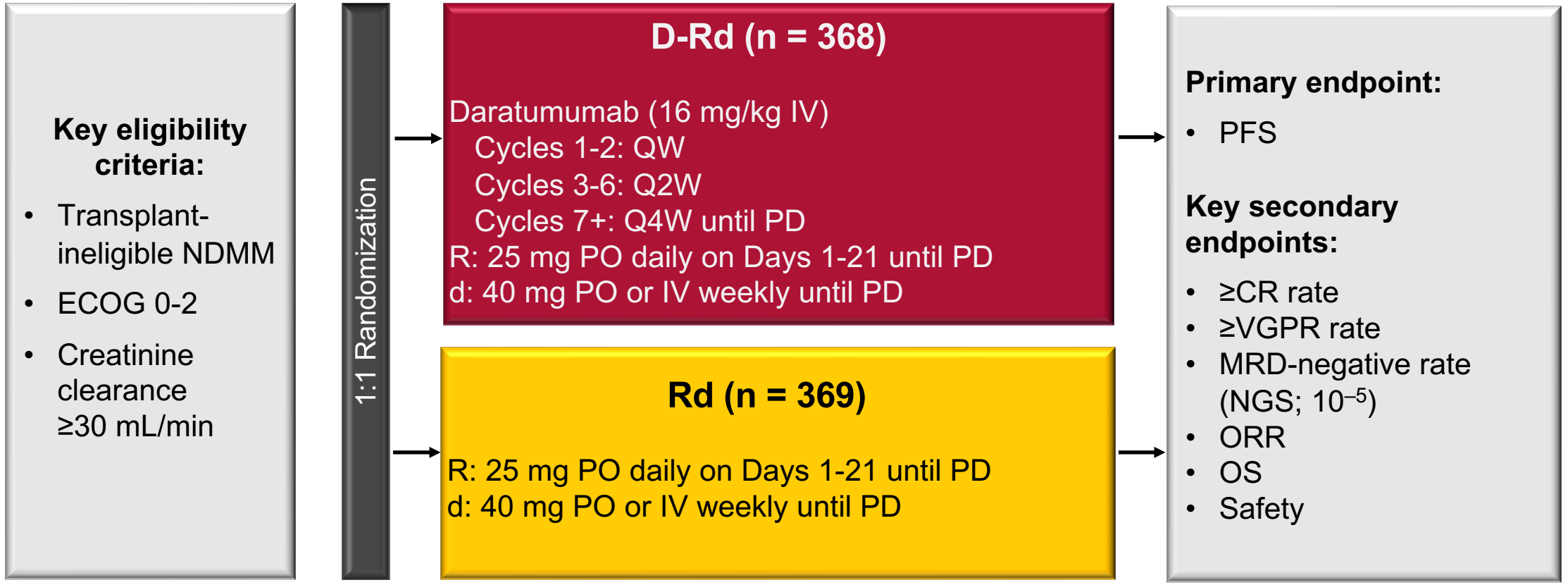
MAIA Study Design

- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)



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Facon T et al NEJM 2019; 380:2104

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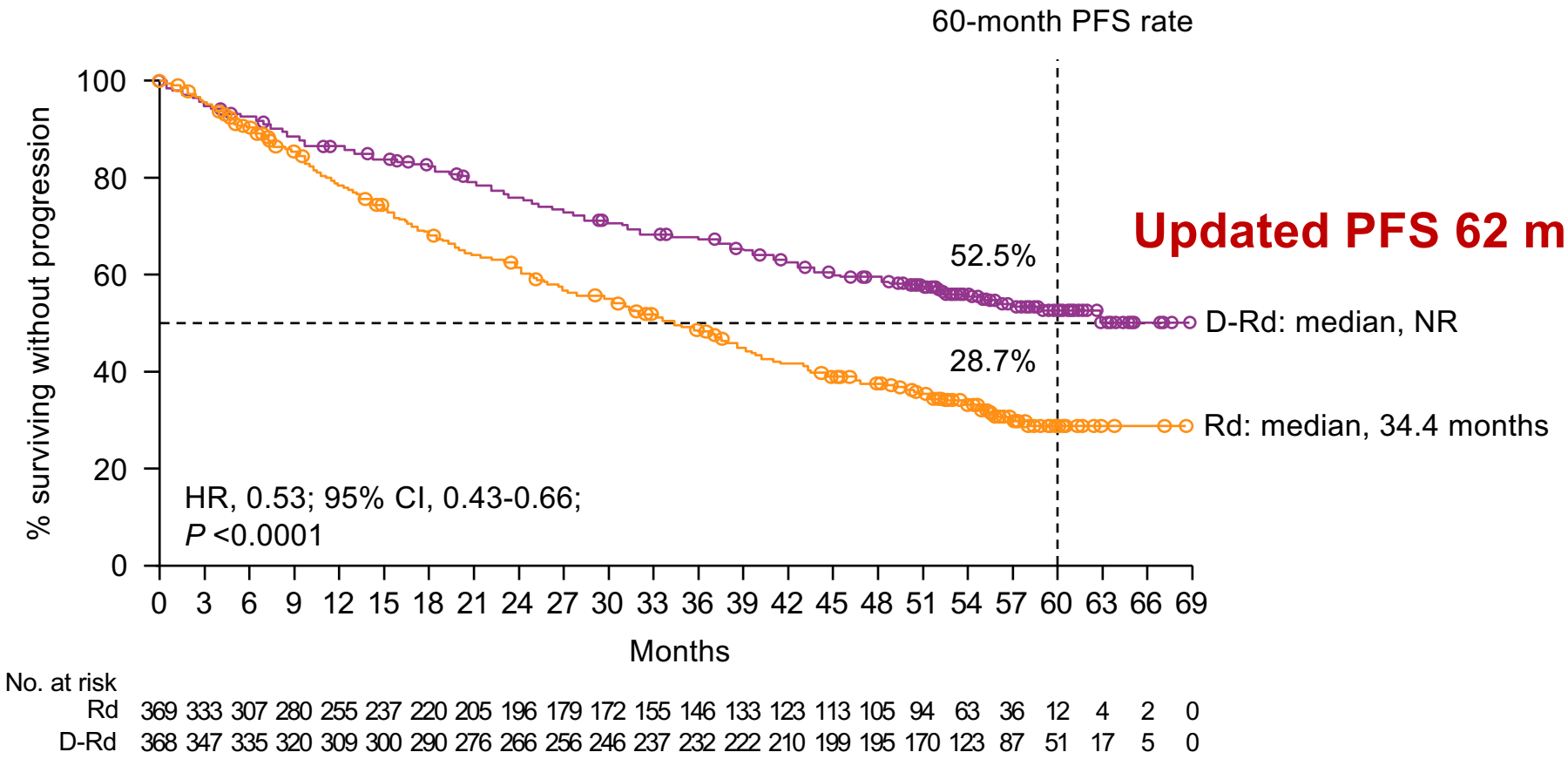
Updated PFS



Updated PFS 62 months

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Usmani et al ASH 2022 and EHA 2023
Usmani, S et al EHA 2021

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IMROZ: Isa-VRd TI Study design: Phase III

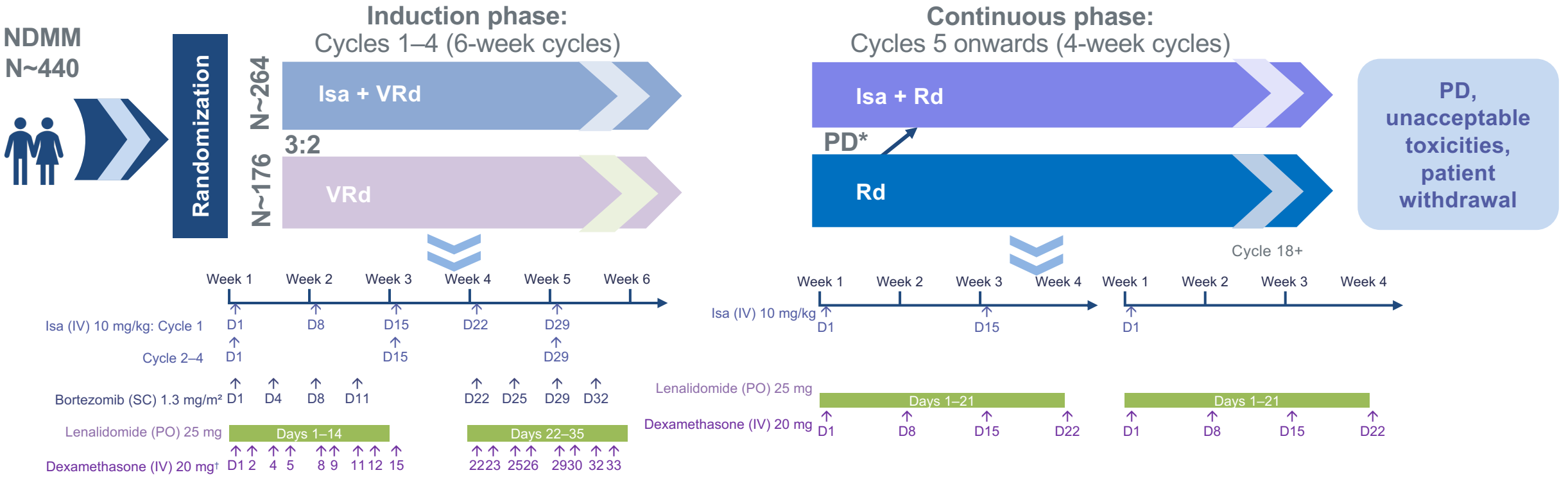
Key eligibility criteria:
- ✓ Age 18–80 years with MM
- ✓ Patients who are newly diagnosed and not considered for HDT
- × ECOG PS >2

Primary endpoint:
- PFS (IRC)

Key secondary endpoints:
- ≥VGPR (IRC)
- MRD neg($\geq 10^{-5}$) if CR or VGPR
- CR (IRC)

Other secondary MRD endpoints:
- MRD status by PFS, TTP and DOR

Exploratory analyses: PET for Imaging-positive MRD-negative response per IMWG criteria



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June 3 – 3:00 PM CDT Hall D1 | Live Stream

Phase 3 study results of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) versus VRd for transplant-ineligible patients with newly diagnosed multiple myeloma (IMROZ).

3:00 PM CDT Thierry Facon, MD Abstract 7500

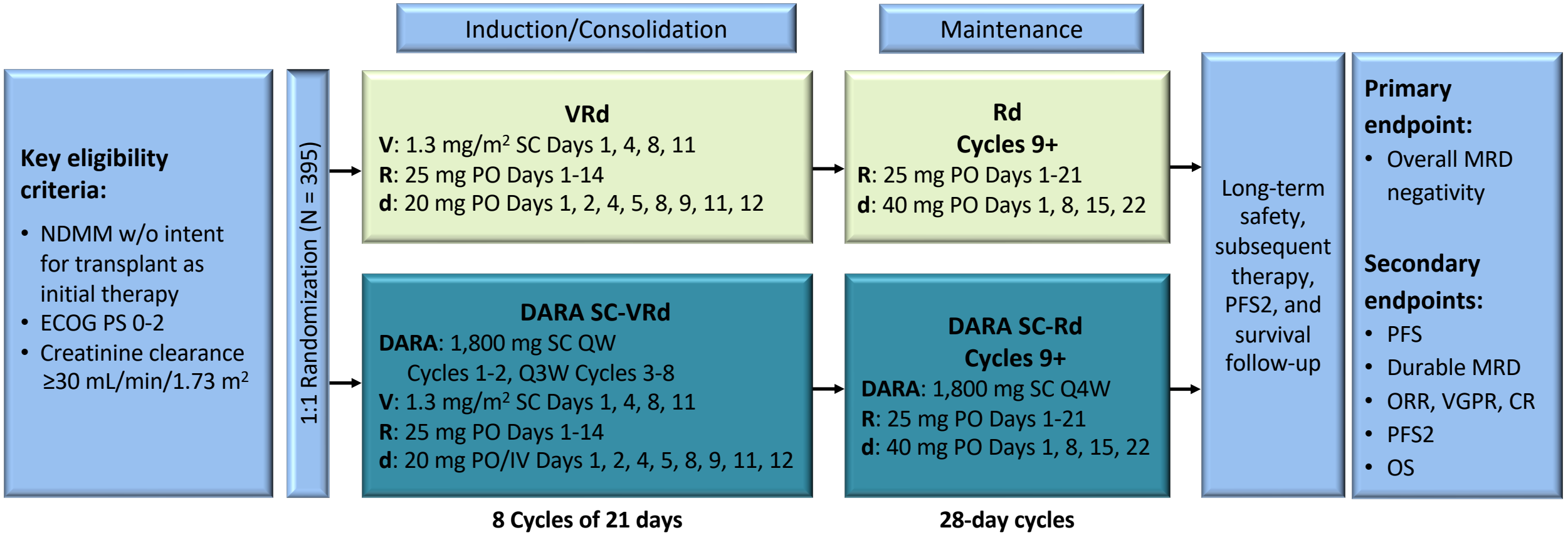
% pts	Isa-VRd (n = 265)	VRd (n = 181)	Stratified odds ratio (95% CI)	1-sided *p*-value
CR	74.7	64.1	1.656 (1.097-2.500)	0.008
MRD- CR	55.5	40.9	1.803 (1.229-2.646)	0.0013
Sustained MRD- for at least 12 mo	46.8	24.3	2.729 (1.799-4.141)	<0.0001
Grade ≥3 TEAE	91.6	84.0	—	
Grade 5 TEAE	11.0	5.5		
Any TEAE leading to tx discontinuation	22.8	26.0		

CR = complete response; MRD = minimal residual disease; TEAE = treatment-emergent adverse event

MAYO CLINIC

CEPHEUS (MMY3019): Study Design

- **Phase 3 study of DARA SC-VRd versus VRd in NDMM without intent for transplant as initial therapy (N = 395)**



@rfonsi1, fonseca.rafael@mayo.edu

Agenda

Module 1: Treatment Approaches for Newly Diagnosed Multiple Myeloma (MM) — Dr Fonseca

Module 2: Role of Chimeric Antigen Receptor (CAR) T-Cell Therapy and Bispecific Antibodies in the Care of Patients with MM — Dr Mateos

Module 3: Incorporation of Other Novel Agents and Strategies into the Management of Relapsed/Refractory MM — Dr O'Donnell

Consulting Faculty Comments

Management of toxicities associated with CAR T-cell therapy and with bispecific antibodies

Dr Kimberly Ku
(Bloomington, Illinois)

Dr Warren Brenner
(Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

For patients to whom you decide to administer CAR T-cell therapy, how do you choose between ciltacabtagene autoleucel (cilta-cel) and idecabtagene vicleucel (ide-cel)?

Indirectly, how would you compare the global efficacy of these agents? What about their tolerability?

QUESTIONS FOR THE FACULTY

Given the recent FDA approvals of cilta-cel and ide-cel earlier in the treatment course, in which line of therapy are you referring your patients with MM for consultation regarding CAR T-cell therapy?

QUESTIONS FOR THE FACULTY

In which line of therapy are you typically employing a bispecific antibody for your patients with MM?

For patients eligible to receive both therapies, would you generally use a bispecific antibody or CAR T-cell therapy first?

HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

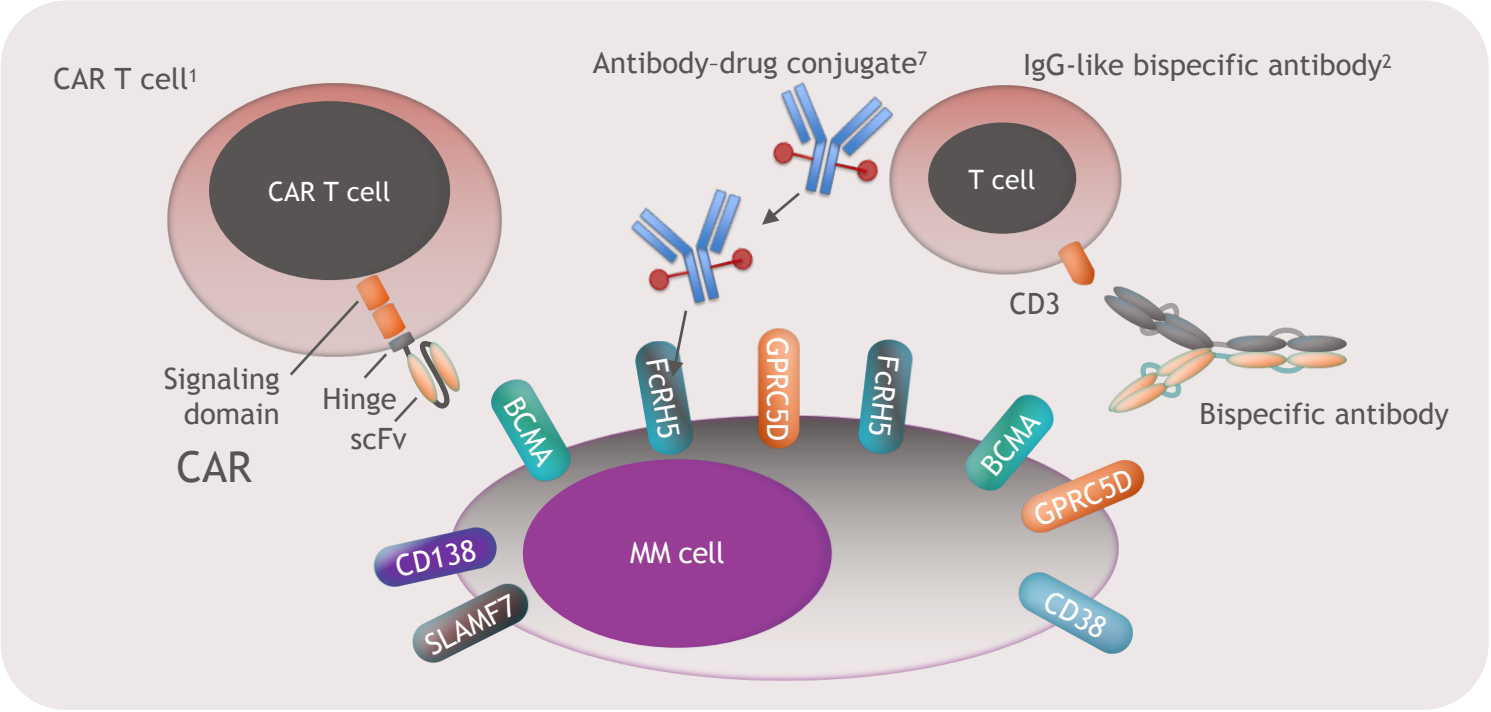
CIC Centro de Investigación del Cáncer

University of Salamanca

Role of CAR-T cell therapy and BsAbs in the care of patients with Multiple Myeloma

María-Victoria Mateos
Salamanca, Spain

New-generation immunotherapies in MM



- **ADC:**
  Belantamab
- **Bispecifics:**
  AMG 701
  Teclistamab, talquetamab
  Elranatamab
  REGN5458
  TNB-383B
  CC-93269
  Cevostamab
- **CAR T:**
  Ide-cel
  Cilta-cel
  p-BCMA-101
  CT053
  ALLO-715

BCMA:[3]
- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

GPRC5D:[4,5]
- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

FCRH5:[6]
- High levels of expression on MM cells
- Normally expressed in plasma cells only

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; FcRH5, Fc receptor-like 5; GPRC5D, ide-cel, idecabtagene vicleucel; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; scFv, single chain variable fragment.

1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538-49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij, et al. Blood Advances, 2020;5(8):2195-2215. 5. Smith EL, et al. Sci Transl Med. 2020;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31:383-395. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155.

Images adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.

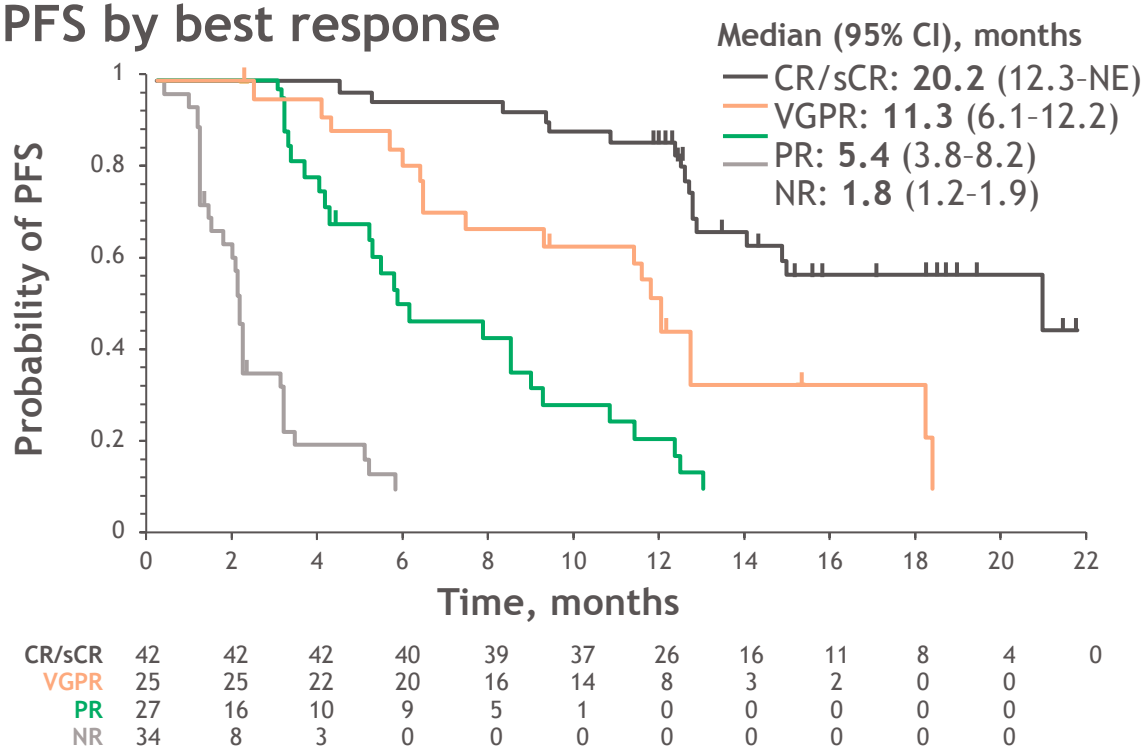
KarMMa Phase 2 study of ide-cel in RRMM

The KarMMa study evaluated the efficacy and safety of ide-cel at doses of **150-450 x 10^6 CAR+ T cells** in 128 patients with RRMM after a median of **6 prior lines of therapy (84% triple refractory)**

All treated patients (N = 128)
ORR: 73% (CR/sCR: 33%)

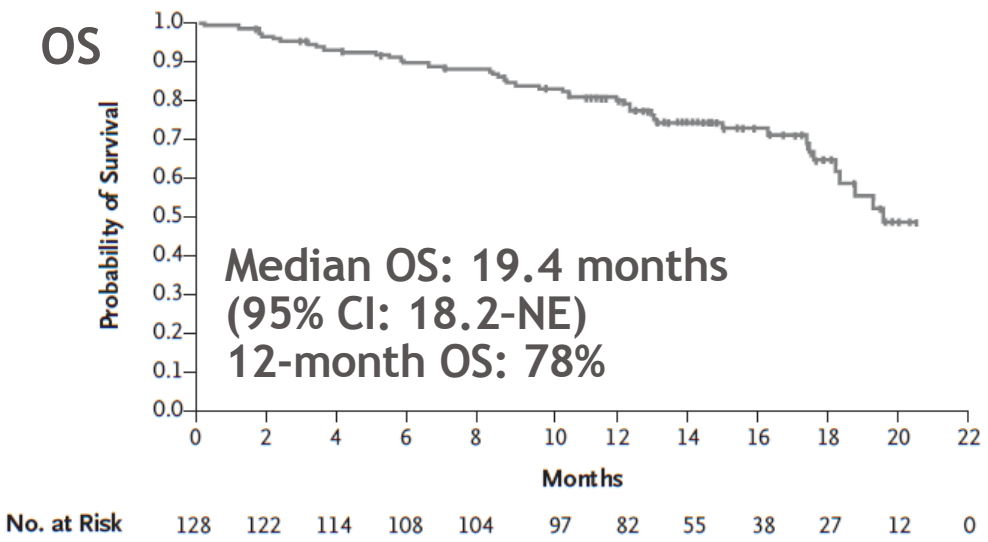
450 x 10^6 dose (n = 54)
ORR: 81% (CR/sCR: 39%)

PFS by best response



Median PFS was 8.8 months in all patients and 20 months in those with CR/sCR

OS



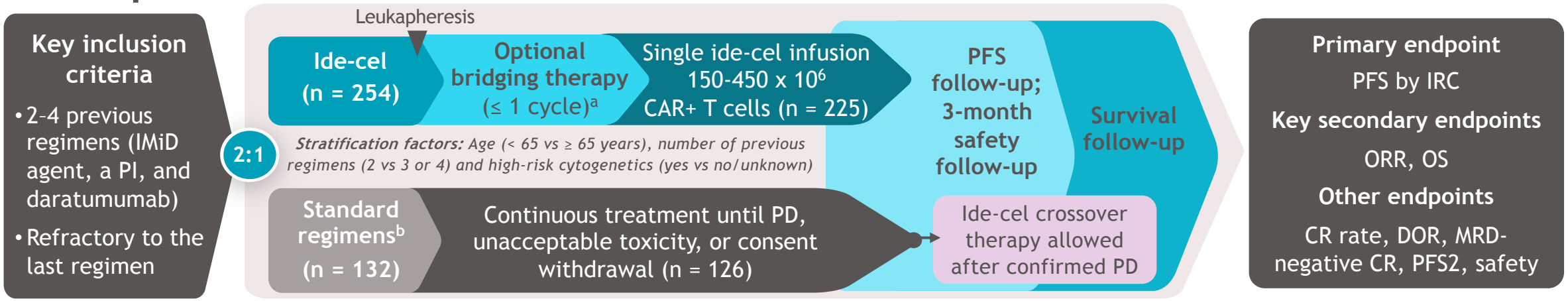
Summary of safety

Key AEs of interest, n (%)	Any grade	Grade 3/4
Infections	88 (69)	28 (22)
CRS	107 (84)	7 (5)
Neurotoxic effect	23 (18)	4 (3)

No new safety signals reported

AE, adverse event; CAR, chimeric antigen receptor; CI, confidence Interval; CR, complete response; CRS, cytokine release syndrome; ide-cel, idecabtagene vicleucel; NE, not estimable; NR, non-responders; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response. Munshi NC, et al. N Engl J Med. 2021;384:705-16.

KarMMa-3 study: Ide-cel versus standard regimens in patients with triple-class-exposed RRMM



Characteristic	Ide-cel (n = 254)	SOC (n = 132)
Median age, years (range)	63 (30–81)	63 (42–83)
Median time from diagnosis to screening, years (range)	4.1 (0.6–21.8)	4.0 (0.7–17.7)
Previous autologous HSCT, n (%)	214 (84)	114 (86)
R-ISS I/II/III, n (%)	50 (20)/150 (59)/31 (12)	26 (20)/82 (62)/14 (11)
EMP, n (%)	61 (24)	32 (24)
High tumor burden, n (%)[c]	71 (28)	34 (26)
High-risk cytogenetics, n (%)[d]		
del(17p)/t(4;14)/t(14;16)/1q gain/amplification	166 (65)/66 (26)/43 (17)/8 (3)/124 (49)	82 (62) /42 (32)/18 (14)/4 (3)/51 (39)
Ultra-high-risk[e]	67 (26)	29 (22)
Median time to progression on last antimyeloma therapy, months (range)	7.1 (0.7–67.7)	6.9 (0.4–66.0)
Daratumumab refractory, n (%)	242 (95)	123 (93)
Triple-class-refractory, n (%)[f]	164 (65)	89 (67)

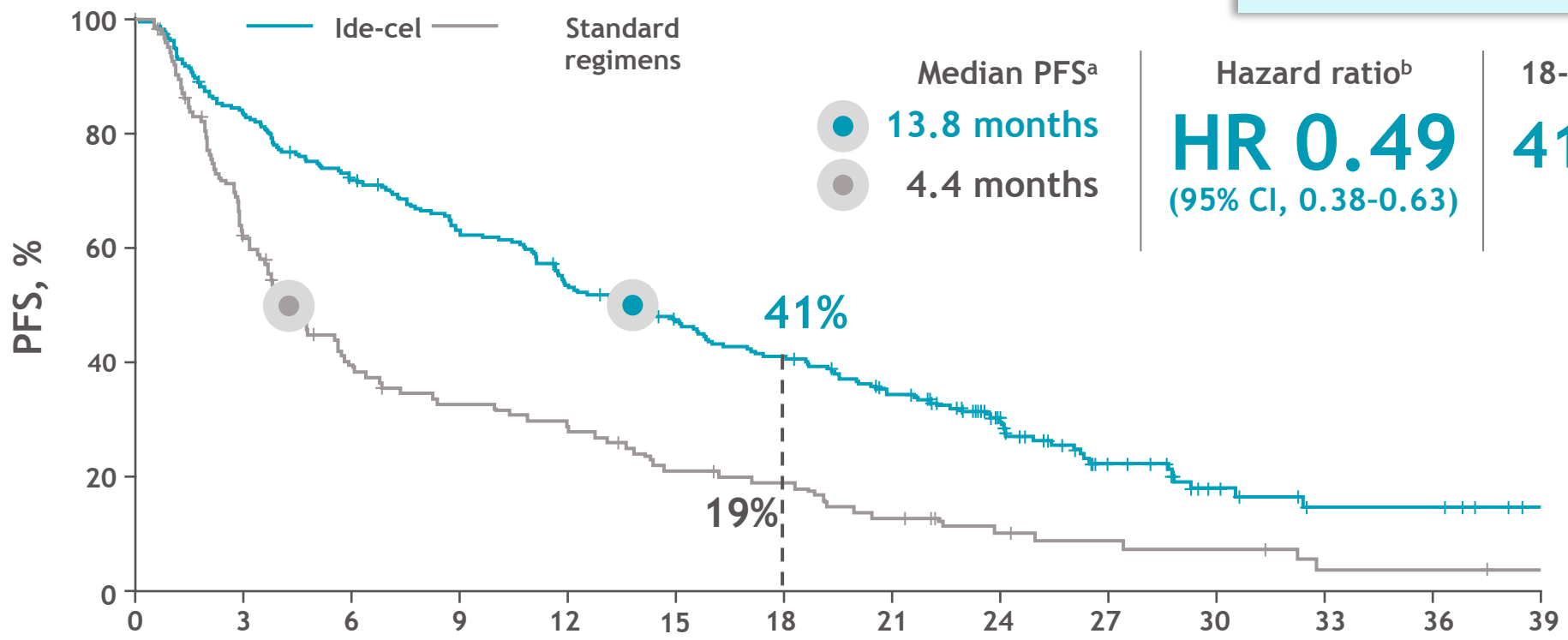
[a] Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as bridging therapy with a minimum 14 days washout; [b] DPd, DVd, IRd, Kd, or EPd; [c] ≥ 50% CD138+ plasma cells in bone marrow; [d] Included del(17p), t(4;14), t(14;16), or 1q gain/amplification; [e] ≥ 2 of del (17p), t(4;14), t(14;16), t(14;20), or 1q gain/amplification; [f] Refractory to ≥ 1 each of an IMiD agent, a PI, and an anti-CD38 antibody. CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; DOR, duration of response; DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EMP, extramedullary plasmacytoma; EPd, elotuzumab/pomalidomide/dexamethasone; HSCT, hematopoietic stem cell transplant; ide-cel, idecabtagene vicleucel; IRC, independent review committee; ITT, intent-to-treat; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PI, proteasome inhibitor; PFS, progression-free survival; PFS2, PFS on next line of therapy; R-ISS, revised International Staging System; RRMM, relapsed or refractory multiple myeloma; SOC, standard of care.

Rodriguez Otero P, et al. ASH 2023. Abstract 1028.

KarMMa-3 study: Efficacy outcomes

ORR was **71%** with ide-cel vs 42% with SOC
- sCR/CR: 44% vs 6%
- MRD-negative CR: 35% vs 2%

Significant benefit with ide-cel at final PFS analysis (ITT population)



	Median PFS[a]	Hazard ratio[b]	18-month PFS rate	
Ide-cel	13.8 months	HR 0.49 (95% CI, 0.38-0.63)	41%	
Standard regimens	4.4 months			19%

Patients at risk

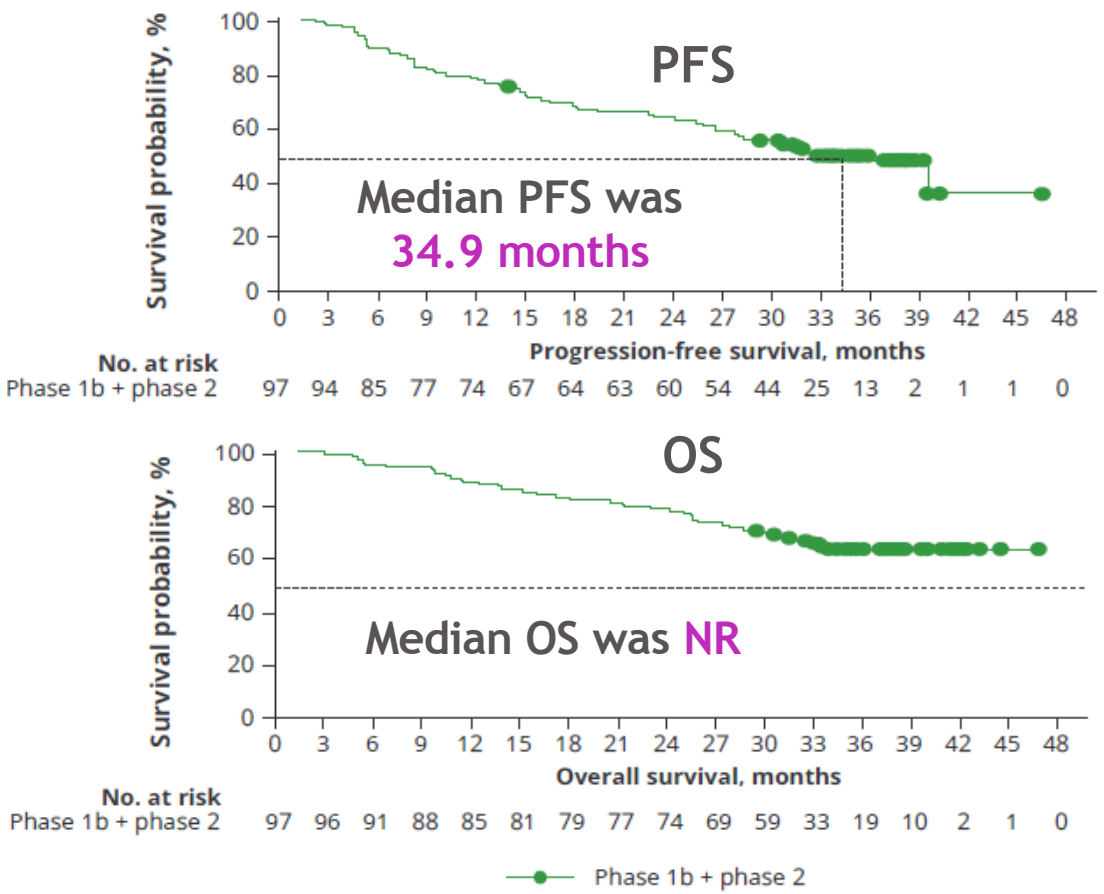
Ide-cel	254	206	177	153	131	111	94	77	54	25	14	7	7	2
Standard regimens	132	76	43	34	31	21	18	12	9	6	5	3	2	1

PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion. PFS based on IMWG criteria per IRC.
[a] Based on Kaplan-Meier approach; [b] Stratified HR based on univariate Cox proportional hazard model. CI is 2-sided. CI, confidence interval; CR, complete response; HR, hazard ratio; ide-cel, idecabtagene vicleucel; ITT, intent-to-treat; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; sCR, stringent complete response; SOC, standard of care.

Rodriguez Otero P, et al. ASH 2023. Abstract 1028.

CARTITUDE-1 final results: Phase 1b/2 study of cilta-cel in heavily pre-treated patients with RRMM

At a median follow-up of 33.4 months, 97 patients with RRMM after a median of **6 prior lines of therapy (88% triple refractory)** were included in the final analysis of the CARTITUDE-1 study



- **ORR: 97.9%** (CR/sCR: 82.5%)
- Of 49 MRD-evaluable patients, 26 and 18 had sustained MRD negativity at 12 and 18 months, respectively

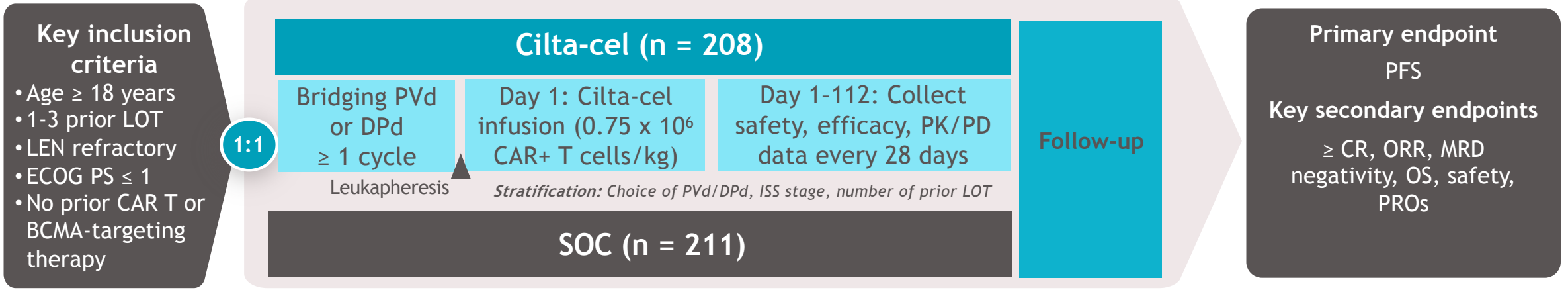
Subgroups	Median PFS, months (95% CI)	30-month PFS, %	36-month PFS, %
All patients	34.9 (25.2-NE)	54.2	47.5
≥ CR[a]	389.2 (34.9-NE)	66.8	59.8
12-month sustained MRD negativity (n = 62)[b]	NR (NE-NE)	74.9	NE
12-month sustained MRD-negative ≥ CR (n = 49)[b]	NR (NE-NE)	78.5	NE

Safety profile

- No new neurotoxic events were reported
- FDA warning about T-cell malignancies and SPMs in general
  - 26 SPMs were reported in 20 patients, including MDS (n = 2), B-cell NHL (n = 1) and AML (n = 3)

[a] Patients had ≥ CR at any time during the study, assessed by computerised algorithm; [b] Patients who were MRD evaluable had a baseline clone identified, sufficient follow-up for assessment and ≥ 2 MRD-negative assessments 12 months apart with no MRD-positive samples in that interval. AML, acute myeloid leukaemia; CI, confidence interval; CR, complete response; FDA, Food and Drug Administration; MDS, myelodysplastic syndromes; MRD, minimal residual disease; NE, not estimable; NHL, non-Hodgkins lymphoma; NR, not reached, OS, overall survival; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; SPM, second primary malignancy. Lin Y, et al. ASCO 2023. Abstract 8009.

CARTITUDE-4 study: Cilta-cel versus PVd/DPd in LEN-refractory MM patients after 1-3 prior LOT[1,2]



Characteristic	Cilta-cel (n = 208)	SOC (n = 211)
Median age, years (range)	61.5 (27-78)	61.0 (35-80)
Median time since diagnoses, years (range)	3.0 (0.3-18.1)	3.4 (0.4-22.1)
ECOG PS 0/1/2, n (%)	114 (54.8)/93 (44.7)/1 (0.5)	121 (57.3)/89 (42.2)/1 (0.5)
ISS I/II/III, n (%)	136 (65.4)/60 (28.8)/12 (5.8)	132 (62.6)/65 (30.8)/14 (6.6)
High-risk cytogenetics, n (%)[a]	123 (59.4)	132 (62.9)
1q gain/amplification/del(17p)/t(4;14)/t(14;16)	89 (43.0)/49 (23.7)/30 (14.5)/3 (1.4)	107 (51.0)/43 (20.5)/30 (14.3)/7 (3.3)
With ≥ 2 high-risk abnormalities	43 (20.8)	49 (23.3)
With del(17p), t(4;14) or t(14;16)	73 (35.5)	69 (32.9)
Triple-class exposure, n (%)	53 (25.5)	55 (26.1)
Daratumumab refractory, n (%)	48 (23.1)	45 (21.3)
Triple-class-refractory, n (%)[b]	30 (14.4)	33 (15.6)
Penta-drug refractory, n (%)[c]	2 (1.0)	1 (0.5)

[a] Data for 207 patients with cilta-cel and 210 patients with SOC; [b] Includes one PI, one IMiD and one anti-CD38 mAb; [c] Includes ≥ 2 PIs, ≥ 2 IMiDs and one anti-CD38 mAb. BCMA, B-cell maturation antigen receptor; CAR, chimeric antigen receptor; CD, cluster of differentiation; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DPd, daratumomab; pomalidomide and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance score; IMiD, immunomodulatory drug; ISS, International Staging System; LEN, lenalidomide; LOT, lines of therapy; mAb, monoclonal antibody; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall safety; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib and dexamethasone. 1. Dhakal B, et al. ASCO 2023 LBA106; 2. San Miguel JF, et al. N Engl J Med. 2023;389:335-47.

CARTITUDE-4: Phase 3 trial of cilta-cel vs PVd/DPd in lena-refractory MM: PFS

- Median number of PL: 2; 33% of pts with HR CA and 21% double hit; 25% TCExposed and 14% TCRefractory; 100% len-refractory

- CR/sCR: 73% 22% and in MRD-evaluable patients, MRD negativity occured in 87.5% vs 32.7% of patients, respectively
- 208 pts assigned to cilta-cel represent the ITT population and 32 pts did not receive cilta-cel as part of the study (20 of them received cilta-cel after disease progression during the bridging therapy)

Figure 1: Progression-Free Survival Per IRC, ITT Population

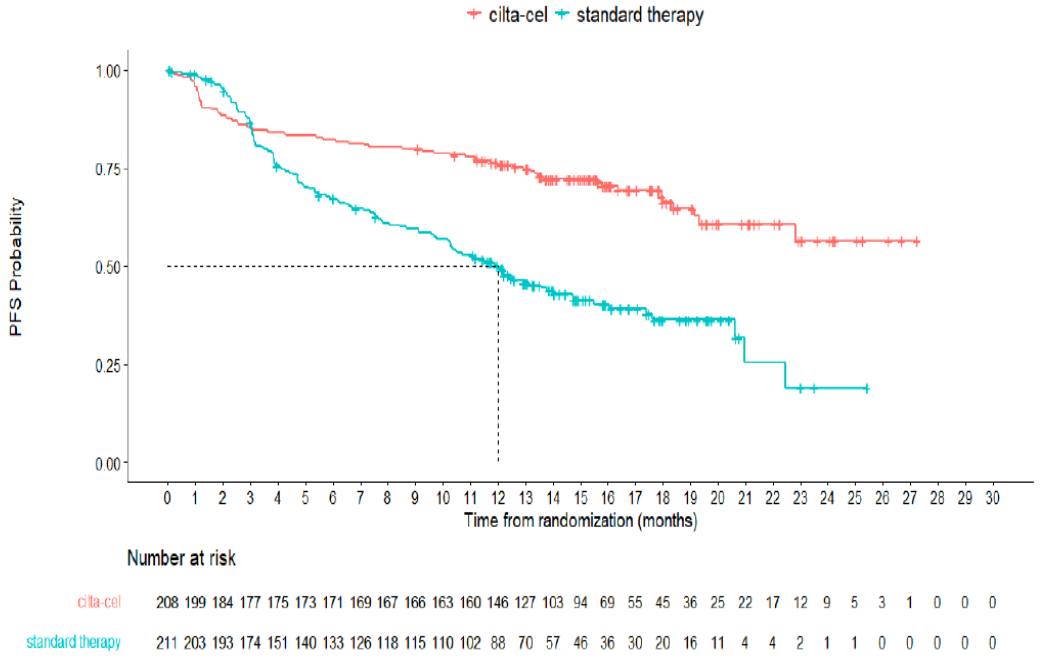
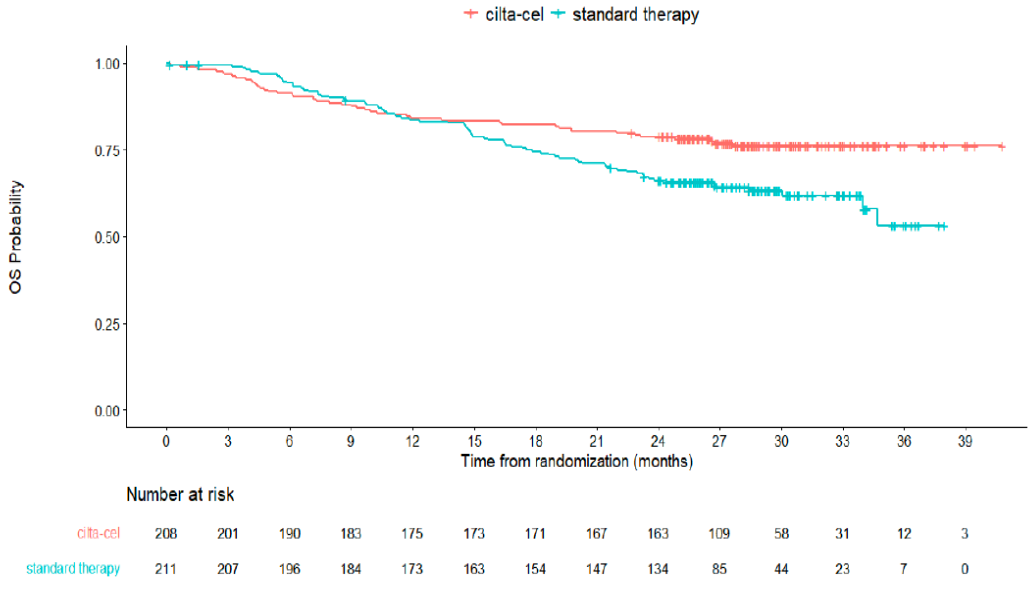


Figure 14: Overall Survival, Data Cutoff of December 13, 2023



Source: FDA analysis
Abbreviation: OS, overall survival

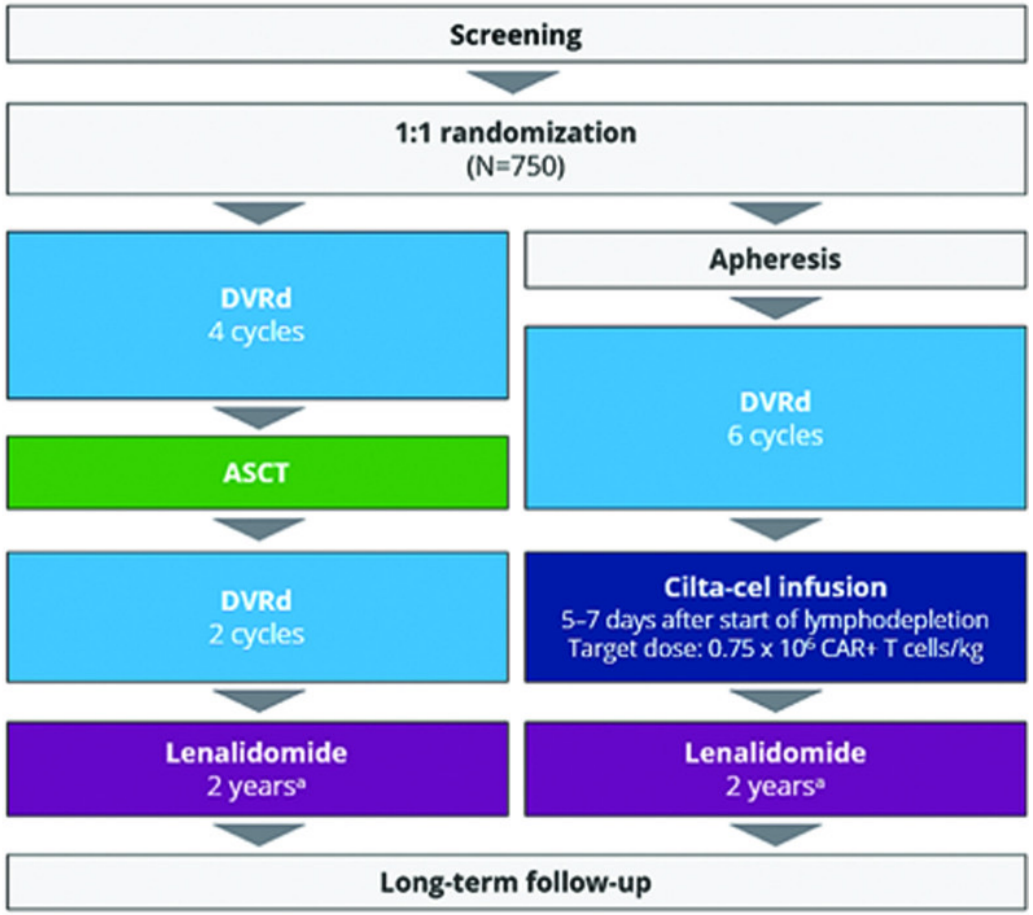
Sustained benefit across the different subgroups of patients

[a]Median follow-up, 15.9 months. [b]Constant piecewise weighted log-rank test. [c]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only progression-free survival events that occurred >8 weeks post randomisation.
Dakhal B, et al. ASCO 2023 (Abstract No. LBA106 – oral presentation).

BCMA-CAR-Ts in NDMM patients TE

CARTITUDE-6 TRIAL

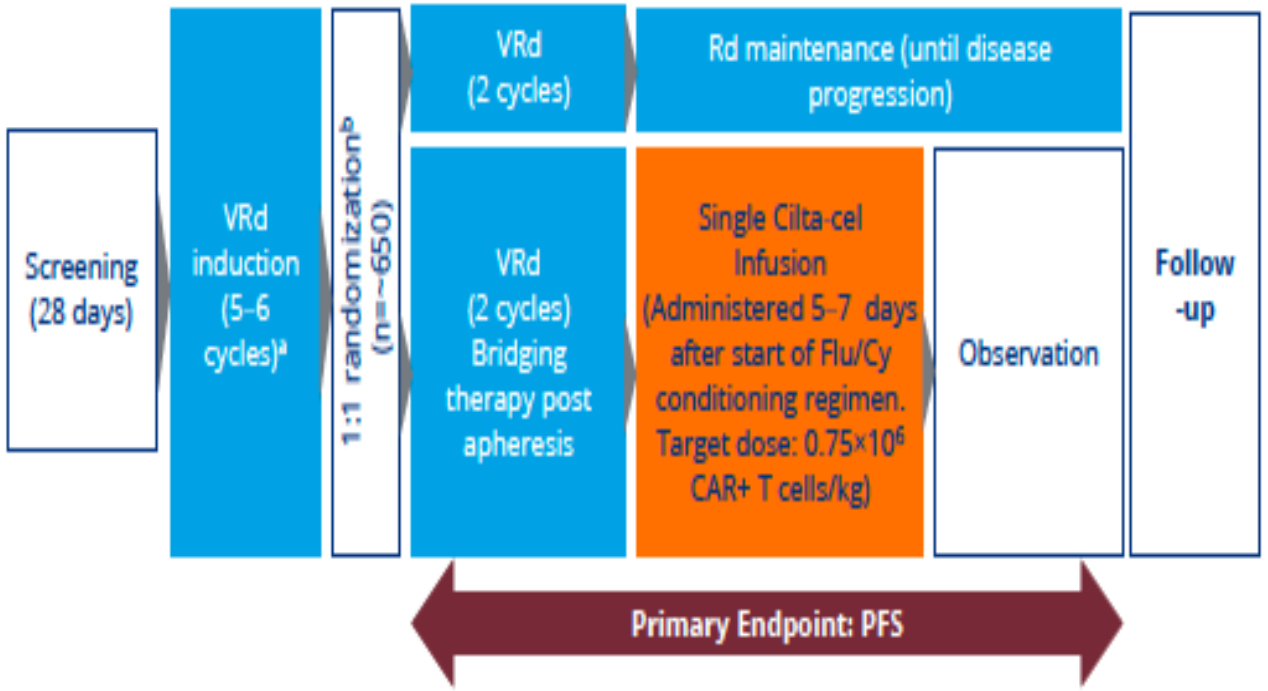
Figure: *EMagine*/CARTITUDE-6 Study Design



[a]Patients benefiting from therapy have the option to continue lenalidomide therapy until progressive disease per investigator's discretion after benefit-risk assessment and review by the medical monitor.

Cartitude-5

FIGURE 1: CARTITUDE-5 Study Design



Flu, fludarabine; Cy, cyclophosphamide
[a] 1 cycle VRd allowed prior to screening
[b] At randomization, patients will be stratified by the following factors: R-ISS (I,II,III); age/transplant eligibility (≥70 years or <70 years and ASCT ineligible due to comorbidities or <70 years and ASCT deferred); response to VRd induction (≥VGPR, ≤PR)

Broijl A et al. EHA 2023. Dytfeld D et al. ASH 2021.

Treatment landscape in Multiple Myeloma today: realistic situation

1st line

ASCT eligible

AntiCD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

AntiCD38 + PI + IMiD + Dex

2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

3rd line

Anti-CD38 + Pomalidomide-dex

Elotuzumab-Pomalidomide-dex

Previous combos if pt elegible

Ide-cel

Other drugs

Melflufen

Sel-dex

4th line

BCMA-targeted therapy

CAR-T

Ide-cel

Cilta-cel

BsAbs

Teclistamab

Elranatamab

GPRC5D-targeted therapy

BsAbs Talquetamab

The label is for RRMM after at least 3 PL of therapy including PI, IMiD and antiCD38 and refractory to the last line of therapy

Treatment landscape in Multiple Myeloma today: realistic situation

1st line

ASCT eligible

AntiCD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

AntiCD38 + PI + IMiD + Dex

2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

3rd line

Anti-CD38 + Pomalidomide-dex

Elotuzumab-Pomalidomide-dex

Previous combos if pt elegible

Ide-cel

Treatment landscape in Multiple Myeloma

1st line

ASCT eligible

AntiCD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

AntiCD38 + PI + IMiD + Dex

2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

Cilta-cel

New combinations:

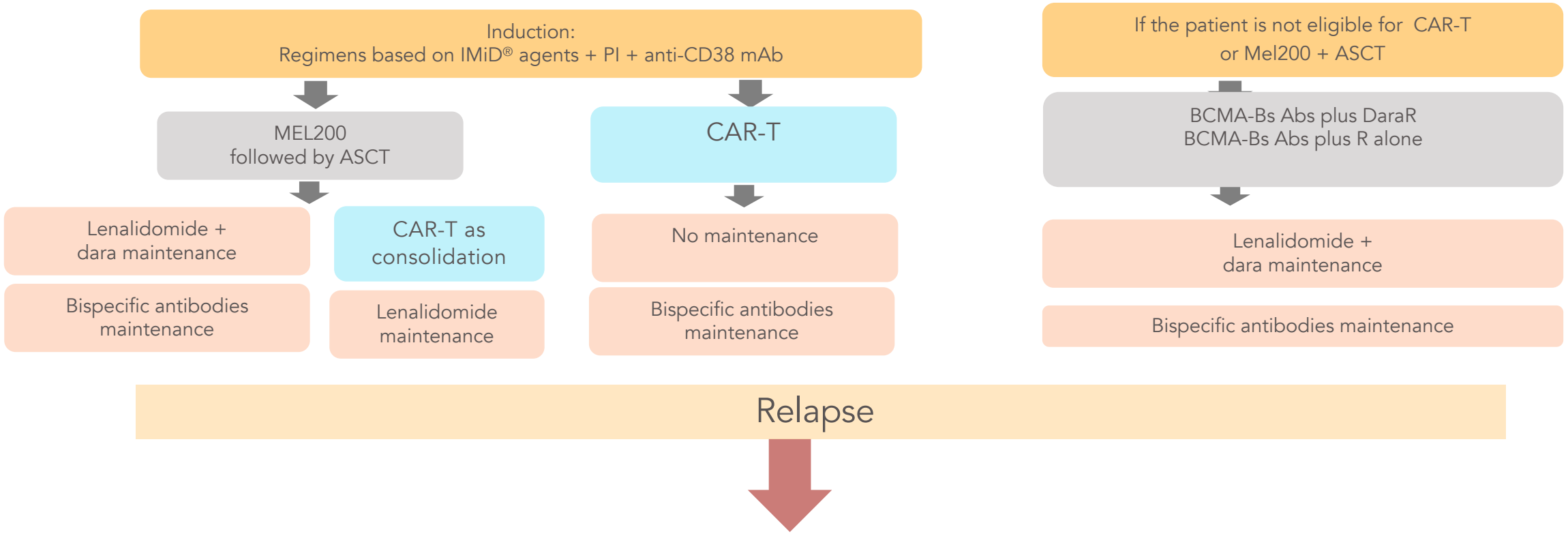
Teclistamab-Dara / Elra-Dara / Elra monotherapy

Talquetamab-Dara or Talquetamab-pom

Belantamab-Vd (DREAMM-7): positive data

Belantamab-Pd (DREAMM-8)

Summary: envisioning the future



BCMA-targeting bsAbs: Efficacy

Product	n	PL/TCR	Efficacy at the RP2D	PFS/DoR/OS (m)	Schedule of administration
Teclistamab[2]	165	5PL/ 77.6%	ORR 63% ≥CR: 45.5%	11.4/24/22.2 months	0.06–0.3–1.5 mg/kg QW SC; switch to Q2W/Q4W dosing (under investigation)
Elranatamab[3]	123	5PL/ 96.7%	ORR 61% ≥CR: 35.0%	17.2m/69% at 12m/24.6m	12–32–76 mg **SC** QW Option to switch to Q2W dosing after ≥2 months if ≥PR and to Q4W dosing after ≥6 Q2W cycles
Linvoseltamab[4]	117 at 200mg	5–6PL/ 80%	ORR 71% (46% ≥CR) (n=117)	69% /87% /75% at 12m	5–25–200 mg **IV** C1–C3 QW C4–C5 Q2W Q4W later if ≥VGPR
ABBV-383[5]	124	5PL/ 82%	ORR 65% (27% ≥CR) @ 40mg ORR 64% (35% ≥CR) @ 60mg	10.4 months/NR in all patients @10.8 month follow-up	60 mg IV Q3W

Most BCMA × CD3 bispecific antibodies have been evaluated in TCR MM patients.
ORR ranges from 50–71% and covers the unmet need. PFS is approx 1 year for most bsAbs

The data presented are provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
BCMA, B-cell maturation antigen; bsAb, bispecific antibody; C, Cycle; CR, complete response; DoR, duration of response; IV, intravenous; mAb, monoclonal antibody; MM, multiple myeloma; MTD, maximum tolerated dose; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PL, prior lines; QW, every week; Q2W, every other week; Q3W, every three weeks; Q4W, every four weeks; RP2D, recommended phase II dose; SC, subcutaneous; sCR, stringent complete response; TCR, triple-class refractory; VGPR, very good partial response.

1. Bar et al. ASH 2023 (abstract 2011); 2. Van de Donk NWCJ, et al. ASCO 2023 (Abstract No. 8011 – presentation); 387:495-505; 3. Tomasson et al. ASH 2023 (Abstract No. 3385 – oral presentation); 4. Lee HC. ASCO 2023 (Abstract No. 8006 – presentation); 5. Vij R et al. ASH 2023 (Abstract No. 3378 – poster).

BCMA-bispecific mAbs: Safety profile

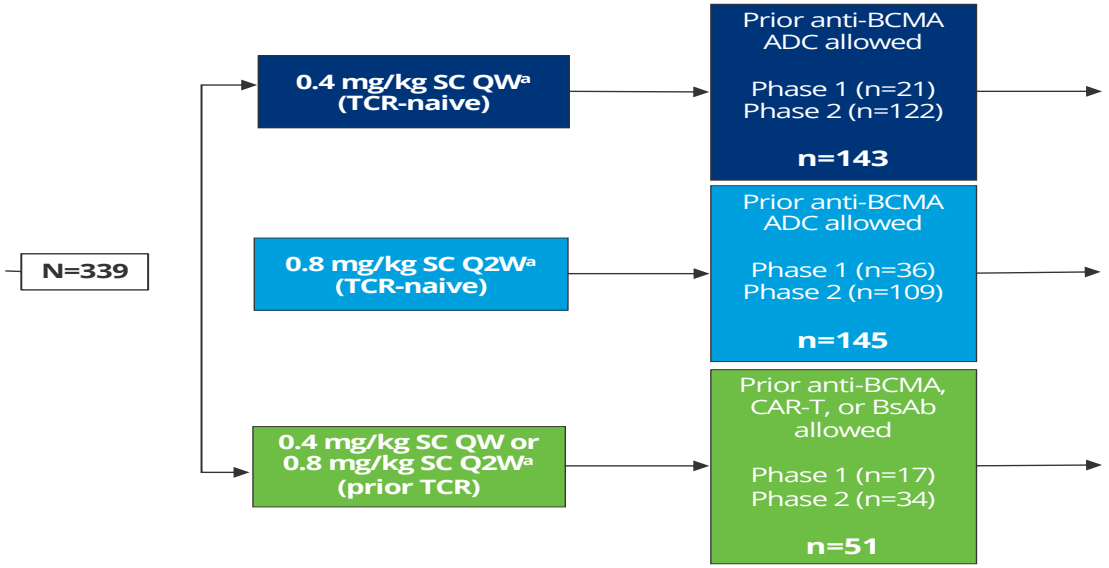
	Teclistamab	Elranatamab	Linvoseltamab	ABVV-3883
CRS (G 3-4)	**71.5% (0.6%)**	**56.3%** (0%)	**44%** (0%)	**43%** (1%)
Median onset	2(1-6)	2	11 hours	1(1-2)
Duration	2(1-9)	2	15 hours	1(1-8)
Tocilizumab	36.4%	40%	18%	NR
NTS	14.5%	NR	NR	NR
ICANS	**3%**	**4%**	**5.6%**	5%
Grade 3-4	**0**	**0**	**1.2%**	0.5%
Median onset	3 days	2.5 days	NR	NR
Duration	7 days	2 days	NR	NR
Treatment required	8.5%	3%	NR	NR
Cytopenias Grade 3-4				
Neutropenia	64%	48%	22%	26%
Anemia	37%	36%	23%	18%
Thrombopenia	21%	22%	13%	11%
Infections	76%	66%	54%	NR
Grade 3-4	**44%**	**35%**	**29%**	**22%**

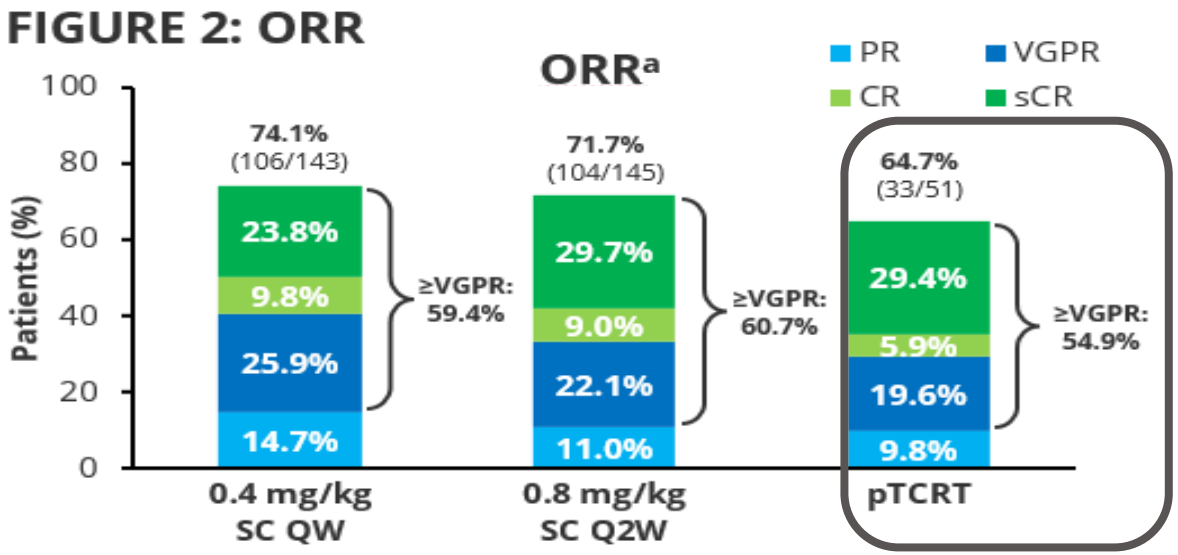
Hypogammaglobulinemia as AEs observed in most patients treated with BCMA-CD3 mABs along with the therapy

1. Wong ASH 2022 Abstract 162; 2.Moreau et al.. NEJM 2022; 3. Bahlis N et al. ASH 2022: Abstr 158; 4. Bumma et al. ASH 2022; Abstract 4555; 5. Voorhes et al. ASH 2022;Absttract 1919

MonumenTAL-1 study: Talquetamab, GPRC5D-CD3 bsAb in RRMM patients[1]

- RRMM patients; median 5–6 PL and ~70% TCR
- ORR was maintained across patient subgroups, except patients with EMD





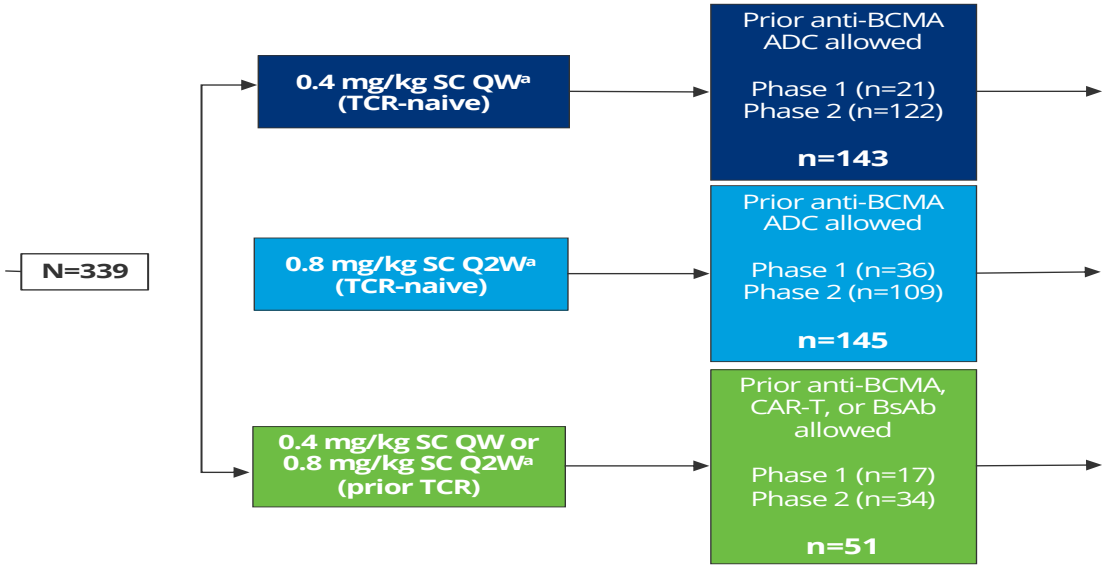
Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
mFU, mo	18.8	12.7	14.8
12-mo DOR rate in patients with ≥CR, %	78.9	90.5	80.5
mPFS, mo (95% CI)	7.5 (5.7–9.4)	14.2 (9.6–NE)[b]	5.1 (3.4–12.3)
12-mo PFS rate, %	34.9	54.4	38.1
12-mo OS rate, %	76.4	77.4	62.9

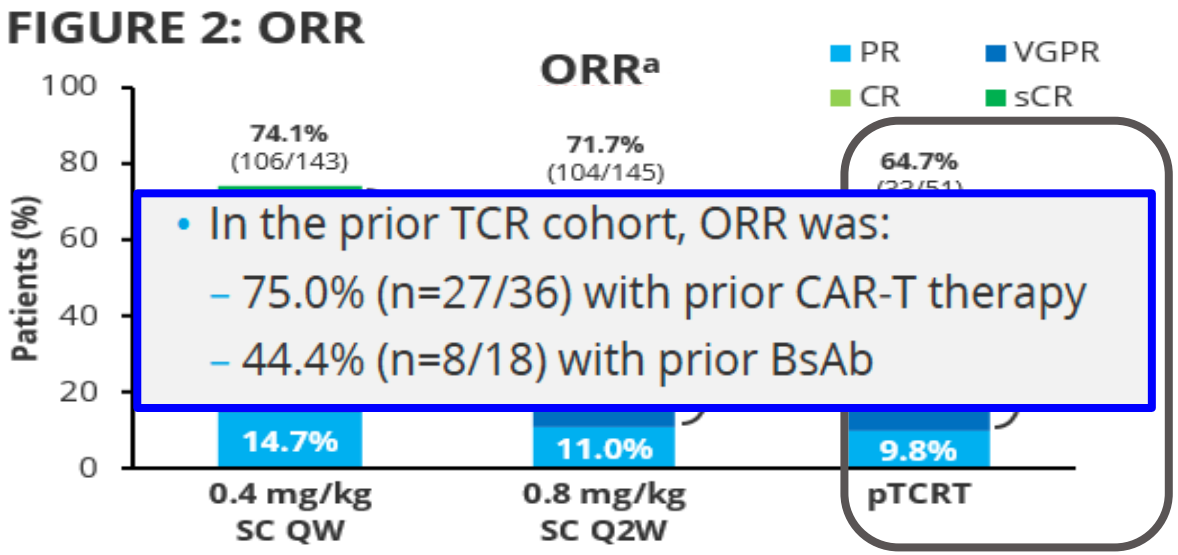
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CD, cluster of differentiation; CI, confidence interval; CR, complete response; DOR, duration of response; EMD, extramedullary disease; FU, follow-up; GPRC5D, G protein coupled-receptor Class 5 group 5; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression–free survival; PL, prior lines; PR, partial response; Q2W, every 2 weeks; QW, weekly; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; sCR, stringent complete response; TCR, T-cell redirection; VGPR, very good partial response.

1. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – poster).

MonumenTAL-1 study: Talquetamab, GPRC5D-CD3 bsAb in RRMM patients[1]

- RRMM patients; median 5–6 PL and ~70% TCR
- ORR was maintained across patient subgroups, except patients with EMD





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1. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – poster).

Talquetamab Safety

Bispecific antibody	Talquetamab Phase 1/2 MonumenTAL-1 Study GPRC x CD3		
Treatment	0.4 mg/kg SC QW	0.8 mg/kg SC Q2W	Either dose
Median follow-up	18.8 months	12.7 months	14. 8 months
AEs, all (Grade 3+)			
CRS	79% (2%)	75% (0.7%)	77% (2.0%)
Infections	59% (20%)	66% (15%)	73% (28%)
Neutropenia	35% (31%)	28% (22%)	55% (53%)
Anemia	45% (32%)	39% (25%)	39% (25%)
Thrombocytopenia	27% (20%)	30% (19%)	37% (29%)
ICANS	11% (1.6%)	10% (1.8%)	10% (1.8%)
# Deaths	0 due to AEs	0 due to AEs	0 due to AEs
Hypogamma/IVIg	NR/13%	NR/10%	NR/10%
Other	Dysgeusia 72% (N/A) Skin 56% (0%) Nail 55% (0%)	Dysgeusia 71% (N/A) Skin 73% (0.7%) Nail 54% (0%)	Dysgeusia 77% (N/A) Skin 69% (0%) Nail 63% (0%)

AEs led to:

- Dose reductions in 14.7%, 8.3%, 9.8%
- Discontinuation in 4.9%, 8.3%, 7.8%

Five patients discontinued due to skin-related AEs (n=3) or dysgeusia (n=2)

- AE, adverse event; CD, cluster of differentiation; CRS, cytokine release syndrome; GPRC, G protein-coupled receptor Class C; ICANS, immune effector cell-associated neurotoxicity syndrome; IVIg, intravenous immunoglobulin; LOT, line of therapy; N/A, not applicable; NR, not reported; QW, once weekly; Q2W, every 2 weeks; SC, subcutaneous.
- Chari A, et al. ASH 2022; Abstract 157; Touzeau C, et al. EHA 2023; Abstract S191.

The future: Bispecific Combinations

Attribute	Key Data Element	Teclistamab + Dara + Len[1] MajesTEC-2 (Cohort E, N=32)		Talquetamab + Dara[2] TRIMM-2 (N=65)	Talquetamab + POM[3] MonumenTAL-2 (N=35)		Teclistamab + Talquetamab[4] RedirecTT-1 (N=93)
		Teclistamab 0.72 mg/kg, SC n=13	Teclistamab 1.5 mg/kg, SC n=19	Talquetamab 0.8 mg/kg, Q2W n=51	Talquetamab 0.4 mg/kg, QW n=16	Talquetamab 0.8 mg/kg, Q2W n=19	Teclistamab 3.0 mg/kg + Talquetamab 0.8 mg/kg, Q2W (n=34)
Characteristics	**High-Risk,** %	**25**	**46.7**	**21.2**	**31.3**	**21.1**	**33.3**
	Median prior LoT, n (range)	**2** (1-3)	**2** (1-3)	5 (2-14)	**3 (2-12)**	**3 (2-5)**	**4 (2-10)**
	Prior PI / IMiD / Anti-CD38, %	**100 / 100 / 38.5**	**100 / 100 / 26.3**	**- / - / 90.2**	**- / - / 75.0**	**- / - / 73.7**	**- / - / -**
	Extramedullary Disease, %	**7.7**	**5.3**	**25.5**	**12.5**	**15.8**	**32.4**
	Prior BCMA, %	-	-	**52.9**	**25.1**	**0**	-
	Prior CAR T / ADC / Bispecific, %	-	-	**17.6 / 21.6 / 19.6**	**18.8 / - / 6.3**	**0 / - / 0**	**2.9[d]/11.8/0**
Efficacy	**Median Follow-Up,** mo (range)	**8.4** (1.1-12.9)		**15.0** (1.0-23.3)	**15.0** (1.2–19.0)	**11.1** (1.2–14.8)	**8.1** (0.7-15.0)
	ORR, %	**100**	**81**	**84.0** [42/50] **82.2** [37/45] (prior anti-CD38) **88.9** [8/9] (prior CAR T) **70.0** [7/10] (prior bispecific)	**93.8** (all patients) **100** [3/3] (prior CAR T) **50.0** [1/2] (EMD) **80.0** [4/5] (HR cytogenetics)	**84.2** (all patients) No prior CAR T **67.0** [2/3] (EMD) **75.0** [3/4] (HR cytogenetics)	**96.3**
	≥VGPR, %	**92**	**Not mature**	**74.0**	**87.5**	**68.4**	**88.8**
	mDoR, mo	**NR**	**NR**	**20.3**	**NR** (12.0-NR)	**NR** (7.4-NR)	**NE** (NE-NE)
Safety	**CRS,** all gr (gr ≥ 3), %	**81.3** (0)		**80.4** (0)	**74.3** (2.9)		**73.5** (0)
	Median onset, d (range)	2 (1-8)		2 (1-4)	-		**2** (1-4)
	Median duration, d (range)	2 (1-22)[a]		2 (1-9)	-		**2** (1-4)
	ICANS NT, all gr (gr ≥ 3), %	**Not reported**		-[b]	**9.0** (0)		**3** (0)
	Non-ICANS NT, all gr (gr ≥ 3), %	-		-	-		-
	Weight decreased, all gr (gr ≥ 3), %	-		**27.5** (0)	-		-
	Infections, all gr (gr ≥ 3), %	**75** (28.1)		**72.5** (25.5)	**80.0** (22.9)		**79.4** (38.2)
	Neutropenia, all gr (gr ≥ 3), %	**84.4** (78.1)		**39.2** (27.5)	**62.9** (54.3)		**55.9** (44.1)
	Dysgeusia, all gr (gr ≥ 3), %	-		-[c]	**85.7** (0)		**47.1[e]** (-)
	Nail and skin disorders, all gr (gr ≥ 3), %	-		Nail: **68.6** (2.0) Skin: **84.3** (7.8)	Nail: **68.6** (0) Skin: **74.3** (5.7)		Nail: **41.2** (0) Skin: **52.9** (0)

[a]The median duration range was confounded by ongoing infection. [b]ICANS in 4.6% of patients (QW and Q2W). [C]76.9% had dysgeusia (QW and Q2W). [d]Includes ide-cel. [e]**Includes ageusia, dysgeusia, hypogeusia, and taste disorder. NE, not estimable.** NR, not reached.

1. Searle et al. ASH 2022. Abstract 160. 2. Dholaria et al. ASCO 2023. Abstract 8003. 3. Matous et al. ASH 2023. Abstract 1014. 4. Cohen et al. ASCO 2023. Abstract 8002.

Treatment landscape in Multiple Myeloma today: realistic situation

1st line

ASCT eligible

Anti-CD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

Anti-CD38 + PI + IMiD + Dex

2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

3rd line

Anti-CD38 + Pomalidomide-dex

Elotuzumab-Pomalidomide-dex

Previous combos if pt elegible

Ide-cel

Other drugs

Melflufen

Sel-dex

4th line

BCMA-targeted therapy

CAR-T

Ide-cel

Cilta-cel

BsAbs

Teclistamab

Elranatamab

GPRC5D-targeted therapy

BsAbs

Talquetamab

The label is for RRMM after at least 3 PL of therapy including PI, IMiD and antiCD38 and refractory to the last line of therapy

Mateos MV, personal communication. Dimopoulos MA et al. EHA/ESMO guidelines. Annals of Oncology 2021

Treatment landscape in Multiple Myeloma

1st line

ASCT eligible

Anti-CD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

Anti-CD38 + PI + IMiD + Dex

2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

Cilta-cel

New combinations:

Teclistamab-Dara /Elra-Dara /Elra monotherapy

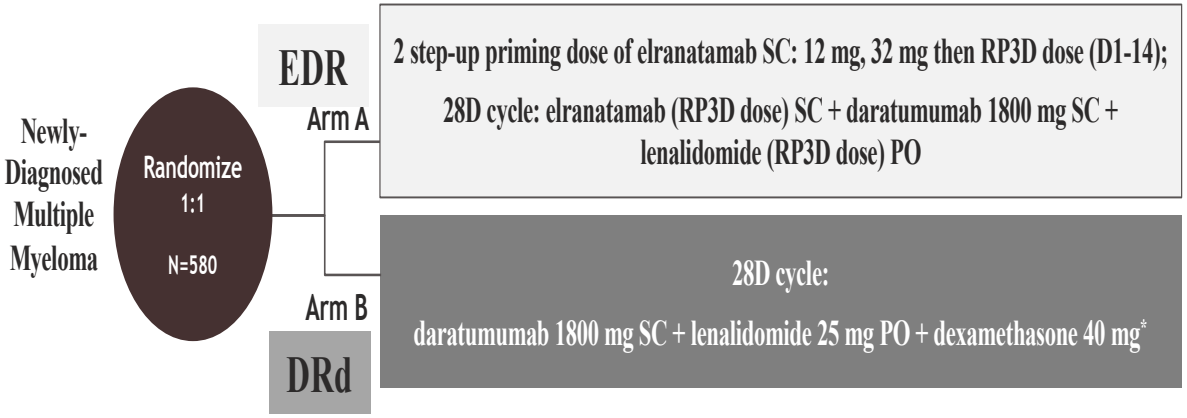
Talquetamab-Dara or Talquetamab-pom

Belantamab-Vd (DREAMM-7): positive data

Belantamab-Pd (DREAMM-8)

Mateos MV, personal communication. Dimopoulos MA et al. EHA/ESMO guidelines. Annals of Oncology 2021

BsAbs in the first line of therapy:



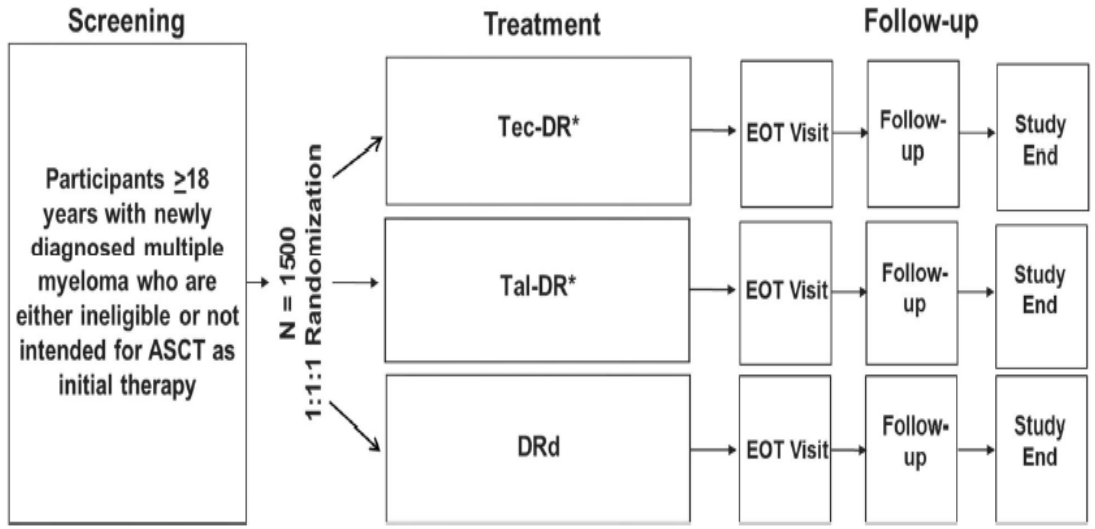
Primary Objective

To compare the efficacy of EDR vs DRd as measured by MRD status and PFS by BICR according to the IMWG

NCT05623020

MajesTEC-7[2]

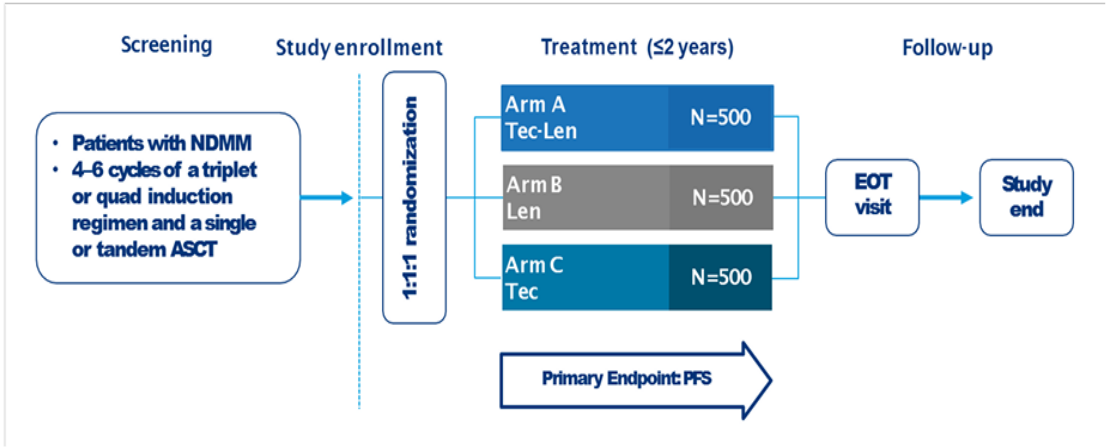
Figure 1: Schematic Overview of the Randomized Part of the Study



NCT05552222

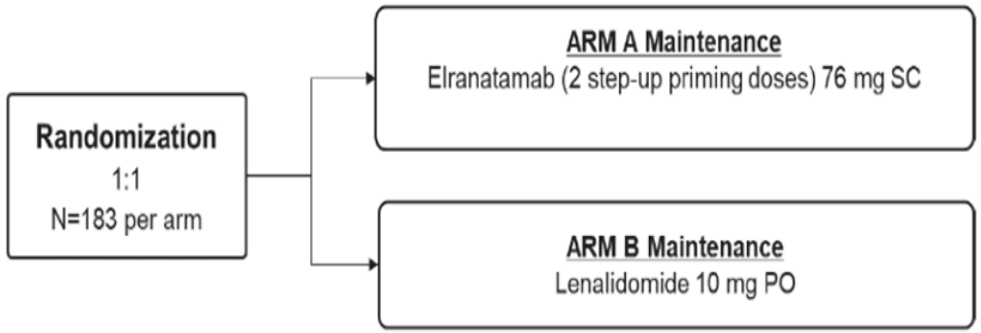
BCMA-CD3 mABs as maintenance

MajesTEC-4: Phase 3 Study Design



Teclistamab + Lenalidomide and Teclistamab Alone Versus Lenalidomide Alone as Maintenance Therapy Following ASCT in NDMM[1]

MagnetisMM-7

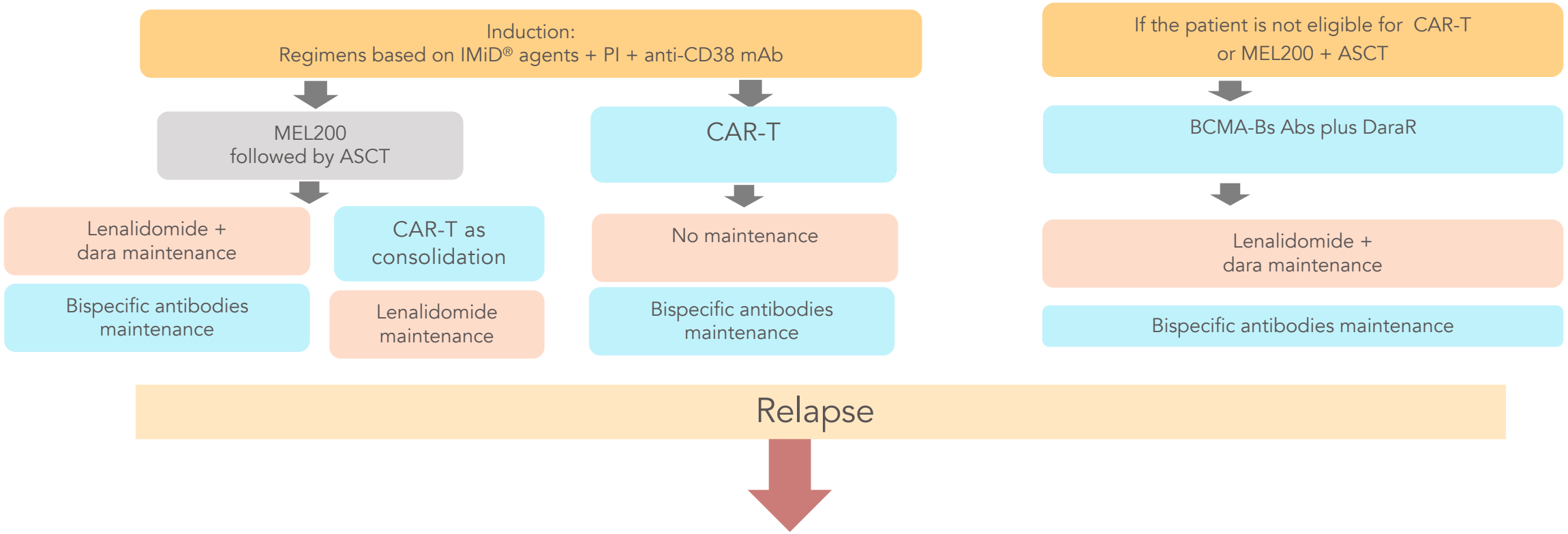


Elranatamab Versus Lenalidomide as Maintenance Therapy Following ASCT in NDMM[2]

Prior debulking to optimize effector: target ratio (rational sequencing)

1. Zamagni E et al. ASH 2022 Poster Presentation 3242; 2. ClinicalTrials.gov NCT05317416

Summary: envisioning the future



How to select the right combination in the near future???

Summary

- BCMA CAR-Ts and BCMA BsAbs together with Talquetamab targeting GPRC5D cover the unmet medical need for the Triple Class Refractory population
- Patient and disease-based factors together with availability, access,.... will drive the selection between CAR-Ts or BsAbs and also if it is better to start with BCMA or GPRC5D as target...
- Sequencing is the challenging situation but we will have more information in the future about mechanisms of resistance and how to overcome them
- In spite of all these problems, we have never seen these efficacy data in a population of MM patients already exposed to PIs, IMiDs and antiCD38 mAbs, and these deserve to be available for our MM patients and to move to earlier lines of therapy.

Agenda

Module 1: Treatment Approaches for Newly Diagnosed Multiple Myeloma (MM) — Dr Fonseca

Module 2: Role of Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies in the Care of Patients with MM — Dr Mateos

Module 3: Incorporation of Other Novel Agents and Strategies into the Management of Relapsed/Refractory MM — Dr O'Donnell

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Comments

Role of venetoclax in therapy for patients with a MM with t(11;14) mutation; clinical experience with ramp-up dosing

Dr Warren Brenner
(Boca Raton, Florida)

Dr Gigi Chen
(Pleasant Hill, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

At what point in the treatment course do you typically employ venetoclax for patients with t(11;14)-positive MM, and what are you generally partnering it with?

QUESTIONS FOR THE FACULTY

Beyond those with t(11;14)-positive MM, are there any other patient subsets (eg, patients with Bcl-2 overexpression) for whom you feel venetoclax might be appropriate?

Consulting Faculty Comments

Integration of selinexor alone or in combination for patients with R/R MM

Dr Warren Brenner (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Where in the treatment sequence are you typically incorporating selinexor for your patients with relapsed/refractory MM, and what are you generally partnering it with?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What is your preferred starting dose and schedule of selinexor for patients with MM?

What strategies do you employ to prevent and manage the adverse events associated with this agent?

Consulting Faculty Comments

Dose reductions or potential elimination of dexamethasone as a component of myeloma therapy

Dr Erik Rupard (St George, Utah)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In which situations are you using lower doses of dexamethasone or eliminating it altogether?

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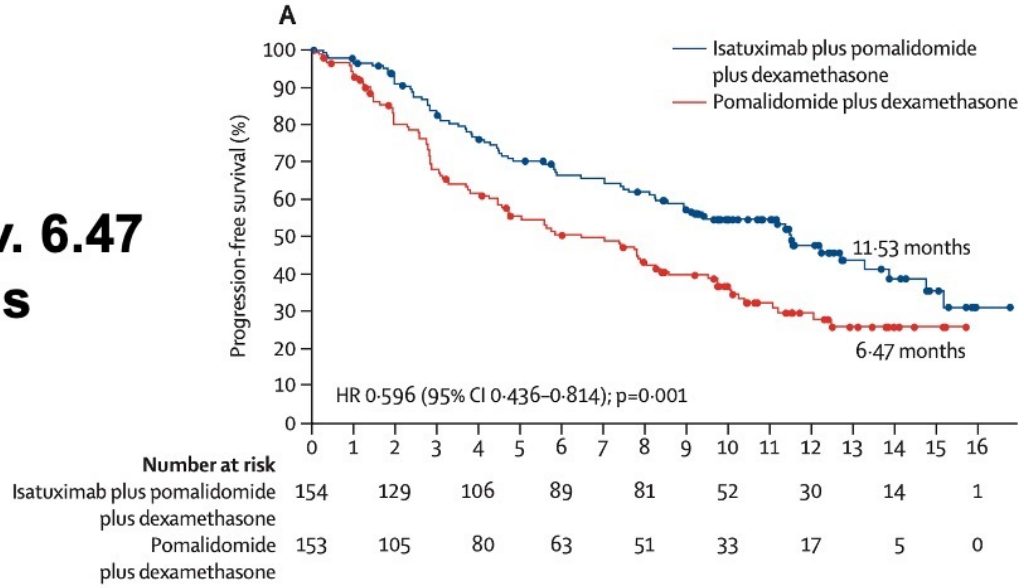
Incorporation of Other Novel Agents and Strategies into the Management of Relapsed/Refractory MM

Elizabeth O'Donnell, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

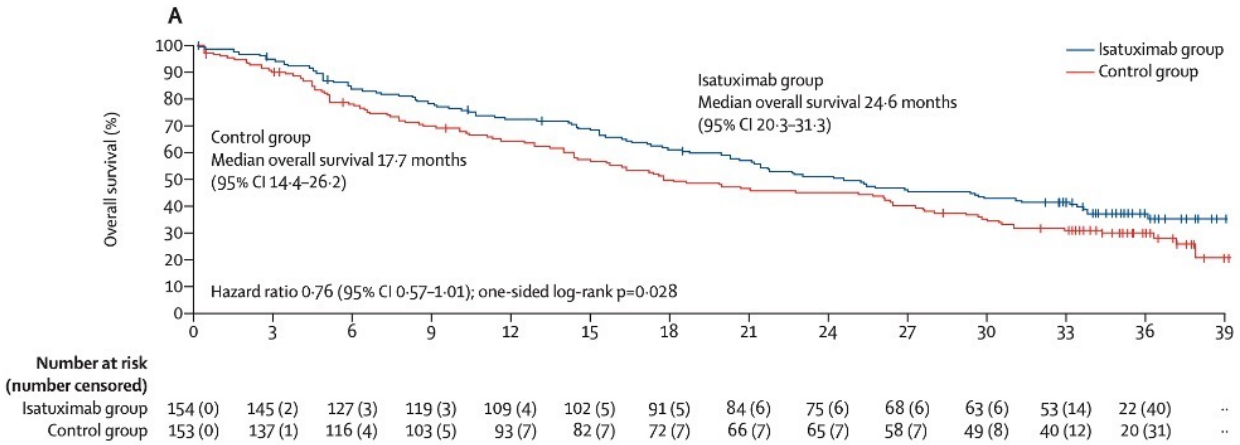
- Updated findings from the Phase III ICARIA-MM and IKEMA studies of isatuximab in combination with standard doublet regimens in R/R MM
- Published efficacy and safety data supporting the use of selinexor in combination with a proteasome inhibitor for patients with R/R MM
- Preliminary data with other selinexor-based combination strategies
- Biologic rationale for the evaluation of venetoclax in MM; available efficacy and safety findings with venetoclax/dexamethasone in patients with t(11;14)-positive or Bcl-2-positive disease
- Early research findings with and ongoing investigation of venetoclax in combination with other systemic agents (eg, proteasome inhibitors, anti-CD38 monoclonal antibodies) employed in MM

ICARIA-MM: isatuximab, pom dex v. pom dex

PFS
11.53 v. 6.47 months



OS



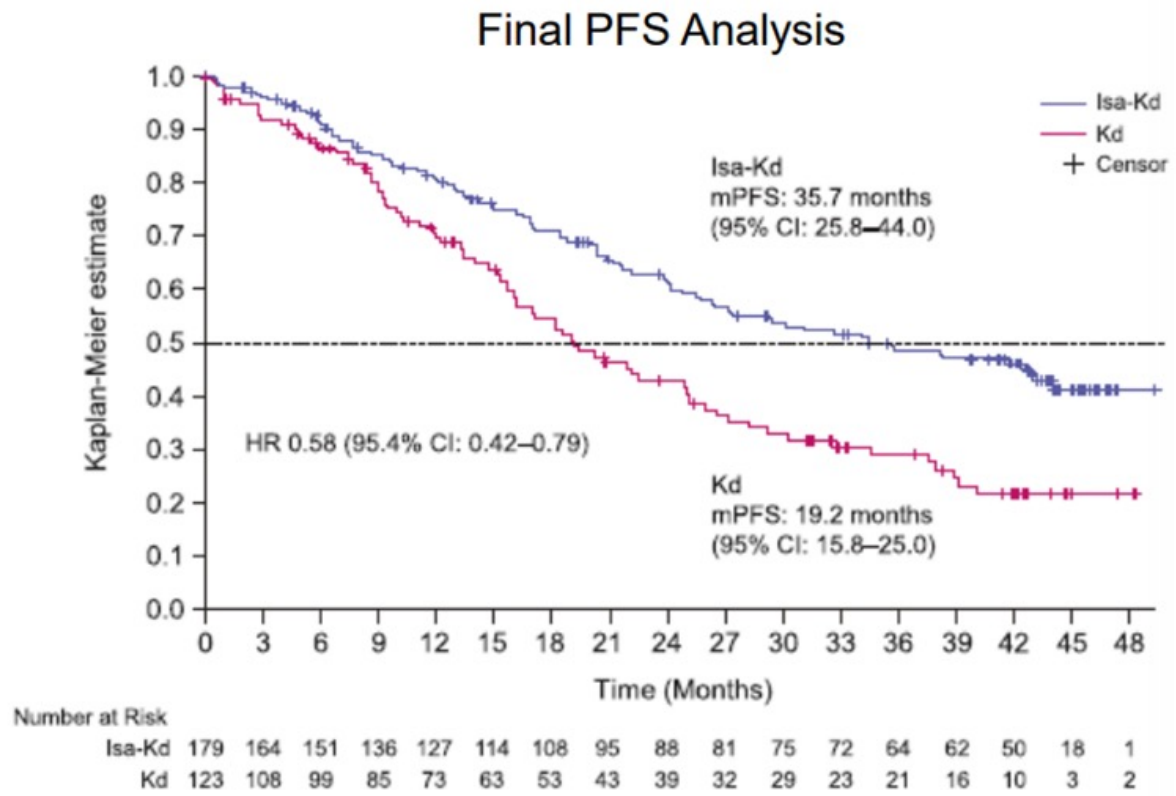
Addition of isatuximab significantly improves progression-free survival and trend in overall survival

	Isa pom dex	Pom dex
ORR	60%	35%
≥VGPR	32%	9%
CR	5%	2%

Attal M et al., *Lancet Oncol* 2019; Richardson PG et al., *Lancet Oncol* 2022

IKEMA: Isatuximab, carfilzomib, dex vs carfilzomib and dex

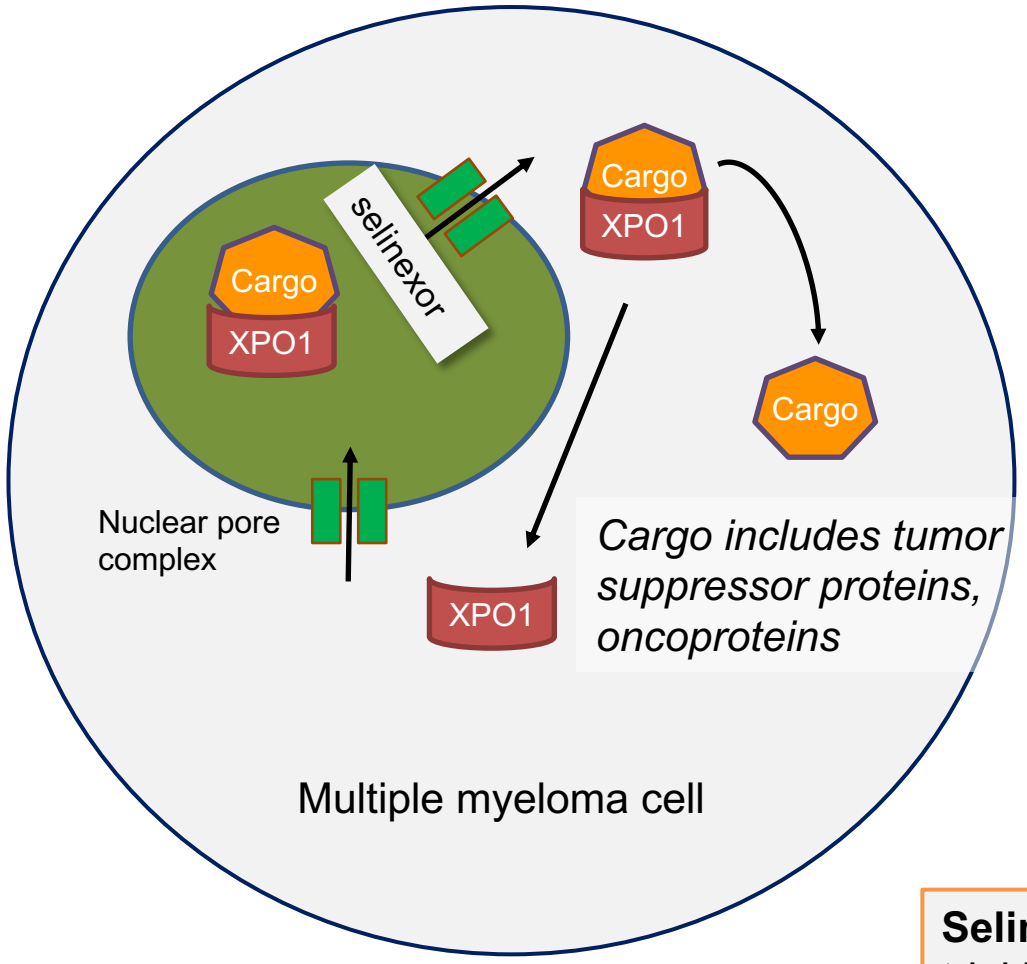
- The primary prespecified interim PFS analysis (median follow-up 20.73 months), demonstrated[1]:
  - A significant improvement in PFS with Isa-Kd versus Kd (HR 0.53; 99% CI 0.32–0.89; one-sided p=0.0007)
- The final PFS analysis (2 years after the prespecified interim analysis; median follow-up 43.96 months) confirmed the results[2]:
  - HR 0.58 (95.4% CI 0.42–0.79)
- **This analysis was planned to occur 3 years after the primary PFS analysis, regardless of the number of OS events, to summarize the OS in IKEMA**



CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; K, carfilzomib; PFS, progression-free survival; mPFS, median PFS.

1. Moreau P, et al. *Lancet*. 2021;397:P2361–P2371; 2. Martin T, et al. *Blood Cancer J*. 2023;13(1):72.

Selinexor



Exportin 1 (XPO1) is the major nuclear export protein for:

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, and FOXO)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)
- Glucocorticoid receptor (GR)

Selinexor is an **oral selective XPO1 inhibitor**

- Prevents nuclear export of tumor suppressor proteins
- Inhibits oncoprotein translation
- Reactivates GR signaling in presence of dexamethasone
- Enhances daratumumab activity in vitro against myeloma cells

Selinexor and dexamethasone approved in July 2019 based on STORM trial in penta drug exposed, triple class refractory patients with selinexor given 80 mg twice/week (Chari A et al., *N Engl J Med* 2019)
ORR 26%; median PFS 3.7 months
GI adverse events are common: all grade, nausea 72%, vomiting 38%

BOSTON: selinexor, bortezomib, dex vs bortezomib, dex

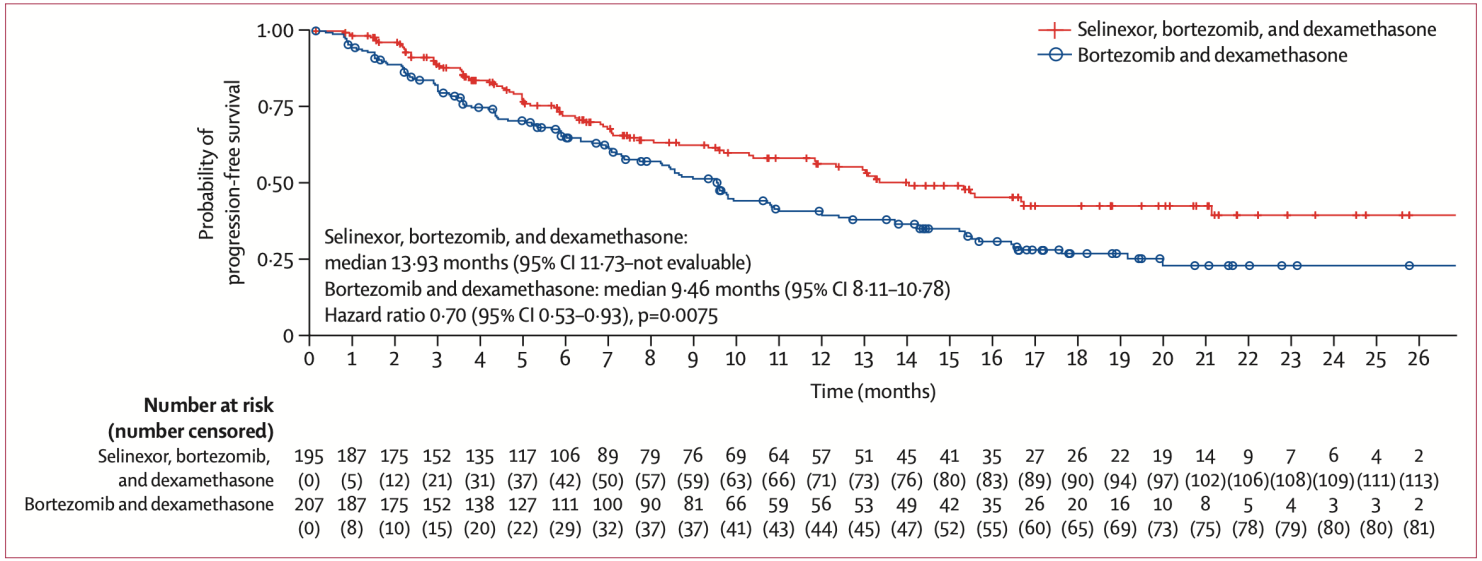


Figure 2: **Kaplan-Meier estimates of progression-free survival among patients in the intention-to-treat population**

Phase III, randomized, 1-3 prior lines

SVd: Selinexor 100 mg weekly, bortezomib **weekly**, dexamethasone 40 mg weekly split over two days (five week cycle)

Vd: Bortezomib **2x/week** with dexamethasone 20 mg day of and day after bortezomib (three week cycle for first 8 cycles)

In SVd arm, 40% less bortezomib and 25% less dexamethasone than control arm

Arm	N	PFS	HR	ORR	≥VGPR	≥CR
SVd	195	13.93	0.7 0.53-0.93	74%	44.6%	24.4%
Vd	207	9.46		62%	32.4%	10.6%

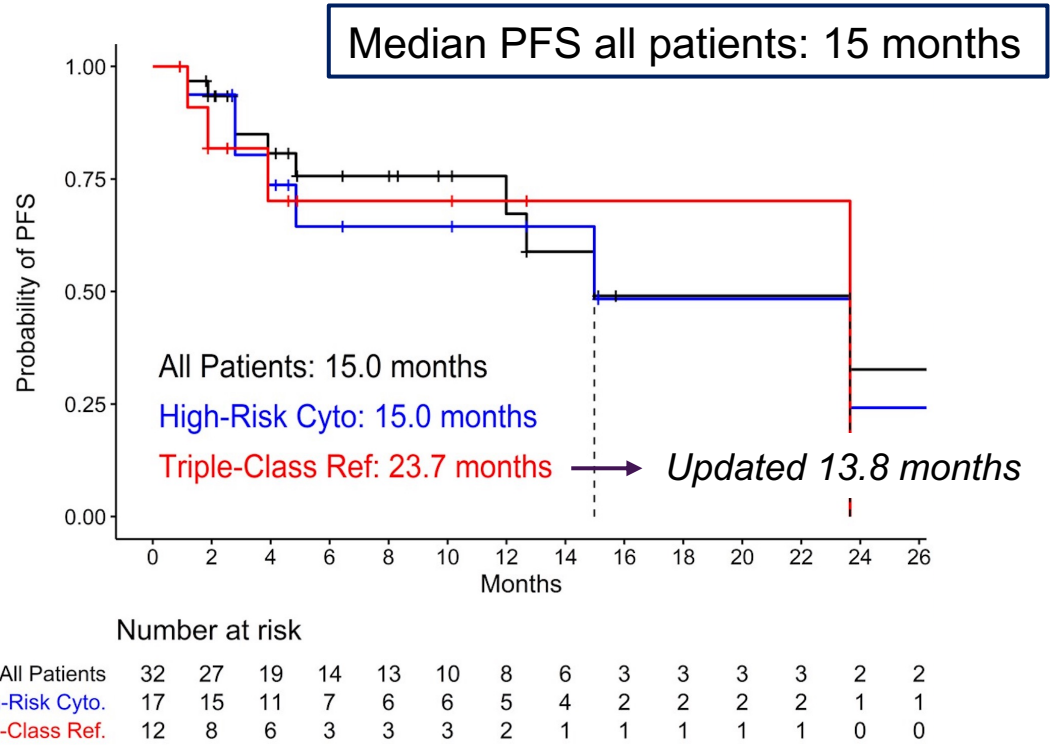
Selinexor significantly adds to the efficacy of bortezomib and dexamethasone

Grosicki S et al., *Lancet* 2020

STOMP: selinexor, carfilzomib, dex

- Median 4 prior lines (1-8)
- Lenalidomide 96.9%
- Pomalidomide 71.9%
- Anti-CD38 antibody 68.8%

Supportive care for nausea, eg, with carfilzomib
- Aprepitant 130 mg IV on days 1, 8, 15
- Palonosetron 0.25 mg IV on days 1, 8, 15
- Olanzapine 5 mg PO QHS on days 1-4
- Prochlorperazine PO PRN
- Ondansetron PO PRN



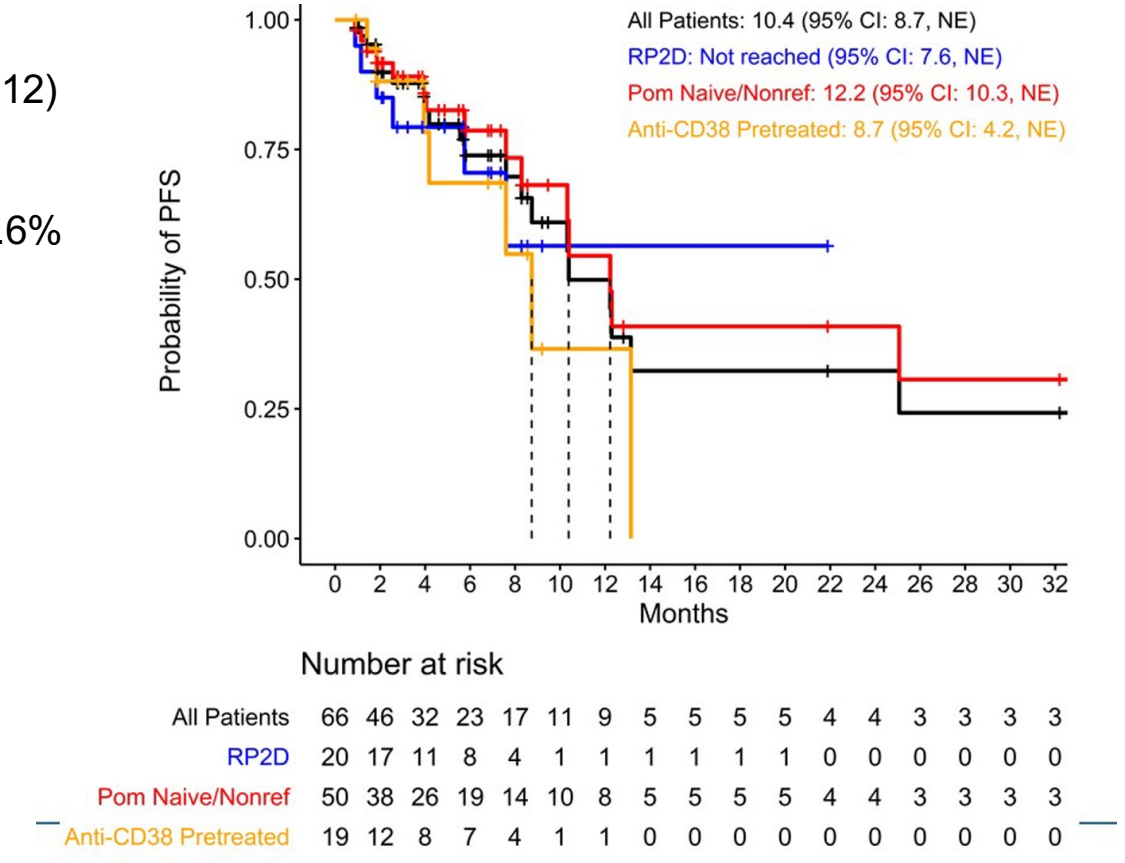
	N = 32
ORR	78%
≥ VGPR	44%
≥ CR	25%

Recommended phase 2 dose: selinexor **80** mg weekly, carfilzomib 56 mg/m^2 weekly

Gasparetto C, et al. *Br J Cancer*. 2022;126(5):718-725; Schiller G et al., ASH 2022

STOMP: selinexor, pomalidomide, dex

- Median 4 prior lines (1-12)
- Lenalidomide 100%
- Pomalidomide 29.2%
- Anti-CD38 antibody 30.6%



Median PFS all patients 10.4 months (N = 66)

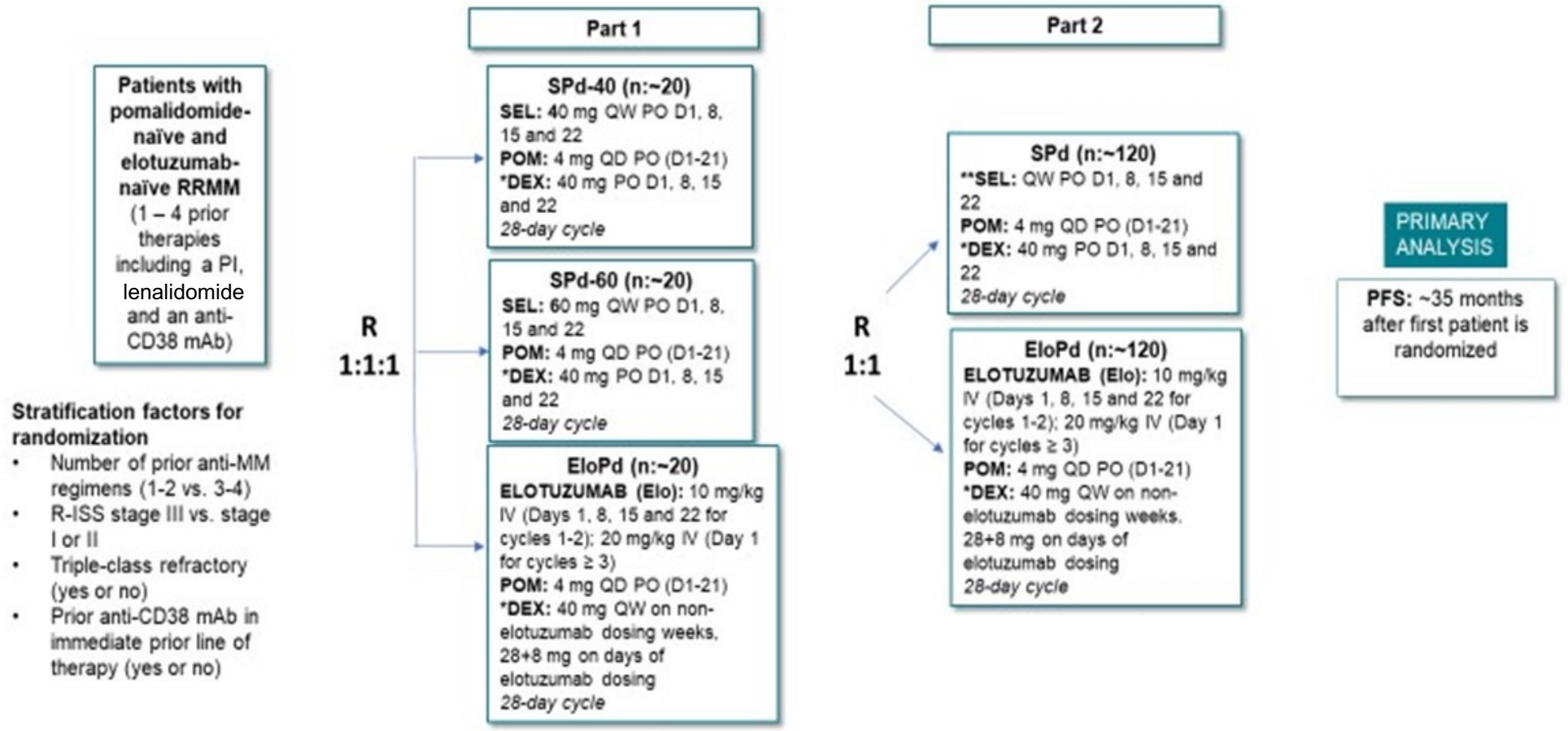
Phase 2 dose

	N = 20
ORR	65%
≥ VGPR	30%
≥ CR	5%

Recommended phase 2 dose, selinexor **60** mg weekly

White D, et al. *J Clin Oncol*. 2021;39(15_suppl):8018.

EMN29/XPORT-MM-031: Phase III Trial Schema

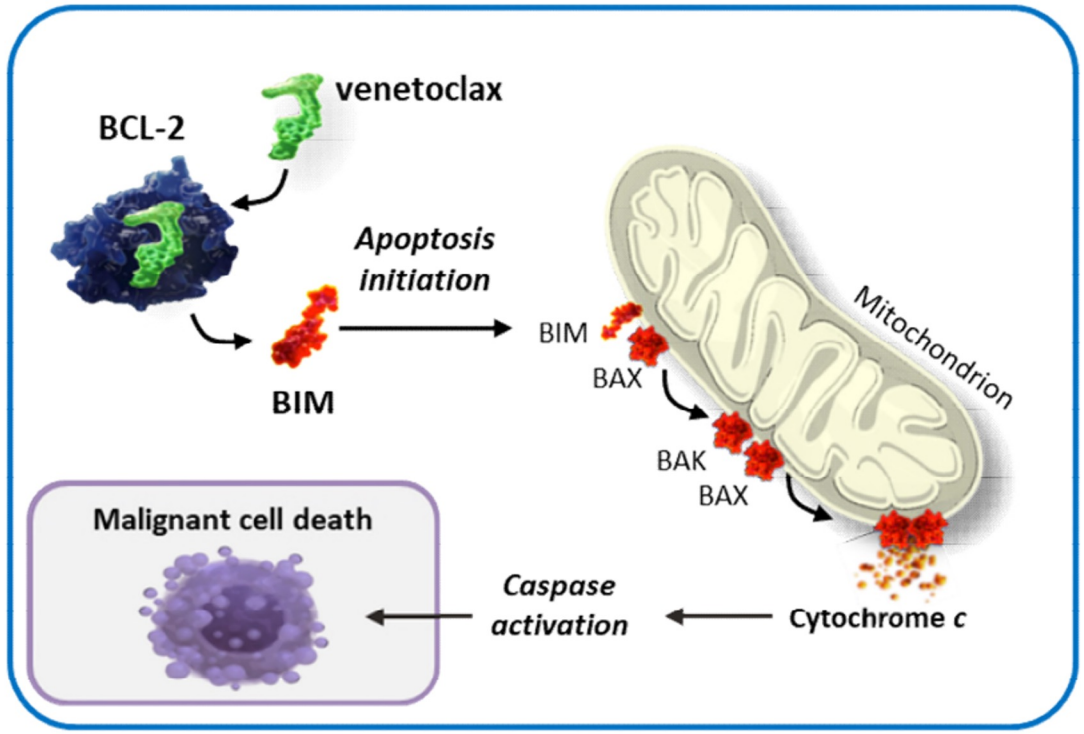


SPd = selinexor/pomalidomide/dexamethasone; SEL = selinexor; POM = pomalidomide; DEX = dexamethasone; EloPd = elotuzumab/pomalidomide/dexamethasone

https://www.myeloma-europe.org/trials/emn29; www.clinicaltrials.gov/NCT05028348; Accessed May 2024.

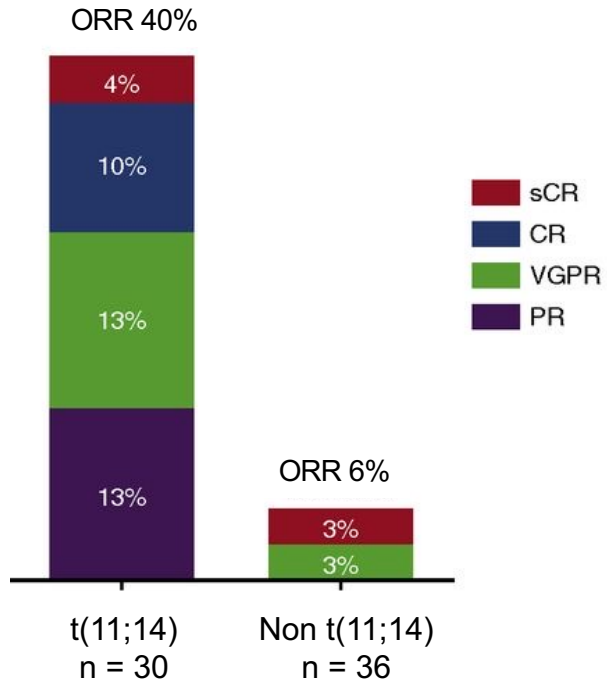
Venetoclax

- MM is a genetically complex disease, and underlying genetic aberrations may influence treatment outcomes as well as inform therapeutic decisions; however, biomarker-directed therapies are lacking
- t(11;14) is the most common translocation in MM, present in approximately 16%–24% of patients[1]
- BCL-2 is an anti-apoptotic protein that promotes cell survival in MM harboring t(11;14)[2]
- Venetoclax is a highly selective, potent, oral BCL-2 inhibitor that has shown encouraging efficacy and safety in patients with t(11;14)-positive RRMM[3-5]
  - In a Phase 1/2 study, 51 patients with t(11;14)-positive RRMM were treated with VenDex, resulting in ORRs of 48%–60%[5]



Venetoclax as single agent in t(11;14) disease

- Venetoclax is an oral inhibitor of BCL2, an anti-apoptotic protein; approved in CLL and AML
- Motivated by in vitro data showing MM cell lines with t(11;14) had higher sensitivity to venetoclax
  - Effect of venetoclax not specifically related to cyclin D1
  - t(11;14) correlates with higher ratios of BCL2:MCL1 mRNA
- 66 patients with a median of 5 prior lines of treatment
  - 77% lenalidomide refractory
- 45% t(11;14); note 15-20% of MM patients in general have t(11;14)
- Daily venetoclax: 300, 600, 900, or 1200 mg
- No dexamethasone (could be added at progression)
- No tumor lysis syndrome

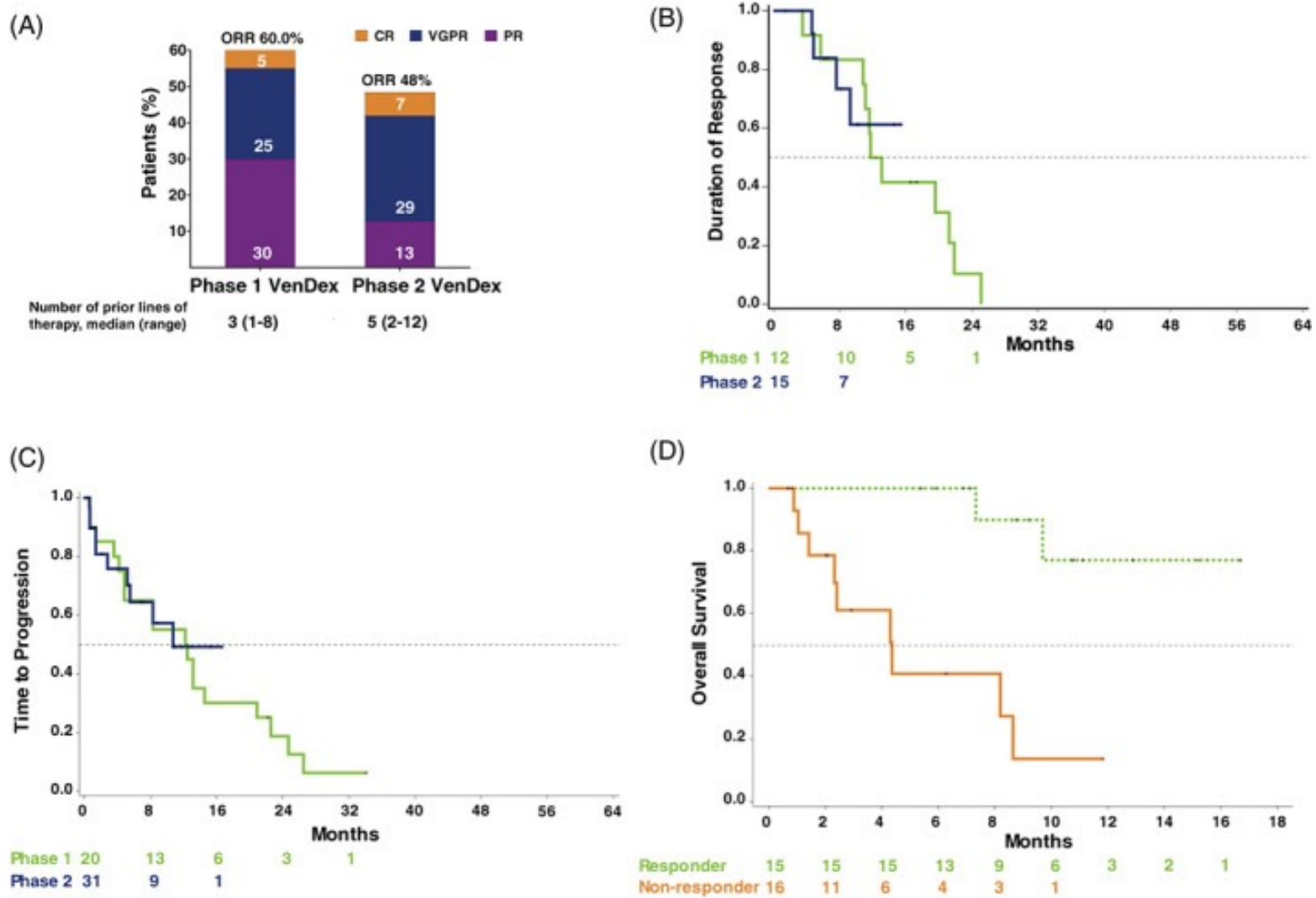


Not shown: higher *BCL2*:*BCL2L1* expression in responders and in t(11;14)

Venetoclax has activity as a single agent in relapsed/refractory disease with t(11;14)

Kumar S, et al. *Blood*. 2017;130(22):2401-2409. Gupta VA, et al. *Blood*. 2021;137(26):3604-3615. Touzeau C, et al. *Leukemia*. 2014;28(1):210-212.

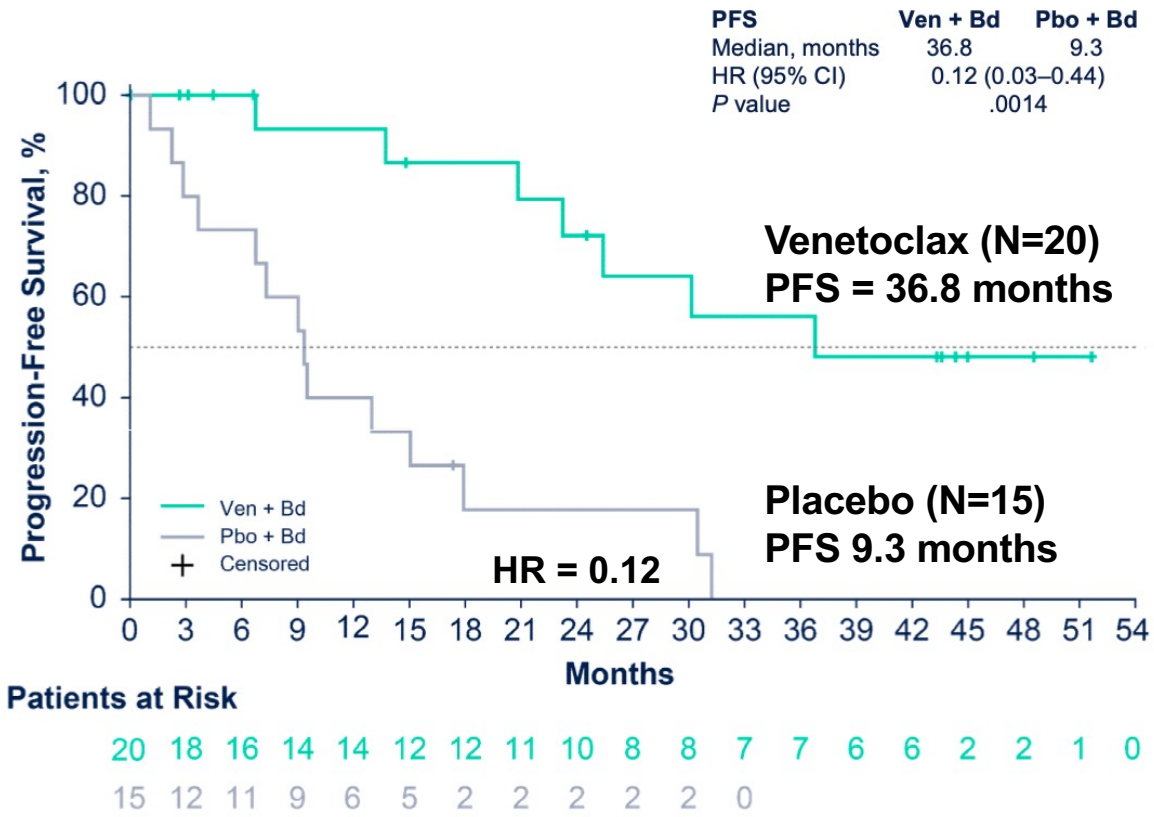
Venetoclax and dex in patients with relapsed/refractory t(11;14) multiple myeloma



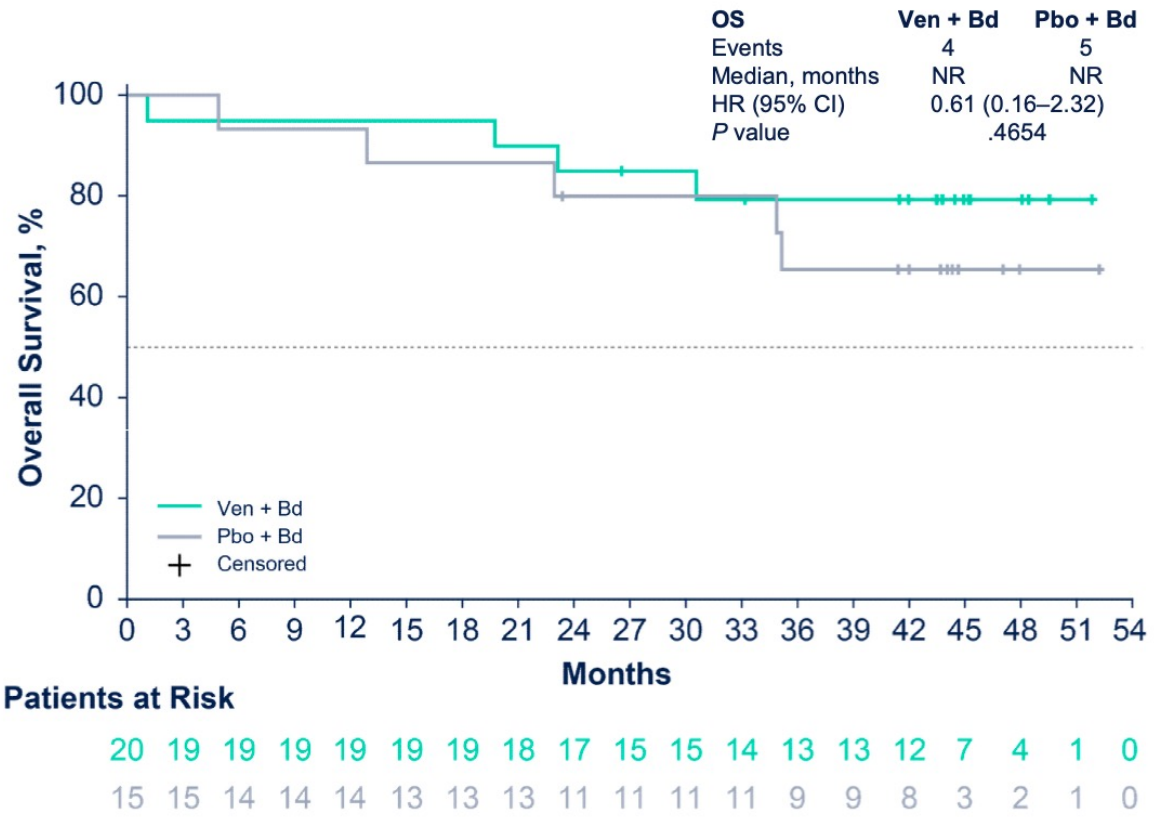
Kaufman et al. Am J Hematol. 2021 Apr 1; 96(4): 418–427.

BELLINI: venetoclax in t(11;14) disease

Investigator-Assessed PFS in Patients With t(11;14)



OS in Patients With t(11;14)

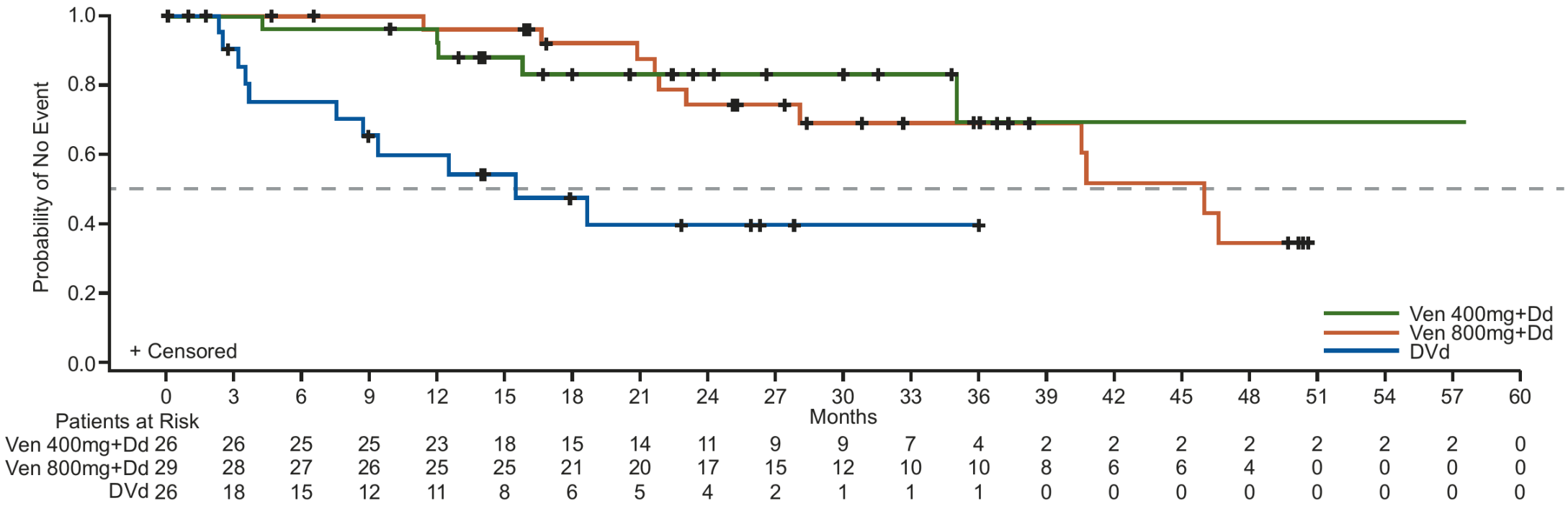


	Ven bort dex	Bortez dex
ORR	95%	47%
≥VGPR	80%	27%
≥CR	55%	7%

Significant improvement in PFS in patients with t(11;14) with HR 0.12

Kumar SK, et al. *Lancet Oncol.* 2020;21(12):1630-1642. Kumar SK, et al. *Blood*. 2021;138(Suppl 1):84.

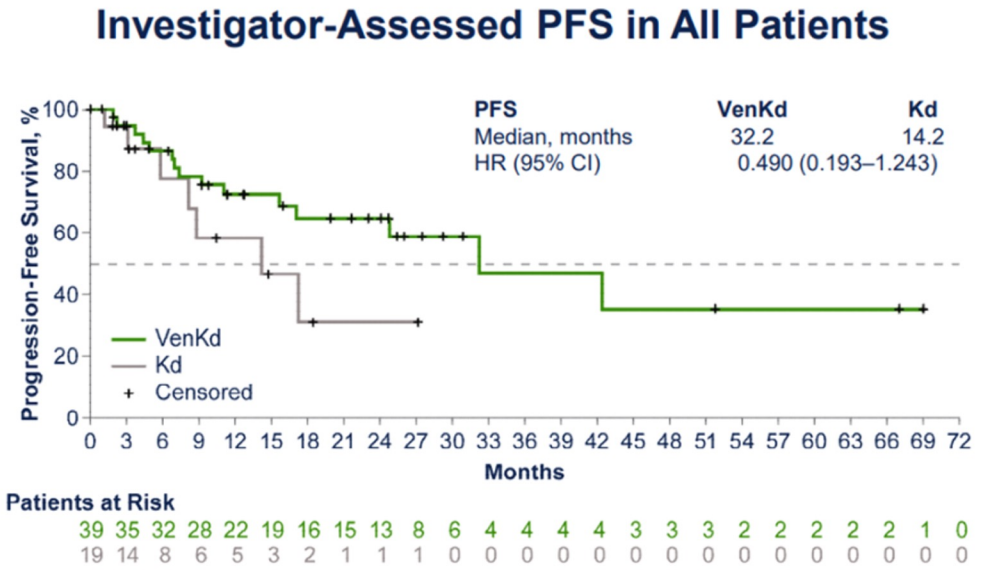
Venetoclax Versus Bortezomib with Daratumumab and Dexamethasone in t(11;14)

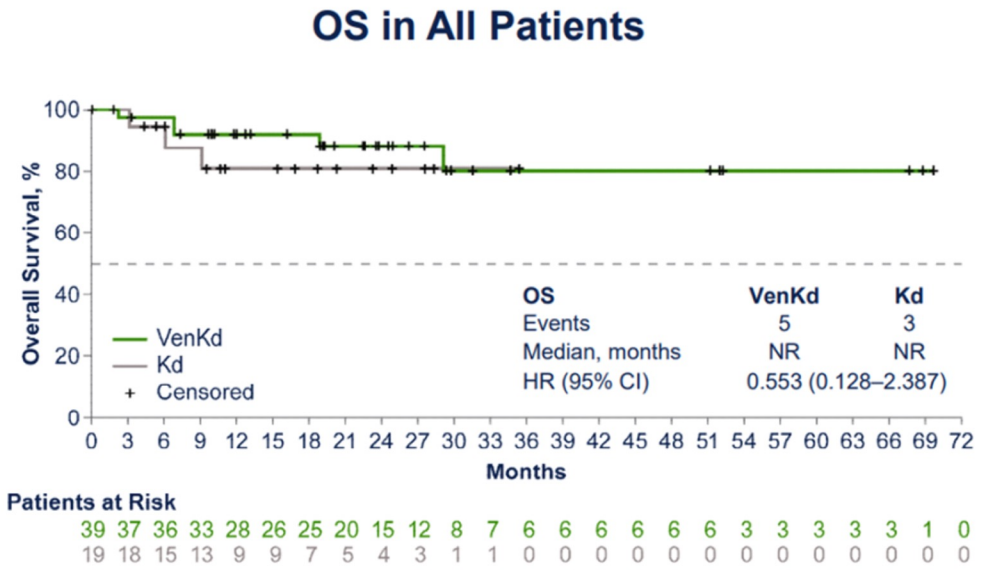


Group	Follow-up time, median (range)	33-month PFS estimate, % (95% CI)
400 mg VenDd (n=26)	24.2 (4.2-57.6)	83.2 (61.0-93.4)
800 mg VenDd (n=29)	32.6 (1.0-50.6)	69.1 (45.6-84.1)
DVd (n=26)	17.8 (0.0-36.0)	39.7 (17.0-61.8)

Data set includes both non-randomized Part 1 patients and randomized Part 3 patients. No statistical comparisons were performed.
Dd, daratumumab and dexamethasone; DVd, bortezomib, daratumumab, and dexamethasone; PFS; progression-free survival; Ven, Venetoclax.

Venetoclax Plus Carfilzomib-Dexamethasone vs Carfilzomib Dexamethasone in t(11;14)





	VenKd (n=39)	Kd (n=19)
Median follow-up, months (range)	22.6 (1.8–69.7)	16.8 (0.0–35.4)
Median DOR, months (95% CI)	41.5 (23.9–NE)	16.3 (6.5–NE)
Median TTR, months (95% CI)	1.0 (1.0–1.1)	1.3 (1.0–4.2)
Median TTP, months (95% CI)	32.2 (17.1–NE)	17.2 (5.8–NE)

Addition of venetoclax to Kd resulted in longer median PFS vs Kd alone, and median OS has not yet been reached in any group

International Myeloma Society Annual Meeting, September 27-30, 2023, Athens, Greece

Meet The Professors Live: Clinical Investigators Provide Perspectives on Actual Cases of Patients with Ovarian and Endometrial Cancer

Sunday, June 2, 2024
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Brian M Slomovitz, MD

Moderator

Angeles Alvarez Secord, MD, MHSc

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