Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

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Faculty

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Director of the Judy and Bernard Briskin
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Anne and Bernard Gray Family Chair in Cancer
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Moderator

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Miami, Florida

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Dr Krishnan — Disclosures

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, Bristol Myers Squibb, GSK, Janssen Biotech Inc, Regeneron Pharmaceuticals Inc, Sanofi
Contracted Research	Janssen Biotech Inc
Speakers Bureau	Bristol Myers Squibb, Takeda Pharmaceuticals USA Inc
Stock Options/Ownership — Public Company	Bristol Myers Squibb

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Dr Lonial — Disclosures

Advisory Committee and Consulting Agreements	AbbVie Inc, Amgen Inc, Bristol Myers Squibb, Celgene Corporation, Genentech, a member of the Roche Group, GSK, Janssen Biotech Inc, Novartis, Pfizer Inc, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Board of Directors with Stock	TG Therapeutics Inc (no cancer agents currently)
Contracted Research	Bristol Myers Squibb, Janssen Biotech Inc, Novartis

Dr Orlowski — Disclosures

Advisory Committee	AbbVie Inc, Adaptive Biotechnologies Corporation, Asylia Therapeutics Inc, BioTheryX Inc, Bristol Myers Squibb, Karyopharm Therapeutics, Meridian Therapeutics, Monte Rosa Therapeutics, Nanjing IASO Biotherapeutics, Neoleukin Therapeutics, Oncopeptides, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi, Sporos Bioventures, Takeda Pharmaceuticals USA Inc
Clinical Research Funding	Bristol Myers Squibb, CARsgen Therapeutics, Exelixis Inc, Heidelberg Pharma, Janssen Biotech Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Laboratory Research Funding	Asylia Therapeutics Inc, BioTheryX Inc, Heidelberg Pharma
Patents	Asylia Therapeutics Inc

Dr Raje — Disclosures

Advisory Committee	Caribou Biosciences Inc, Immuneel Therapeutics
Consulting Agreements	AbbVie Inc, Amgen Inc, Bristol Myers Squibb, Janssen Biotech Inc, Pfizer Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Contracted Research	bluebird bio

Dr Richardson — Disclosures

Advisory Committee	Bristol Myers Squibb, Celgene Corporation, GSK, Karyopharm Therapeutics, Oncopeptides, Sanofi
Research Grants	Bristol Myers Squibb, Celgene Corporation, Karyopharm Therapeutics, Oncopeptides, Takeda Pharmaceuticals USA Inc

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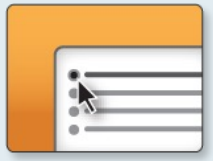
Clinicians in the Meeting Room

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 premeeting survey.

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.

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Clinicians Attending via Zoom

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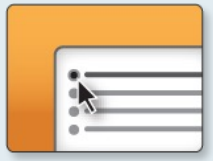

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About the Enduring Program

- 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.
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Moderator

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Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Richardson

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) MM — Dr Lonial

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies in the Treatment of MM — Dr Krishnan

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Orlowski

MM Survey Respondents

Melissa Alsina, MD
Jesús Berdeja, MD
Natalie Callander, MD
Rafael Fonseca, MD
Carol Ann Huff, MD
Jonathan Kaufman, MD
Amrita Krishnan, MD
Shaji Kumar, MD
Ola Landgren, MD, PhD
Sagar Lonial, MD
Tom Martin, MD
Joseph Mikhael, MD, MEd
Philippe Moreau, MD
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Krina Patel, MD, MSc
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Paul Richardson, MD
Keith Stewart, MB, ChB
Sascha Tuchman, MD, MHS
Jeffrey Zonder, MD

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Consulting Faculty

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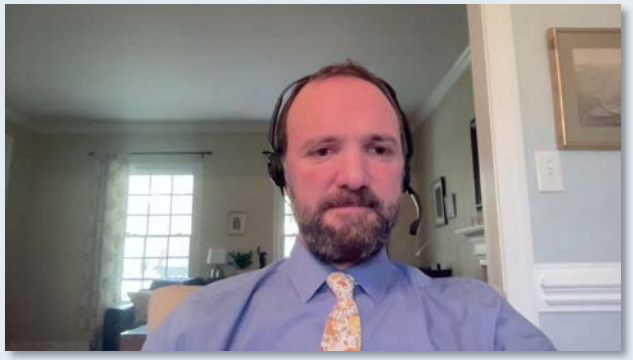
Tampa, Florida

C Ola Landgren, MD, PhD
Sylvester Comprehensive Cancer Center
University of Miami
Miami, Florida



Sascha A Tuchman, MD, MHS
UNC Lineberger Comprehensive Cancer Center
Chapel Hill, North Carolina

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FDA Investigating 'Serious Risk' of Secondary Cancer After CAR-T Therapy

Press Release: November 29, 2023

“The FDA has launched an investigation into what it called a ‘serious risk’ of T-cell malignancies in patients treated with autologous chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA) or CD19.

The agency has received multiple reports of T-cell malignancies, including CAR-positive lymphomas, from clinical trials and postmarketing adverse event data sources, according to a statement posted on the FDA website. Serious outcomes of these secondary malignancies have included hospitalization and death. The notice and investigation pertain to all currently approved BCMA- and CD19-targeted CAR T-cell products.

‘Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalizations and death, and is evaluating the need for regulatory action,’ agency officials said in the statement. ‘As with all gene therapy products with integrating vectors (lentiviral or retroviral vectors), the potential risk of developing secondary malignancies is labeled as a class warning in the US prescribing information for approved BCMA-directed and CD19-directed genetically modified autologous T-cell immunotherapies.’”

https://www.medpagetoday.com/hematologyoncology/hematology/107569

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Agenda

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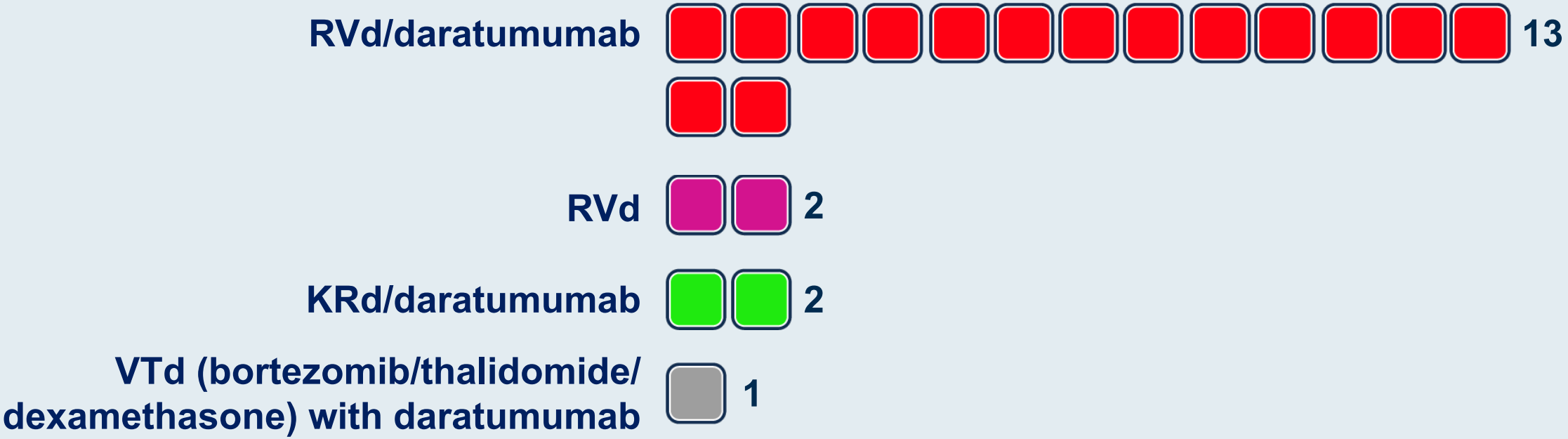
Module 4: Bispecific Antibodies in the Treatment of MM — Dr Krishnan

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Orlowski

Regulatory and reimbursement issues aside, what is your preferred induction regimen for a younger (65-year-old) patient with standard-risk multiple myeloma (MM)?



Survey of 20 US-based clinical investigators November 2023

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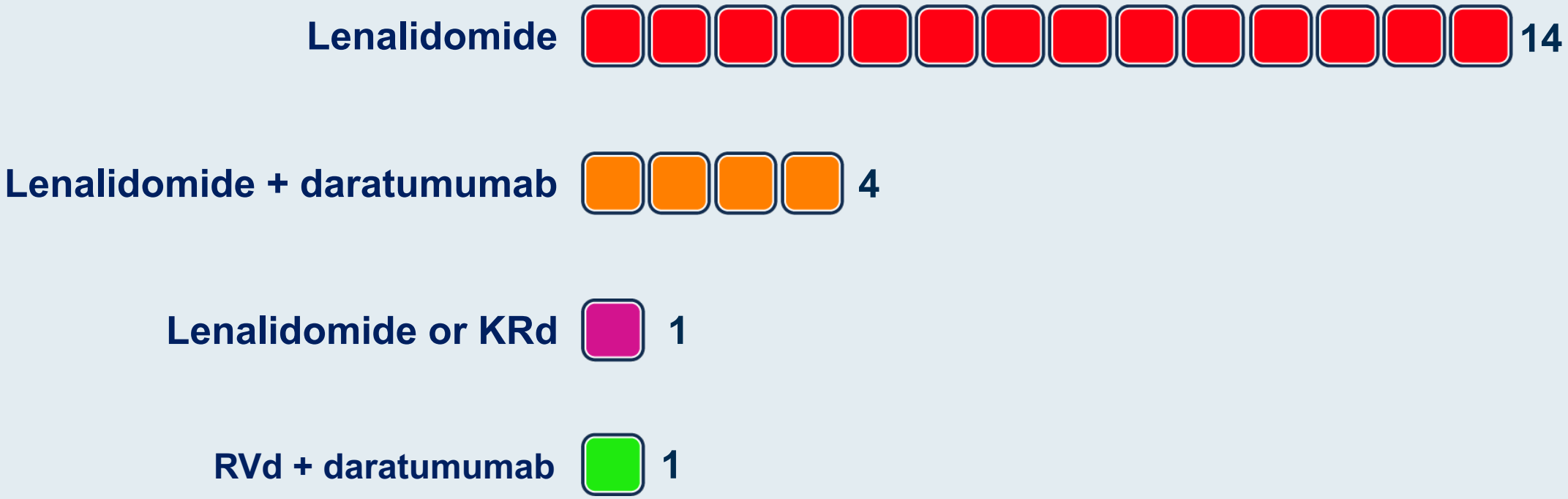
What post-transplant maintenance therapy regimen would you recommend for a younger (65-year-old) patient with standard-risk MM?



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How long would you continue maintenance therapy?

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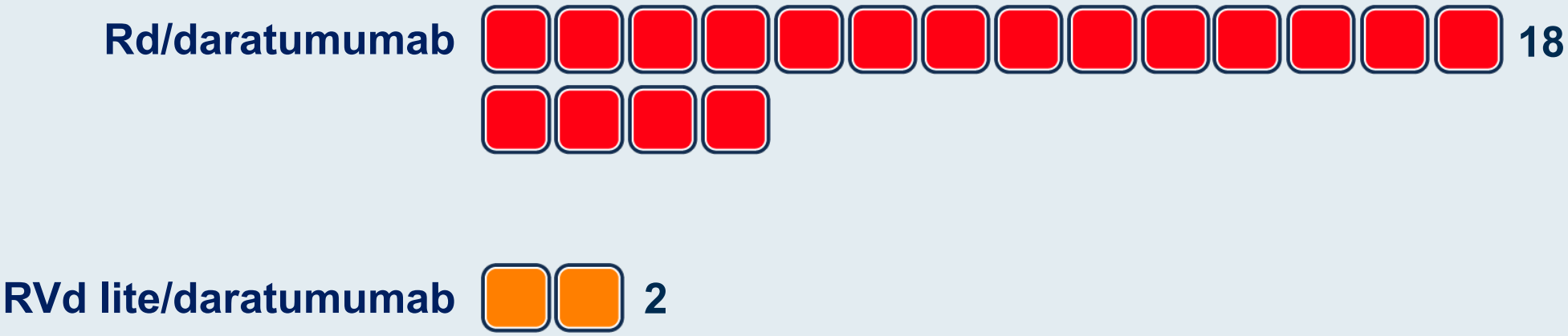
Regulatory and reimbursement issues aside, what is your preferred initial regimen for an older (80-year-old) patient with standard-risk MM who is transplant ineligible?



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What maintenance therapy would you recommend for an older (80-year-old) patient with standard-risk MM who is transplant ineligible?

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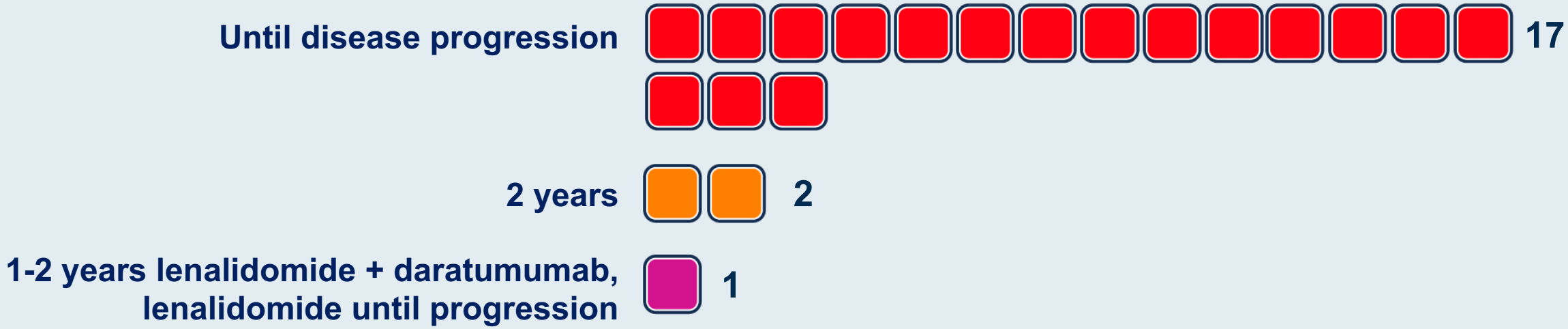
How long would you continue maintenance therapy?



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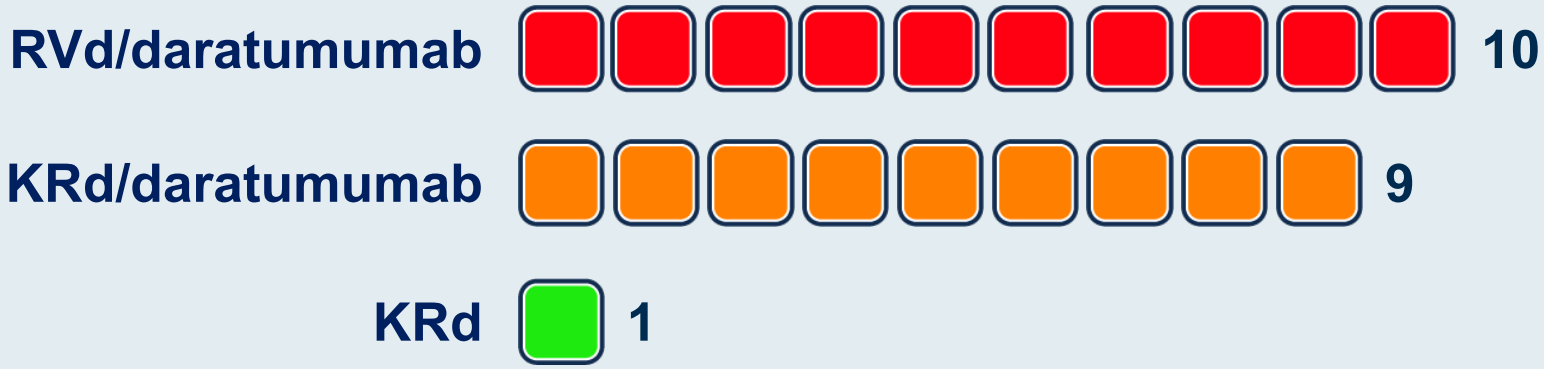
Regulatory and reimbursement issues aside, what would be your preferred induction treatment for a younger, transplant-eligible patient with high-risk (eg, del[17p]) MM?



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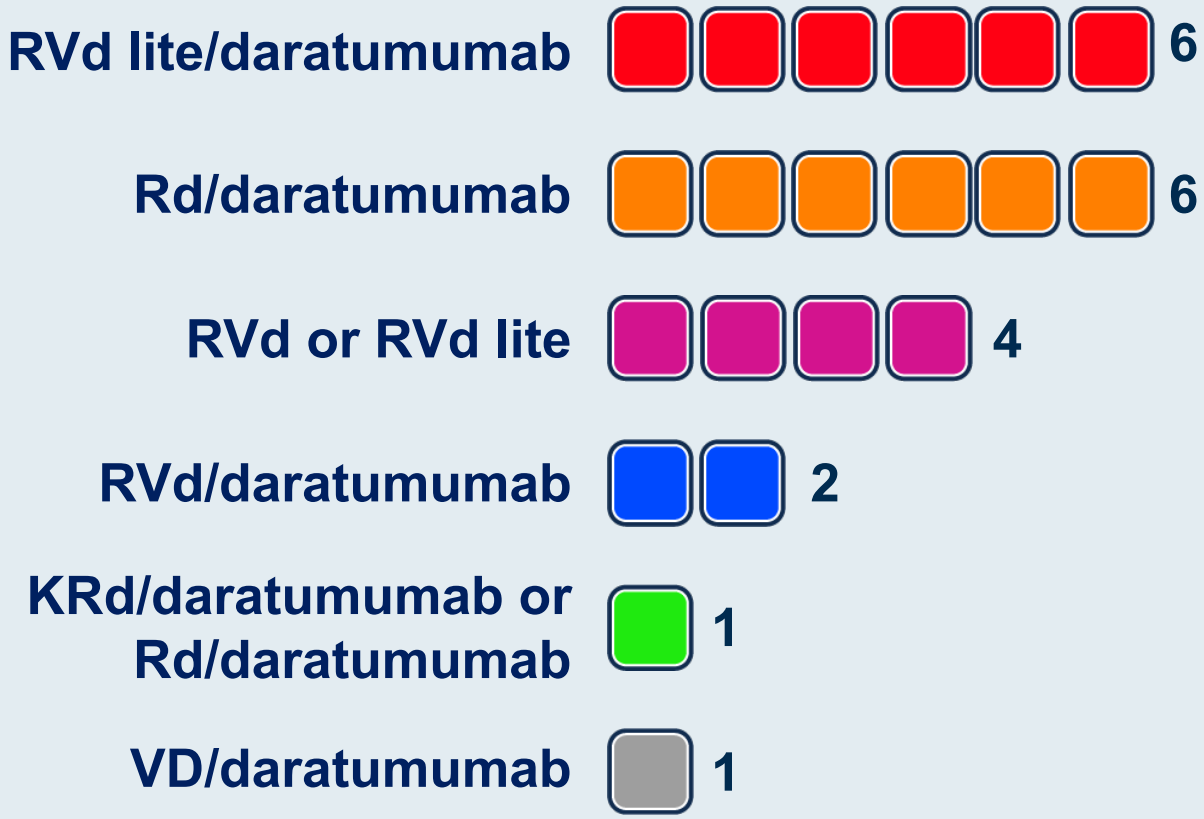

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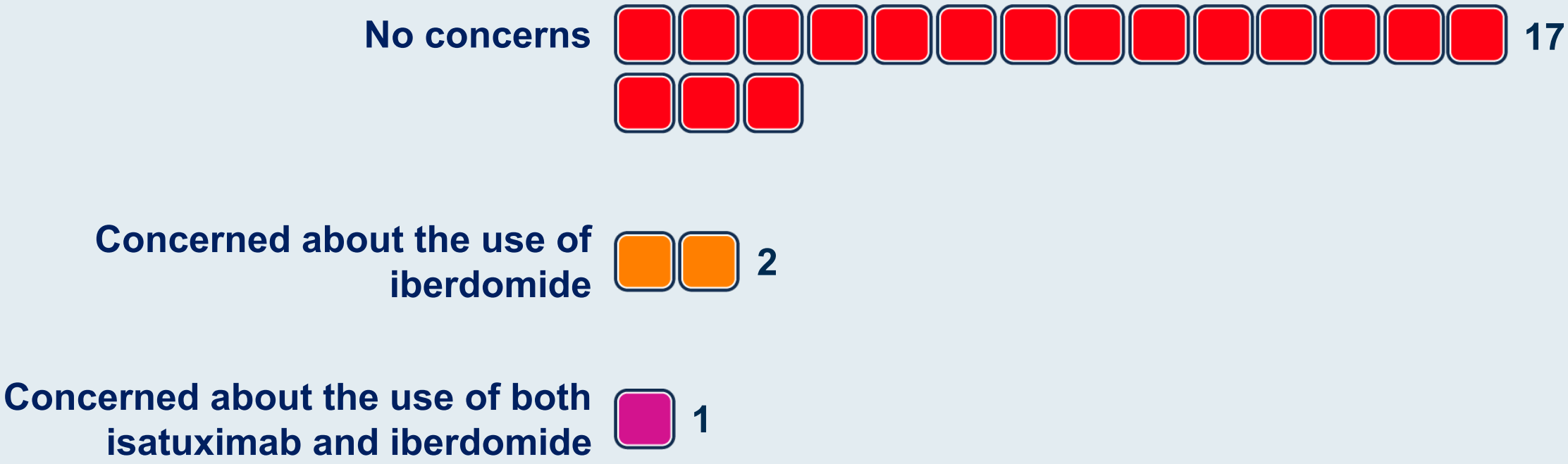
How would you feel about participating in a clinical trial evaluating the role of transplant (eg, DETERMINATION) in which the induction regimen was isatuximab/iberdomide/bortezomib/dexamethasone?



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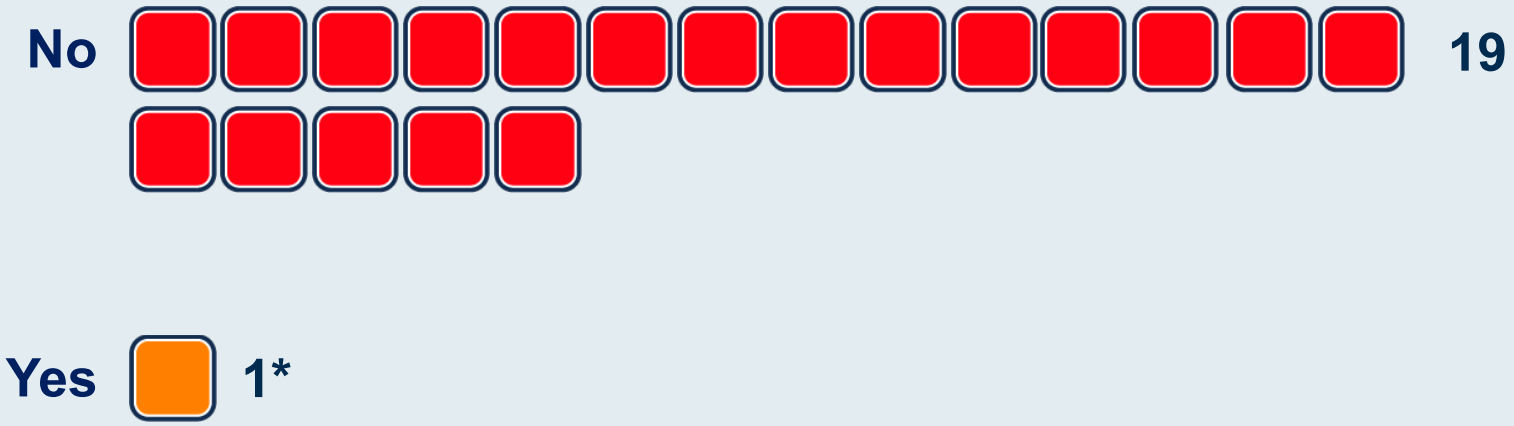
Does your transplant approach differ for an African American patient?



* Especially if high BMI and/or female sex, more likely to keep ASCT in reserve

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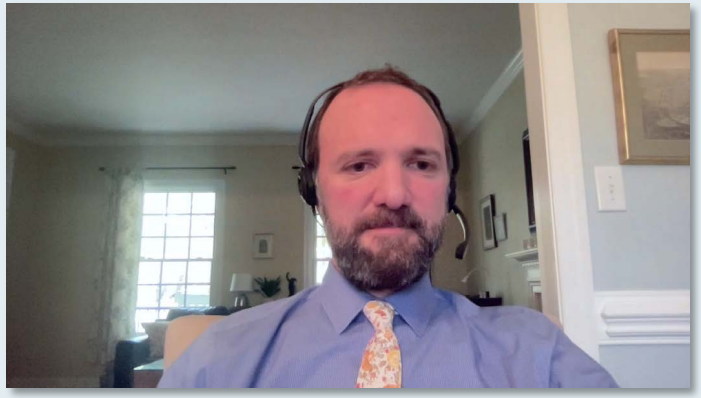
Approach to first-line therapy for transplant-eligible patients with MM

Melissa Alsina, MD

C Ola Landgren, MD, PhD



Sascha A Tuchman, MD, MHS

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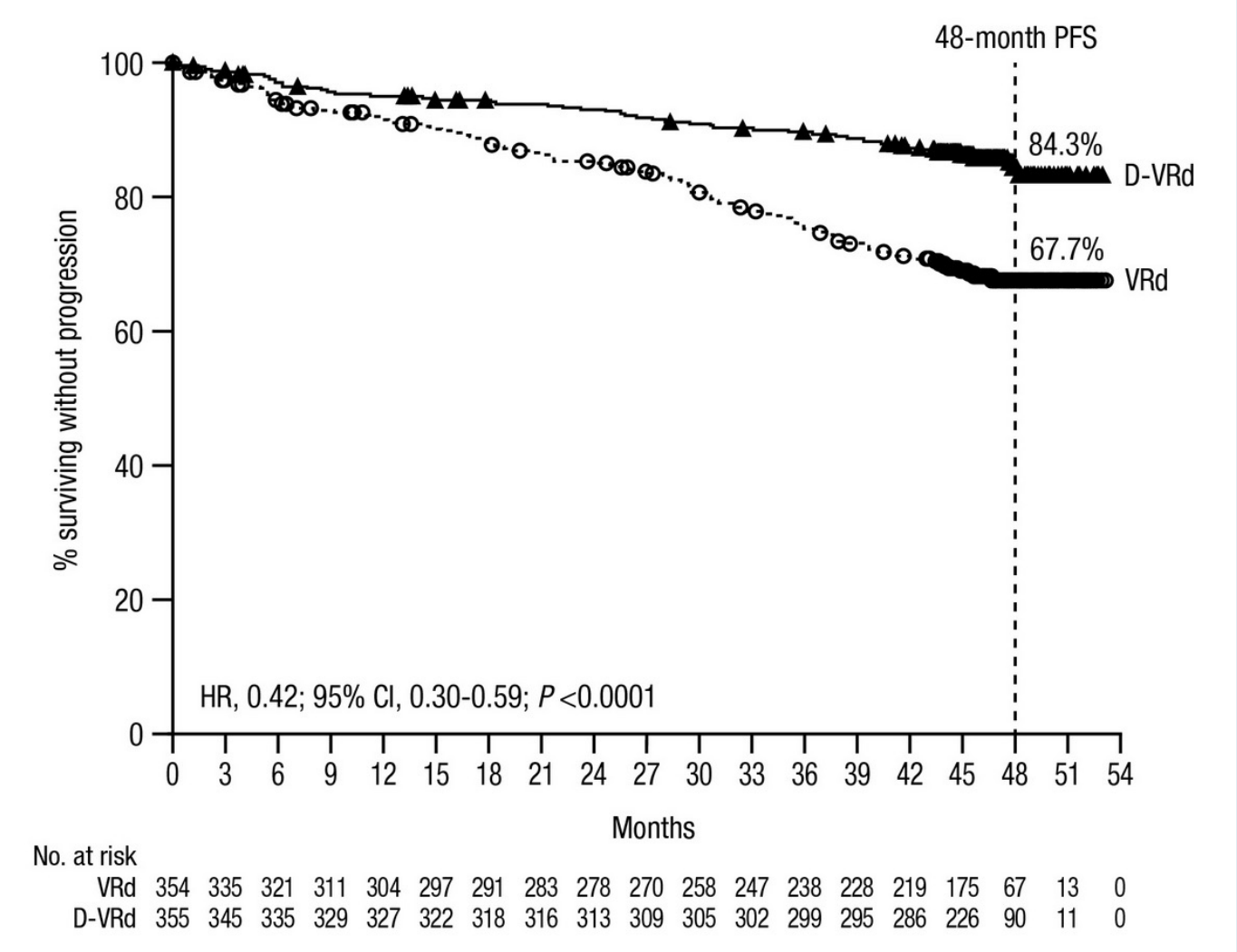
Phase 3 Randomized Study of Daratumumab (DARA) + Bortezomib, Lenalidomide, and Dexamethasone (VRd) versus VRd Alone in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Who Are Eligible for Autologous Stem Cell Transplantation (ASCT): Primary Results of the PERSEUS Trial

Sonneveld P et al.

ASH 2023;Abstract LBA-1.

LATE BREAKING ABSTRACTS| TUESDAY, DECEMBER 12 | 9:00 AM — 10:30 AM PT

PERSEUS: Progression-Free Survival with D-VRd versus VRd for Transplant-Eligible Patients with MM



Sonneveld P et al. ASH 2023;Abstract LBA-1.

Therapeutic options for older patients not eligible for transplant

Melissa Alsina, MD

C Ola Landgren, MD, PhD

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Approach to transplant for younger patients with standard-risk MM

Melissa Alsina, MD

C Ola Landgren, MD, PhD

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Management of Newly Diagnosed Multiple Myeloma (MM)

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RJ Corman Professor of Medicine
Harvard Medical School

Clinical Program Leader, Director of Clinical Research
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Boston, Massachusetts

Dana-Farber Cancer Institute

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VE RI TAS

Treatment landscape in NDMM is evolving – from doublets/triplets to triplets/quadruplets

IMiDs	Thalidomide Lenalidomide Pomalidomide
PIs	Bortezomib Carfilzomib Ixazomib
Anti-CD38 mAbs	Daratumumab

Transplant-eligible		Transplant-ineligible
VAD, Dex	Pre-novel agents	MP, Dex, VAD
Vd, PAD, VDd, VCd, Td, RCd	1 novel agent, doublet/triplet therapy	MPT, VMP, MPR, Rd, Vd, VCd
VTd, RVd, KRd	2 novel agents, triplet therapy	Dara-Rd, RVd, KRd, IRd
Dara-VTd, Dara/Isa-RVd, Dara/Isa-KRd, Isa-IberVd	2/3 novel agents, quadruplet therapy	Dara-VMP, Dara/Isa-RVd, Dara-VCd

Anti-CD38 mAb-based quadruplets: emerging SOCs building on existing triplet backbones

NCCN Guidelines[1]

Transplant-eligible patients

Preferred / recommended	Others	Maintenance
RVd	Dara-VTd	R
Dara-RVd	Dara-VCd	V
KRd	Dara-KRd	RV / RK
	Isa-RVd	Dara±R
	VDd/VCd/KCd	Ixa
	VTD-PACE	

Transplant-ineligible patients

Preferred / recommended	Others	Maintenance
RVd	Rd	R
Dara-Rd	Vd	V
Dara-VMP	VCd	RV
Dara-VCd	KCd	Ixa
KRd	RVd-lite	
	RCd	

+ Isa-RVd, Dara-KRd, Isa-KRd… under ongoing investigation in NDMM

1. Callander NS, et al. J Natl Compr Cancer Netw 2022;20(1):8–19 (updated per V2.2024;https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf).

Immune-based therapy approaches in MM: CD38 as a critical target[1,2]

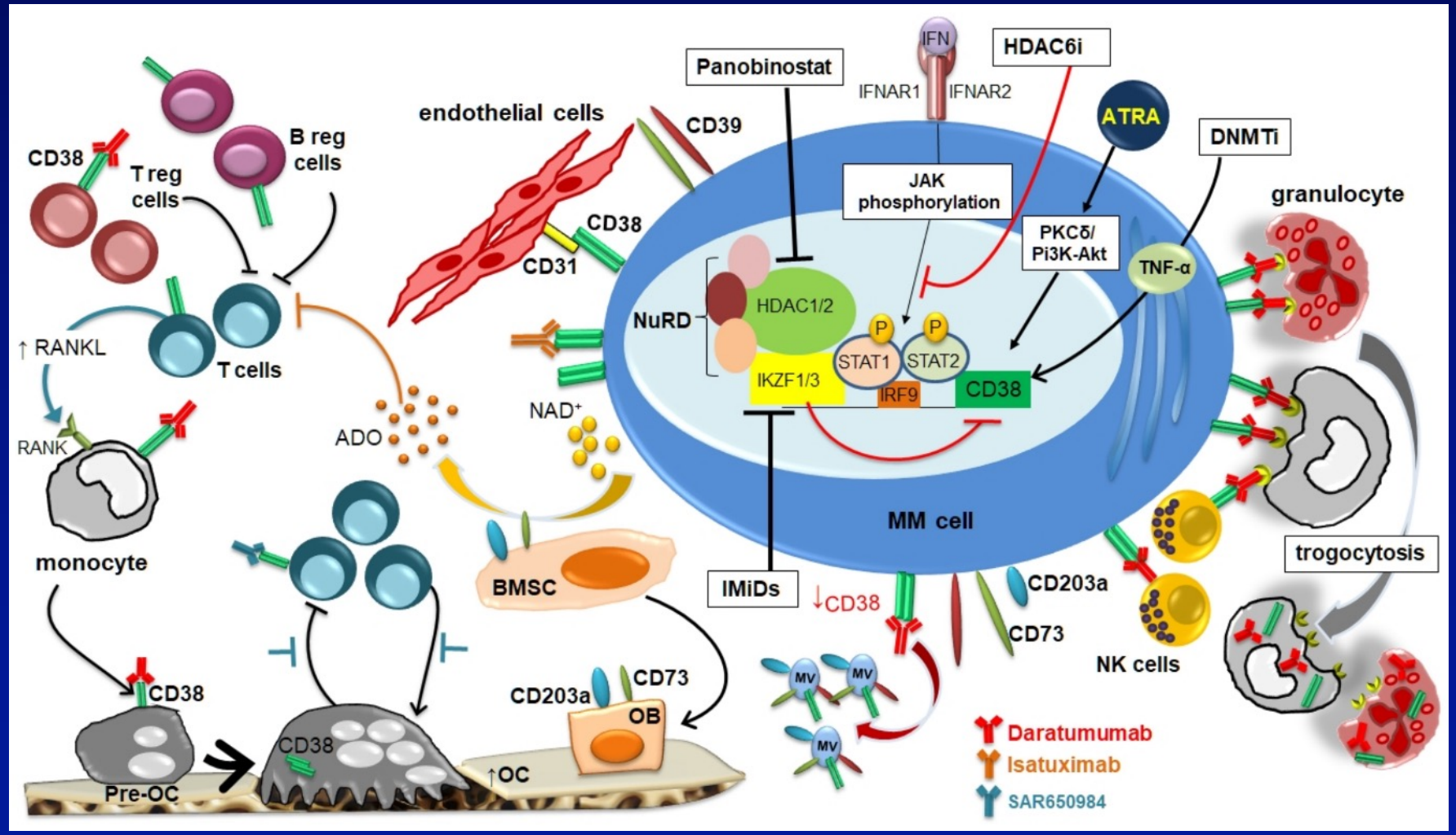
CD38 highly expressed by MM cells

Functions as a receptor, an adhesion molecule, and an ectoenzyme mediating immunosuppression

CD38 expressed in bone marrow microenvironment

CD38 also expressed by immune cells – T cells, T regs, B regs, NK cells, MDSCs

CD38 is thus a critical target in MM therapy, and anti-CD38 mAbs are transforming NDMM treatment



1. Costa F, et al. Cells 2019;8:1632. Figure reproduced under Creative Commons license CC BY 4.0.
2. van de Donk NWCJ, et al. Blood 2018;131(1):13–29.

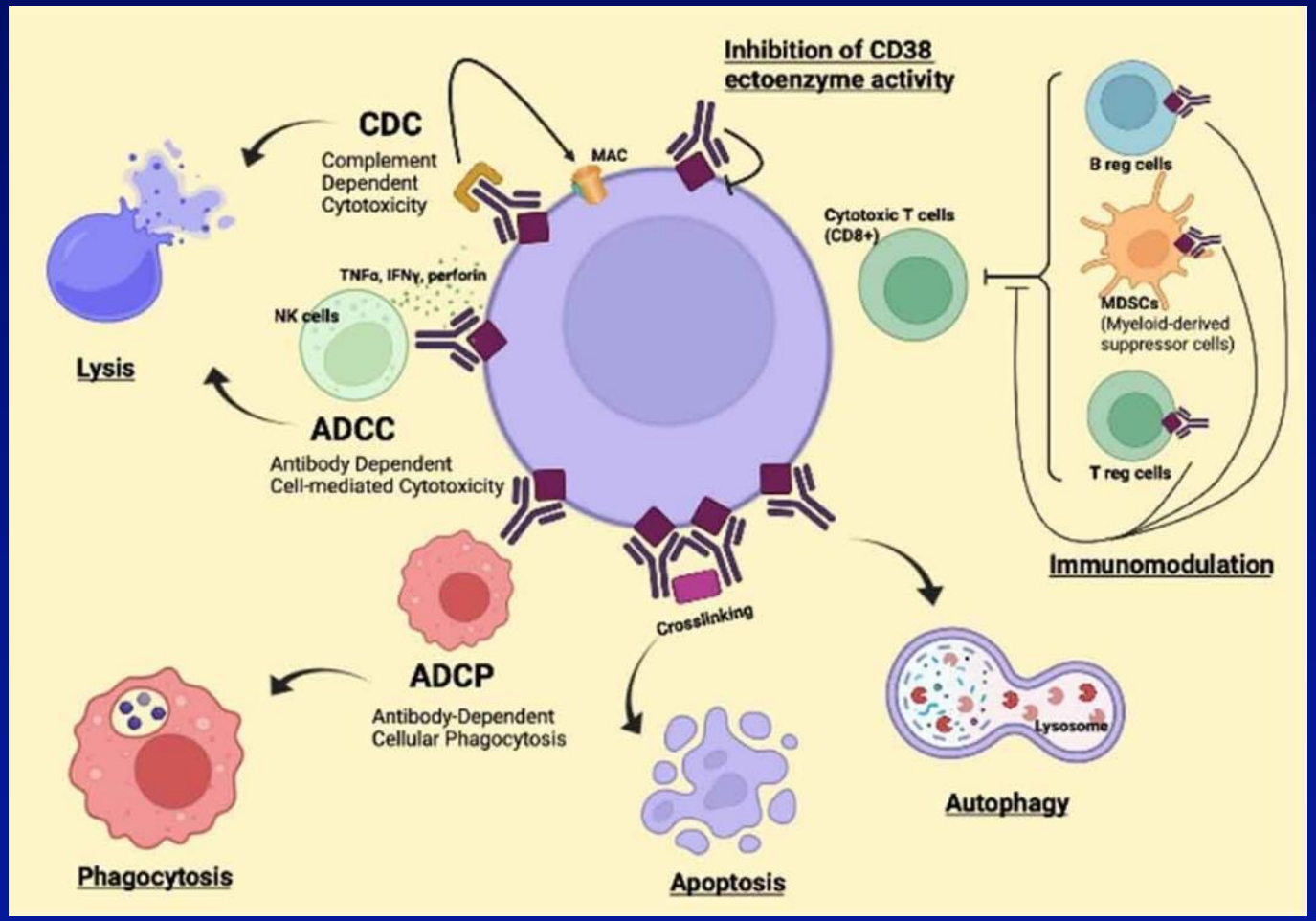
Anti-CD38 mAbs in NDMM: MOA[1]

Activity against MM cells via multiple mechanisms

- CDC
- ADCC
- ADCP
- Direct pro-apoptotic activity via cross-linking

Immunomodulatory activity

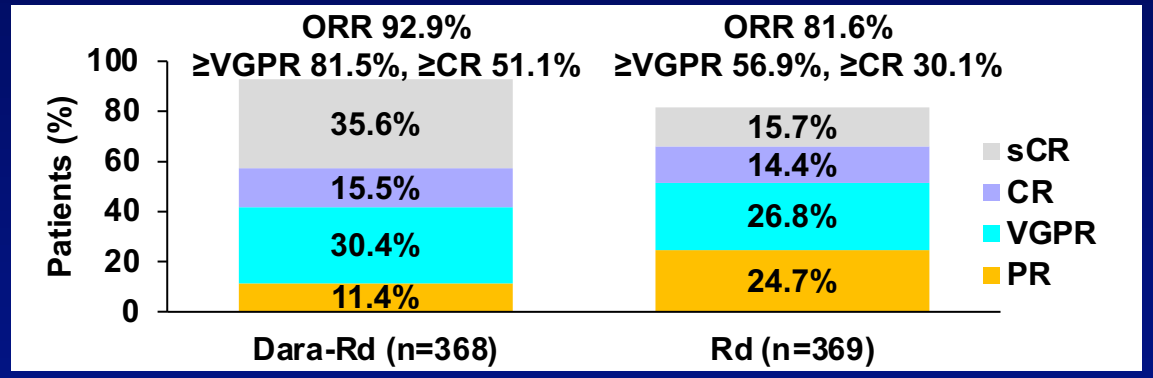
- Eradication of CD38+ T regs, B regs, MDSCs
- Shift away from immunosuppressive tumor microenvironment
- Better antitumor immune response

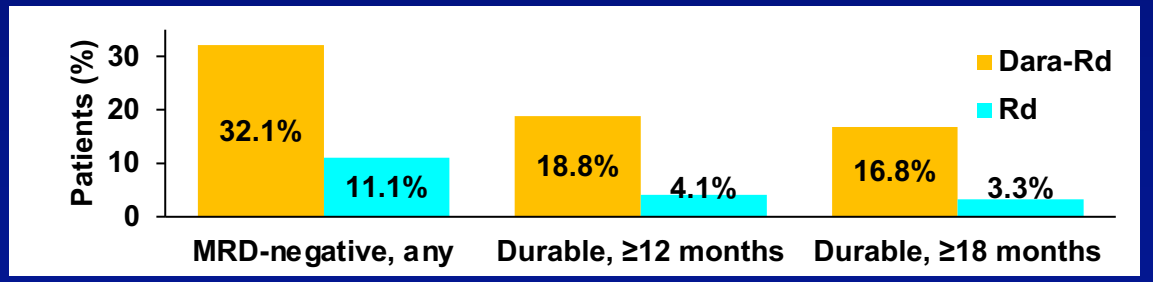


1. van de Donk NWCJ, et al. Blood 2018;131(1):13–29.

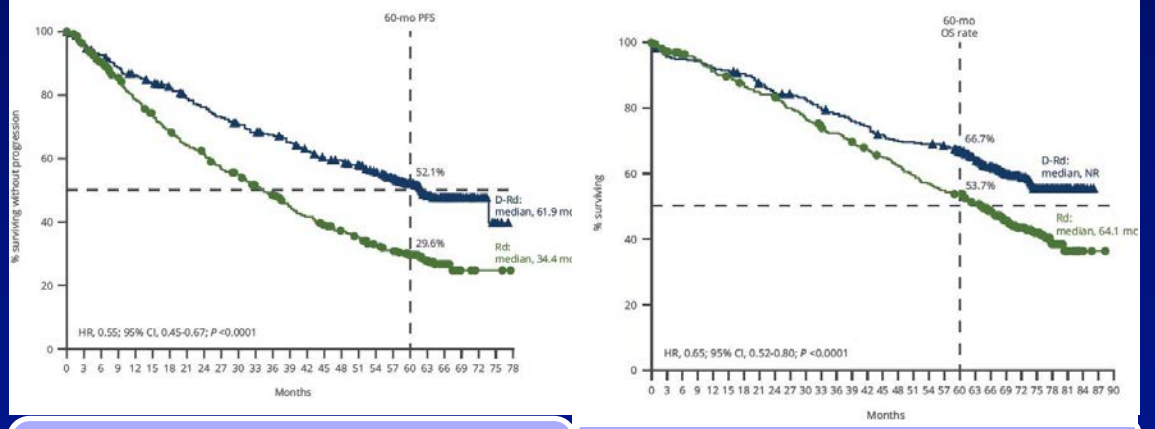
Anti-CD38 mAb-based triplet, transplant-ineligible patients

MAIA: Dara-Rd vs Rd[1–4]





After median follow-up of 64.5 (PFS) / 73.6 (OS) months:[3]



Median PFS 61.9 vs 34.4 months (HR 0.55)

Median OS not reached vs 64.1 months (HR 0.65)

Common grade 3/4 AEs (Dara-Rd vs Rd):

- Neutropenia 54.1% vs 37.0%
- Anemia 17.0% vs 21.6%
- Any infection 42.6% vs 29.6%
- Pneumonia 19.5% vs 10.7%
- Diarrhea 9.1% vs 6.0%
- Fatigue 9.1% vs 4.7%

PFS, ORR, and MRD-negative benefit in multiple subgroups:[5–7]

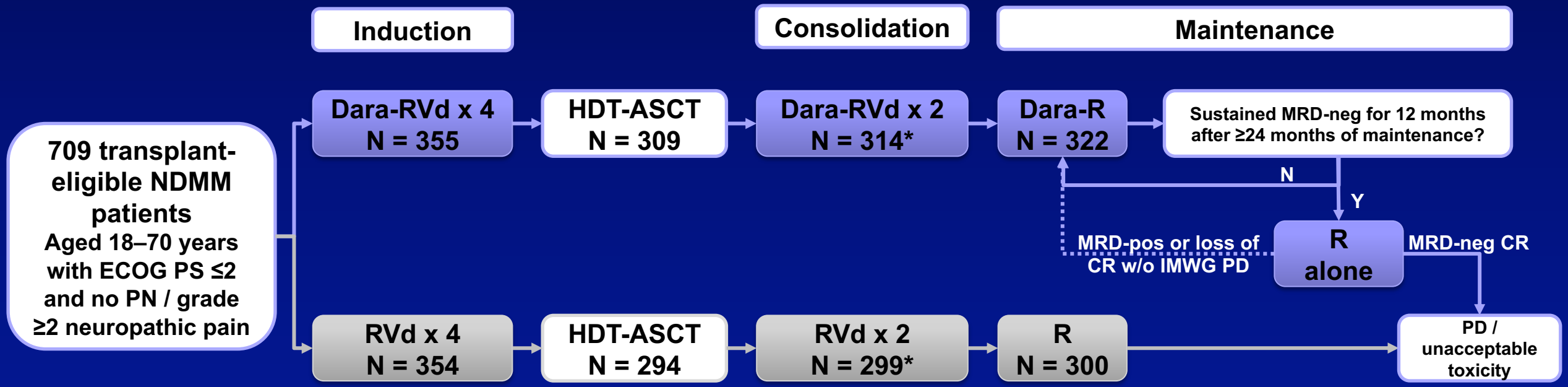
- Elderly / frail
- ISS III
- Renal insufficiency
- EMD
- High-risk cytogenetics

Adjusted indirect treatment comparison using patient-level data suggests significantly longer PFS with Dara-Rd vs RVd[8]

1. Facon T, et al. N Engl J Med 2019;380(22):2104–15. 2. San Miguel J, et al. Blood 2022;139(4):492–501. 3. Kumar SK, et al. Blood 2022;140(suppl 1):abstract 4559.
4. https://www.darzalexhcp.com/drd-maia-trial 5. Moreau P, et al. Blood 2022;140(suppl 1):abstract 3245. 6. Facon T, et al. Blood 2022;140(suppl 1):abstract 4553.
7. Facon T, et al. Leukemia 2022;36(4):1066–77. 8. Durie BG, et al. J Clin Oncol 2023;41(16_suppl):8037.

Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT

PERSEUS: Dara-RVd vs RVd – prolonged PFS, deepened responses



Patients (N = 709)

- Median age 60 years
- ISS Stage III 14.8%
- High-risk cytogenetics [t(4;14), t(14;16), del17p] 21.7%

AMERICAN SOCIETY OF HEMATOLOGY® 2023

Late-breaking abstracts session
Tuesday, Dec 12, 2023, 9:00–10:30 AM
Abstract LBA-1.
Presenter: Pieter Sonneveld

Sonneveld P, et al. ASH 2023, abstract LBA-1.
ClinicalTrials.gov, NCT03710603.

*Completed 4 x induction and 2 x maintenance cycles at data cut-off.

Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT

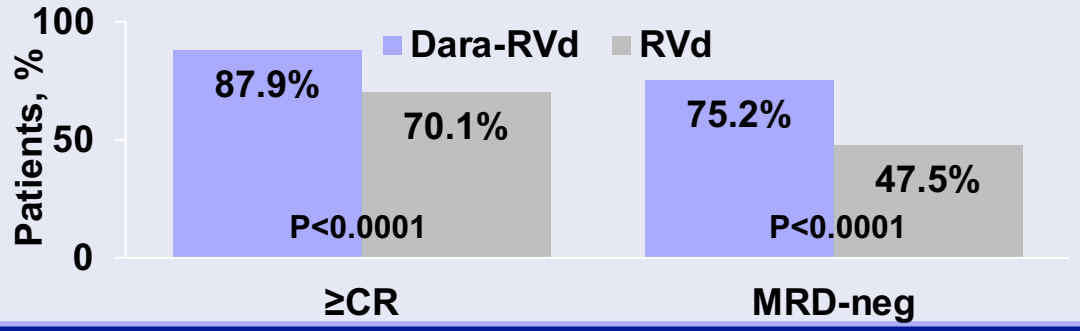
PERSEUS: Dara-RVd vs RVd – prolonged PFS, deepened responses

Median follow-up 47.5 months

PFS (primary endpoint), Dara-RVd vs RVd

- 48-month rate 84.3% vs 67.7%
- HR 0.42 (95% CI 0.30–0.59), P<0.0001
- Consistent PFS benefit across subgroups including ISS III and high-risk cytogenetics

Overall rates of ≥CR and MRD-neg



Safety

AEs, %	Dara-RVd (N = 355)	RVd (N = 354)
Grade 3/4 AEs		
Neutropenia	62.1%	51.0%
Thrombocytopenia	29.1%	17.3%
Diarrhea	10.5%	7.8%
Pneumonia	10.5%	6.1%
Febrile neutropenia	9.4%	10.1%
SAEs	57.0%	49.3%
AEs leading to discontinuation	8.8%	21.3%

AMERICAN SOCIETY OF HEMATOLOGY®
2023

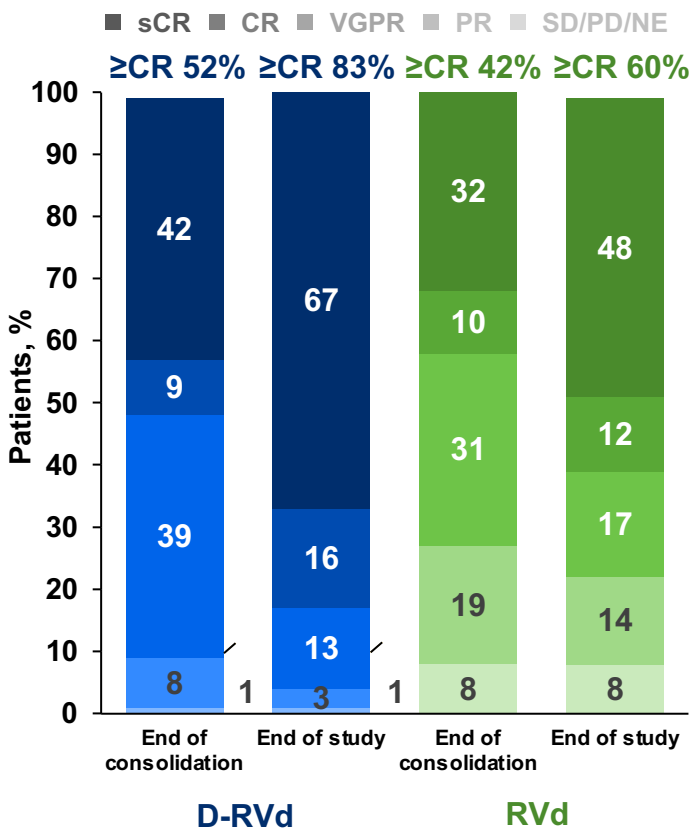
Late-breaking abstracts session
Tuesday, Dec 12, 2023, 9:00–10:30 AM
Abstract LBA-1.
Presenter: Pieter Sonneveld

Sonneveld P, et al. ASH 2023, abstract LBA-1.
ClinicalTrials.gov, NCT03710603.

Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT

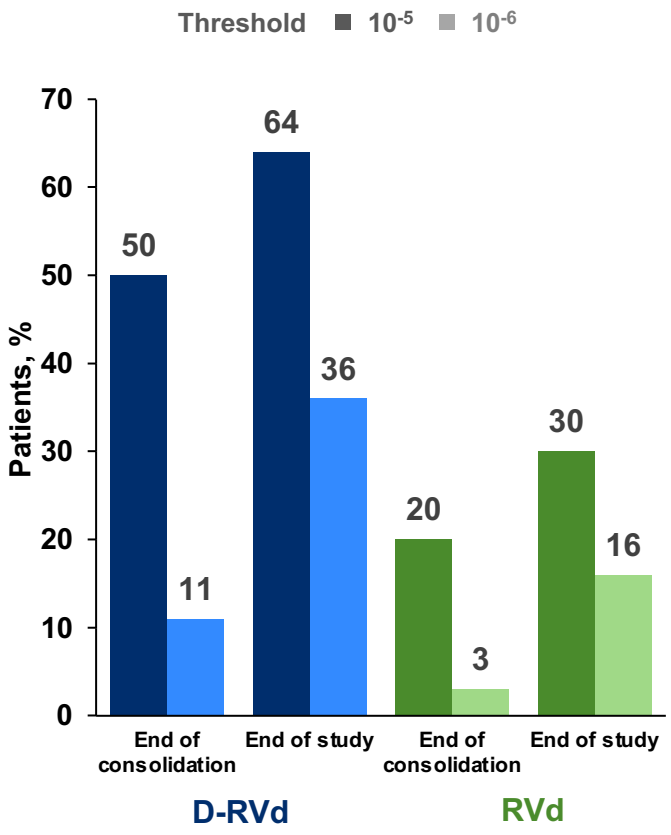
GRIFFIN: Dara-RVd vs RVd – prolonged PFS, deepened responses

ORR



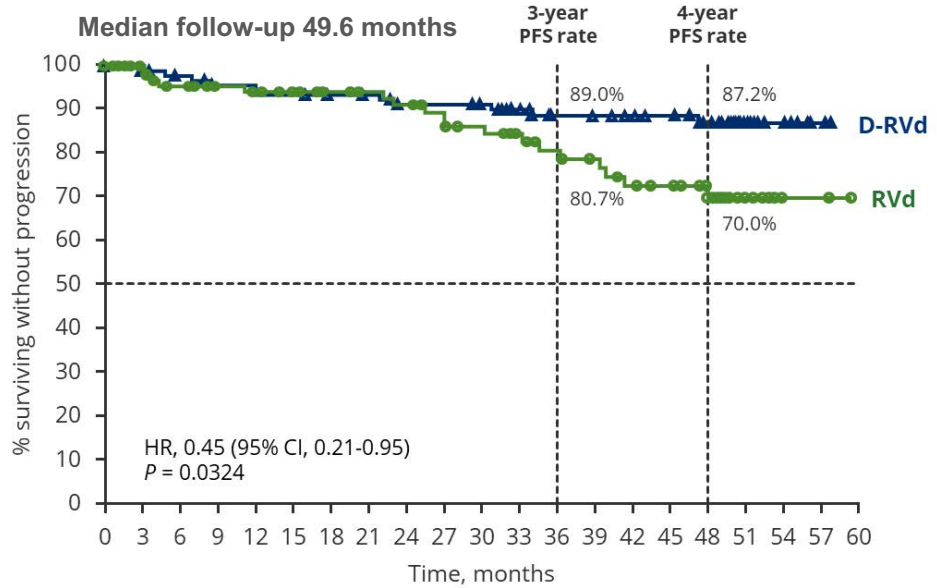
≥CR rates increased over time, with deepest responses at end of study

MRD-neg rate



14% vs 10% of patients converted from MRD-pos at end of consolidation to MRD-neg by end of study

PFS/OS in the ITT population for D-RVd versus RVd



- **Median OS not reached in either arm; 4-year OS with D-RVd vs RVd: 92.7% vs 92.2% (HR 0.90)**

Safety data

- **Hematologic Grade 3/4 AEs with D-RVd vs RVd: neutropenia (46% vs 23%), lymphopenia (23% vs 23%), leukopenia (17% vs 8%), thrombocytopenia (16% vs 9%), anemia (9% vs 6%)(**
- **Non-hematologic Grade 3/4 AEs: PN (7% vs 9%), fatigue (7% vs 6%), diarrhea (7% vs 5%)**
- **AEs led to discontinuation in 33% vs 31% of patients (due to infections in 2% vs 3%)**
- **Minimal impact on stem cell mobilization, predictable stem cell harvesting and engraftment in all patients who underwent ASCT[2]**

1. Voorhees PM, et al. Lancet Haematol 2023;10(10):e825–37. 2. Chhabra S, et al. Transplant Cell Ther 2023;29(3):174.e1–10.

Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT

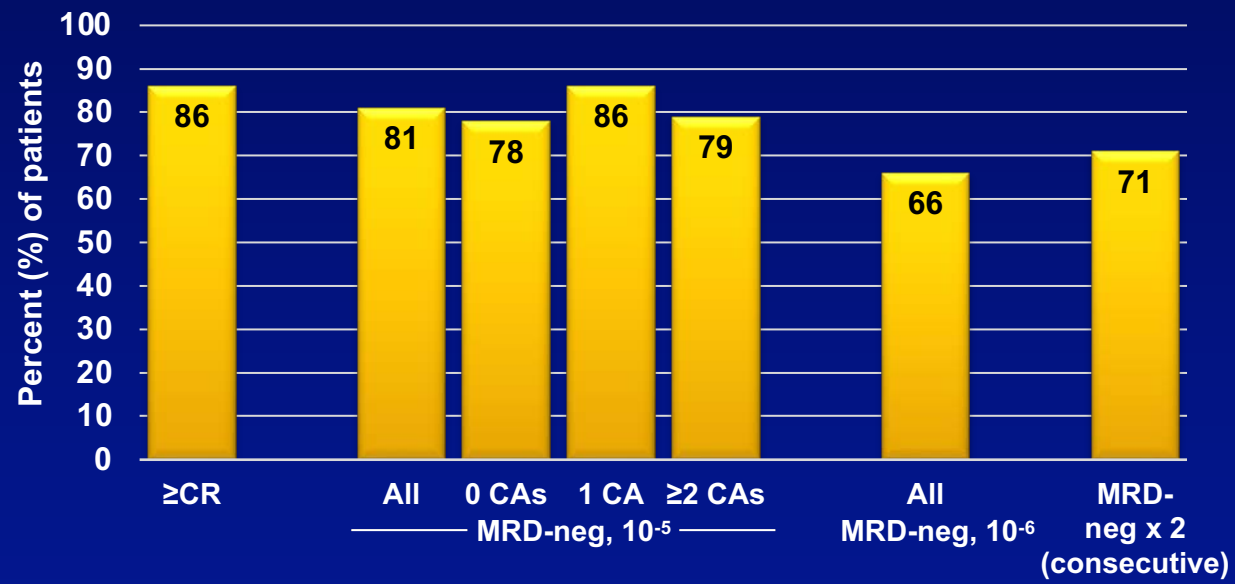
MASTER: Dara-KRd in NDMM patients with high-risk cytogenetics[1,2]

MASTER study design

- Induction: 4 x Dara-KRd
- Stem cell collection, ASCT
- Consolidation: 0, 4, or 8 x Dara-KRd according to MRD status
- Two consecutive MRD-neg results → treatment-free surveillance
- MRD-pos after consolidation → R maintenance

123 patients, 57% with high-risk cytogenetics

- Median age 60 years (range 36–79); 24 aged ≥70 years
- 37% with 1 high-risk cytogenetic abnormality (HRCA)
- 20% with ≥2 HRCAs
- MRD trackable by NGS in 96%



Median follow-up 35.9 months[2]

- Older vs younger (≥70 vs <70 years)
- 3-year PFS: 86.3% vs 80.3%
- 3-year OS: 95.8% vs 88.7%

Median follow-up 42.2 months[3]

- 0 vs 1 vs ≥2 HRCA:
- 3-year PFS: 88.4 %, 78.9%, 50.0%
- 3-year OS: 94%, 92%, 75%

Minimal impact on stem cell mobilization, predictable stem cell harvesting and engraftment in all patients who underwent ASCT[4]

1. Costa LJ, et al. J Clin Oncol 2022;40(25):2901–12. 2. Giri S, et al. Blood 2022;140(suppl 1):abstract 1930.
3. Costa L, et al. Lancet Haematol 2023;10(11):e890–901. 4. Chhabra S, et al. Transplant Cell Ther 2023;29(3):174.e1–10

CA, cytogenetic abnormality

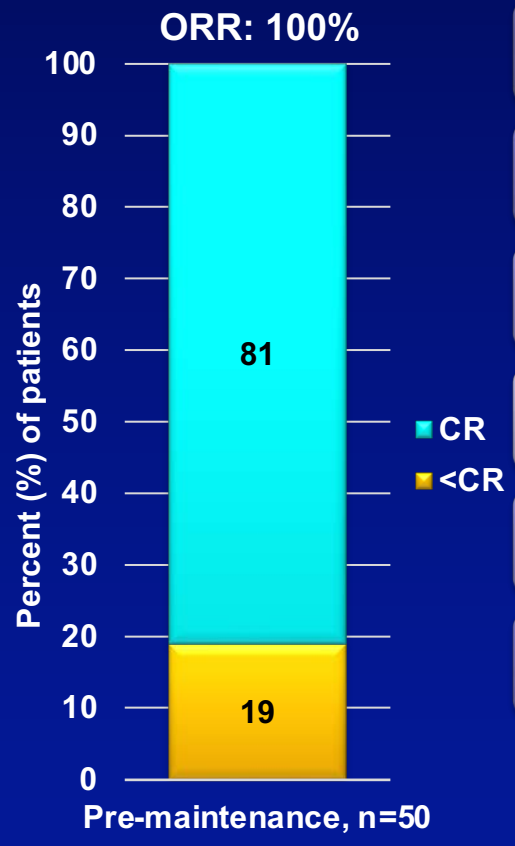
Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT
IFM 2018-04: Dara-KRd in NDMM patients with high-risk cytogenetics

IFM 2018-04 study design

- Induction: 6 x Dara-KRd
- Stem cell collection, ASCT 1
- Consolidation: 4 x Dara-KRd
- ASCT 2
- Maintenance: Dara-R x 2 years

50 patients with high-risk cytogenetics

- Median age 57 years
- 40% del(17p)
- 52% t(4;14), 20% t(14;16)
- 50% 1q gain
- 68% with 2 abnormalities
- 8% EMD



- Primary endpoint met: 72% of patients completed ASCT 2
- MRD-neg (10^{-6}), pre-maintenance: 94% (n=31/33)
- Median follow-up 32 months
- 24-month PFS: 87%
- 24-month OS: 94%
- Grade 3/4 AEs:
  - Neutropenia 44%
  - Thrombocytopenia 24%
  - Anemia 22%
  - Infection 14%

1. Touzeau C, et al. ASH 2023, abstract 207.
2. Touzeau C, et al. J Clin Oncol 2022;40(suppl 16):abstract 8002.

2023
Oral session 653. Multiple Myeloma: Prospective Therapeutic Trials: Smoldering and Newly Diagnosed Myeloma
Saturday, Dec 9, 2023, 2:30 PM
Abstract 207. Presenter: Cyrille Touzeau

Anti-CD38 mAb-based quadruplet induction alone, no ASCT

MANHATTAN: Dara-KRd – high response and MRD-neg rates

41 NDMM patients received Dara-KRd regimen for 8 cycles

- Patients could then receive ASCT (n=12) or standard-of-care maintenance

MRD-negative rate after 8 cycles: 71%

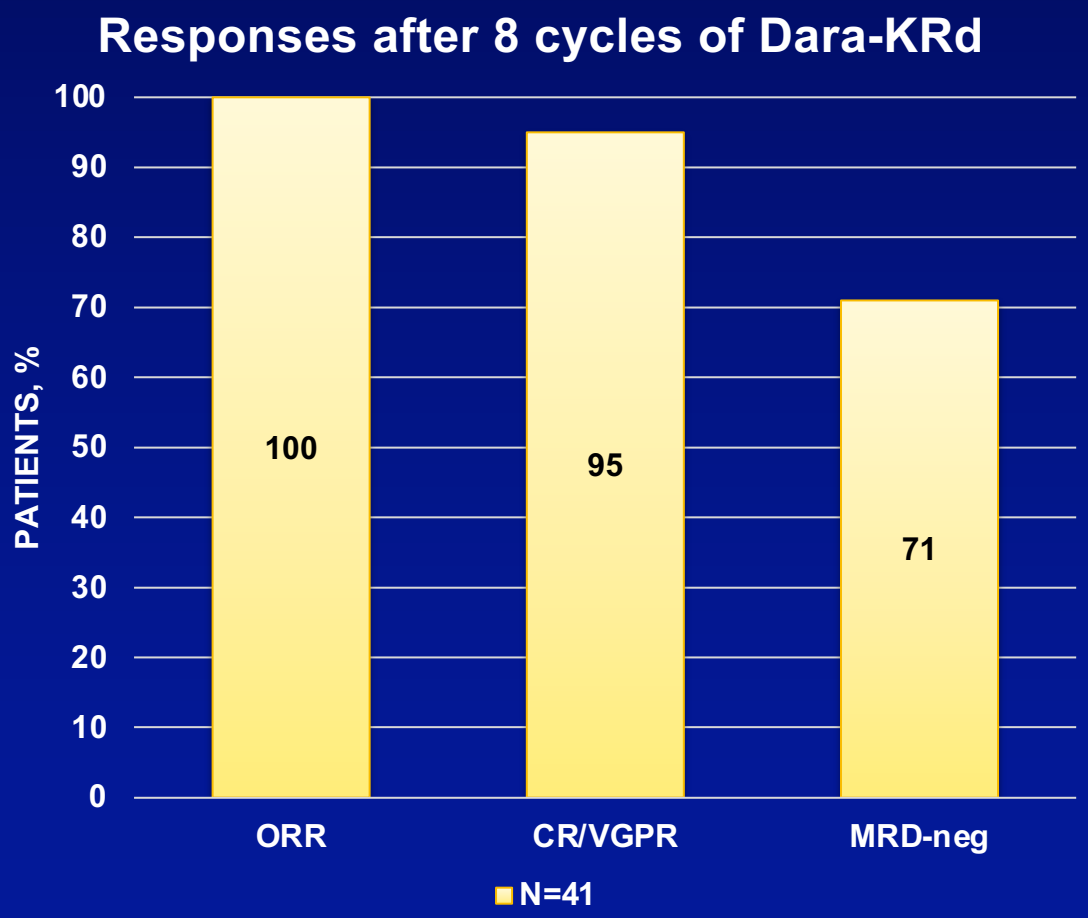
- No significant differences by age or cytogenetics
- At 1 year, 7/8 patients assessed remained MRD-negative

After median follow-up of 11 months:

- 1-year PFS 98%
- 1-year OS 100%

Safety

- Common grade 3/4 AEs: 27% neutropenia, 9% rash, 7% lung infection
- Dara infusion-related reactions in 40%
- Serious AEs in 18%



Landgren O, et al. JAMA Oncol 2021;7(6):862–8.

Anti-CD38 mAb-based quadruplet induction, fit transplant-ineligible patients

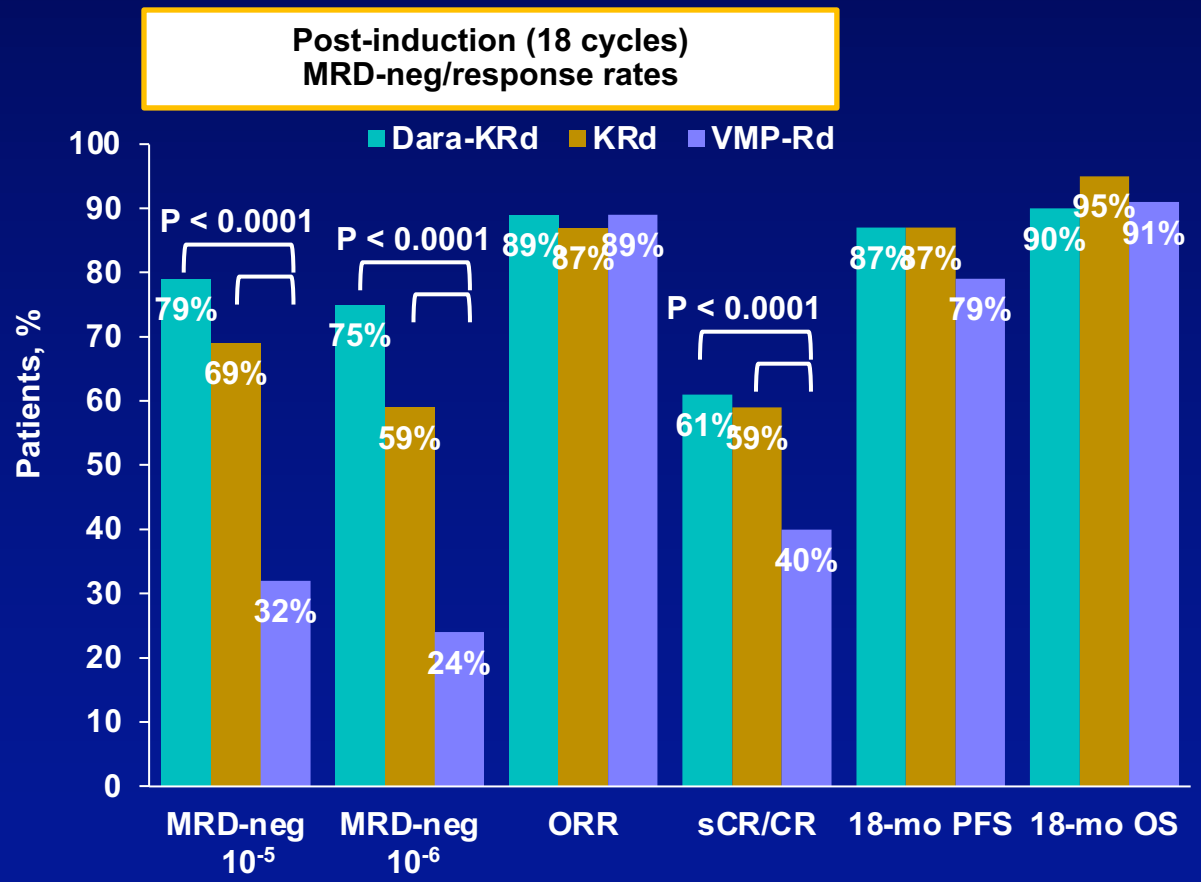
GEM2017FIT: Dara-KRd vs KRd vs VMP-Rd

GEM2017FIT study design and patients

- 'Fit' per Geriatric Assessment in Hematology scale, aged 65–80 years
- 462 patients randomized to 18 induction cycles of Dara-KRd vs KRd vs VMP-Rd (n=154 each)
- Overall median age 72 years, ~33% aged >75 years, ~33% ISS III, 15% EMD

Grade 3/4 AEs during Dara-KRd vs KRd vs VMP-Rd induction

- Neutropenia 47% vs 24% vs 50%
- Thrombocytopenia 17% vs 16% vs 34%
- Infections 16% vs 15% vs 12%
- Cardiovascular AEs 14% vs 11% vs 5%



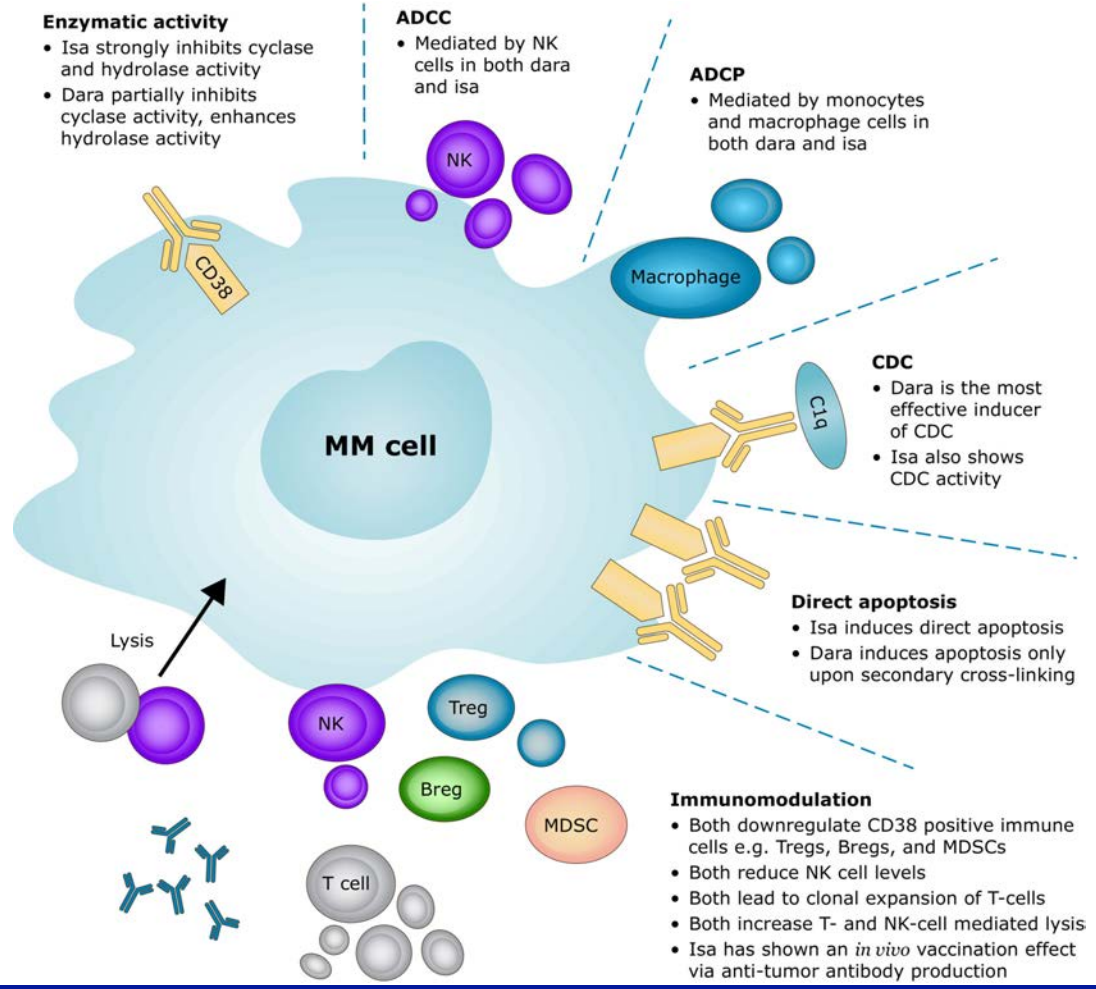
2023 American Society of Hematology

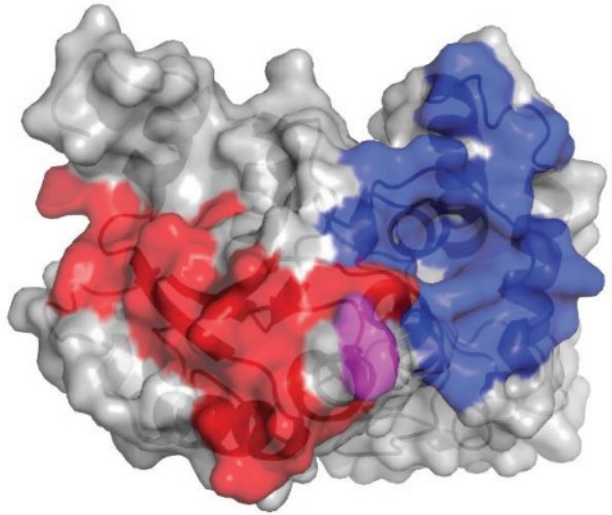
Oral session 653. Multiple Myeloma: Prospective Therapeutic Trials: Smoldering and Newly Diagnosed Myeloma
Saturday, Dec 9, 2023, 3:00 PM
Abstract 209. Presenter: Maria-Victoria Mateos

Mateos M-V, et al. ASH 2023, abstract 209.

Isatuximab: a distinct anti-CD38 mAb vs daratumumab

Differing relative contributions to mechanisms of action of daratumumab and isatuximab[1–3]





Distinct epitopes on human CD38 interact with daratumumab (red) and isatuximab (blue), potentially contributing to distinct mechanisms of action[3]

Isatuximab epitope includes catalytic domain of CD38 – isatuximab inhibits NAD+ substrate and thus the production of immune-suppressing adenosine[4]

Distinct characteristics[3,5-7]

Isatuximab saturates membrane CD38 and can be internalized – different membrane dynamics vs daratumumab	ADCC, ADCP, CDC with isatuximab triggered at threshold of surface CD38	Isatuximab inhibits CD38 enzymatic features	Isatuximab can directly induce cell death without crosslinking[7]	Isatuximab induces NK cell activation and NK cell-mediated cytotoxicity through CD38 and CD16 crosslinking[3]

Daratumumab and isatuximab potentially valuable as complementary / alternative therapies[5]

1. Bisht K, et al. Cancer Med 2023;doi:10.1002/cam4.6619. 2. van de Donk NWCJ, et al. Blood 2018;131(1):13–29. 3. Zhu C, et al. Front Immunol 2020;11:1771. 4. Martin TG, et al. Cells 2019;8(12):1522. 5. Malavasi F, Faini AC. Clin Cancer Res 2019;25(10):2946–8. 6. Moreno L, et al. Clin Cancer Res 2019;25(10):3176–87. 7. Martino EA, et al. Expert Opin Biol Ther 2023;23(4):315–8.

Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT

IsKia: Isa-KRd vs KRd in transplant-eligible NDMM patients

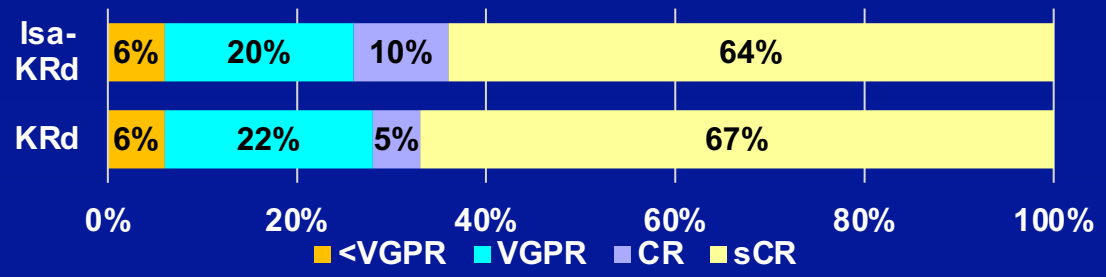
IsKia study design (NCT04483739)

- Induction: 4 x Isa-KRd/KRd
  - MEL200+ASCT
- Consolidation: 4 x Isa-KRd/KRd → 12 x Isa-KRd/KRd light
- Maintenance: R
- Primary endpoint: MRD-neg rate post consolidation

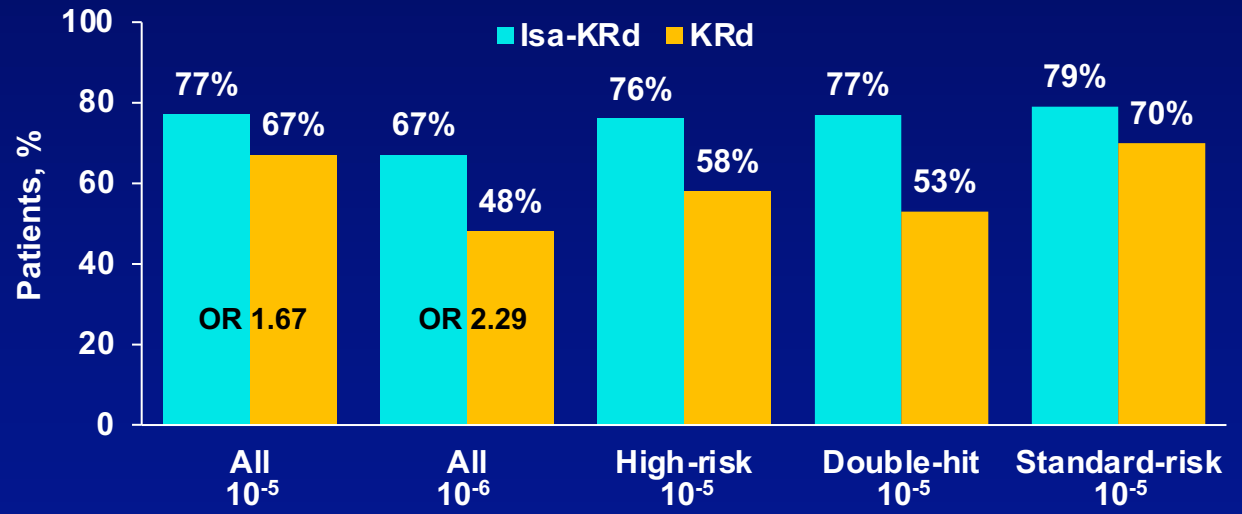
302 NDMM patients randomized (1:1)
Isa-KRd vs KRd
151 vs 151

- Median age 61 vs 60 years
- 18% vs 19% high-risk cytogenetics [del17p, t(4;14), t(14;16)]
- 9% vs 8% ≥2 high-risk cytogenetic abnormalities (including gain/amp 1q) – 'double-hit'

Response rates post consolidation



MRD-neg rates post consolidation



Median follow-up 20 months

1-year PFS 95% in both arms

Grade 3-4 neutropenia 37% vs 22%

Grade 3-4 thrombo-cytopenia 15% vs 17%

Infections 16% vs 12%

Gay F, et al. ASH 2023, abstract 4.

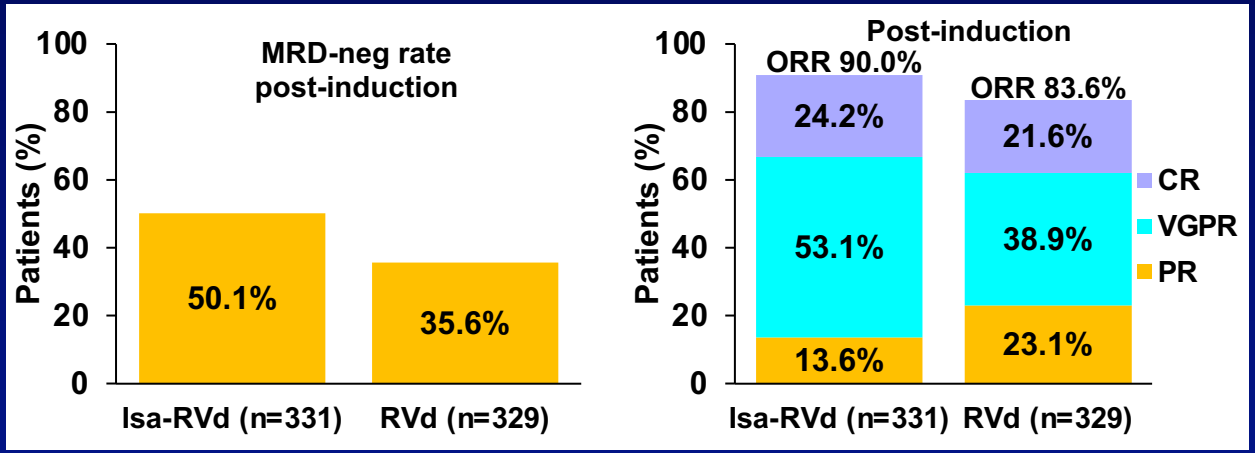
2023

Plenary Scientific Session
Sunday, Dec 10, 2023, 2:00 PM-4:00 PM
Abstract 4. Presenter: Francesca Gay

Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT

GMMG-HD7/SKylaRk: Isa-RVd/KRd in transplant-eligible NDMM patients

GMMG-HD7[1,2]



660 NDMM patients

- Median age 59 vs 60 years
- 24% vs 20% ISS III
- 18% vs 20% high-risk cytogenetics

Safety (induction)

- Grade 3/4 AEs 63% vs 61%
- Grade 3/4 neutropenia 23% vs 7%
- Grade 3/4 infections 12% vs 10%

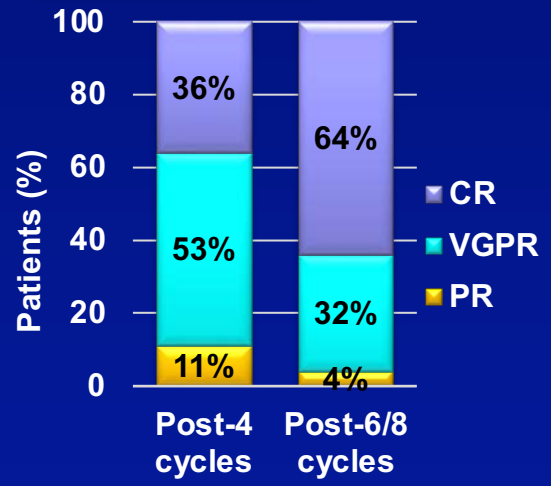
SKylaRk[3,4]

SKylarRk study design

- Induction: 4 x Isa-KRd
- Stem cell collection, ASCT or defer
- Consolidation: 2 x Isa-KRd (post-ASCT) or 4 x Isa-KRd (if ASCT deferred)
- Maintenance: R (standard-risk cytogenetics), Isa-KR (high-risk cytogenetics)

50 transplant-eligible NDMM patients

- Median age 59 years
- 46% high-risk cytogenetics
- 12% ISS III
- 4% R-ISS III



Post-4 cycles: MRD-neg (10^{-5}) 43% (n=12/28)

Post-6 cycles: MRD-neg (10^{-5}) 66% (n=27/41)

24-month PFS: 91.3%; 24-month OS: 95.8%

ASCT deferred in 89% (n=40/45)

Most common grade 3/4 AEs: neutropenia 24%, ALT elevated 10%, acute kidney injury 6%, thrombocytopenia 6%

1. Goldschmidt H, et al. Blood 2021;138(suppl 1):abstract 463. 2. Goldschmidt H, et al. Lancet Haematol 2022;9(11):E810–21. 3. O'Donnell EK, et al. Blood 2022;140(suppl 1):abstract 3239. 4. O'Donnell EK, et al. Blood 2023, abstract 4671.

AMERICAN SOCIETY OF HEMATOLOGY® 2023

Session 651. Multiple Myeloma and Plasma Cell Dyscrasias: Basic and Translational: Poster III
Monday, Dec 11, 2023, 6:00 PM-8:00 PM
Abstract 4671. Presenter: Elizabeth O'Donnell

Anti-CD38 mAb-based quadruplet induction/consolidation + ASCT

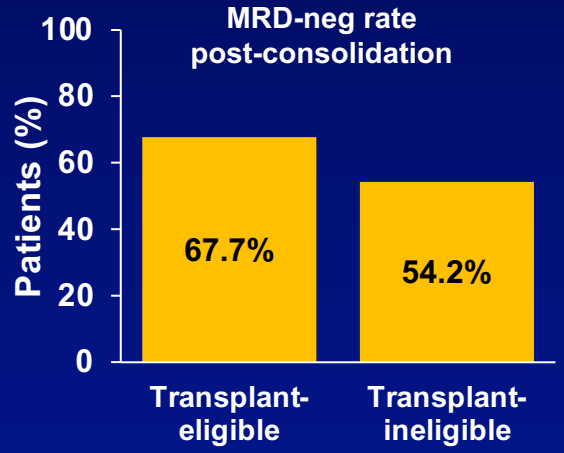
GMMG-CONCEPT: Isa-KRd in high-risk NDMM

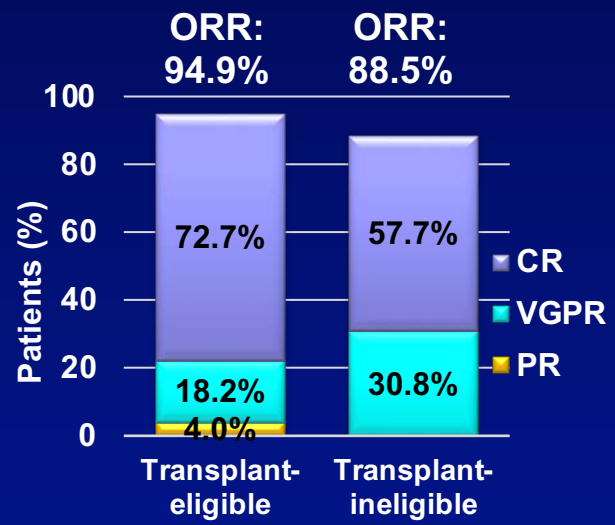
GMMG-CONCEPT study design

- Induction: 6 x Isa-KRd
  - Transplant-eligible: ASCT
  - Transplant-ineligible: 2 x Isa-KRd
- Consolidation: 4 x Isa-KRd
- Maintenance: Isa-KR

125 NDMM patients: 99 transplant-eligible, 26 transplant-ineligible

- Median age (transplant-eligible/ineligible) 58/74 years
- 100% high-risk cytogenetics
  - 44%/42% del17p
  - 38% t(4;14), 15% t(14;16)
  - 36% >3 copies 1q21
  - 30% >1 abnormality





Among transplant-eligible/-ineligible patients:			
82%/69% MRD-neg at any point	Sustained (≥1 year) MRD-neg in 63%/42%	3-year PFS 68.9%/58.4%	2-year OS 83.9%/71.0%

Grade ≥3 AEs (transplant eligible/ineligible): 78.4% / 72.0%

Common grade ≥3 AEs

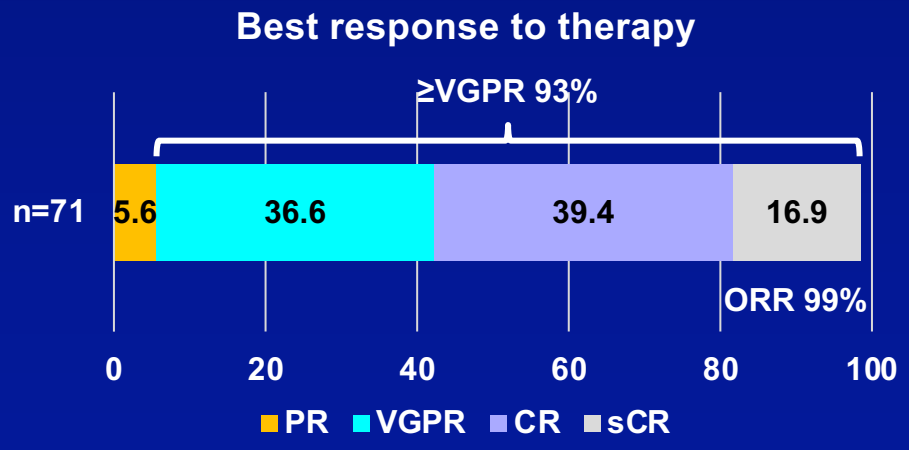
- Neutropenia 39.2% / 28.0%
- Thrombocytopenia 26.8% / 16.0%
- Anemia 14.4% / 12.0%
- Infections 27.8% / 28.0%

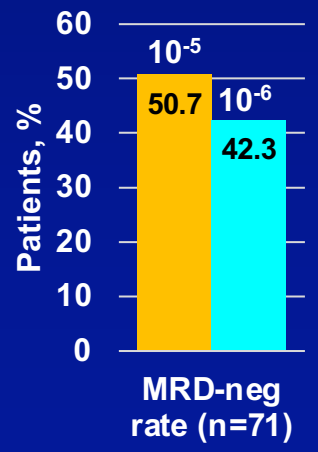
Leypoldt LB, et al. J Clin Oncol 2023;doi:10.1200/JCO.23.01696.

Anti-CD38 mAb-based quadruplet induction, non-ASCT patients

Isa-RVd/Isa-VCd in patients ineligible for / with no immediate intent for transplant[1]

Patients	N = 73
Median age, years (range)	71 (49–87)
Age ≥75 years, %	20.5
ISS stage III, %	8.2
High-risk cytogenetics, %	20.4
1q21+, %	34.2





2-year PFS: 83.1%

Grade ≥3 TEAEs: 79.5%

- Neutropenia 16.4%
- Diarrhea 11.0%
- Asthenia 9.6%
- PN 5.5%

Isa-VCd in transplant-ineligible NDMM[2]

- 17 patients; median age 71 years, 23.5% aged ≥75 years, 35/.3% ISS III, 5.9% high-risk cytogenetics, 5.9% 1q21+
- Best response (n=15): ORR 93.3%, ≥VGPR 80.0%, sCR/CR 66.6%; MRD-neg (10^{-5}) 53.5%
- Median PFS 63.3 months; 5-year OS 79%
- Grade ≥3 TEAEs 82.4%
  - Pneumonia 26.7%, neutropenia 18.8%, hypertension 17.6%, anemia 12.5%

1. Ocio EM, et al. Leukemia 2023; doi: 10.1038/s41375-023-01936-7.
2. Ocio EM, et al. HemaSphere 2023;7(2):e829.

Building on Dara-Rd/RVd backbones: ongoing randomized phase 2/3 studies of anti-CD38 mAb-based quadruplets vs triplets in NDMM

Study	ClinicalTrials.gov	Regimens	Population	Primary endpoint	Initial completion
PERSEUS / EMN17	NCT03710603	Dara-RVd vs RVd	690 transplant-eligible patients	PFS	May 2025
ADVANCE[1]	NCT04268498	Dara-KRd vs KRd	Transplant-eligible patients, MRD-adapted therapy (no ASCT if MRD-negative after 8 cycles)	MRD-neg rate	February 2027
EMN18	NCT03896737	Dara-VCd vs VTd, then Dara-Ixa vs Ixa maintenance	401 transplant-eligible patients	PFS MRD-neg rate	May 2024
GEM21menos65	NCT05558319	Isa-Vd + iberdomide vs Isa-RVd vs RVd	ASCT candidates	MRD-neg rate	April 2027
CEPHEUS	NCT03652064	Dara-RVd vs RVd	395 transplant-eligible patients without intent for upfront ASCT + transplant-ineligible patients	MRD-negative rate	August 2025
EQUATE	NCT04566328	Dara-RVd vs Dara-Rd	Transplant-eligible patients without intent for upfront ASCT + transplant-ineligible patients	OS	December 2027
IMROZ	NCT03319667	Isa-RVd vs RVd	475 transplant-ineligible patients	PFS	April 2026
BENEFIT – IFM2020-05[1]	NCT04751877	Isa-RVd vs Isa-Rd	270 transplant-ineligible fit patients aged 65–80 years	MRD rate at 18 months	April 2024

Data awaited from ongoing Phase 3 studies of anti-CD38 mAb-based quadruplets vs triplets

→

MRD evaluation key in all studies:
Primary endpoint in ADVANCE, EMN18, GEM21menos65, CEPHEUS
Secondary endpoint in PERSEUS

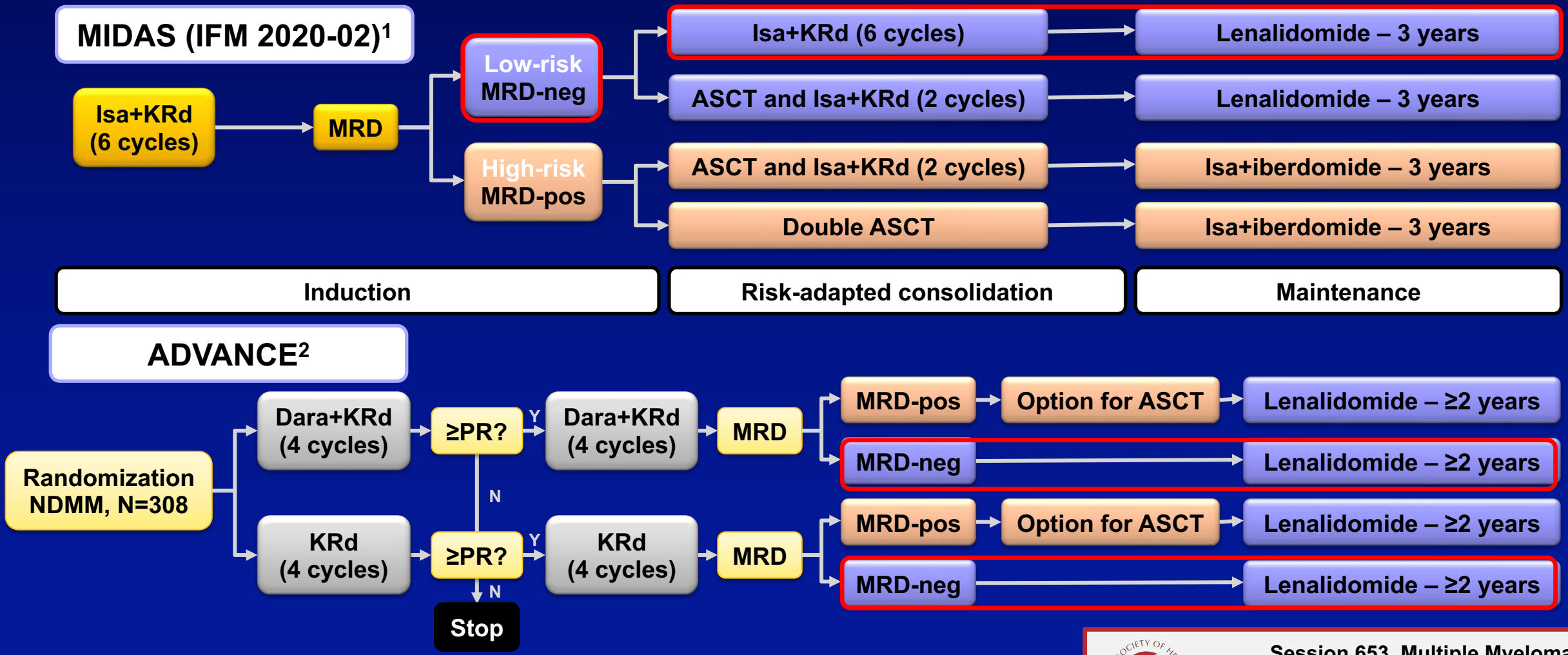
→

MRD negativity a key goal of therapy in this setting as a research tool

ClinicalTrials.gov, November 9, 2023

1. Landgren O, et al. IMS 2022;abstract P-047. 2. Bobin A, et al. Blood 2022;140(suppl 1):abstract 1927.

MRD-adapted therapeutic approaches with anti-CD38 mAb-based quadruplets – MIDAS (IFM 2020-02) / ADVANCE (University of Miami)



1. Perrot A, et al. COMy 2021. https://clinicaltrials.gov/ct2/show/NCT04934475.
2. Landgren O, et al. ASH 2023, abstract 3392.

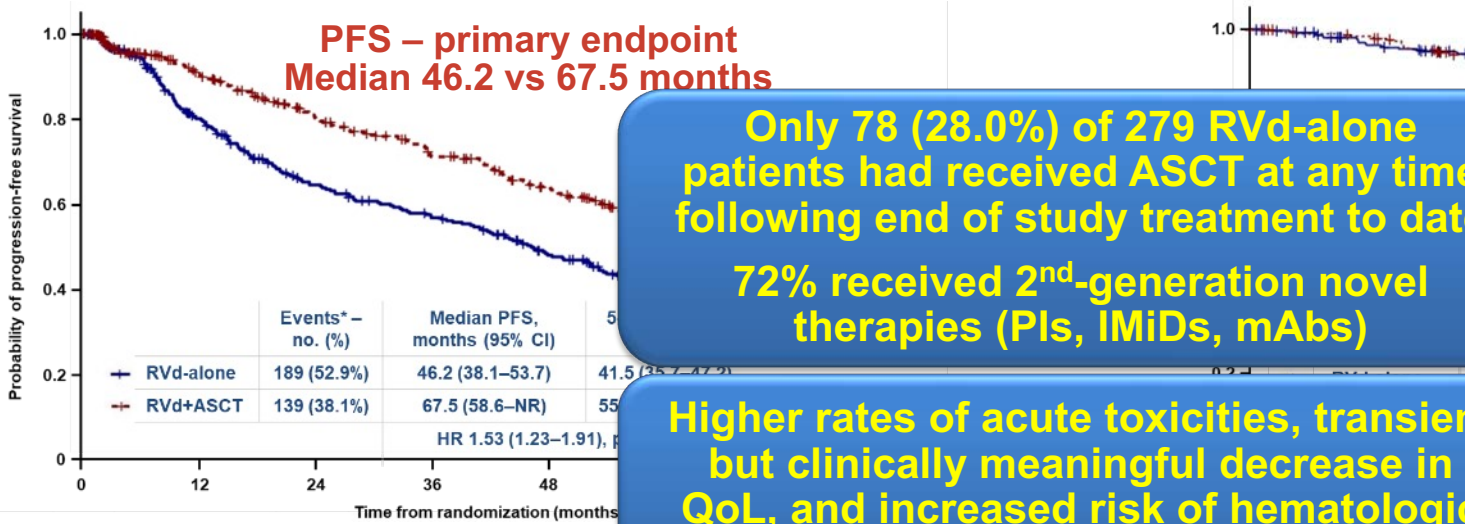
2023

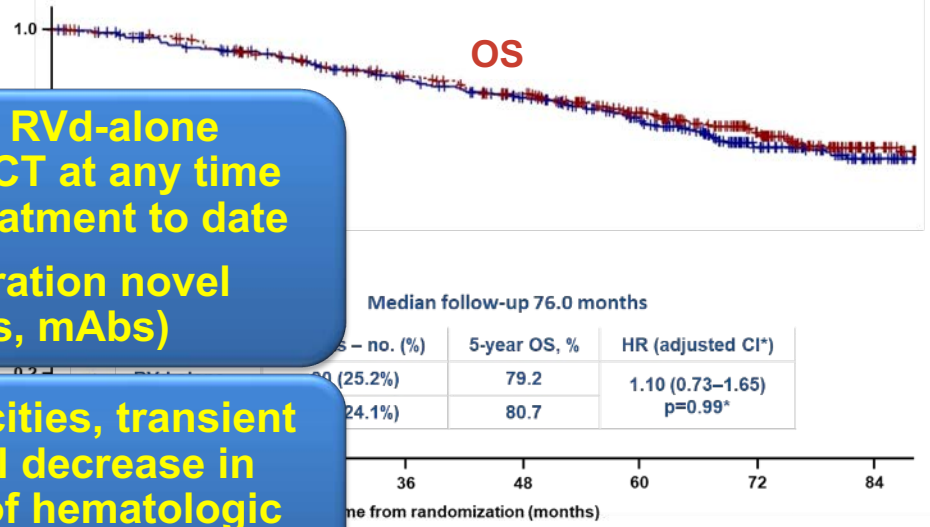
Session 653. Multiple Myeloma: Prospective Therapeutic Trials: Poster II
Sunday, Dec 10, 2023, 6:00 PM-8:00 PM
Abstract 3392. Presenter: Ola Landgren

Increasing rationale for deferred ASCT approach in NDMM

DETERMINATION phase 3 trial: Improved PFS with RVd+ASCT vs RVd-alone, but no OS advantage

DETERMINATION: RVd-alone vs RVd+ASCT, plus lenalidomide maintenance until progression; 28.0% RVd-alone patients received subsequent ASCT

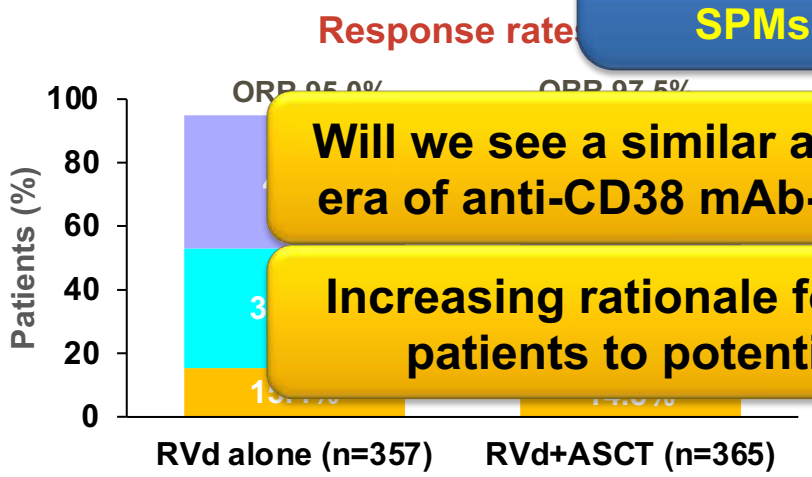


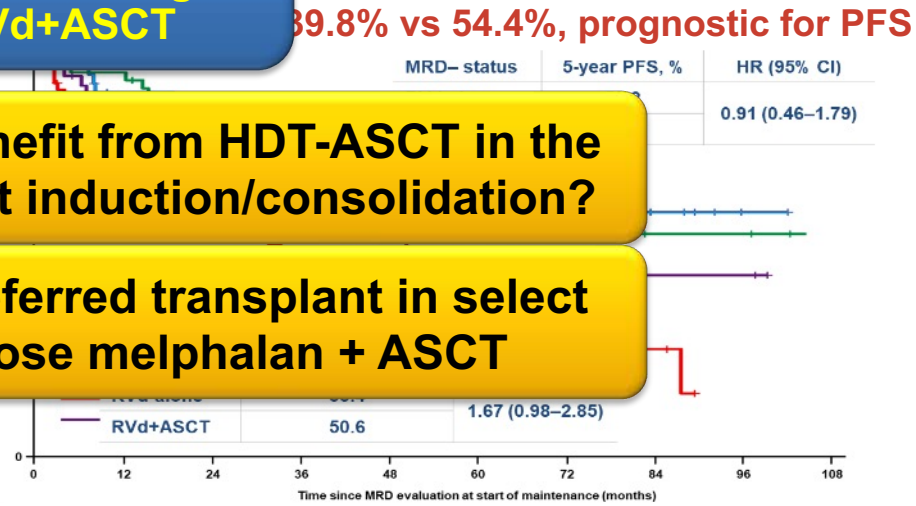


Only 78 (28.0%) of 279 RVd-alone patients had received ASCT at any time following end of study treatment to date

72% received 2nd-generation novel therapies (PIs, IMiDs, mAbs)

Higher rates of acute toxicities, transient but clinically meaningful decrease in QoL, and increased risk of hematologic SPMs (AML/MDS) with RVd+ASCT





Will we see a similar absence of OS benefit from HDT-ASCT in the era of anti-CD38 mAb-based quadruplet induction/consolidation?

Increasing rationale for considering deferred transplant in select patients to potentially avoid high-dose melphalan + ASCT

Richardson PG, et al. N Engl J Med 2022;387(2):132–47.

*Preliminary data in 198 patients from the start of lenalidomide maintenance

DETERMINATION: subgroup analyses indicate patients with potentially differential benefit from different treatment approaches

PFS subgroup analysis

		RVd-alone	RVd+
All	ITT analysis	189/357	13
Age	<60 years	122/235	1
	≥60 years	67/122	
Sex	Male	107/202	
	Female	82/155	
Race	White/Caucasian	150/268	
	Black/African American	24/66	
	Other		
ECOG	0		
	1–2		
BMI	<25		
	25 to <30		
	≥30		
MM	IgG		
	IgA		
	Light chain		
ISS	I		
	II		
	III		
LDH	Not elevated (<225 U/L)		
	Elevated (≥225 U/L)		
FISH	High risk		
	t(4;14)		
	Del(17p)		
	Standard risk		
R-ISS	I		
	II		
	III		

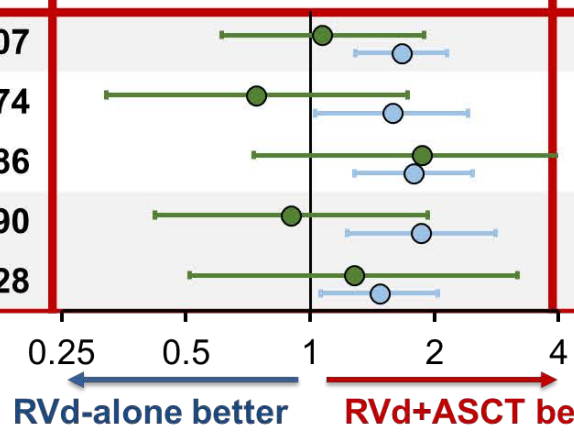
Richardson PG, et al. N Engl J

Multiva

Subgroup	Comp
Age	≥60 y
Sex	Fema
Race	Black
	Othe
BMI	25–<3
	≥30
ECOG PS	>0
ISS stage	II
	III
Cytogenetics	High
	Unkn
LDH	>ULN
Hemoglobin	≤10 g
Calcium	≥10.5 m

ASH 2023: Subgroup analysis of PFS by race and BMI or sex suggest similar PFS, EFS, and OS with RVd-alone and RVd+ASCT in African American patients

Subgroup	AA patients			HR (95% CI)	White patients		
	RVd-alone	RVd+ASCT	HR	RVd-alone vs RVd+ASCT	RVd-alone	RVd+ASCT	HR
All	NR	61.4	1.07		44.3	67.2	1.67
BMI ≥30	NR	58.6	0.74		41.1	64.4	1.58
BMI <30	66.4	NR	1.86		45.3	82.3	1.78
Female	NR	58.6	0.90		42.0	NR	1.85
Male	66.4	NR	1.28		46.2	64.3	1.47



2023

653. Multiple Myeloma: Prospective Therapeutic Trials: Poster III
Monday, Dec 11, 2023, 6:00 PM-8:00 PM
Abstract 4672. Presenter: Jeffrey A. Zonder

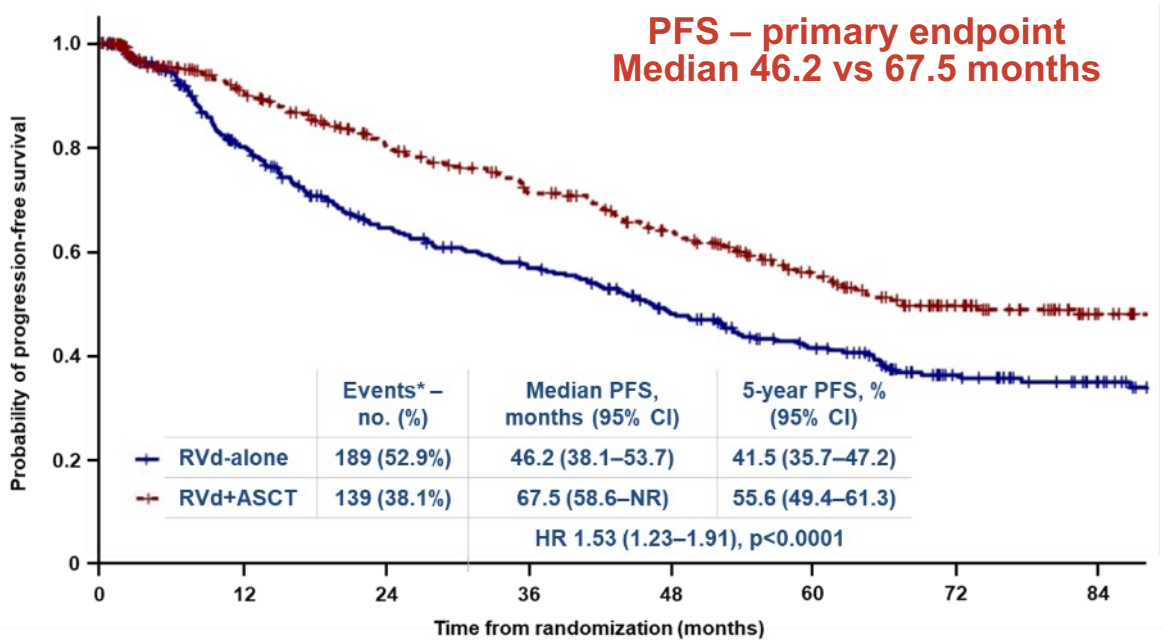
1. Richardson PG, et al. N Engl J Med 2022;387(2):132–47. 2. Hassoun H, et al. ASH 2022;poster presentation 2110. 3. Hassoun H, et al. Tandem Meetings 2023; poster presentation.
4. Hassoun H, et al. EBMT 2023; updated oral presentation. 5. Zonder JA, et al. ASH 2023; poster presentation 4762.

Duration of maintenance: DETERMINATION / IFM 2009

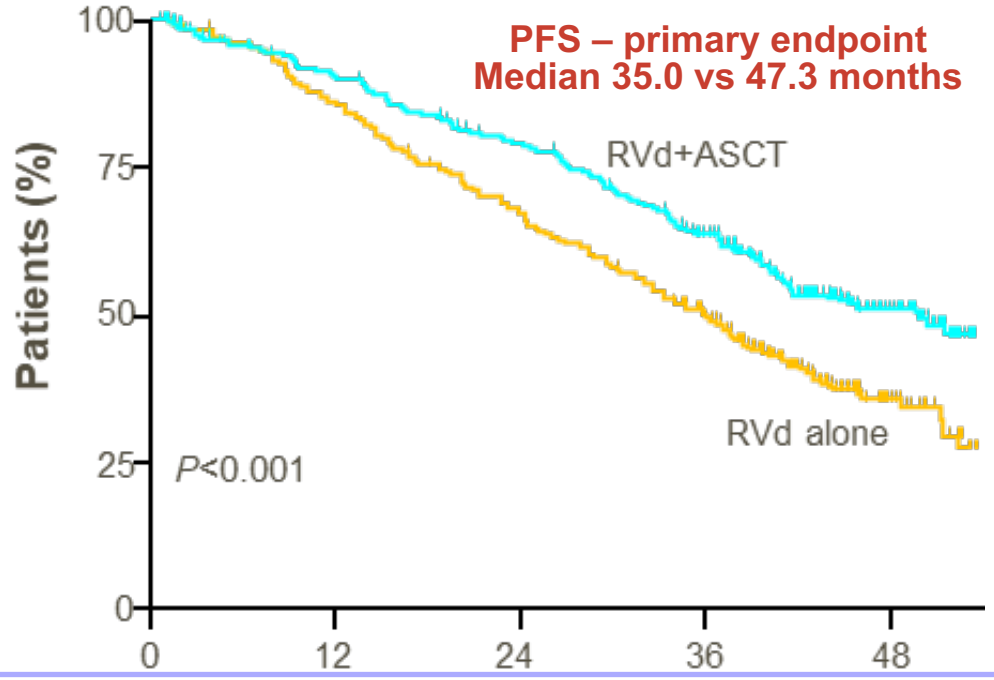
Parallel study designs: RVd-alone vs RVd+ASCT

- **DETERMINATION: R maintenance to progression[1]**
- **IFM 2009: R maintenance for 1 year[2,3]**

DETERMINATION[1]



IFM 2009[2,3]



- **Increased PFS with greater duration of maintenance therapy**
- **Median PFS Δ between arms: DETERMINATION 20.3 months[1] vs IFM 2009 12.3 months[2,3]**
- **Enhanced benefit from HDM plus long-term lenalidomide in driving deep and durable responses, enhancing cytoreduction, and improving antitumor immune microenvironment and tumor-specific immunity after cellular reconstitution[1]**

1. Richardson PG, et al. N Engl J Med 2022;387(2):132–47. 2. Perrot A, et al. Blood 2020;136(suppl 1): abstract 39. 3. Attal M, et al. N Engl J Med 2017;376(14):1311–20.

FORTE / ATLAS: building on R maintenance backbone

FORTE[1]

474 NDMM patients

- 158 KRd+ASCT
- 157 KRd12
- 159 KCd+ASCT

356 patients randomized to KR vs R maintenance

- 178 per arm

PFS, KR vs R

- 3-year rate 75% vs 65%
- HR 0.64, p=0.023

Common grade 3/4 AEs during KR vs R maintenance

- Any 49% vs 39%
- Neutropenia 20% vs 23%
- Infections 5% vs 7%
- Vascular events 7% vs 1%

ATLAS[2]

180 NDMM patients

- Post-induction plus ASCT
- 93 KRd
- 87 R

Response, KRd vs R

- Improved depth of response after 6 months 54% vs 44%
- MRD-neg rate post-cycle 6 53% vs 31%

Outcomes, KRd vs R

- Median follow-up 33.8 months
- Median PFS 59.1 vs 41.4 months
- HR 0.51, p=0.012
- Median OS not reached vs 61.8 months, HR 0.83, p=0.68

Safety, KRd vs R

- Grade 3/4 neutropenia 48% vs 60%
- Grade 3/4 thrombocytopenia 13% vs 7%
- Grade 3/4 lower respiratory tract infections 8% vs 1%
- SAEs 30% vs 22%

1. Gay F, et al. Lancet Oncol 2021;22(12):1705–20.
2. Dytfeld D, et al. Lancet Oncol 2023;24(2):139–50.

Building on maintenance backbones: ongoing studies of anti-CD38 mAb-based doublet/triplet maintenance in NDMM

Study	ClinicalTrials.gov	Phase	Maintenance regimens	Setting	Primary endpoint	Initial completion
AURIGA	NCT03901963	3	Dara-R vs R	Post-ASCT	MRD-neg rate	June 2024
DRAMMATIC[1]	NCT04071457	3	Dara-R vs R	Post-ASCT	OS	July 2029
MDACC 2022-0028	NCT05776979	2	Isa-R	Post-ASCT in high-risk NDMM	3-year PFS	December 2025
HEME-18	NCT05344833	2	Isa-R	MRD-pos patients post-ASCT	MRD-neg CR rate	December 2030
GMMG-CONCEPT	NCT03104842	2	Isa-KR	Post-ASCT in high-risk NDMM	MRD-neg rate	February 2025
GEM-OPTIMAL	NCT05218603	n/a	Dara-V	Post-Dara-VMP in non-transplant patients	PFS	November 2025

Multiple studies investigating anti-CD38 mAb-based doublet or triplet maintenance therapy → Some studies using doublet/triplet therapy to disease progression → Strategic impact on subsequent treatment approaches in patients refractory to an anti-CD38 mAb

ClinicalTrials.gov, November 9, 2023

1. Dhakal B, et al. Hematologist 2021;18(6):doi:10.1182/hem.V18.6.202166

Alternative maintenance approaches: ongoing studies of novel combinations and therapies in NDMM

Study	ClinicalTrials.gov	Phase	Maintenance regimens	Setting	Primary endpoint	Initial completion
FiTNEss (UK-MRA Myeloma XIV)	NCT03720041	3	Ixazomib + R vs R	Transplant-ineligible patients, post-ixazomib-Rd induction therapy	PFS	December 2024
EXCALIBER-Maintenance	NCT05827016	3	Iberdomide vs R	Post-ASCT	PFS	March 2029
IBEX	NCT06107738	2	Iberdomide + Dara	Post-ASCT	MRD-neg rate at 12 months	December 2025
KarMMa-9	NCT06045806	3	Ide-cel + R vs R	Suboptimal response post-ASCT	PFS	March 2031
CARTITUDE-5	NCT04923893	3	Cilta-cel vs Rd	Post-RVd induction, non-transplant setting	PFS	June 2026
MajesTEC-4	NCT05243797	3	Teclistamab + R vs Teclistamab vs R	Post-ASCT	PFS	April 2028
MajesTEC-5	NCT05695508	2	Teclistamab + Dara + R	Post-ASCT	Safety	May 2026
ISA-HC-NK	NCT04558931	2	CellProtect NK cells + Isa vs Isa	Post-ASCT	VGPR rate MRD-neg rate	December 2027

ClinicalTrials.gov, November 9, 2023

MRD-directed / alternative maintenance therapy approaches at ASH 2023

UK-MRA RADAR[1]	• MRD-neg post-ASCT and after isa maintenance for 1 year – continued isatuximab vs stop maintenance • MRD-pos post-ASCT: Isa-RVd x 4 cycles + Isa-R maintenance vs RVd x 4 cycles + R maintenance vs Isa-R maintenance vs R maintenance
FREEDMM (NCT05192122)[2]	• ≥2 years lenalidomide maintenance • Sustained MRD-negativity (2 x NGS, 10^{-6} threshold, 1 year apart) → stop maintenance
RAMP UP (NCT05344833)[3]	• MRD-pos patients post-ASCT • Isa-R maintenance for 3 years • MRD testing every 12 months
EMN26 (NCT04564703)[4]	• Iberdomide maintenance post-ASCT • 48%/45% response improvement in iberdomide 1.0/1.3 mg cohorts after 6 months
SeaLAND (ALLG MM23) study (ANZCTR12620000291987)[5]	• Selinexor-R vs R maintenance post-ASCT • Selinexor 40 mg weekly generally tolerable in combination with R

1. Ramasamy K, et al. ASH 2023, abstract 3390. Poster presentation, Sunday Dec 10.
2. Avila Rodriguez AM, et al. ASH 2023, abstract 3395. Poster presentation, Sunday Dec 10.
3. Sweiss K, et al. ASH 2023, abstract 4974. Poster presentation, Monday Dec 11.
4. van de Donk NWCJ, et al. ASH 2023, abstract 208. Oral presentation, Saturday Dec 9.
5. Quach H, et al. ASH 2023, abstract 2023. Poster presentation, Saturday Dec 9.

Isatuximab Phase 3 Trial Meets Primary Endpoint of Progression Free Survival in Patients with Newly Diagnosed Multiple Myeloma Not Eligible for Transplant

Press Release – December 7, 2023

"The Phase 3 IMROZ trial evaluating the investigational use of isatuximab in combination with standard-of-care bortezomib, lenalidomide and dexamethasone (VRd) met its primary endpoint at a planned interim analysis for efficacy, demonstrating statistically significant improvement in progression-free survival (PFS) compared with VRd alone in transplant-ineligible patients with newly diagnosed multiple myeloma (MM). This is also the second Phase 3 trial investigating isatuximab in newly diagnosed patients to show superiority versus standard of care.

The safety and tolerability of isatuximab observed in this trial was consistent with the established safety profile of isatuximab and VRd.

https://www.sanofi.com/en/media-room/press-releases/2023/2023-12-07-06-35-00-2792221

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Richardson

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) MM — Dr Lonial

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies in the Treatment of MM — Dr Krishnan

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Orlowski

To approximately how many patients with MM have you administered belantamab mafodotin on or off protocol?

Median number of patients: 15 (range 5-40)

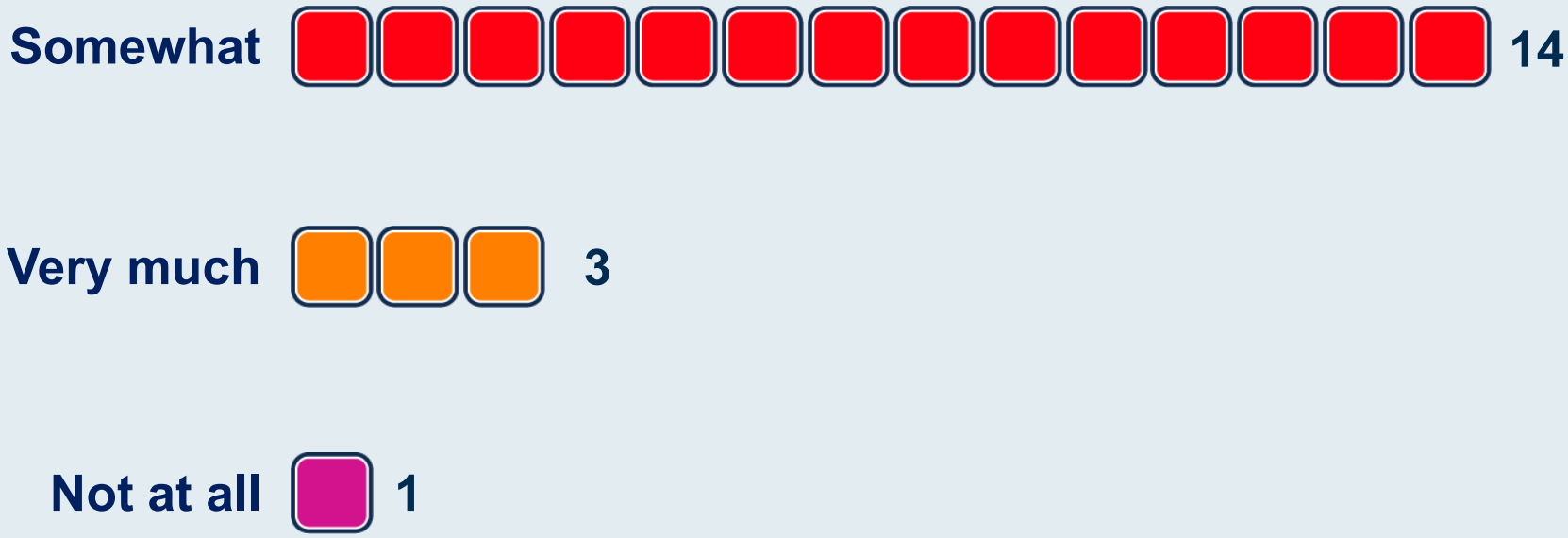
What is the longest duration of clinical benefit you have observed with belantamab mafodotin?

Median number of months: 24 (range 5-63)

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

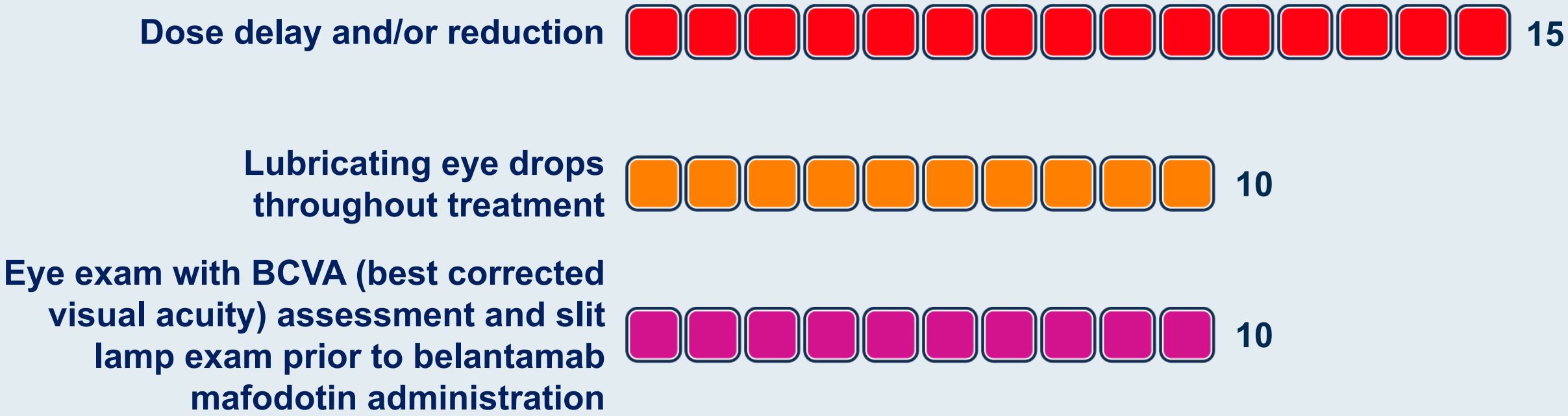
How much of an obstacle to use are the ophthalmic issues associated with belantamab mafodotin?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

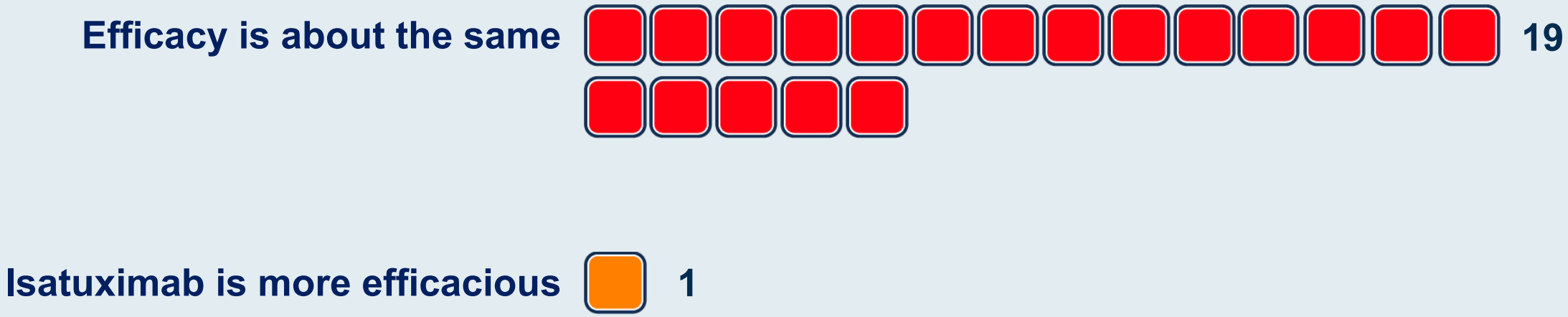
Which of the following strategies do you recommend for mitigation of corneal toxicities associated with belantamab mafodotin in patients with relapsed/refractory (R/R) MM? (Select all that apply)



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

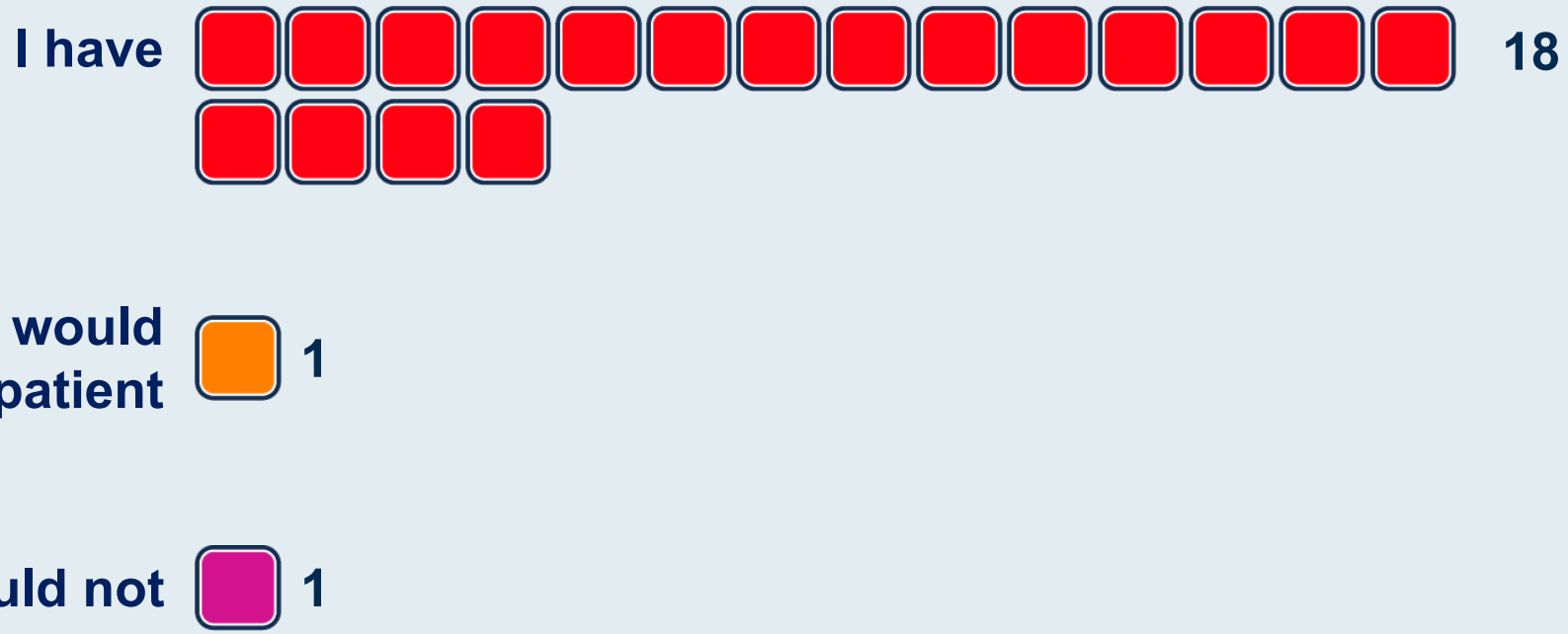
Based on your personal clinical experience and knowledge of available data, how would you compare the global efficacy of daratumumab to that of isatuximab for R/R MM?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Have you rechallenged or would you rechallenge relapsed disease with an anti-CD38 antibody in a patient who has previously received one as a component of induction therapy (eg, 2 years ago)?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

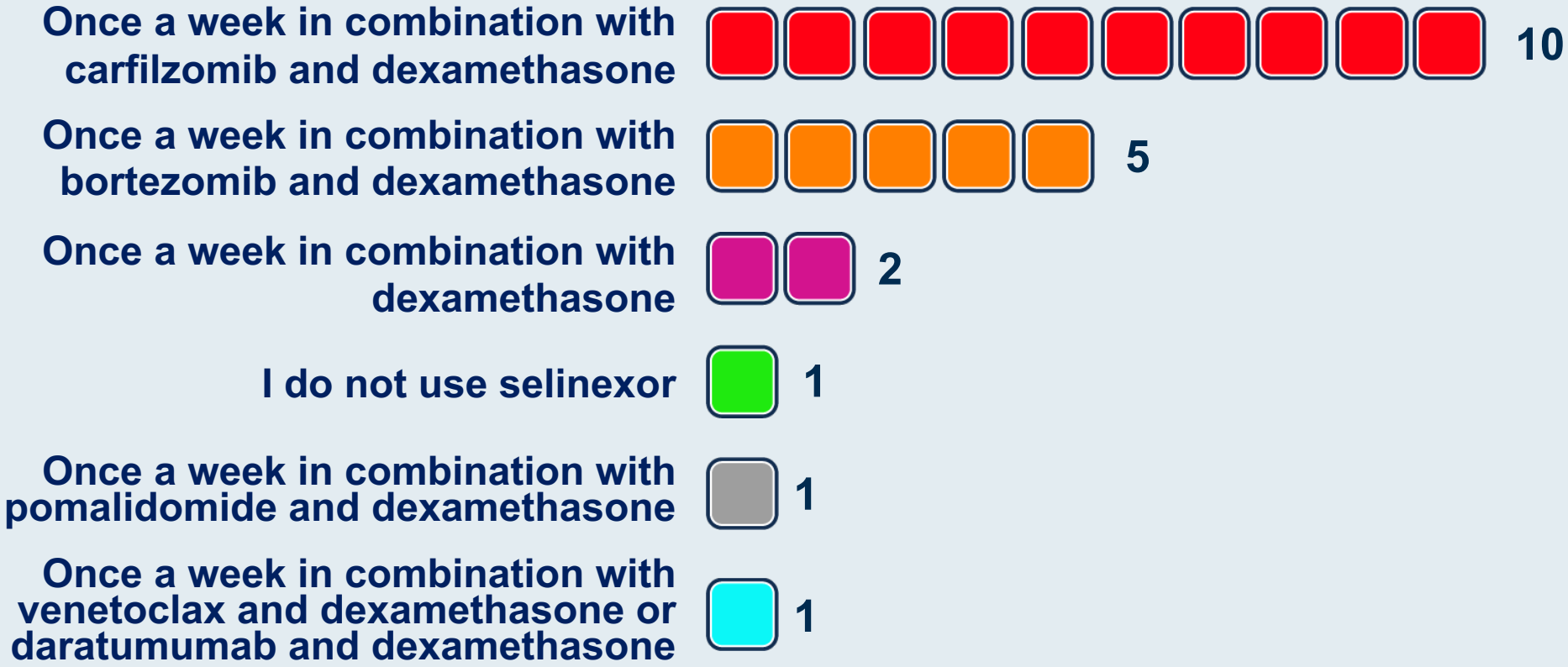
To approximately how many patients with MM have you administered selinexor on or off protocol?

Median number of patients: 30 (range 3-100)

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

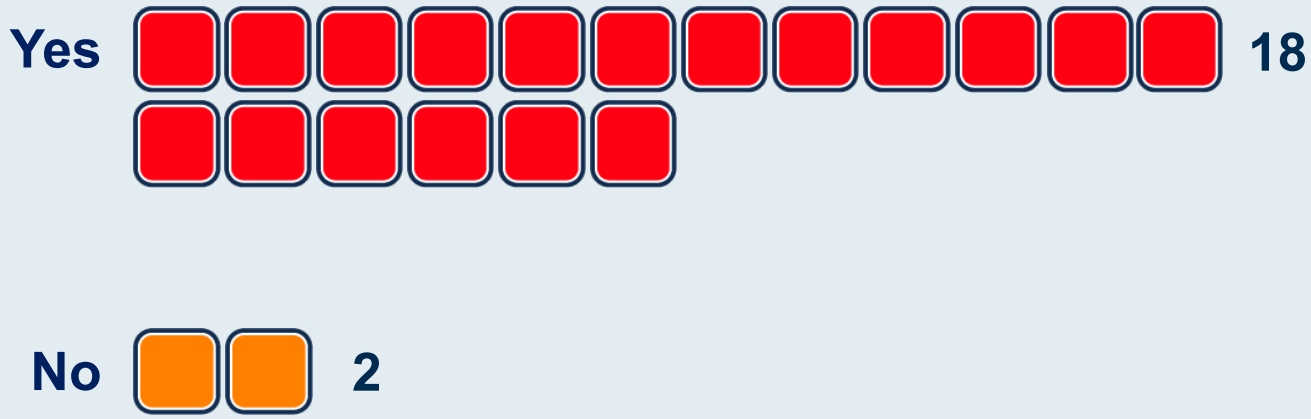
In general, what is the optimal method to administer selinexor in the treatment of R/R MM?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

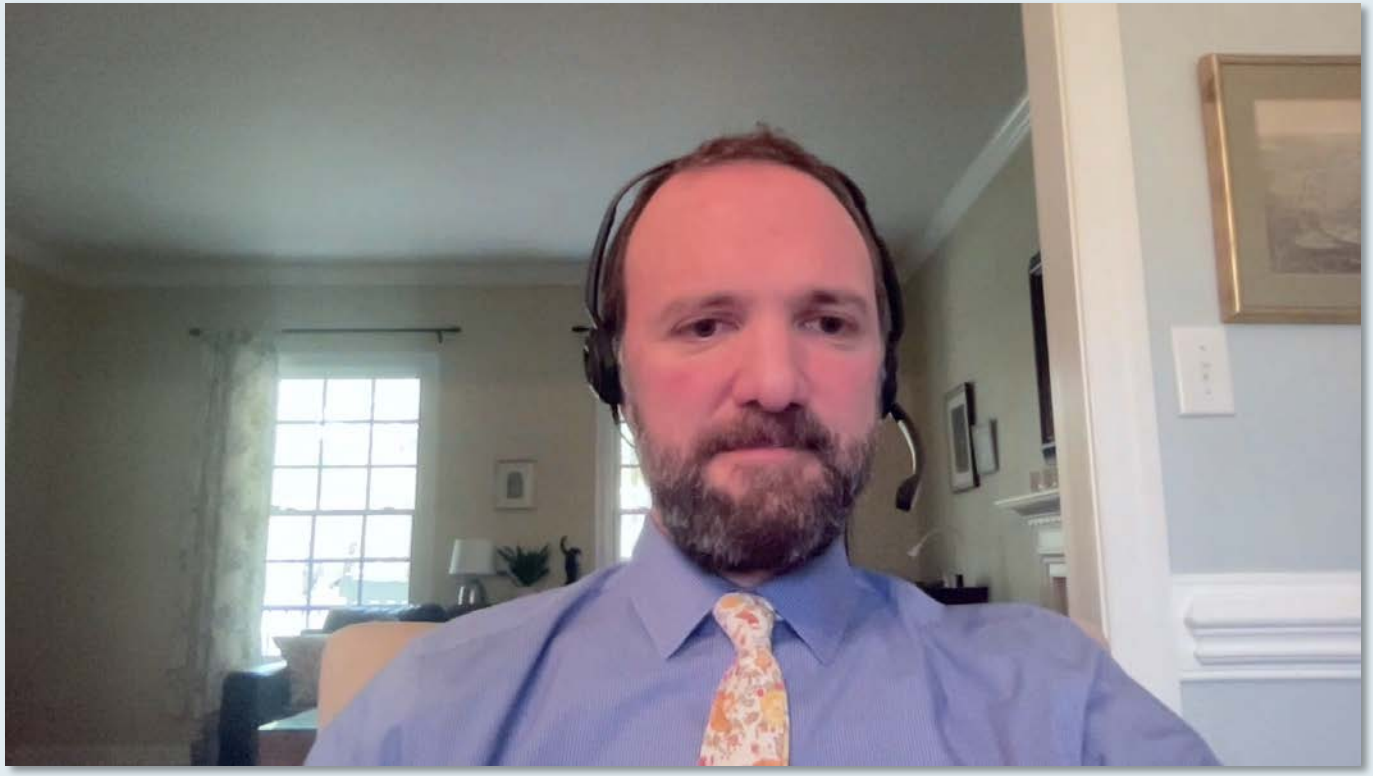
In general, should preemptive medications for gastrointestinal toxicities be initiated prior to administering selinexor?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Approach for patients with R/R MM



Sascha A Tuchman, MD, MHS

RTP
RESEARCH
TO PRACTICE

Clinical experience with belantamab mafodotin for R/R MM; incidence of ophthalmic toxicities

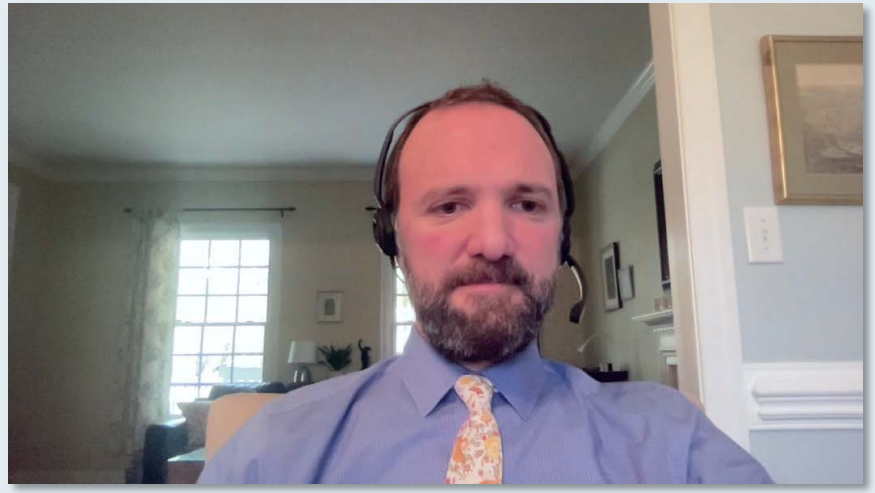
C Ola Landgren, MD, PhD

Melissa Alsina, MD

RTP
RESEARCH
TO PRACTICE

Efficacy and tolerability of selinexor in combination with a proteasome inhibitor (eg, bortezomib, carfilzomib) for patients with R/R MM

C Ola Landgren, MD, PhD



Sascha A Tuchman, MD, MHS

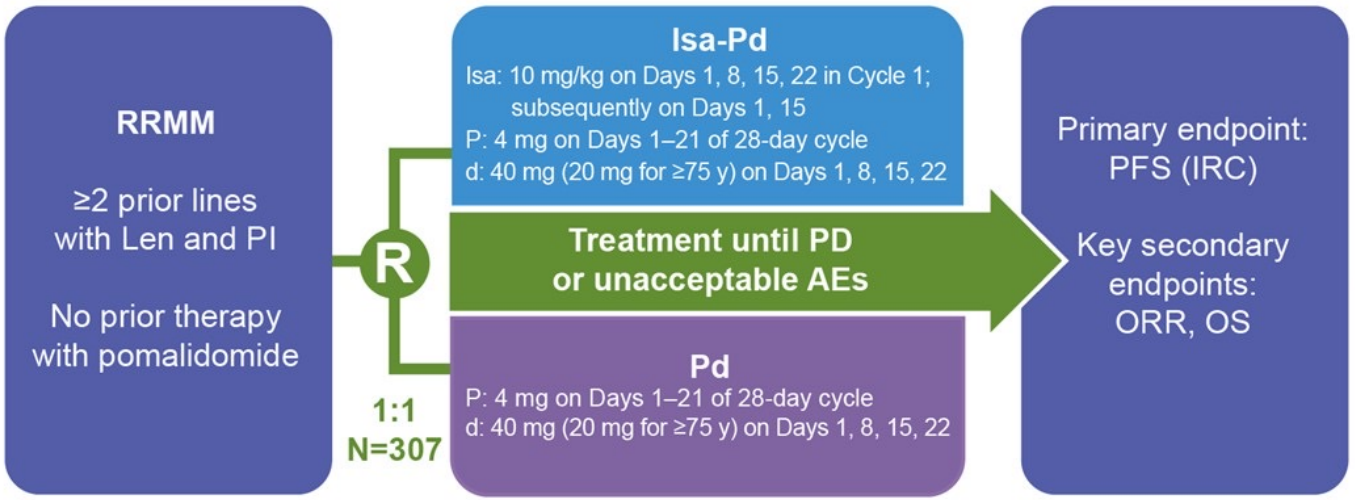
RTP
RESEARCH
TO PRACTICE

Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Sagar Lonial, MD

ICARIA-MM Updated Results

Study design[1] and pre-planned second interim analysis



PRIMARY ANALYSIS[2]
(data cut-off October 11, 2018; median follow-up of 11.6 months):

Significant improvement in PFS with Isa-Pd vs Pd alone (11.5 vs 6.5 months, respectively; **HR 0.596**; 95% CI 0.436–0.814; p=0.001)

At 35.3 months follow-up, 17.5% of patients in the Isa-Pd arm remained on treatment vs 7.8% in the Pd arm

SECOND INTERIM ANALYSIS:

- Time to next treatment
- OS
- PFS2
- Safety

Data cut-off date of October 1, 2020 (90% OS analysis at 198 OS events; median follow-up of 35.3 months) and October 7, 2020 for all other analyses

ICARIA-MM study: NCT02990338

AE, adverse event; d, dexamethasone; HR, hazard ratio; IRC, independent review committee; Isa, isatuximab; Len, lenalidomide; ORR, overall response rate; OS, overall survival; P, pomalidomide; PD, progressive disease; PFS, progression-free survival; PFS2, time from randomization to disease progression on first subsequent therapy or death; PI, proteasome inhibitor; R, randomization; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; y, years

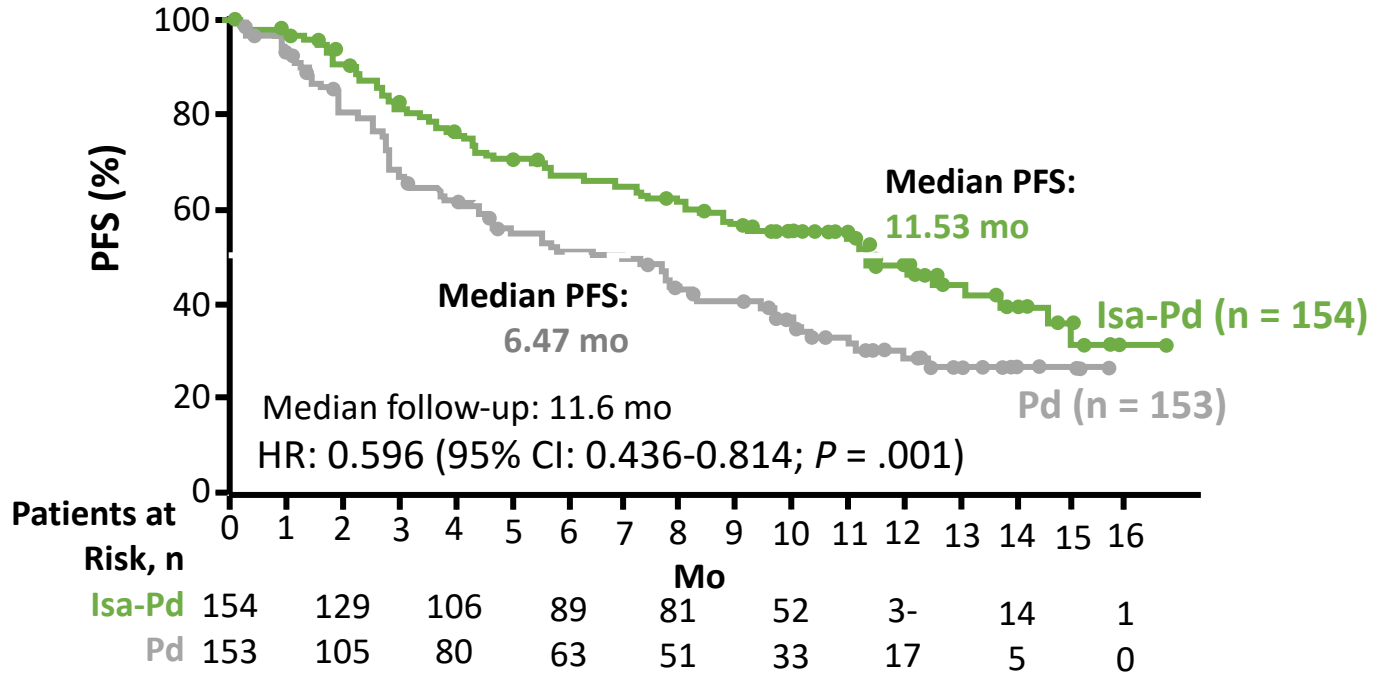
1. Richardson PG, et al. *Future Oncol*. 2018;14:1035–47. 2. Attal M, et al. *Lancet*. 2019;394:2096–2107

Phase III ICARIA-MM: Isa-Pd vs Pd in R/R MM After ≥2 Prior Therapy Lines Including Len and a PI

Isa-Pd group

- 3 prior lines of therapy
- 94% Len refractory (60% in last line)
- 77% PI refractory
- 72% double refractory

Response, %	Isa-Pd (n = 154)	Pd (n = 153)
ORR	63	33
▪ sCR	<1	<1
▪ CR	9	2
▪ VGPR	29	8
▪ PR	25	12



- At median 35.3-mo follow-up, mOS: 24.6 mo for Isa-Pd vs 17.7 mo for Pd; HR: 0.776 (95% CI: 0.594-1.102; log-rank *P* = .0319)

Attal. Lancet. 2019;394:2096. Richardson. Lancet Oncol. 2022;23:416. Richardson. IMS 2022. Abstr OAB-052.

ICARIA-MM Updated Results
Updated safety

	Isa-Pd (n=152)		Pd (n=149)	
Exposure to study treatments				
Cumulative exposure to treatment, patient-years	184.9		124.5	
Median treatment duration, weeks (range)	47.6 (1.3–171.6)		24.0 (1.0–168.6)	
Patients with, n (%)				
Any TEAE	151 (99.3)		146 (98.0)	
Any Grade ≥3 TEAE	138 (90.8)		112 (75.2)	
Treatment-related Grade ≥3 TEAE	115 (75.7)		75 (50.3)	
Any Grade 5 TEAE[a]	14 (9.2)		15 (10.1)	
Any SAE	111 (73.0)		90 (60.4)	
Any TEAE leading to definitive discontinuation	18 (11.8)		21 (14.1)	
Top 3 non-hematologic TEAEs occurring in ≥20% of patients in either arm				
Preferred term, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Infusion reaction	57 (37.5)	4 (2.6)	2 (1.3)	0
URTI	52 (34.2)	5 (3.3)	29 (19.5)	2 (1.3)
Diarrhea	46 (30.3)	3 (2.0)	33 (22.1)	2 (1.3)
Grade 3–4 hematologic abnormalities (from laboratory values), %				
Thrombocytopenia	34.2		25.2	
Neutropenia	84.9		71.5	

No new safety signals were identified. The incidence of TEAEs with fatal outcome and TEAEs leading to definitive discontinuation remained similar between the 2 arms

[a]TEAE with fatal outcome during the treatment period

d, dexamethasone; HR, hazard ratio; Isa, isatuximab; P, pomalidomide; SAE, serious adverse event; TEAE, treatment-related adverse event; URTI, upper respiratory tract infection

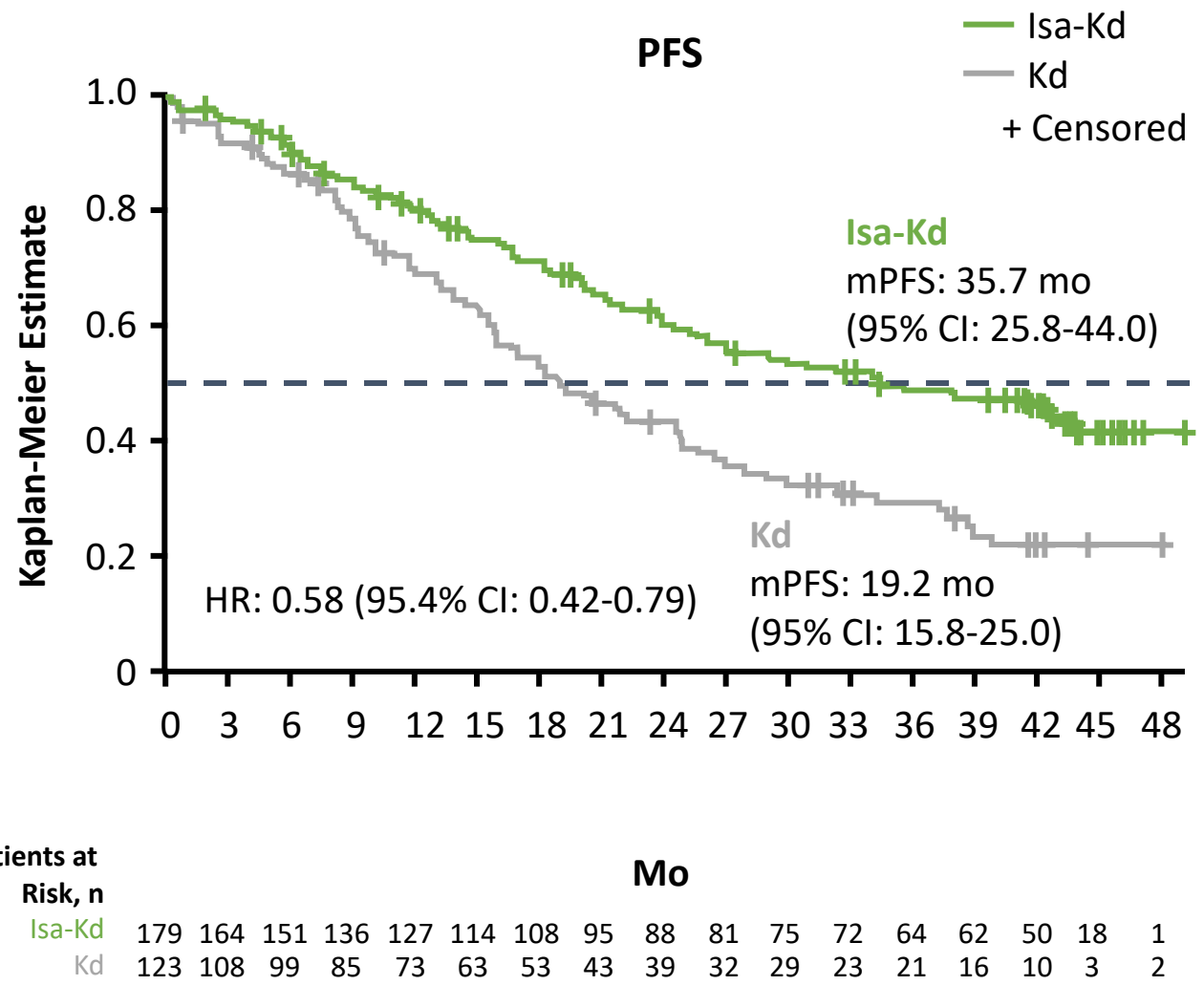
Phase III IKEMA: Isa-Kd vs Kd in R/R MM After 1-3 Prior Therapy Lines

Isa-Kd group

- 2 prior lines of therapy
- 32% Len refractory
- 31.3% PI refractory
- 49.7% refractory to last regimen

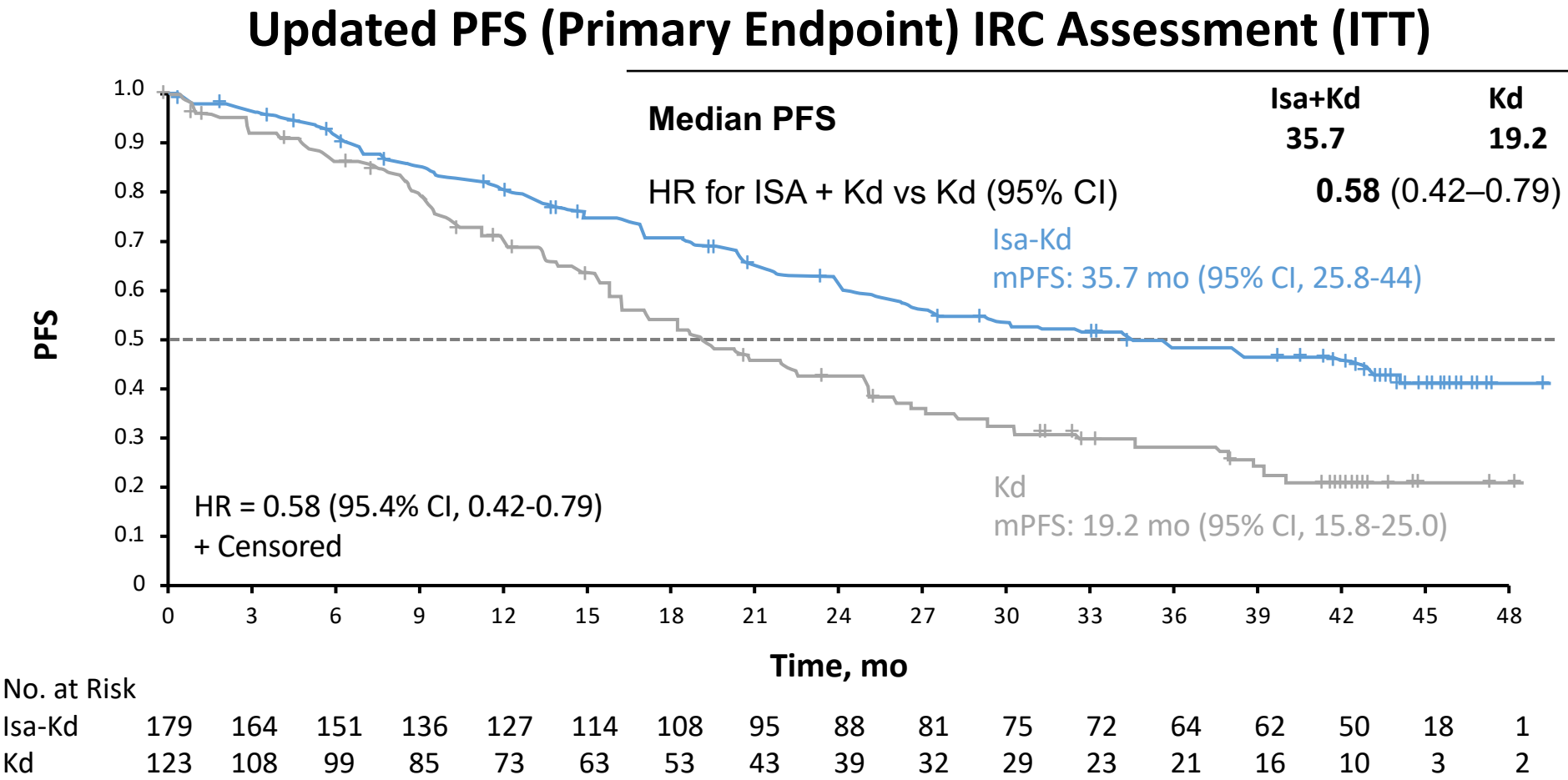
Parameter	Isa-Kd (n = 179)	Kd (n = 123)
ORR, %	86.6	83.7
CR, %	44.1	28.5
MRD negative, %	33.5	15.4
MRD negative and CR rate, %	26.3	12.2
mPFS2, mo (95% CI)	47.2 (38.1-NC)	35.6 (24.1-40.5)
	HR: 0.68 (95% CI: 0.50-0.94)	
mOS, mo (95% CI)*	NR (52.17-NR)	50.6 (18.9-NR)
	HR: 0.855 (95% CI: 0.608-1.202) P = .184	

*Median follow-up: 56.6 mo.



Martin. Blood Cancer J. 2023;13:72. Yong. IMS 2023. Abstr OA-48.

IKEMA: Updated PFS After Additional 2 Years of Follow-Up[1]



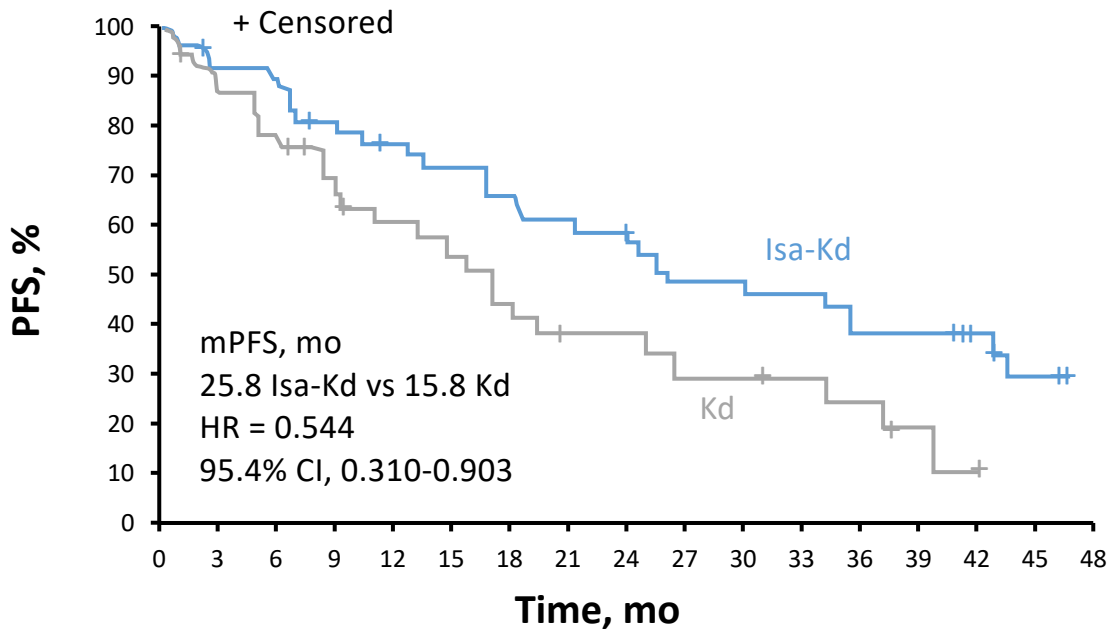
Isa-Kd showed the longest PFS on a PI-based backbone in RRMM, with 42% reduction vs Kd in the risk of progression or death

1. Moreau P et al. 2022 ESMO Virtual Plenary. Abstract VP5-2022.

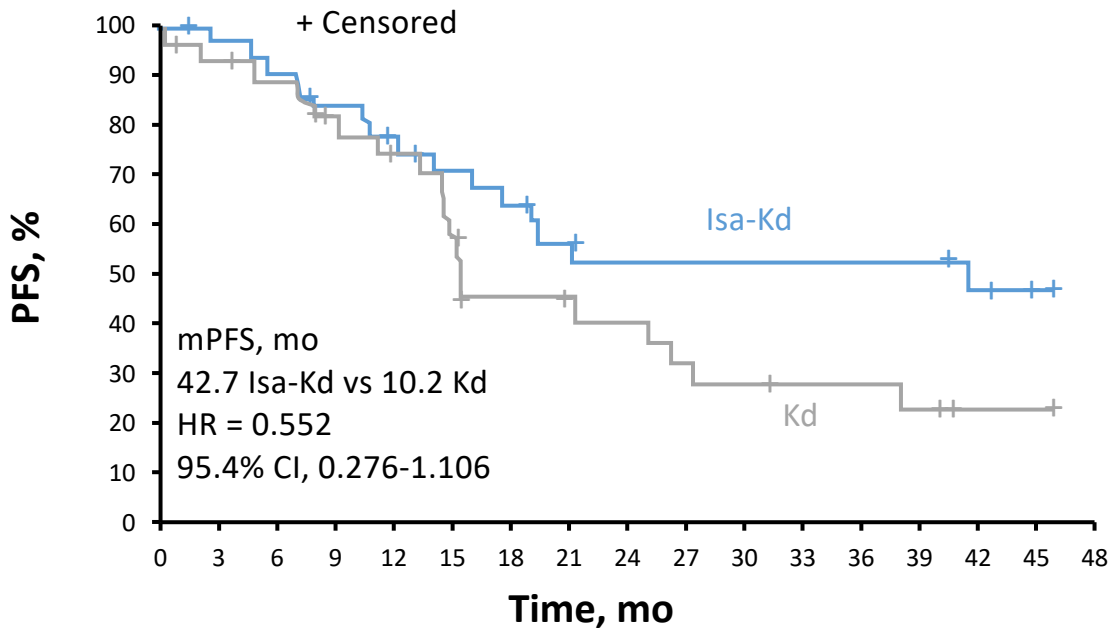
IKEMA: The Addition of Isa to Kd Improved PFS and Depth of Response in Both Early and Late Relapse Patients[1]

Subgroup results were consistent with those observed in the overall IKEMA study population

Early Relapse and Refractory to Last Regimen



Late Relapse and Refractory to Last Regimen

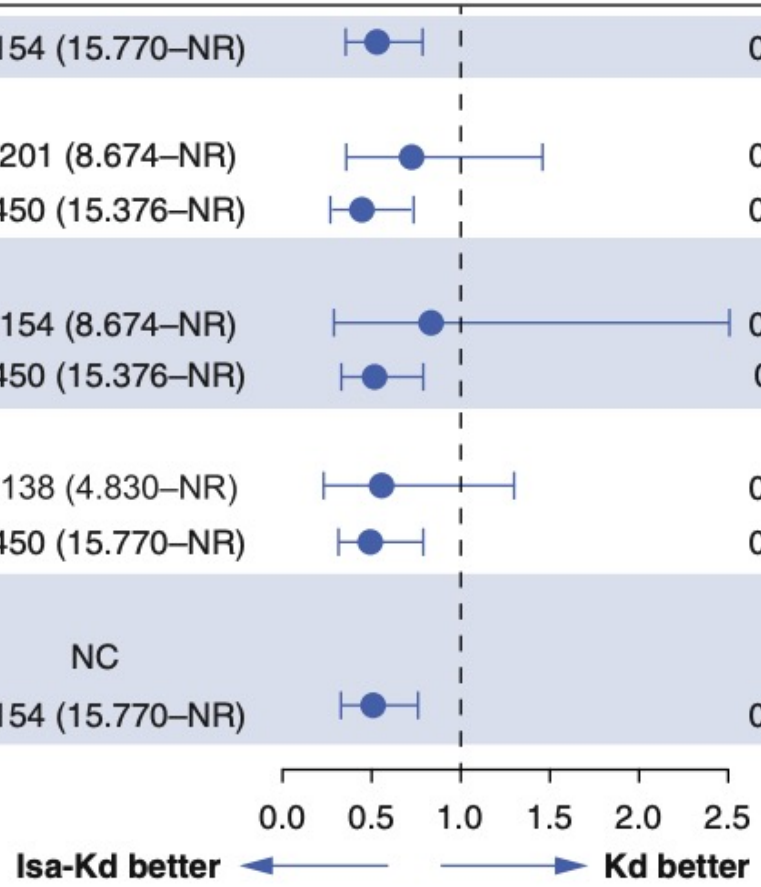


PFS in patients refractory to the last regimen was similar between early (HR = 0.544) and late relapse (HR = 0.552) patients, favoring Isa-Kd over Kd

1. Facon T et al. ASH 2022. Abstract 753.

IKEMA: Efficacy of Isa-Kd in Patients with High-risk RRMM[1]

Subgroup	Isa-Kd Group (n/N)	Median PFS (95% CI)	Kd Group (n/N)	Median PFS (95% CI)	Hazard ratio (95% CI)
All patients	48/179	NR (NR–NR)	55/123	19.154 (15.770–NR)	0.531 (0.359–0.786)
High-risk chromosomal abnormality*					
At least one	17/42	NR (13.076–NR)	15/31	18.201 (8.674–NR)	0.724 (0.361–1.451)
None	27/114	NR (NR–NR)	35/77	19.450 (15.376–NR)	0.440 (0.266–0.728)
del(17p)					
Present	6/18	NR (9.232–NR)	7/16	19.154 (8.674–NR)	0.837 (0.281–2.496)
Absent	39/143	NR (NR–NR)	43/96	19.450 (15.376–NR)	0.510 (0.330–0.788
t(4;14)					
Present	10/22	NR (11.433–NR)	11/20	11.138 (4.830–NR)	0.549 (0.232–1.301)
Absent	34/137	NR (NR–NR)	39/89	19.450 (15.770–NR)	0.491 (0.310–0.778)
t(14;16)					
Present	4/6	7.129 (2.530–NR)	0/0	NC	NC
Absent	41/153	NR (NR–NR)	50/111	19.154 (15.770–NR)	0.501 (0.331–0.757)



1. Spicka I, et al. Eur J Haematol. 2022 Nov;109(5):504-512

IKEMA: Safety Profile of Isa-Kd vs Kd

AE, n (%)	Isa-Kd (n = 177)		Kd (n = 122)	
	All Gr	Gr ≥3	All Gr	Gr ≥3
Hematologic				
Anemia	177 (100)	43 (24.3)	121 (99.2)	26 (21.3)
Neutropenia	100 (56.5)	36 (20.4)	55 (45.1)	9 (7.4)
Thrombocytopenia	168 (94.9)	53 (30)	109 (89.3)	29 (23.8)
Nonhematologic				
Infusion reaction	81 (45.8)	1 (0.6)	4 (3.3)	0
Diarrhea	70 (39.5)	5 (2.8)	39 (32)	3 (2.5)
Hypertension	67 (37.9)	30 (22.6)	43 (35.2)	28 (23)
URT infection	66 (37.3)	6 (3.4)	33 (27)	2 (1.6)
Fatigue	56 (31.6)	10 (5.6)	25 (20.5)	1 (0.8)
Dyspnea	54 (30.5)	10 (5.6)	27 (22.1)	1 (0.8)
Pneumonia	48 (27.1)	33(18.6)	26 (21.3)	15 (12.3)
Back pain	45 (25.4)	3 (1.7)	26 (21.3)	1 (0.8)
Insomnia	45 (25.4)	11 (6.2)	30 (24.6)	3 (2.5)
Bronchitis	43 (24.3)	4 (2.3)	15 (12.3)	1 (0.8)
Arthralgia	39 (22)	4 (2.3)	15 (12.3)	2 (1.6)
Cough	39 (22)	0	17 (13.9)	0
Asthenia	36 (20.3)	4 (2.3)	20 (16.4)	4 (3.3)

- Incidence of SPMs was 9% for Isa-Kd and 7.4% for Kd
  - Skin cancers were 6.2% in Isa-Kd and 3.3% in Kd
  - None led to treatment discontinuation
- Treatment-related deaths were 5.6% for Isa-Kd and 4.9% for Kd

Martin. Blood Cancer J. 2023;13:72.

Investigational SC Isatuximab Shows Comparable Efficacy Compared With IV Administration

In an assessment of an on-body delivery system (OBDS), a wearable bolus injector applied to the abdomen by a healthcare professional, SC isatuximab at RP2D of 1,400 mg demonstrated[1]

- Safety profile consistent with IV administration
- No IRs; excellent local tolerability
- Efficacy comparable to that observed in the ICARIA study
- Convenience of a hands-free option with controlled delivery

	ISA IV 10 + Pd (n = 12)	ISA SC 1,000 + Pd (n = 12)	ISA SC 1,400 (RP2D) + Pd (n = 10)	ISA OBDS + Pd (n = 22)	ISA OBDS and SC (RP2D) + Pd (n = 32)
ORR, n (%)	8 (66.7)	8 (66.7)	8 (80.0)	16 (72.7)	24 (75.0)
sCR/CR, n (%)	2 (16.7)	3 (25.0)	2 (20.0)	5 (22.7)	7 (21.9)

SC formations are being investigated in MM (NCT05405166; phase 3 noninferiority trial)[2]

1. Quach H et al. ASH 2022. Abstract 1923. 2. https://clinicaltrials.gov/ct2/show/NCT05405166.

Phase Ib Study of Isatuximab SC Administration With Wearable Bolus Injector

- SC isatuximab (with WBI or IP) or IV isatuximab with Pd
- Median duration of WBI injection was 10 min* (range: 6.6-49.5) with comparable ORRs

	Isa IV + Pd (n = 12)		Isa IP + Pd (n = 10)		Isa WBI + Pd (n = 22)	
Adverse Event, n (%)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
URT infection	0	0	2 (20)	0	1 (4.5)	0
COVID-19	0	0	4 (40)	0	6 (27.3)	3 (13.6)
Injection-site erythema	0	0	5 (50)	0	4 (18.2)	0
Injection-site bruising	0	0	3 (30)	0	0	0
Infusion reaction	1 (8.3)	0	1 (10)	0	0	0
Laboratory Abnormalities, n (%)	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	2 (16.7)	0	2 (20)	0	3 (13.6)	0
Neutropenia	3 (25)	7 (58.3)	3 (30)	6 (60)	7 (31.8)	15 (59.1)
Thrombocytopenia	3 (25)	2 (16.7)	1 (10)	2 (20)	4 (18.2)	4 (18.2)

Quach. IMS 2023. Abstr P-306. Isatuximab PI.

Selinexor-Based Regimens

	Sd[a]	SVd[b]		SPd[c]	SDd[d]
Study arm	-	**Tx**	**Control**	**Tx**	**Tx**
Selinexor dose	**80 mg 2x/w**	**100 mg 1x/w**	-	**60 mg 1x/w**	**100 mg 1x/w**
N	**123**	**402**		**20**	**31**
Median prior lines of therapy	7	2		4	3
% triple-refractory	100%	-		-	-
% penta-refractory	68%	-		-	-
Efficacy					
ORR	26%	76.4%	62.3%	65%	75%
≥ CR rate	2%	17%	10%	5%	0%
Median PFS, mos	3.7	13.93	9.46	10.4	12.5
PFS HR (95% CI)	-	0.70 (0.53–0.93)		-	-
Median OS, mos	8.6	NR	25	NR	NR
OS HR (95% CI)	-	0.84 (0.57–1.23)		-	-
NCCN recommendation[e]	**Penta-refractory**	**1 – 3 prior**		**2 prior inc IMiD+PI**	**1 – 3 prior**
FDA indication[f]	**Penta-refractory**	**1 prior**		**None**	**None**

a. Chari A, et al. N Engl J Med. 2019;381:727-738; b. Grosicki S, et al. Lancet. 2020;396:1563-1573; c. White D, et al. J Clin Oncol. 2021;39:8018; d. Gasparetto C, et al. EJHaem. 2021;2:56-65; e. NCCN. Multiple Myeloma (V2.2023). 2022. Accessed November 4, 2022. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf; f. Selinexor [PI]. Revised July 2022.

Managing Gastrointestinal Toxicities With Selinexor

- **GI events with selinexor are common, but manageable with prophylaxis, early intervention and dose adjustment[a]**

Early and aggressive supportive care

- Nausea prophylaxis with 2 agents
  - (5-HT3 antagonist, low-dose olanzapine, NK1 receptor antagonist)
- Hydration and dietary counseling
- Antidiarrheals

Dose adjustment

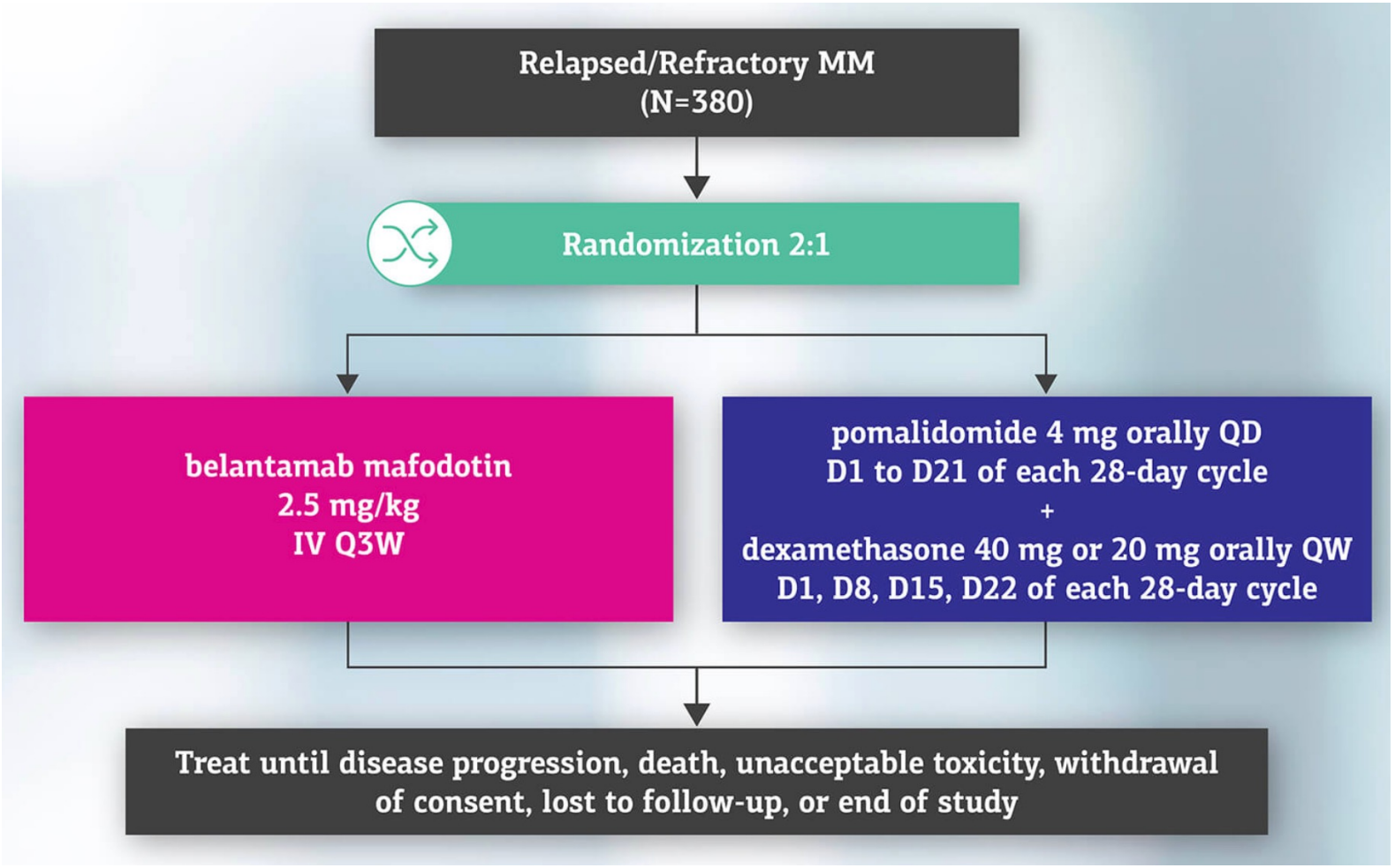
- Interrupt and dose reduce for increasing nausea, diarrhea, weight loss, hyponatremia, fatigue

	Sd[a]		SVd[b]		SPd[c]		SDd[d]	
Selinexor dose	**80 mg twice weekly**		**100 mg weekly**		**60 mg weekly**		**100 mg weekly**	
Adverse event, %	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Nausea	72	10	50	8	70	0	71	9
Diarrhea	46	7	32	6	25	0	35	3
Vomiting	38	3	21	4	20	0	29	3
Constipation	22	2	17	0	-	-	29	0
Anorexia	56	5	35	4	-	-	35	0
Weight loss	50	1	26	2	25	0	24	3
Hyponatremia	37	22	-	-	-	-	32	12

a. Mikhael J, et al. Clin Lymphoma Myeloma Leuk. 2020;20:351-357; b. Chari A, et al. N Engl J Med. 2019;381:727-738; c. Grosicki S, et al. Lancet. 2020;396:1563-1573; d. White D, et al. J Clin Oncol. 2021;39:8018; e. Gasparetto C, et al. EJHaem. 2021;2:56-65.

DREAMM-3 Trial: Primary Endpoint Was Not Met

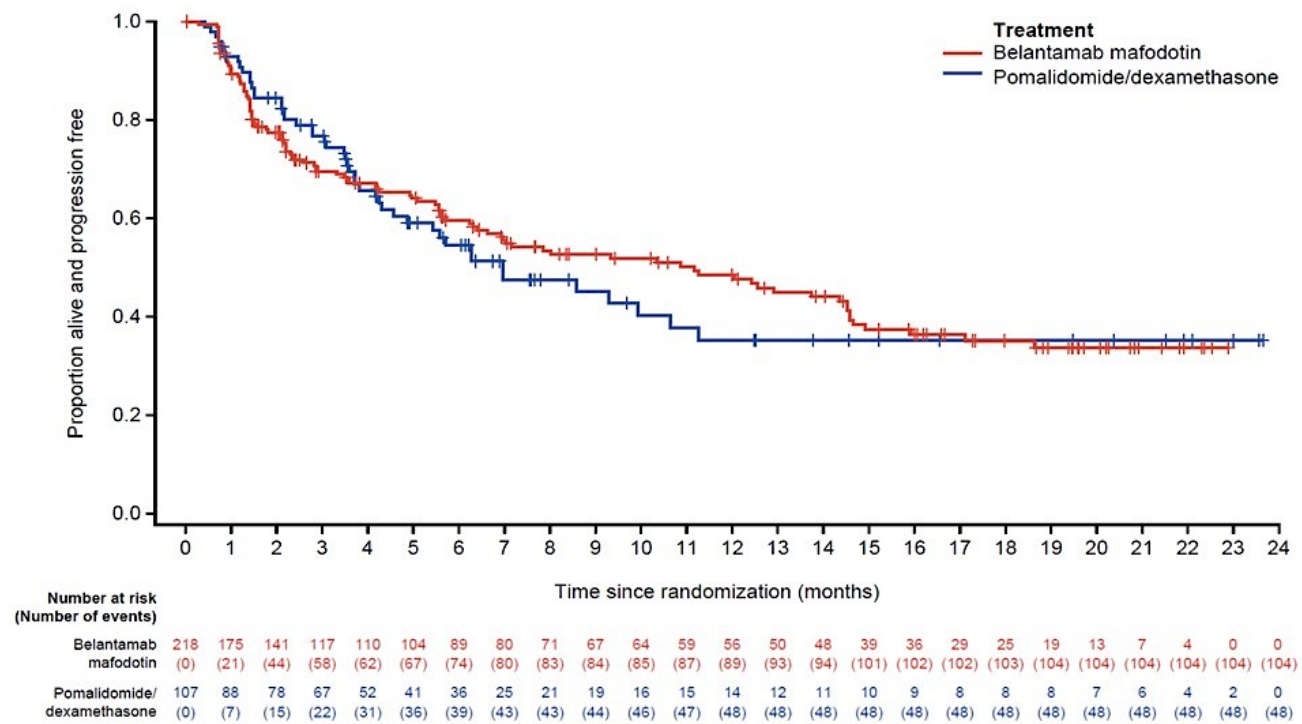
- The primary endpoint of improved PFS was not met in the phase 3 DREAMM-3 study of belantamab mafodotin monotherapy versus pomalidomide plus low-dose dexamethasone for patients with R/R MM.[1]
- The median progression-free survival for belantamab mafodotin was 11.2 months vs 7 months with PomDex (HR, 1.03; 95% CI, 0.72-1.47). [1]



1. https://bit.ly/3FYNEnB 2. https://dreammtrials.com/dreamm3.html

Median PFS was longer for belamaf vs Pd, but PFS HR was 1.03

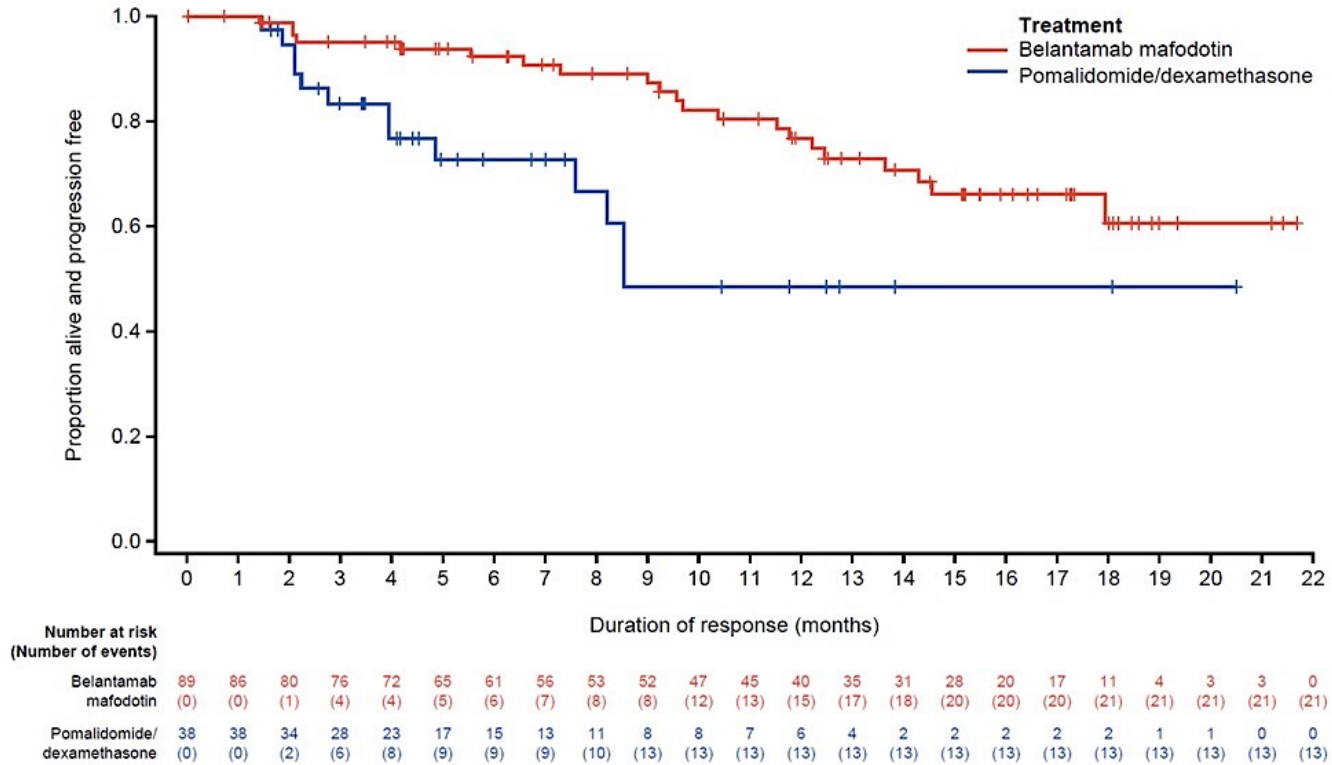
- Median follow-up was 11.5 months for belamaf and 10.8 months for Pd.
- Median PFS was longer for belamaf than for Pd, but PFS HR did not reach statistical significance.
  - Belamaf: **11.2** months (95% CI 6.4 – 14.5).
  - Pd: **7.0** months (95% CI 4.6 – 10.6).
  - HR of 1.03 (95% CI: 0.72, 1.47, p=0.558).
  - KM curves cross over at ~4 months.



CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; Pd, pomalidomide plus dexamethasone; PFS, progression-free survival.

Belamaf demonstrated longer duration of response

- Overall, median follow-up was 11.5 months for belamaf and 10.8 months for Pd.
- Median DoR* was longer for belamaf than for Pd:
  - Belamaf: **NR** (95% CI 17.9, NR).
  - Pd: **8.5** months (95% CI 7.6, NR).
  - Rates at
    - 6-month: 93% vs 75%.
    - 12-month: 77% vs 50%.
    - 18-month: 63% vs 50%.
- KM curves show clear and early separation.



*DoR was a secondary endpoint and was not tested for statistical significance. CI, confidence interval; DoR, duration of response; KM, Kaplan-Meier; NR, not reached; Pd, pomalidomide plus dexamethasone.

Belantamab Mafodotin Summary

Study	DREAMM-1	DREAMM-2	DREAMM-4	DREAMM-6	DREAMM 7/8
Phase	I	**II**	I/II	I/II	III/III
Treatment (All are IV q 3wk)	Belamaf dose escalation, expansion 3.4 mg/kg	Belamaf 2.5 or 3.4 mg/kg	Belamaf 2.5 or 3.4 mg/kg + pembro	Belamaf 2.5 mg/kg + bortezomib-dex	Bela + VD vs DaraVD Bela + PD Vs PVD
Patients	n=35	n=196	n=34	n=18	N=494/300
Median prior lines	5	6-7	5	3	UNK
Triple-class refractory	37%	100%	NR	NR	UNK
ORR %	60% (38.5% if prior dara exposure)	31% / 34%	47%	78%	UNK
PFS	12 mos (6.8 mos if prior dara)	2.9 / 4.9 months	3.4 months	NR	UNK
AEs- all grade (gr3+)					
Keratopathy	52% (3%)	70% (27%)/ 75% (21%)	76% (38%)	100% (56%)	UNK
Thrombocytopenia	63% (35%)	35% (20%)/ 58% (34%)	35%(29%)	67% (61%)	
Anemia	28% (17%)	24% (20) / 37% (25%)			
Infusion reaction	12% (3%)	21% (3%) / 16% (1%)	50% (0%)/14% (0%)	17% (0%)	
Other			Blurred vision: 38% (0%)		

NOTE: Cross-trial comparisons are for discussion purposes only. This is a summary slide to highlight trials in a similar space.

Trudel, et al. *Blood Cancer J* 2019; Lonial, et al. *Lancet Oncol* 2019; Nooka, et al. *Hematology Reports* 2020; Suvannasankha et al. ASCO 2022; Popat, et al. ASH 2020; Quach H, et al, ASCO 2022; Kumar, et al. ASH 2020

Positive Results from the DREAMM-7 Head-to-Head Phase III Trial of Belantamab Mafodotin for R/R MM

Press Release – November 27, 2023

"The manufacturer today announced positive headline results from a planned interim efficacy analysis of the DREAMM-7 head-to-head phase III trial evaluating belantamab mafodotin as a second-line treatment for relapsed or refractory multiple myeloma. The trial met its primary endpoint of progression-free survival (PFS) and showed that belantamab mafodotin when combined with bortezomib plus dexamethasone (BorDex) significantly extended the time to disease progression or death versus daratumumab plus BorDex, an existing standard of care for relapsed/refractory multiple myeloma. A strong and clinically meaningful overall survival (OS) trend with nominal *p*-value <0.0005 was also observed at the time of this analysis, and the trial continues to follow up for OS.

The safety and tolerability of the belantamab mafodotin regimen was consistent with the known safety profile of the individual agents. Results from the interim analysis will be presented at an upcoming scientific meeting and shared with health authorities."

https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-results-from-dreamm-7-head-to-head-phase-iii-trial-for-blenrep/

Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Richardson

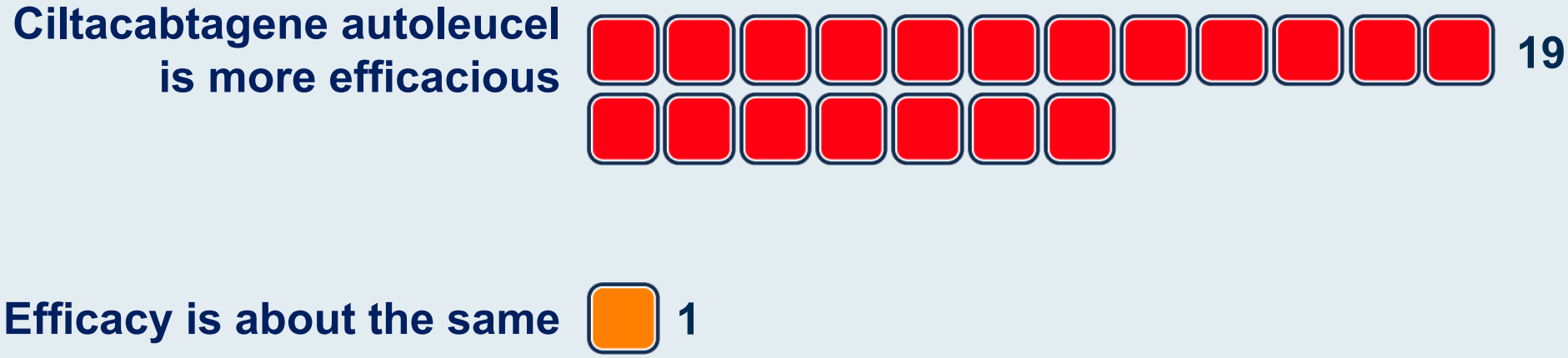
Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) MM — Dr Lonial

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies in the Treatment of MM — Dr Krishnan

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Orlowski

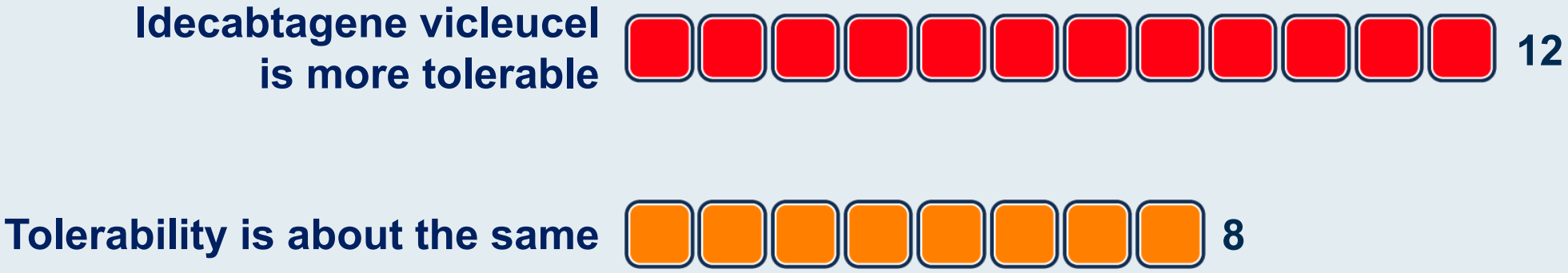
Based on your personal clinical experience and knowledge of available data, how would you compare the global efficacy of idecabtagene vicleucel to that of ciltacabtagene autoleucel for R/R MM?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, how would you compare the tolerability of idecabtagene vicleucel to that of ciltacabtagene autoleucel for R/R MM?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

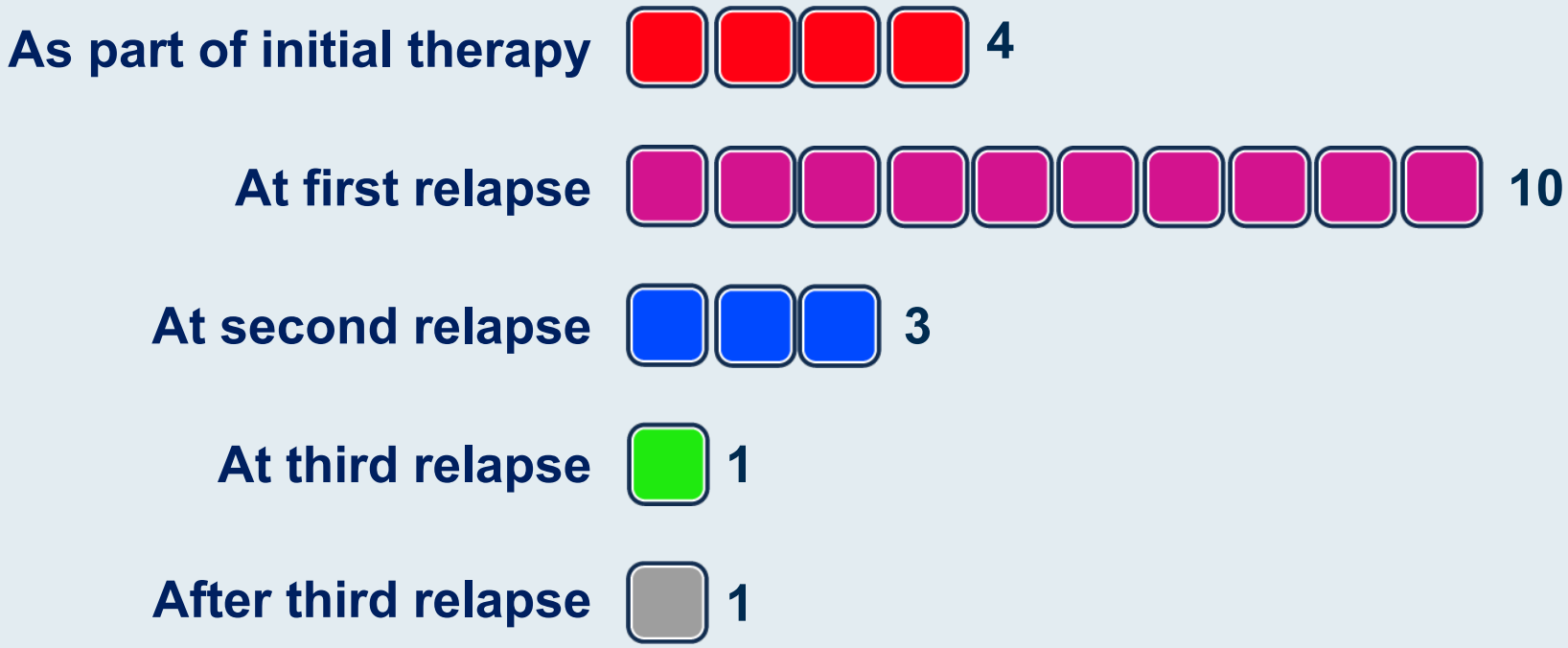
Regulatory and reimbursement issues aside, what do you currently believe is the optimal point at which CAR T-cell therapy should be administered for standard-risk MM (ie, at what point would you like to see your patients enter a trial or receive it off protocol)?

Respondent comment:
Remaining challenge is the mortality/morbidity (death, 2nd malignancies, hemophagocytosis, Parkinsonism, other ICANS, etc) for CAR T cells in relation to all other treatment options out there. We need more solid data (larger datasets with longer follow-up) to be able to better counsel patients on optimal treatment strategies. Many options available; eg, combinations of bispecific antibodies are highly effective and have lower mortality (also lower morbidity). These issues get more complex for earlier lines, in particular newly diagnosed patients. We need more data.

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what do you currently believe is the optimal point at which CAR T-cell therapy should be administered for high-risk (eg, del[17p]) MM (ie, at what point would you like to see your patients enter a trial or receive it off protocol)?



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RTP RESEARCH TO PRACTICE

What is the age of the oldest patient to whom you have administered or whom you have referred for CAR T-cell therapy?

Patient age: 81 (median; range 72-90)

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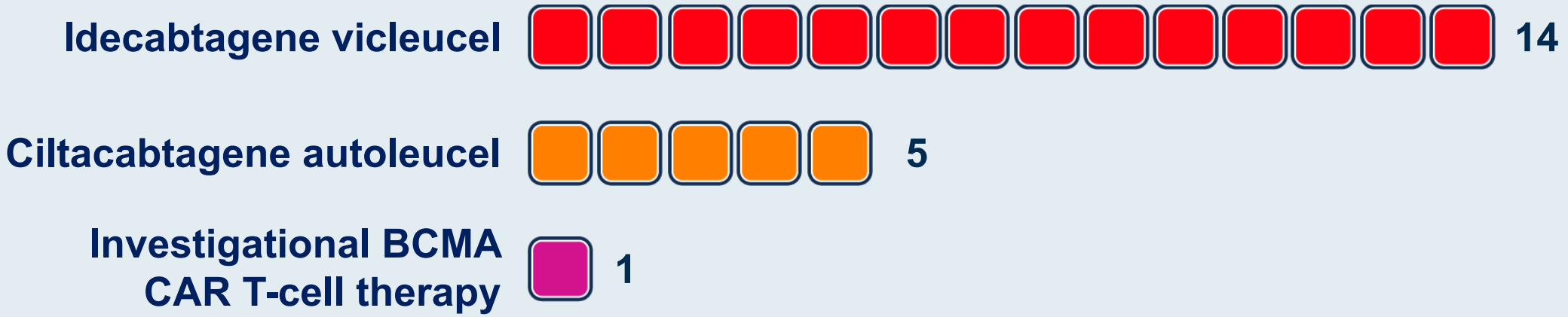
RTP RESEARCH TO PRACTICE

CAR T-cell platform the patient received:



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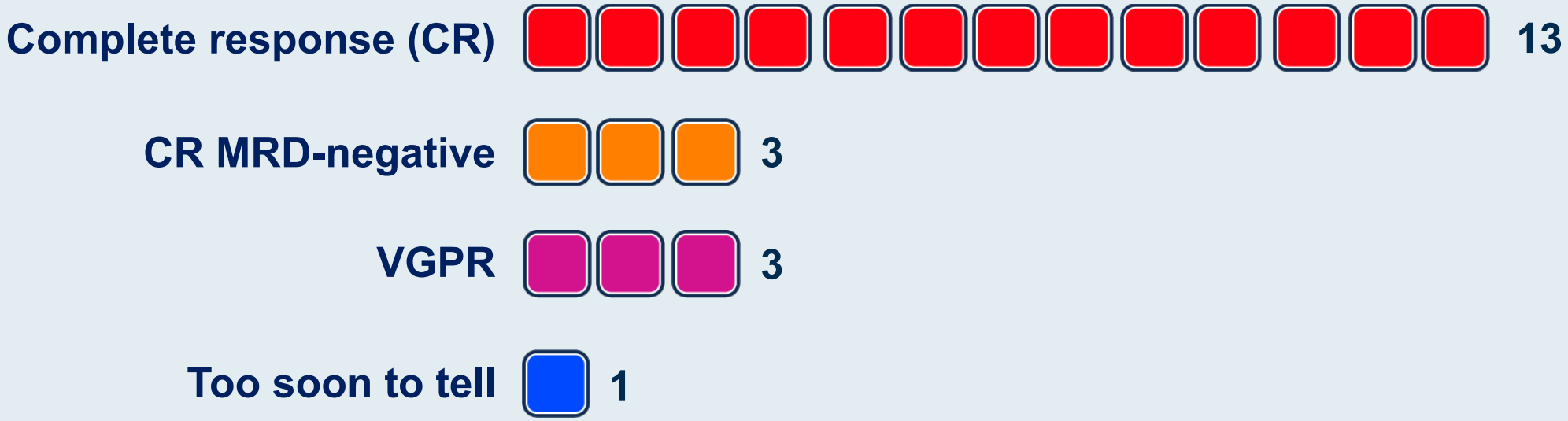
RTP RESEARCH TO PRACTICE

Please describe the oldest patient to whom you have administered or whom you have referred for CAR T-cell therapy.

Patient's response to therapy:



MRD = minimal residual disease; VGPR = very good partial response

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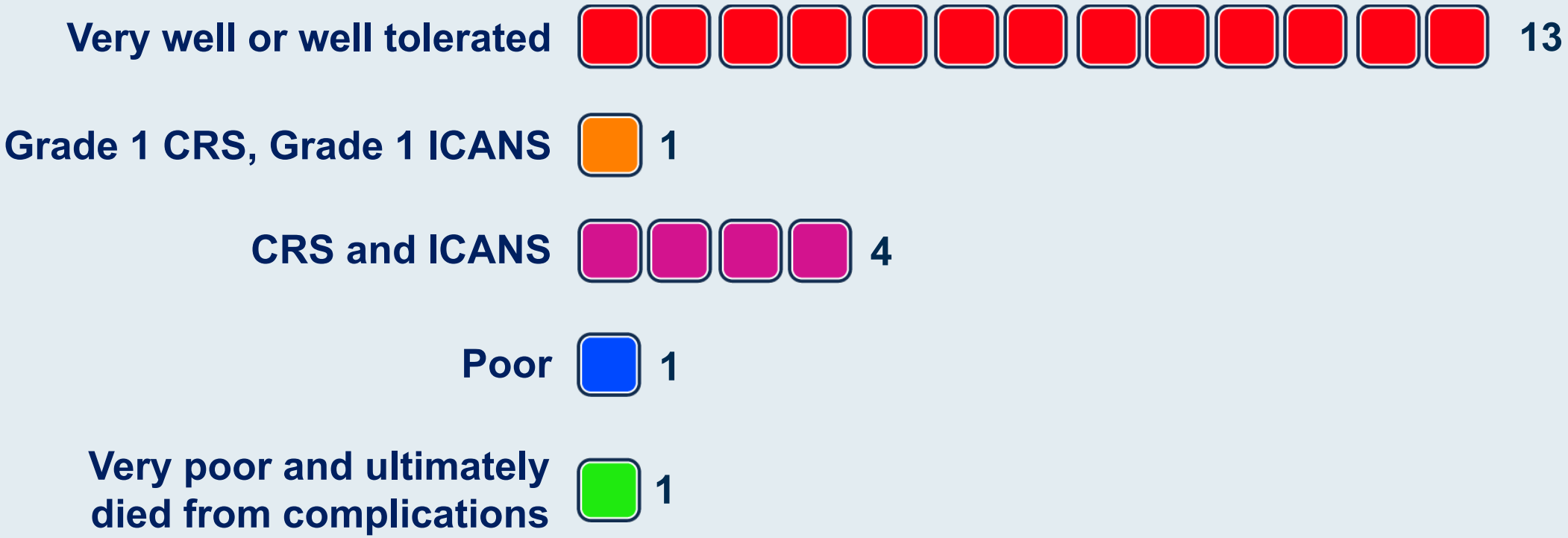
RTP RESEARCH TO PRACTICE

Please describe the oldest patient to whom you have administered or whom you have referred for CAR T-cell therapy.

Patient's tolerance of therapy:



CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome

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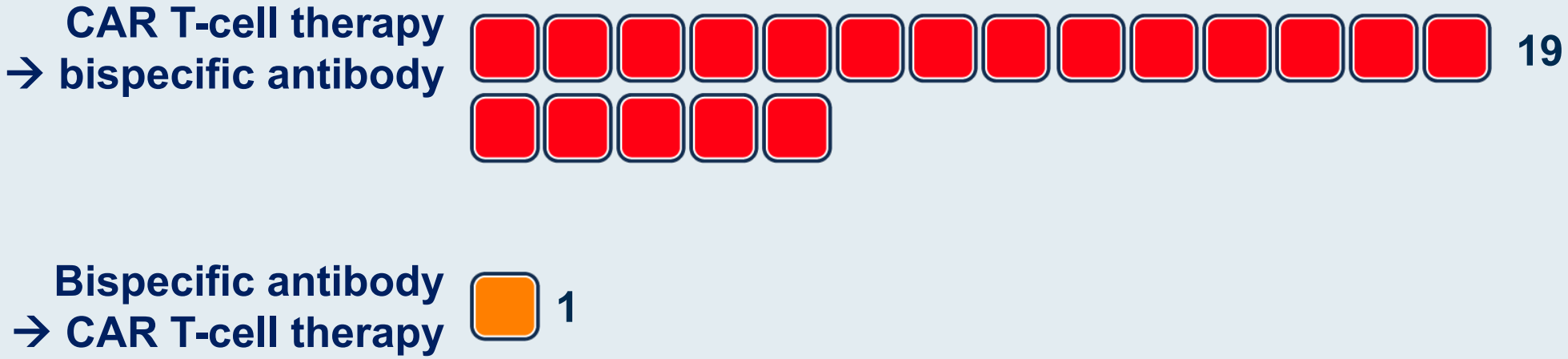
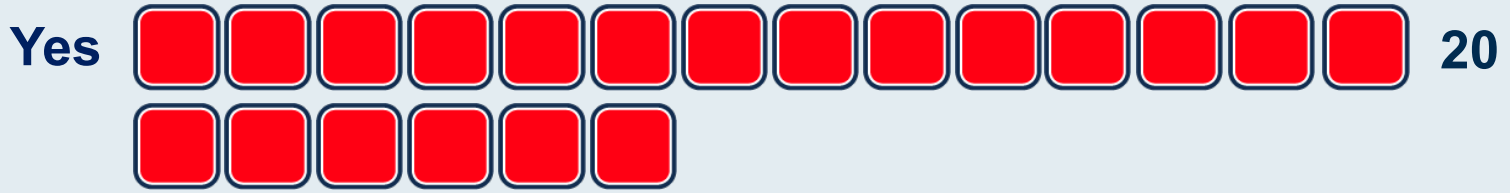
Regulatory and reimbursement issues aside, for a patient with R/R MM who is eligible to receive both, how would you generally sequence the following?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, does the administration of a BCMA-targeted bispecific antibody affect a subsequent response to BCMA-targeted CAR T-cell therapy?



Based on your personal clinical experience and knowledge of available data, does the administration of belantamab mafodotin affect a subsequent response to BCMA-targeted CAR T-cell therapy?

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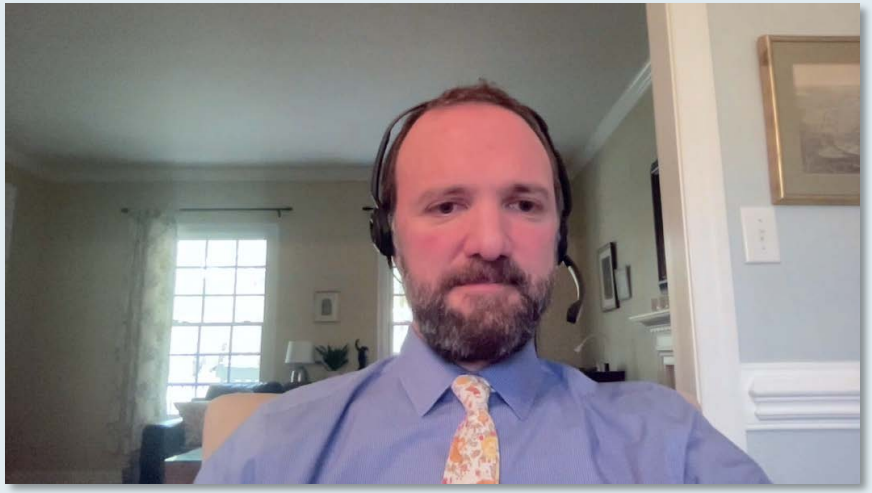
RTP RESEARCH TO PRACTICE

Similarities and differences between the BCMA CAR T-cell therapies idecabtagene vicleucel and ciltacabtagene autoleucel

C Ola Landgren, MD, PhD



Sascha A Tuchman, MD, MHS

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TO PRACTICE

Effectiveness of FDA-approved BCMA CAR T-cell therapies in clinical practice

Melissa Alsina, MD

RTP
RESEARCH
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Role of CAR T cells in Myeloma

Noopur Raje, MD
Center for Multiple Myeloma
MGH Cancer Center

Professor of Medicine
Harvard Medical School

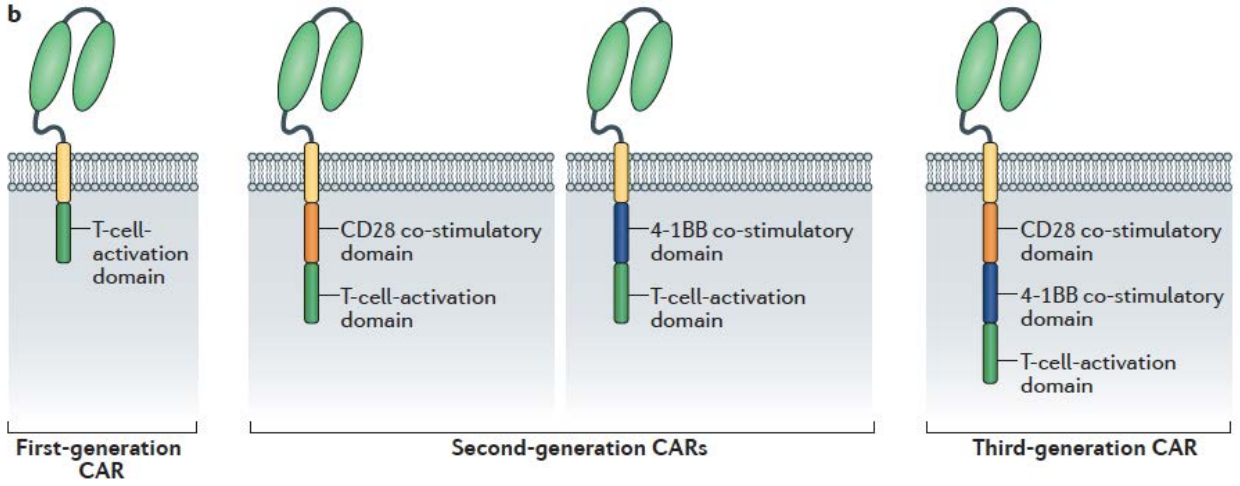
MASSACHUSETTS GENERAL HOSPITAL

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Chimeric antigen receptors (CAR) and CAR-T technology

- CARs are engineered transmembrane receptors with two distinct functional components:
  - Antibody fragment or target binding domain that recognizes targets on the surface of cancer cells
  - Signaling domains that rapidly and powerfully activate the T cell to attack and kill cancer cells

- CAR structure:
  - Extracellular domain: antibody domain (scFv) against a tumor antigen
  - Transmembrane domain
  - Intracellular domain:
    - First generation CARs: CD3ζ (T cell coreceptor necessary for T cell activation)
    - Second generation CARs: CD3ζ + either CD28 or 4-1BB (costimulatory domain)
    - Third generation CARs to come: CD3ζ + two costimulatory domains (CD28, 4-1BB, OX40, ICOS, CD27)

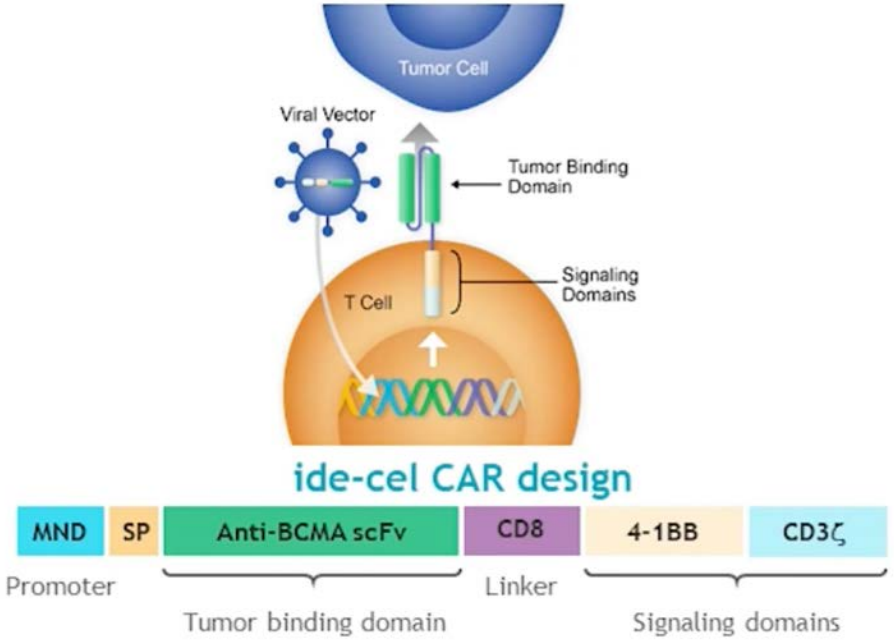


CAR, chimeric antigen receptor.

Maus and Levine The Oncologist 2016; Li and Zhao Protein Cell 2017; Chang and Chen Trends Mol Med 2017; Brudno JN & Kochenderfer N. Nat Rev Clin Onc 2018;15:31–46.

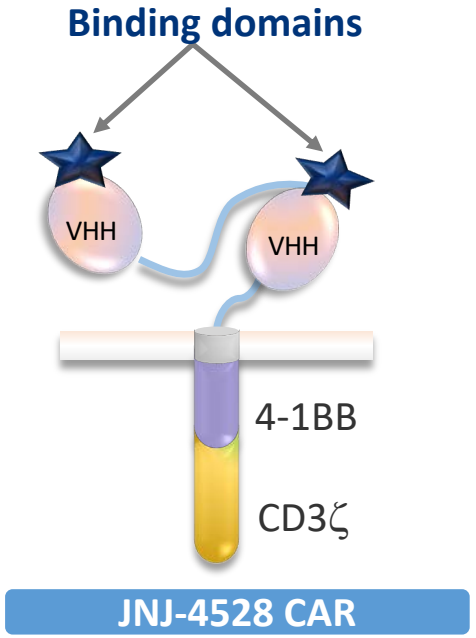
Idecabtagene-Vicleucel (ide-cel): Approved March 2021

- Autologous CAR T-cell
- Anti-BCMA scFv
- 4-1BB costimulatory domain
- CD3z intracellular signaling domain



Ciltacabtagene Autoleucel (cilta-cel): Approved Feb 2022

- Autologous CAR T-cell
- **Two BCMA-targeting sites (increased avidity)**
- 4-1BB signaling domain
- CD3z intracellular signaling domain

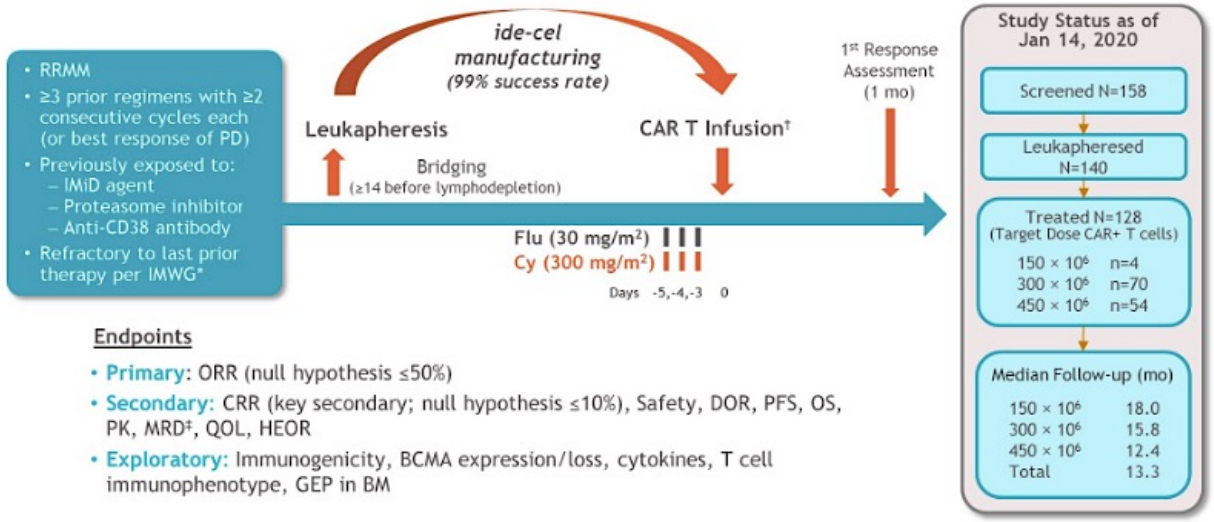


****FDA Label:**

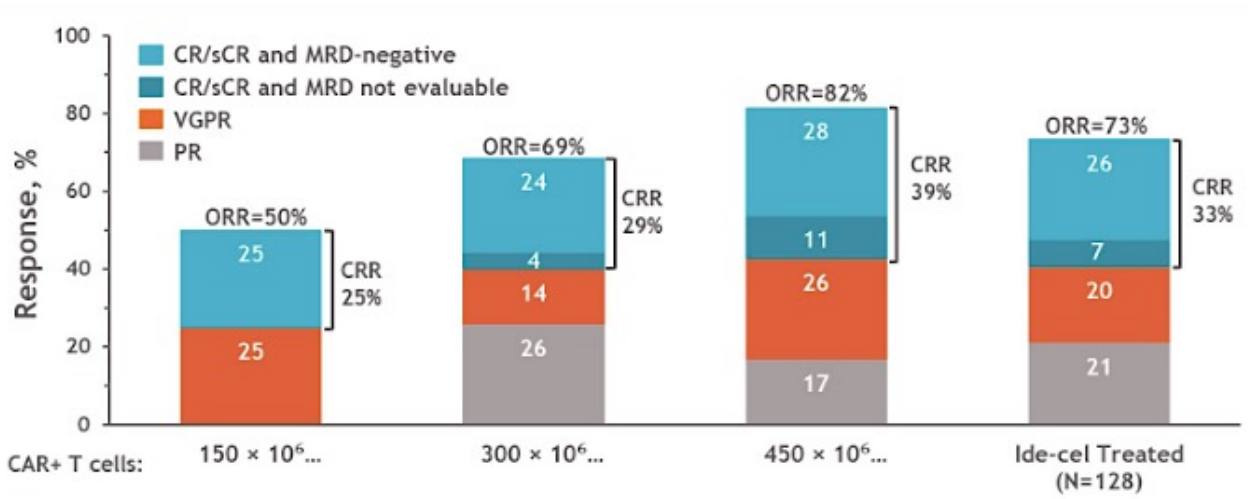
- **Four or More Prior Lines of Therapy**
- **Previously treated with IMID, PI and anti-CD38 monoclonal antibody**

KarMMa: Ide-cel Registration Study

Trial design



Response

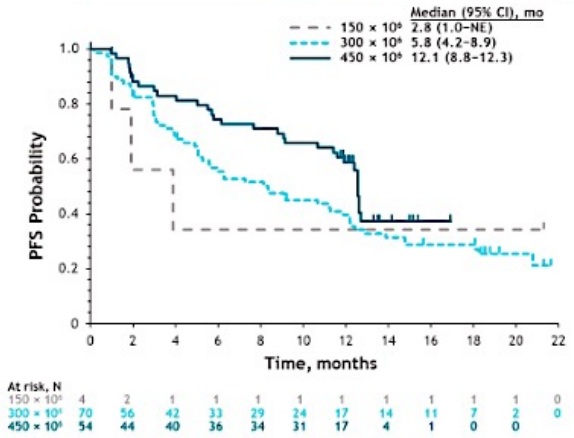


- Primary (ORR > 50%) and key secondary (CRR >10%) endpoints met in the Ide-cel treated population
  - *ORR of 73% (95% CI, 65.8-81.1; P<0.0001)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7-40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5-8.8); median time to CR of 2.8 mo (range, 1.0-11.8)
- Median follow-up of 13.3 mo across target dose levels

Munshi et al. N Engl J Med 2021;384:705-16.

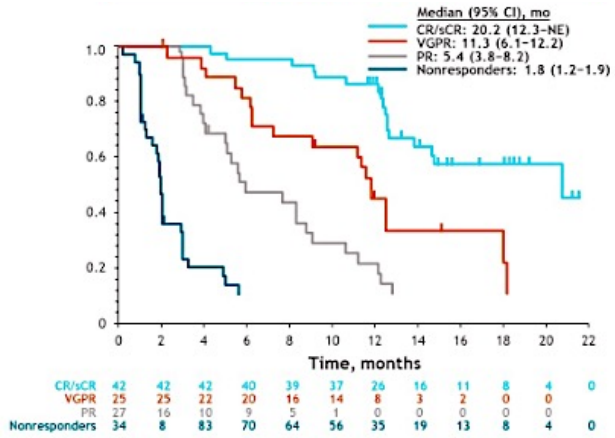
KarMMa: PFS and MRD-negativity

PFS by Target Dose



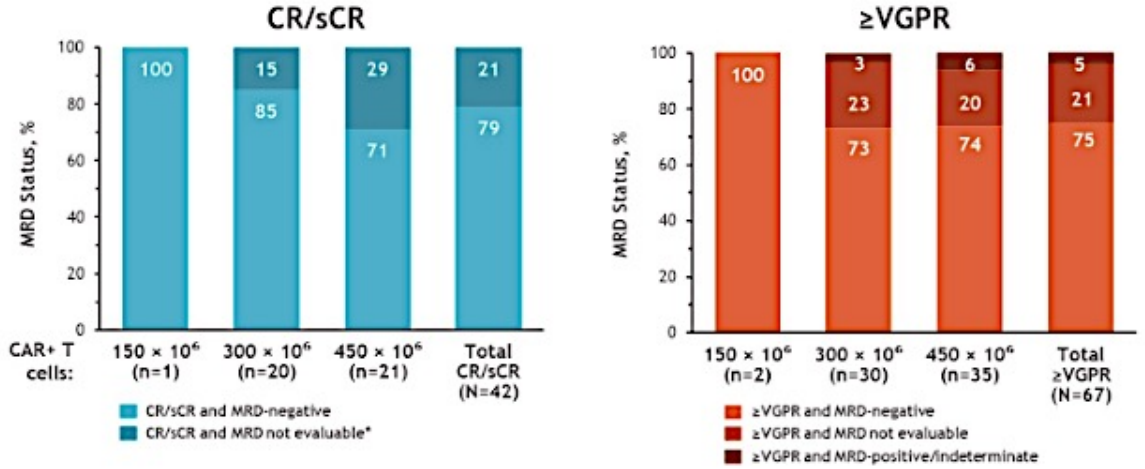
- PFS increased with higher target dose
- Median PFS was 12 mo at 450 x 10^6 CAR+ T cells

PFS by Best Response



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

MRD-negativity by target dose



- mOS 24.8 months (95% CI: 19.9-31.2) among all treated patients

Target Dose, CAR+ T cells	150 x 10^6	300 x 10^6	450 x 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]

CARTITUDE-1: Cilta-cel Registration Study

Trial design

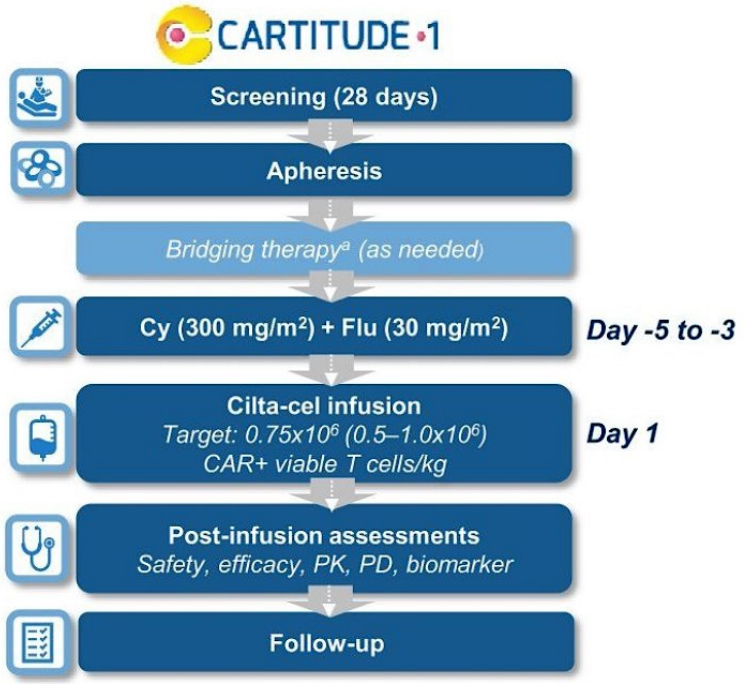
Primary objectives

- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel by ORR

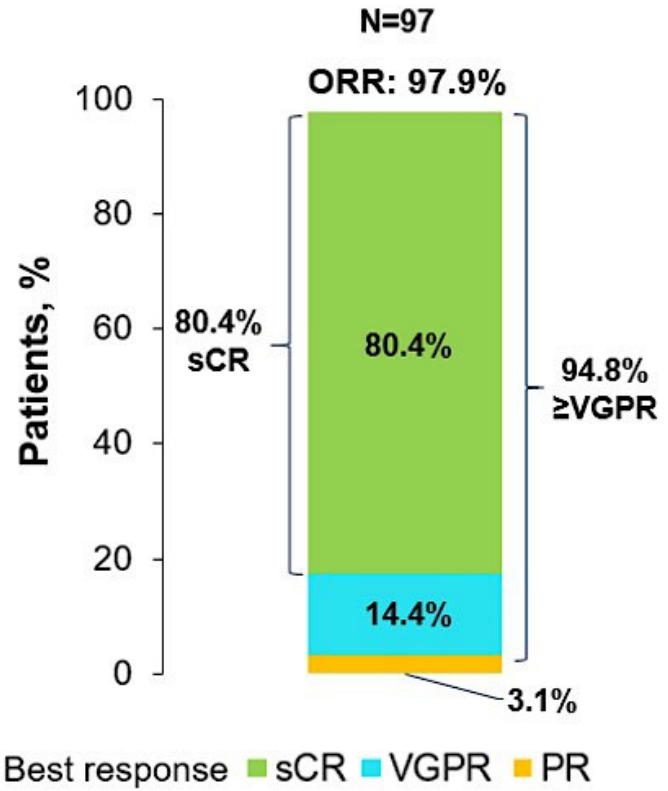
Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 therapy

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



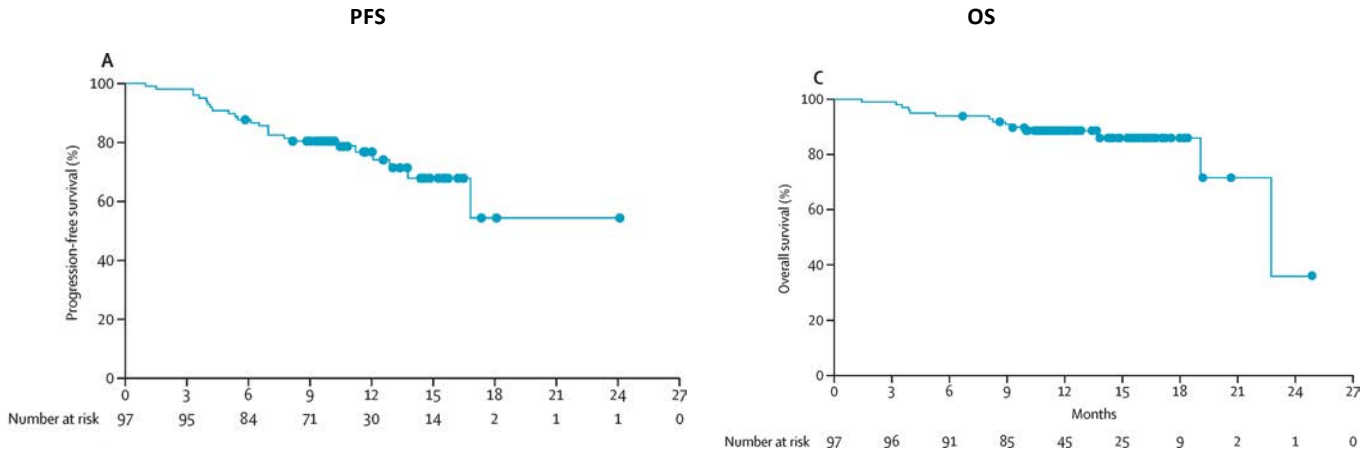
Response



Berdeja et al. Lancet 2021; 398: 314–24

CARTITUDE-1 Follow Up

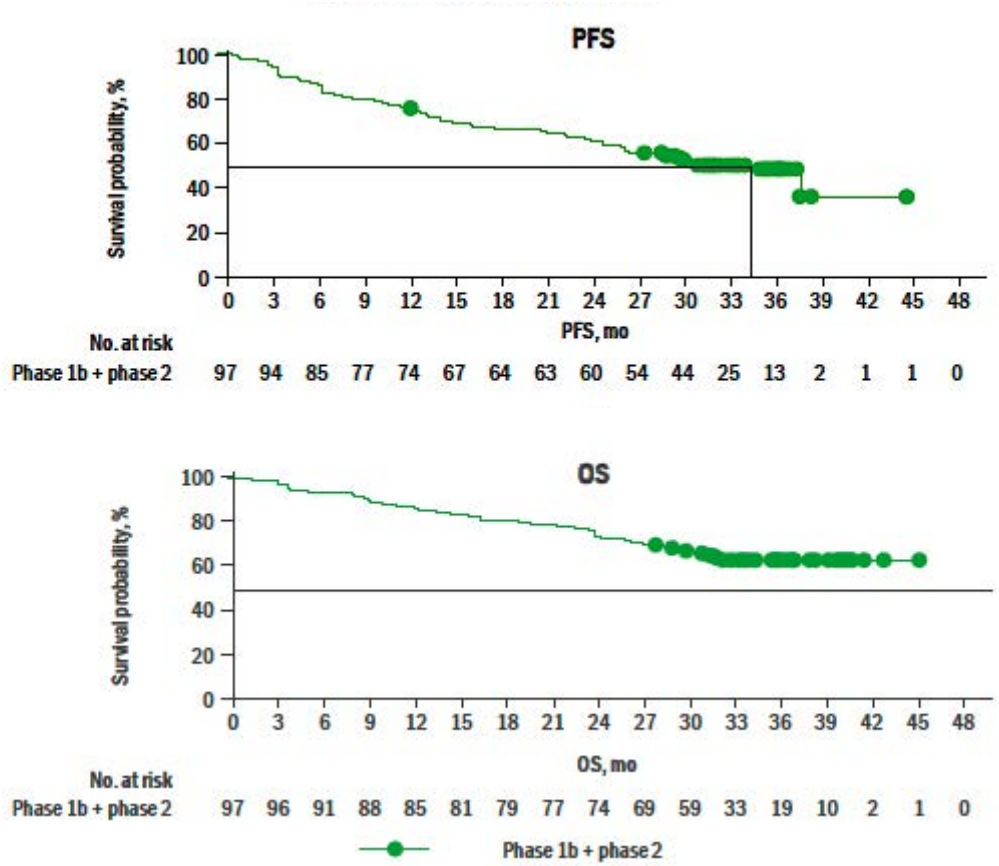
~27 months



PFS by CR and sustained MRD negativity

Subgroups	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All patients	34.9 (25.2–NE)	54.2%	47.5%
≥CR[a]	38.2 (34.9–NE)	66.8%	59.8%
12-mo sustained MRD negativity[b]	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative ≥CR[b]	NR (NE–NE)	78.5%	NE

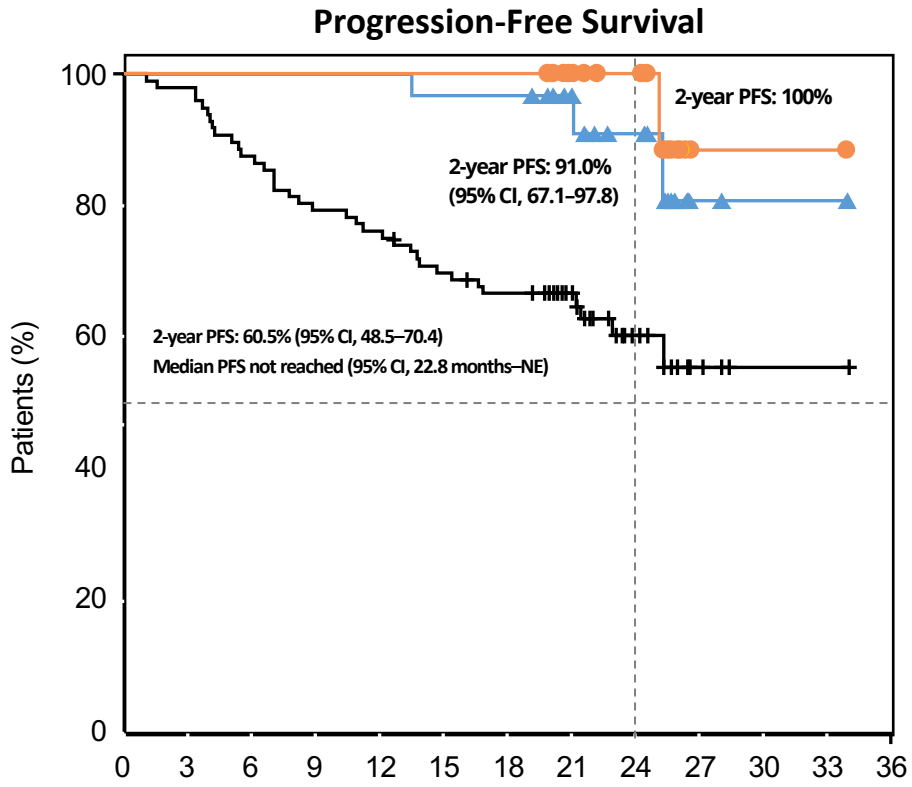
~3 years

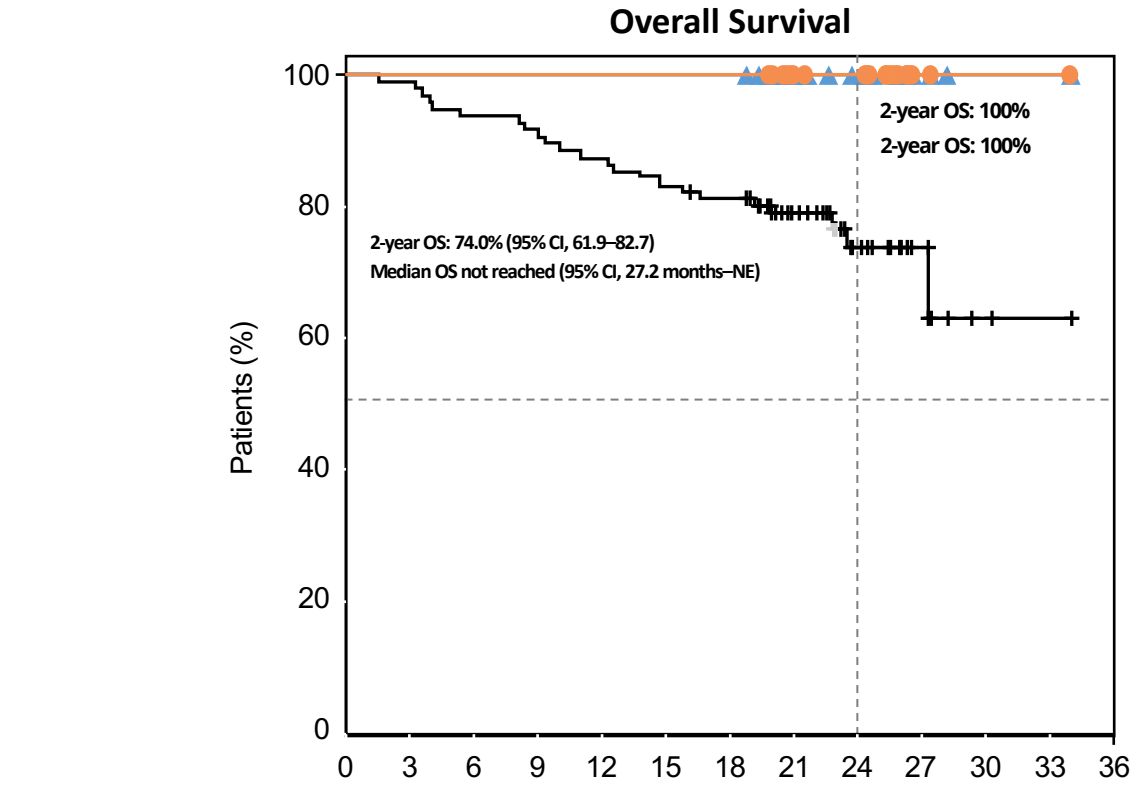


Berdeja et al. Lancet 2021; 398: 314–24

CARTITUDE-1: Progression-Free Survival and Overall Survival by MRD Negativity (10^{-5}) sustained for ≥ 6 and 12 months

- Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})





All patients | MRD negativity sustained ≥6 months | MRD negativity sustained ≥12 months

Usmani SZ et al. SOHO 2022; Abstract MM-181.

KarMMa and CARTITUDE-1 CRS and NT

	Ide-cel	Cilta-cel
FDA approval Trial, Reference Publication	KarMMa (n=124) Munshi NEJM 2021	CARTITUDE-1 (n=97) Berdeja Lancet 2021
Safety		
CRS (all; grades 3–4)	84% (5%)	95% (5%)
Median onset of CRS	1 day	7 days
ICANS (all; grades 3–4)	18% (3%)	17% (2%)
Delayed neurotoxicity (all; grades 3-4)	None	12% (9%)
Infections (all; grades 3–4)	69% (22%)	58% (20%)
Grades 3–4 neutropenia > 1 month Grades 3–4 thrombocytopenia > 1 month	41% 48%	10% 25%

Berdeja et al. Lancet 2021; 398: 314–24
Munshi et al. N Engl J Med 2021;384:705-16.

CARTITUDE-1: Safety

- **No new treatment-related deaths**
- **A total of 20 SPMs were reported in 16 patients**
  - Nine patients with hematologic malignancies (1 low-grade B-cell lymphoma, 6 MDS, 3 fatal AML[one patient had both MDS and fatal AML])
  - One patient each with malignant melanoma, adenocarcinoma, myxofibrosarcoma, and prostate cancer
  - Six non-melanoma skin cancers
- **One new case of signs and symptoms of parkinsonism (previously termed movement and neurocognitive TEAEs) (total n=6)**
  - On day 914, patient experienced cognitive slowing, gait instability, and neuropathy (all grade 1), and tremor (grade 3); he is currently stable and functioning, and remains in sCR with no steroids or anticytokine therapies given
  - Work-up is ongoing, including a differential diagnosis as post-encephalitis syndrome
  - Had 2 risk factors for parkinsonism (grade 2 CRS and grade 3 ICANS) after cilta-cel[5,6]
- **Outcomes in the previously reported 5 patients with parkinsonism[1,2]**
  - 3 have died (two from other underlying causes [sepsis and lung abscess] and one related to parkinsonism)
  - One patient has recovered, and one is recovering (ongoing grade 2 symptoms) at the time of the data cut
- **Following implementation of patient management strategies, the incidence of parkinsonism has decreased from 6% in CARTITUDE-1 to <0.5% across the CARTITUDE program**

Deaths

	Total (N=97)	Time of death post cilta-cel infusion (days)
Total deaths during the study	30	45–917
Due to progressive disease	14	253–746
AEs unrelated to treatment (n=9)		
Pneumonia	1	109
Acute myeloid leukemia[a]	3	418, 582, 718
Ascites[b]	1	445
Myelodysplastic syndrome	1	803
Respiratory failure	3	733, 793, 829
Septic shock	1	917
AEs related to treatment (n=6)		
Sepsis and/or septic shock	2	45, 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

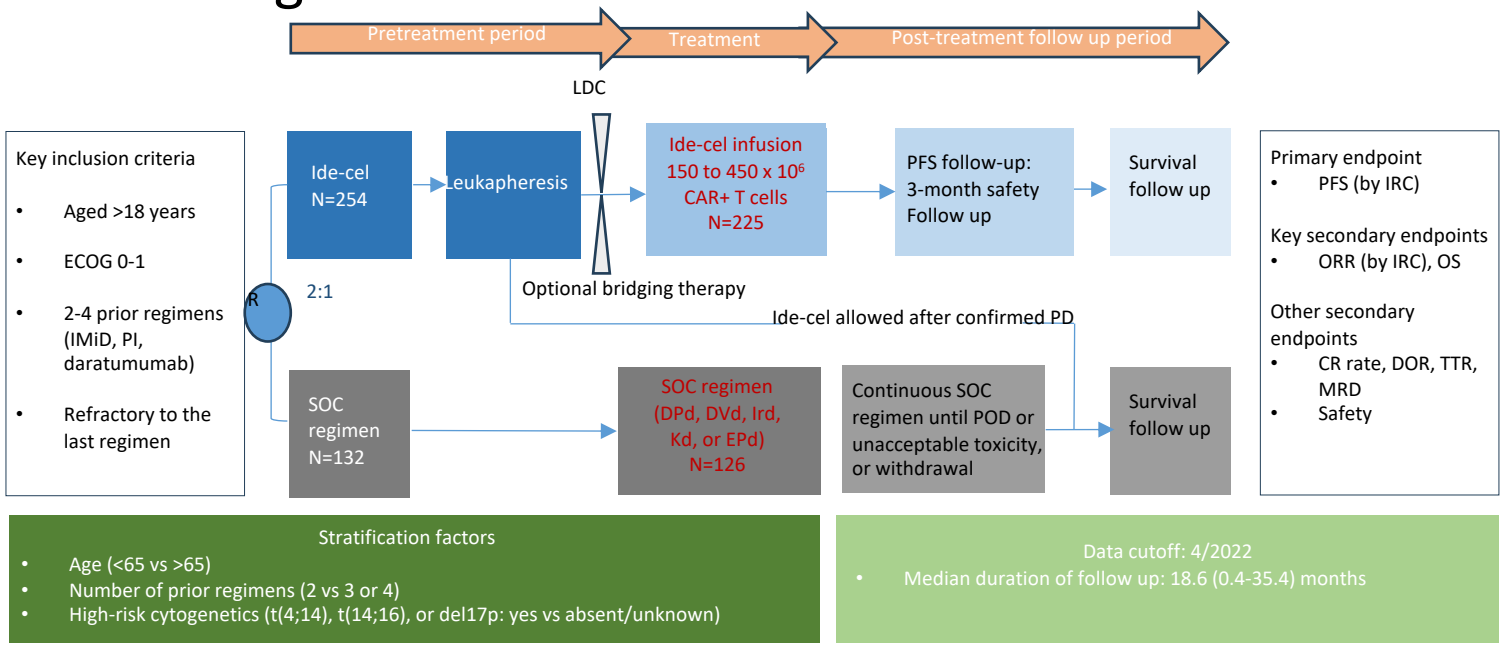
[a]One patient with AML also had MDS and a cytogenetic profile consistent with MDS (del20q [present before cilta-cel infusion], loss of 5q); another patient who died from AML had both prostate cancer and squamous cell carcinoma of the scalp. [b]Patient died from ascites unrelated to cilta-cel as assessed by the investigator due to noncirrhotic portal fibrosis and nonalcoholic steatosis that was present for many years preceding the study.
AML, acute myelogenous leukemia; AEs, adverse events; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; MDS, myelodysplastic syndrome; sCR, stringent complete response; SPM, secondary primary malignancies; TEAE, treatment-emergent AE

1. Berdeja JG, et al. *Lancet* 2021; 398:314-24. 2. Cohen AD, et al. *Blood Cancer J* 2022; 12:32.

CAR T-cell therapy in earlier lines

KarMMa-3: Ide-cel vs SOC After 2-4 Lines

Trial design



Baseline characteristics

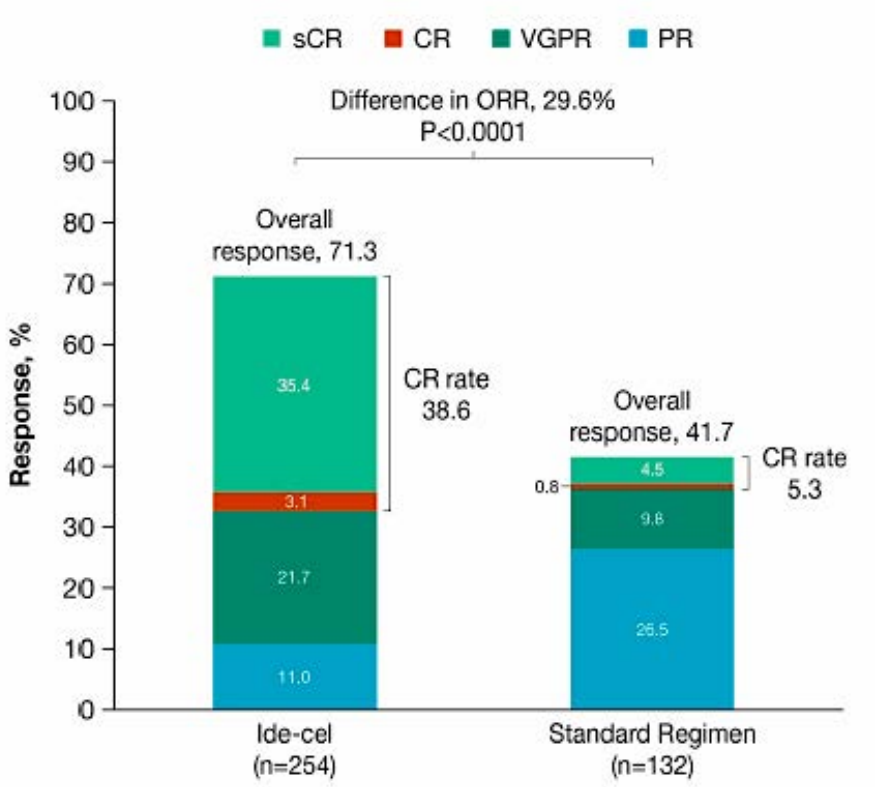
Median age	63 yrs
Median time since diagnosis	4.1 yrs
Median prior therapies	N=3
Triple-class refractoriness	66%
Daratumumab refractoriness	95%
High-risk cytogenetics	44%

Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

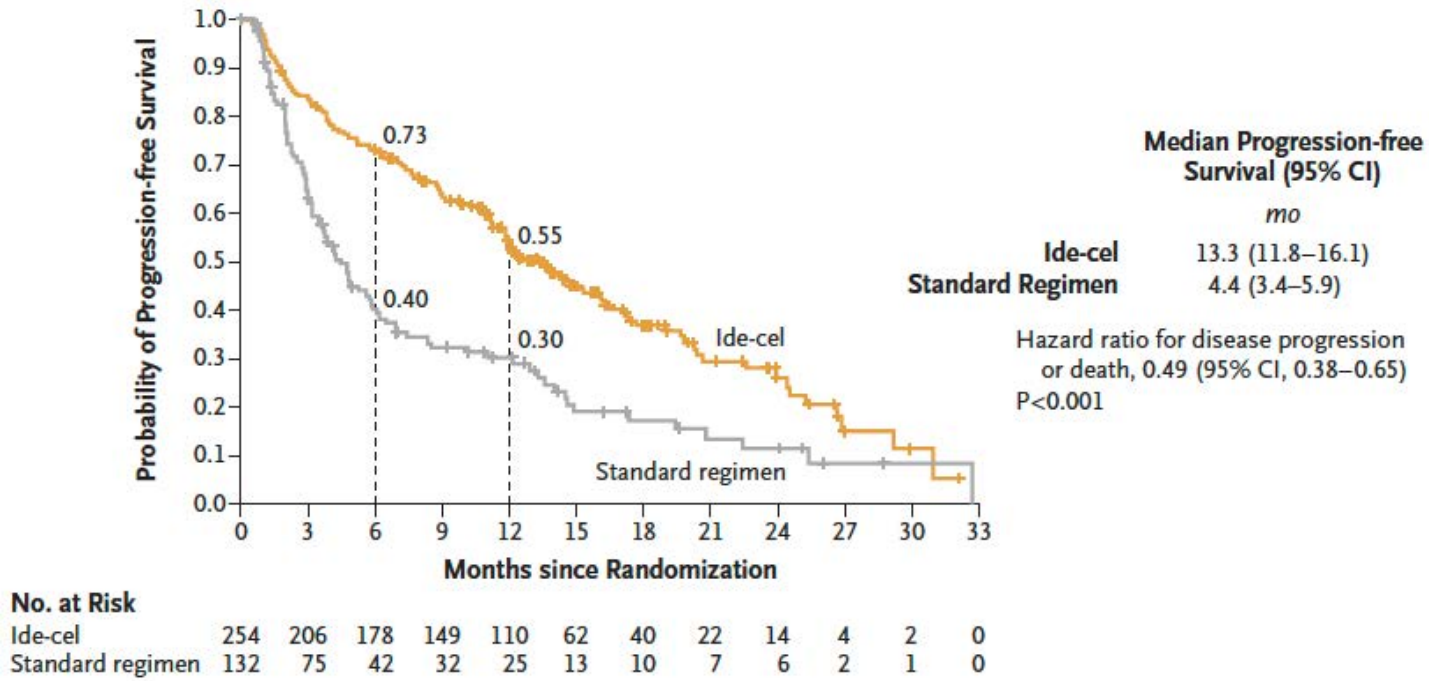
Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

KarMMa-3: Response and PFS

Response



PFS

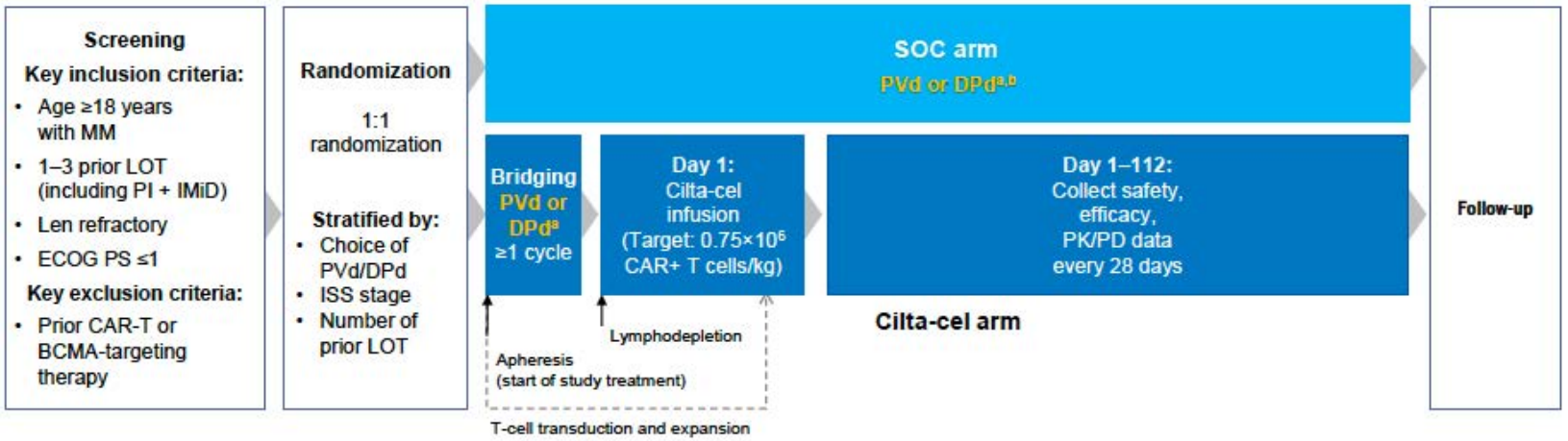


Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

CARTITUDE-4: Cilta-cel vs DPd/PVd After 1-3 Lines

Trial design



Primary endpoint
- PFS[c]

Secondary endpoints
- Efficacy: ≥CR, ORR, MRD negativity, OS
- Safety
- PROs

Baseline characteristics

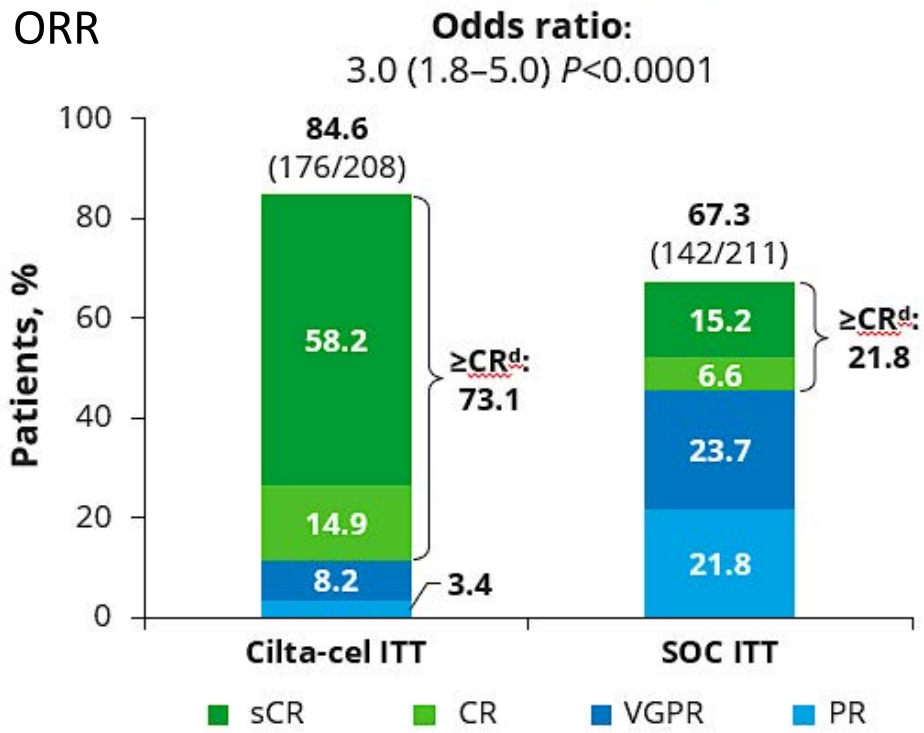
Median age	61.5 yrs
Median time since diagnosis	3 yrs
Median prior therapies	N=2
Triple-class refractoriness	14.4%
Daratumumab refractoriness	23.1%
High-risk cytogenetics	59.4%

Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

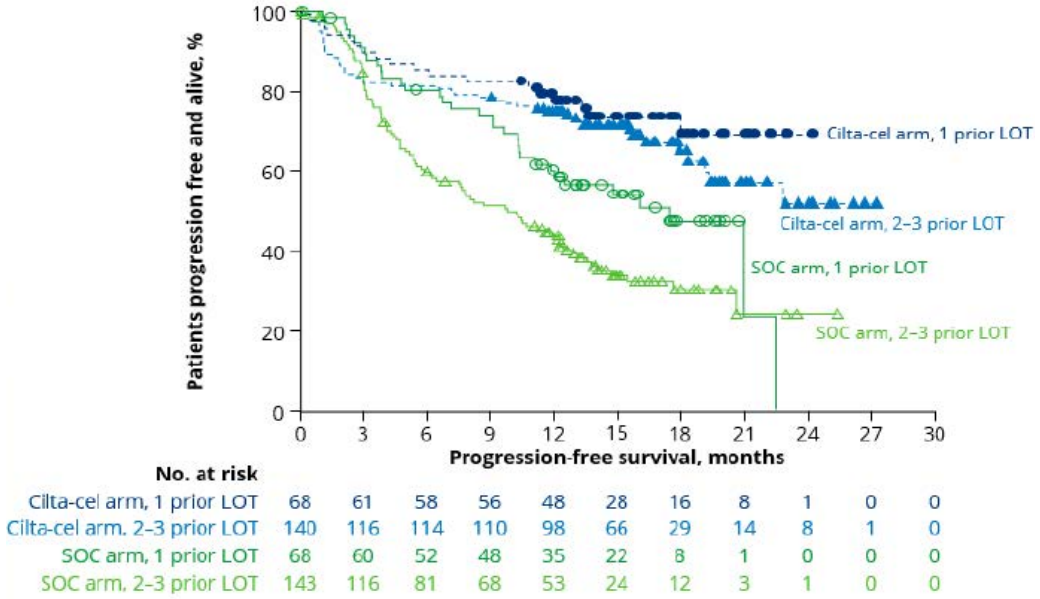
Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

CARTITUDE-4: Response and PFS

ORR



PFS by treatment and number of prior lines



No. at risk

Cilta-cel arm, 1 prior LOT	68	61	58	56	48	28	16	8	1	0	0
Cilta-cel arm, 2–3 prior LOT	140	116	114	110	98	66	29	14	8	1	0
SOC arm, 1 prior LOT	68	60	52	48	35	22	8	1	0	0	0
SOC arm, 2–3 prior LOT	143	116	81	68	53	24	12	3	1	0	0

Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

KarMMa-3 / CARTITUDE-4: CRS and NT

KarMMa-3

	Ide-cel (n = 225)
CRS,[a] n (%)	
Any grade	197 (88)
Grade 3/4	9 (4)
Grade 5	2 (1)
Median (range) time to first onset, days[b]	1.0 (1.0–14.0)
Median (range) duration, days	3.5 (1.0–51.0)
iiNT,[c] n (%)	
Any grade	34 (15)
Grade 3/4	7 (3)
Grade 5	0
Median (range) time to first onset, days[b]	3.0 (1.0–317.0)
Median (range) duration, days	2.0 (1.0–37.0)

CARTITUDE-4

AEs, n (%)	As-treated patients (n=176)				
	Any grade	Grade 3/4	Median time to onset, days	Median duration, days	Resolved, n
CRS	134 (76.1)	2 (1.1)	8	3	134
Neurotoxicity[a]	36 (20.5)	5 (2.8)			
ICANS	8 (4.5)	0[b]	10	2	8
Other[c]	30 (17.0)	4 (2.3)			
Cranial nerve palsy[d]	16 (9.1)	2 (1.1)	21	77	14
Peripheral neuropathy	5 (2.8)	1 (0.6)	63	201	3
MNT	1 (0.6)	0	85	–	0

Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014
Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

KarMMa-2 cohort 2 study design

Cohort 2 (N=99)
Clinical high-risk MM (1 regimen)

Cohort 2a (n = 37)

- **Early relapse: PD < 18m from initiation of frontline therapy containing induction, ASCT (single or tandem) and LEN-containing maintenance**
- **≥ 18 years of age**
- **Measurable disease**
- **One prior anti-myeloma treatment regimen[b]**
- **ECOG status score ≤ 1**

Cohort 2b (n = 31)
Early relapse (PD < 18m from frontline therapy without ASCT)

Cohort 2c (n = 31)
Inadequate response (< VGPR) post-ASCT

Primary endpoint

Cohort 2a: CRR (CR and sCR; by investigator per IMWG criteria)

Secondary endpoints

Cohort 2a: ORR, TTR, DOR, PFS, TTP, OS, safety, PK, immunogenicity (anti-CAR antibody response), HRQoL

Exploratory endpoints

Cohort 2a: MRD, biomarkers (serum level of soluble BCMA)

- Efficacy and safety were analyzed in all patients who received ide-cel

ClinicalTrials.gov Identifier: NCT03651128

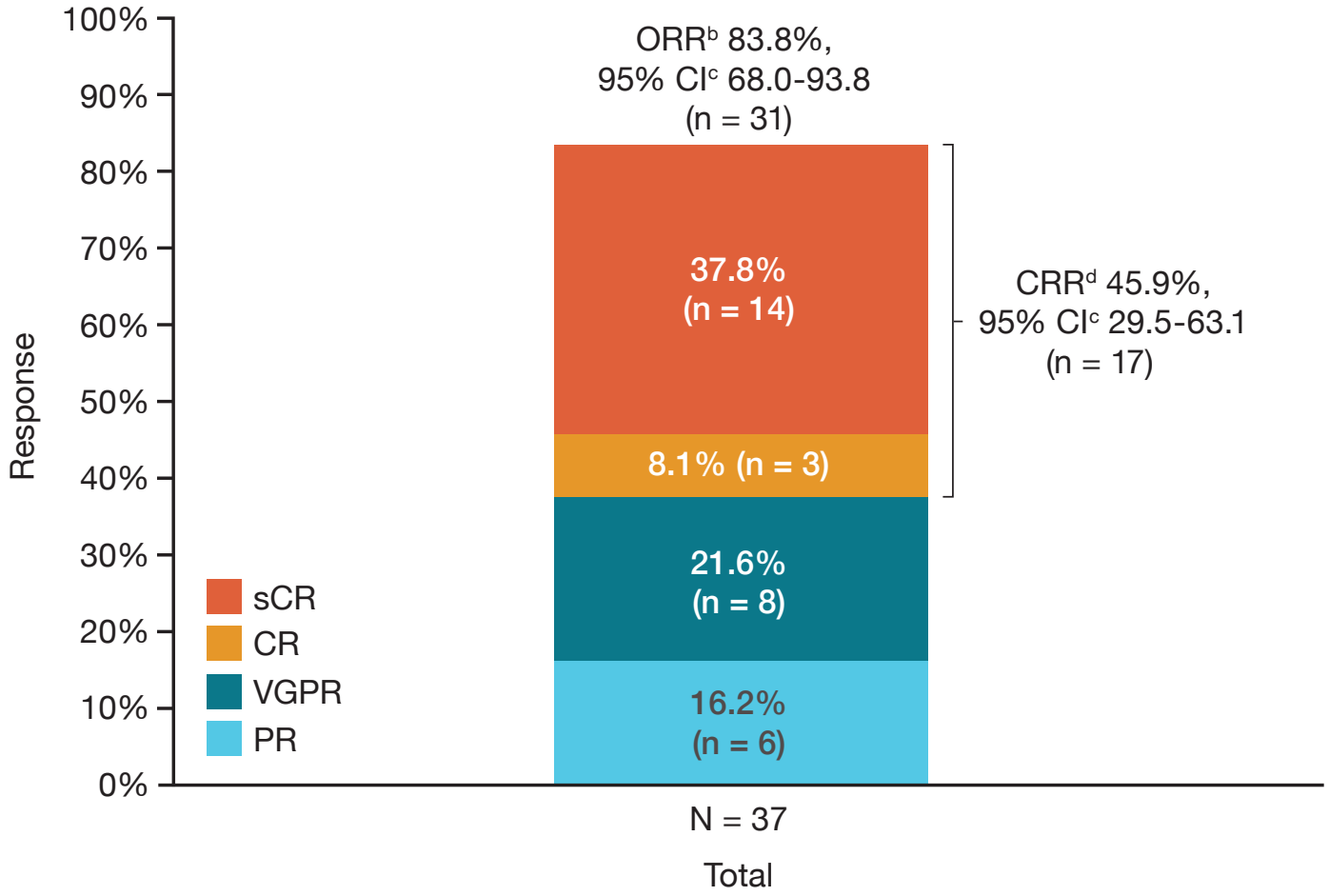
CR, complete response; CRR, complete response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; LEN, lenalidomide; MRD, minimal residual disease; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; sBCMA, soluble BCMA; sCR, stringent complete response; TTP, time to progression; TTR, time to response; VGPR, very good partial response.

[a]After lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 × 3), patients received a single infusion of ide-cel at a range of 150-450 × 10^6 CAR+ T cells (up to an additional 20%; ≥ 20% considered over the protocol-specified doses). [b]Induction with or without HSCT and with or without maintenance therapy is considered a single regimen

Usmani S, et al. ASH 2022 [Abstract 361]

Best overall response

- Primary endpoint was met, with 45.9% achieving ≥ CR ($P < 0.0001$)
- ORR was 83.8% (95% CI 68.0–93.8)
- Median time to first response[a] was 1.0 month (range 0.9–2.9 months)

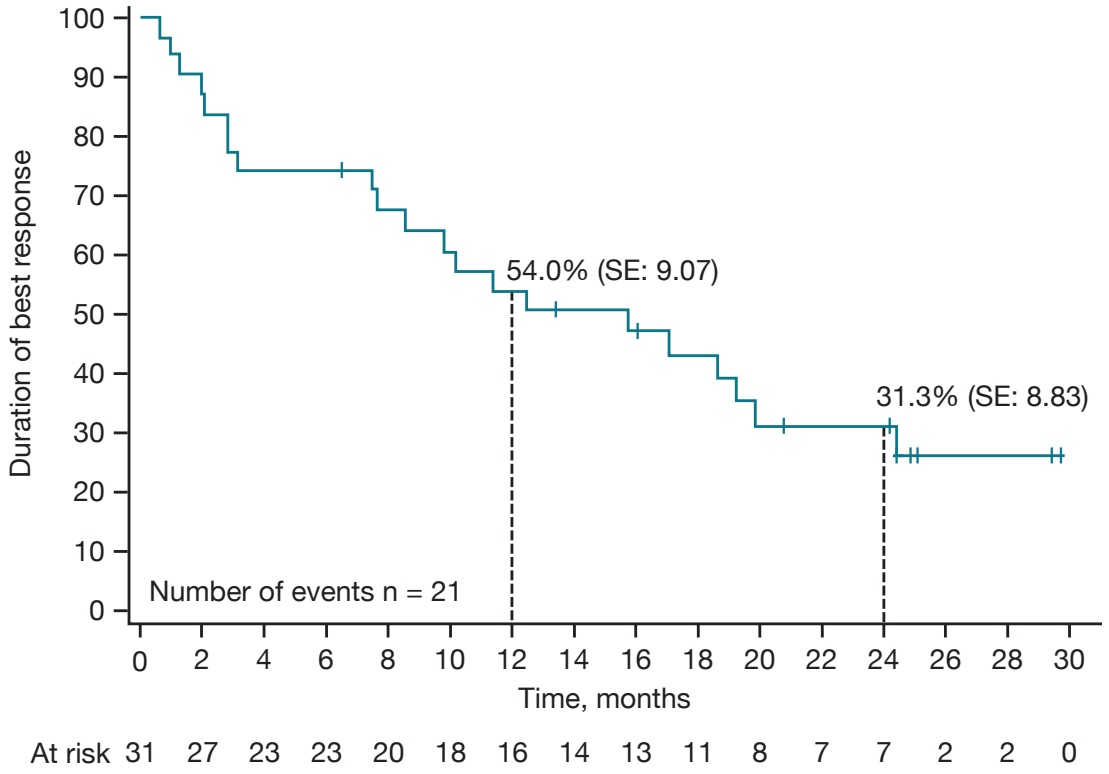


The primary efficacy endpoint was the complete response (CR) rate (proportion of patients who achieved CR or sCR); the primary analysis was planned for at least 6 months after the last patient received ide-cel infusion.
[a]Response defined as PR or better based on IMWG Criteria by investigator assessment; measured from infusion. [b]Patients with PR or better (2 patients had minimal response; 4 had stable disease and 0 had PD). [c]Clopper-Pearson CI. [d]Patients with sCR or CR.

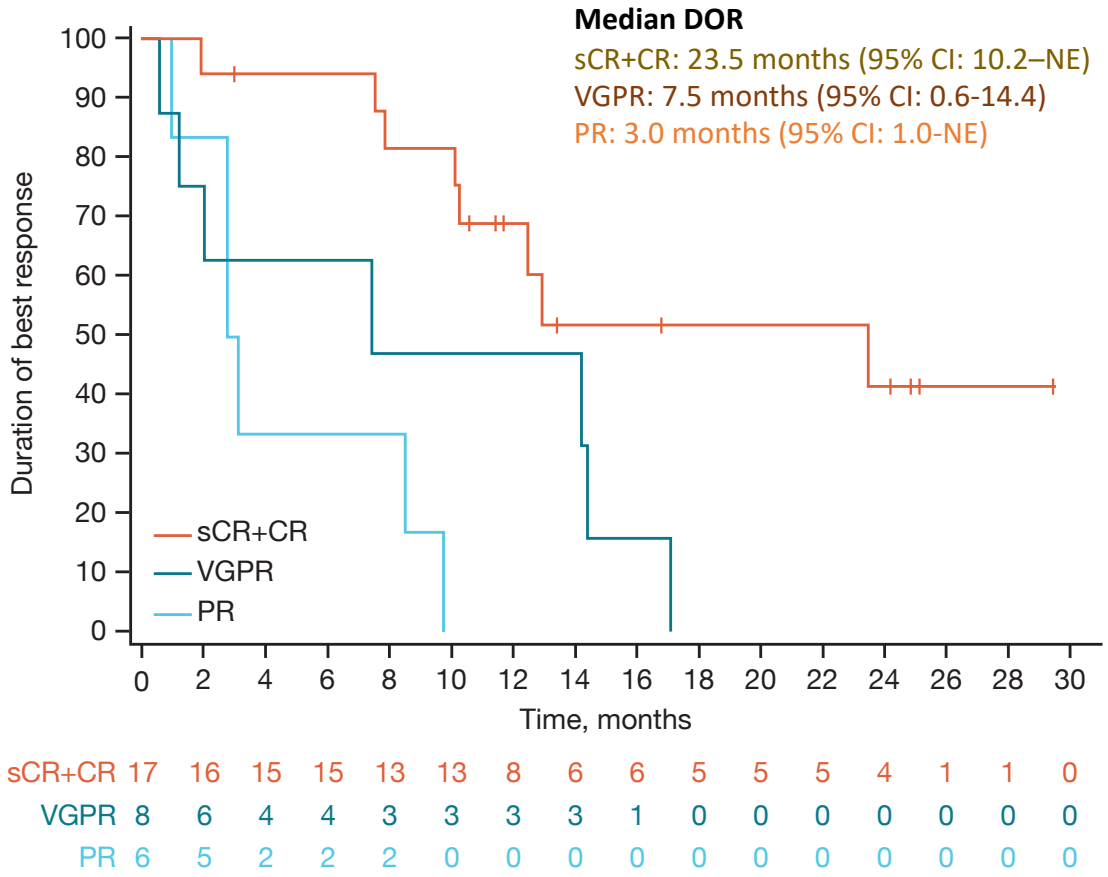
Usmani S, et al. ASH 2022 [Abstract 361]

Duration of best response[a]

- Median duration of best response in all patients who responded was 15.7 months (95% CI: 7.6–19.8)



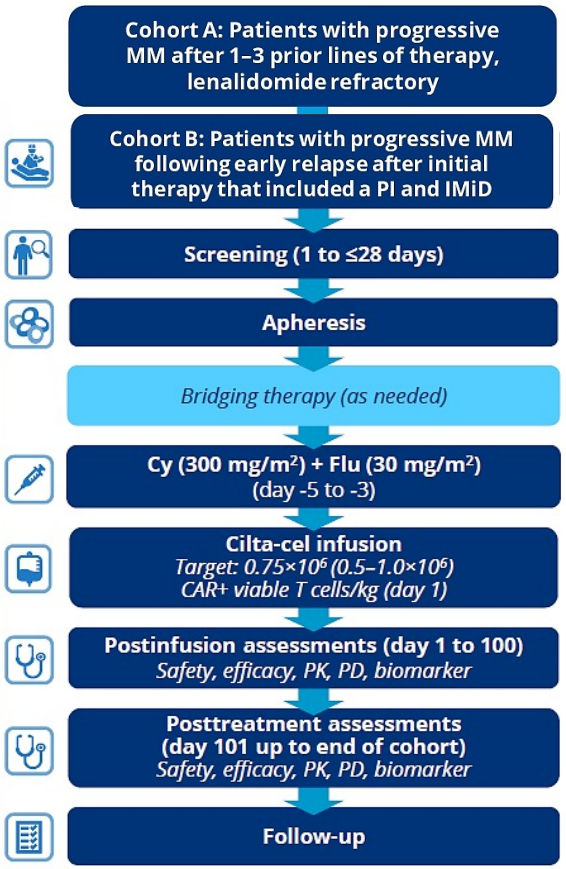
- Median duration of best response in patients who achieved ≥ CR was 23.5 months (95% CI: 10.2–NE)

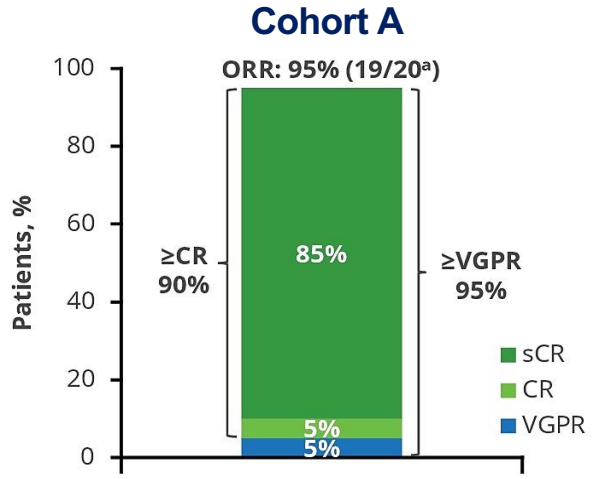


NE, not evaluable; SE, standard deviation.
[a]Responders only, based on IMWG criteria: investigator assessment

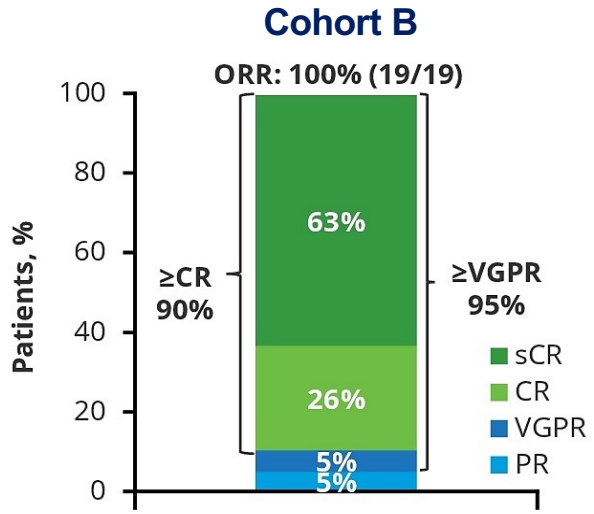
Usmani S, et al. ASH 2022 [Abstract 361]

Using CAR T-cell therapy at earlier lines of therapy: CARTITUDE-2





[a]One patient demonstrated a minimal response.
sCR, stringent CR



AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (95)	19 (95)
Thrombocytopenia	16 (80)	7 (35)
Anemia	15 (75)	9 (45)
Lymphopenia	14 (70)	14 (70)
Leukopenia	11 (55)	11 (55)
CAR-T–related AEs		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15)[a]	1 (5)

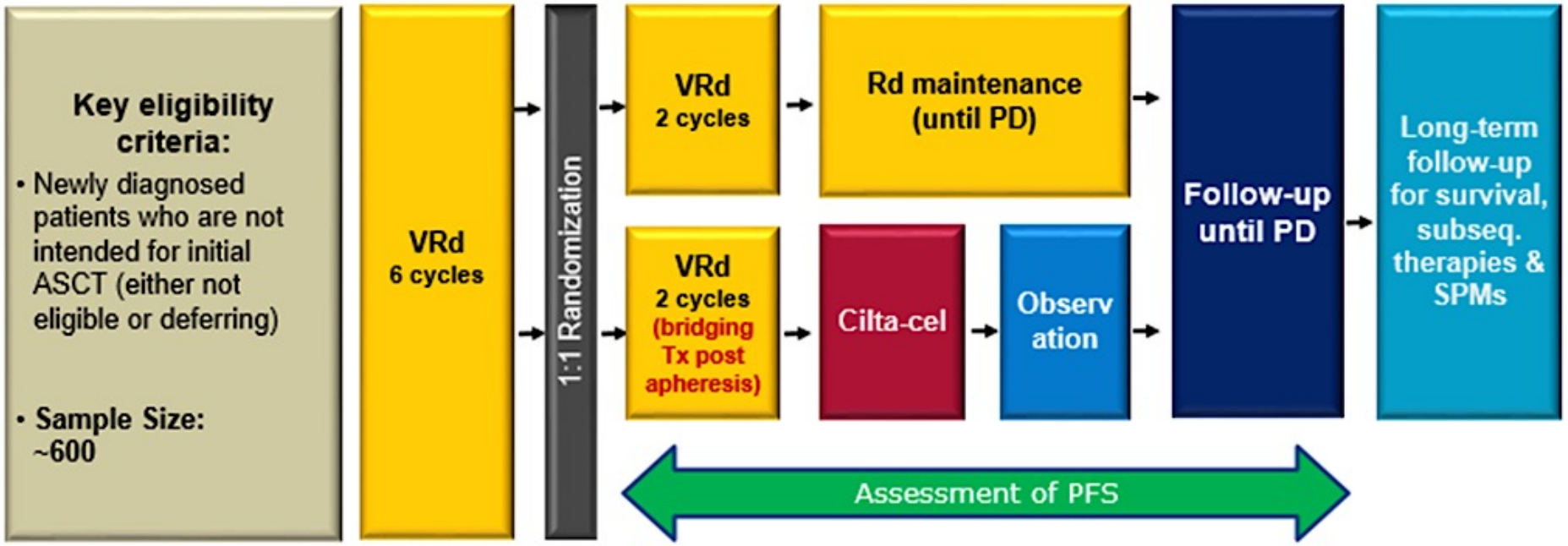
[a]One patient had peripheral sensorimotor neuropathy, one had anosmia and dysgeusia, and one had facial paralysis.

AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	18 (95)	17 (90)
Anemia	11 (58)	9 (47)
Thrombocytopenia	11 (58)	5 (26)
Lymphopenia	6 (32)	6 (32)
Leukopenia	5 (26)	5 (26)
CAR-T–related AEs		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
Parkinsonism	1 (5)	1 (5)

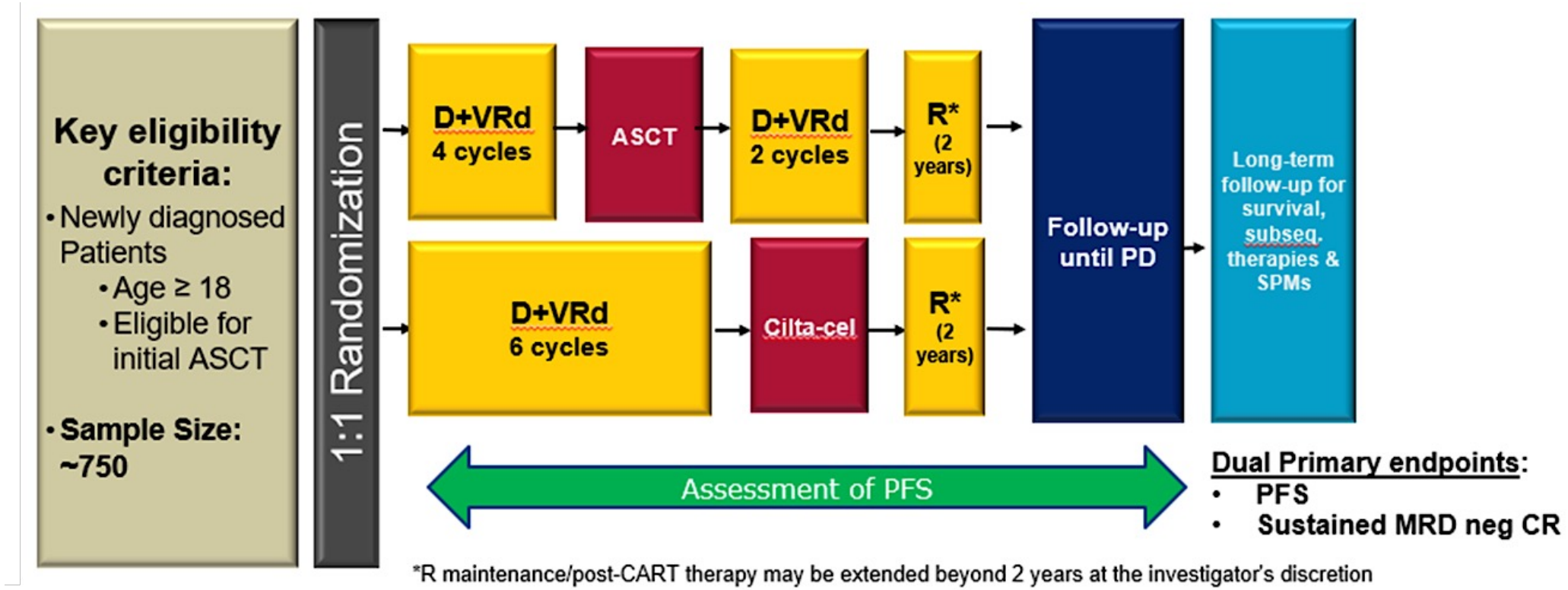
CR, complete response; CRS, cytokine release syndrome; Cy, cytarabine; Flu, fludarabine; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; sCR, stringent CR; VGPR, very good partial response

Hillengass J et al. EHA 2022;abstract P959 (poster presentation)
Agha M et al. EHA 2022;abstract S185 (oral presentation)

CARTITUDE-5: Randomized, phase 3 in NDMM, not intended for transplant



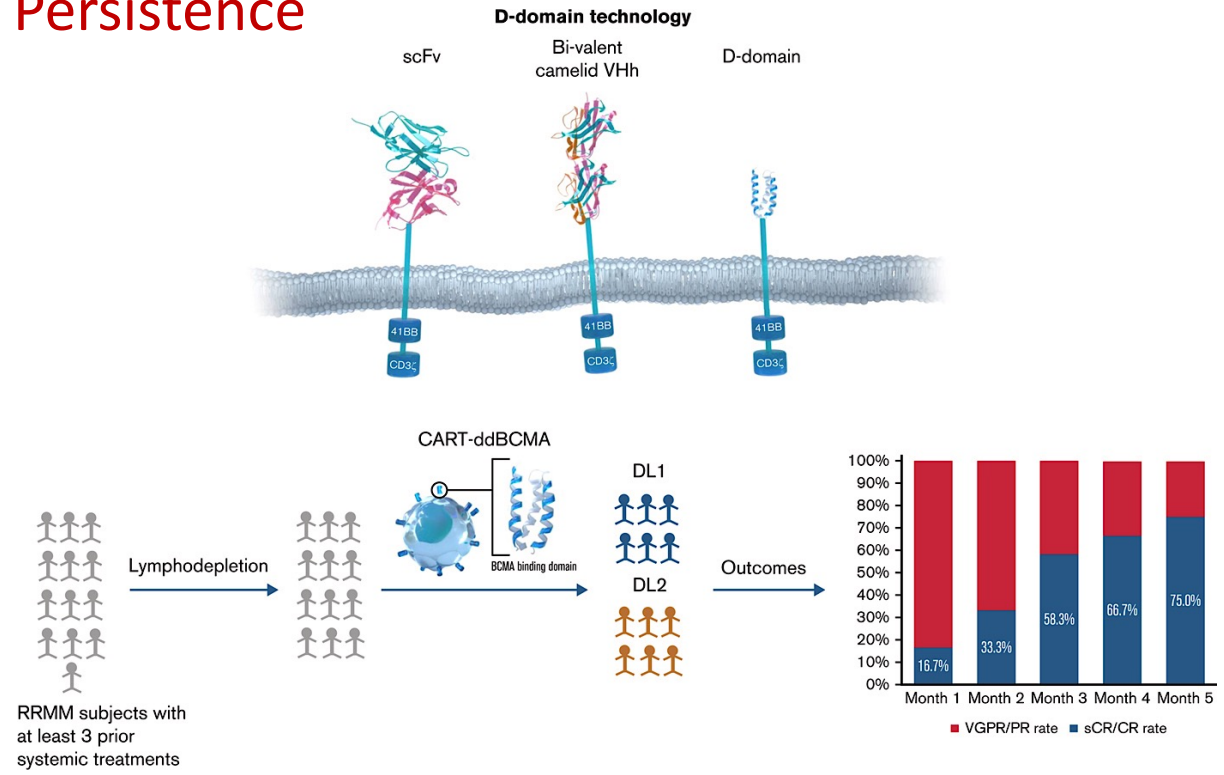
CARTITUDE-6: Randomized, phase 3 in NDMM, transplant eligible



Emerging CART therapies in R/R myeloma

ddBCMA CART in R/R MM

- Reduced Immunogenicity, Enhance Activity and Persistence



ddBCMA phase 1 trial

- N=25 RR MM patients
- LoT median ~5 (3-16)
- EMD 40%
- ORR 100%
- CR/sCR 67%
- ≥VGPR 88%
- Responses beyond 18 months including in patients with EMD
- CRS 100%, most Gr ≤2; 4 patients had ICANS (2 had Gr3)

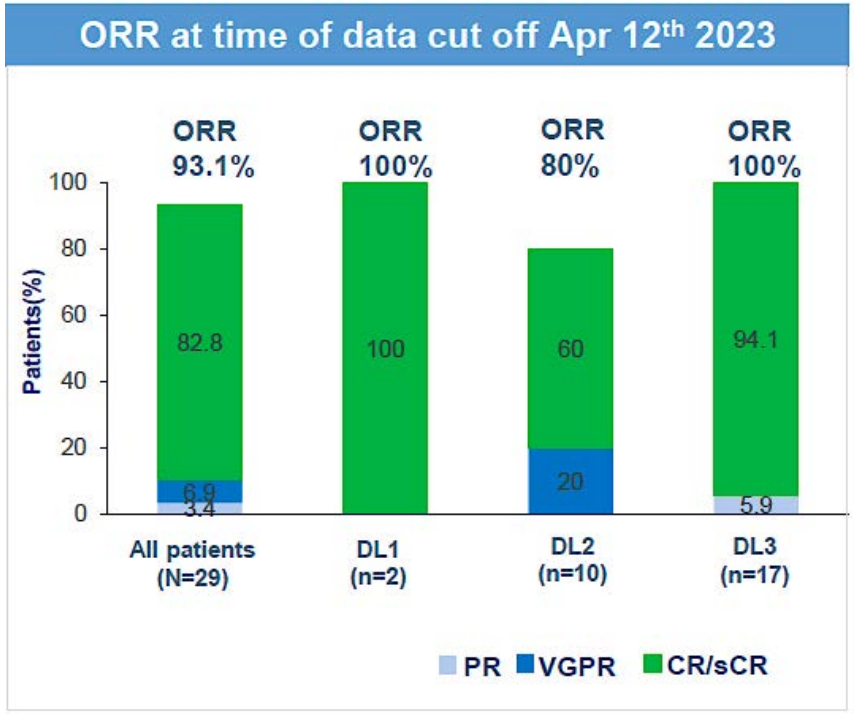
Phase 2 ddBCMA-CAR T currently open and actively enrolling patients at MGH site

M. Frigault et al, Phase 1 Study of CART-Ddbcma for the Treatment of Patients with Relapsed and/or Refractory Multiple Myeloma: Results from at Least 1-Year Follow-up in All Patients, Abstract 1023, ASH 2023

BCMA/CD19 Fast CART GC012F

- **Dual targeting**
  - GC012F targets both BCMA and CD19
  - Dual specificity approach to maximize efficacy
  - GC012F showed stable CAR expansion and effective functionality

- BCMA/CD19 FAST phase 1 trial



- N=29 R/R MM, 97% heavily pre-treated, with 93% refractory to their last therapy.
- ORR 93%, with 38% of patients achieving MRD negativity
- Median DOR 38 mos
- CRS 86.2%, mostly Gr ≤2; no ICANS

A phase 2 is currently underway in ND HR MM

Juan Du et al. UPDATED RESULTS OF A PHASE I, OPEN-LABEL STUDY OF BCMA/CD19 DUAL-TARGETING FASTCAR-T GC012F FOR PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM), Hemasphere. 2023 Aug; 7(Suppl): e84060bf.

What’s next?

Anti-GPRC5D CAR T-cells

Anti-GPRC5D CAR T-cells
MCARH109

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

GPRC5D-Targeted CAR T Cells for Myeloma

Sham Mailankody, M.B., B.S., Sean M. Devlin, Ph.D., Jonathan Landa, D.O., Karthik Nath, M.B., B.S., Ph.D., Claudia Diamonte, B.S.N., R.N., O.C.N., Elizabeth J. Carstens, M.D., Douglas Russo, M.S., Romany Auclair, M.D., Lisa Fitzgerald, M.S.N., Briana Cadzin, B.S.N., R.N., Xiuyan Wang, Ph.D., Devanjan Sikder, Ph.D., Brigitte Senechal, Ph.D., Vladimir P. Bermudez, Ph.D., Terence J. Purdon, M.S., Kinga Hosszu, Ph.D., Devin P. McAvoy, B.S., Tasmin Farzana, M.P.H., Elena Mead, M.D., Jessica A. Wilcox, M.D., Bianca D. Santomasso, M.D., Ph.D., Gunjan L. Shah, M.D., Urvi A. Shah, M.D., Neha Korde, M.D., Alexander Lesokhin, M.D., Carlyn R. Tan, M.D., Malin Hultcrantz, M.D., Ph.D., Hani Hassoun, M.D., Mikhail Roshal, M.D., Filiz Sen, M.D., Ahmet Dogan, M.D., Ph.D., Ola Landgren, M.D., Ph.D., Sergio A. Giralt, M.D., Jae H. Park, M.D., Saad Z. Usmani, M.D., Isabelle Rivière, Ph.D., Renier J. Brentjens, M.D., Ph.D., and Eric L. Smith, M.D., Ph.D.

ABSTRACT

BACKGROUND

B-cell maturation antigen (BCMA)–directed chimeric antigen receptor (CAR) T-cell therapies have generated responses in patients with advanced myeloma, but relapses are common. G protein–coupled receptor, class C, group 5, member D (GPRC5D) has been identified as an immunotherapeutic target in multiple myeloma. Preclinical studies have shown the efficacy of GPRC5D-targeted CAR T cells, including activity in a BCMA antigen escape model.

METHODS

In this phase 1 dose-escalation study, we administered a GPRC5D-targeted CAR T-cell therapy (MCARH109) at four dose levels to patients with heavily pretreated multiple myeloma, including patients with relapse after BCMA CAR T-cell therapy.

RESULTS

A total of 17 patients were enrolled and received MCARH109 therapy. The maximum tolerated dose was identified at 150×10^6 CAR T cells. At the 450×10^6 CAR T-cell dose, 1 patient had grade 4 cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome (ICANS), and 2 patients had a grade 3 cerebellar disorder of unclear cause. No cerebellar disorder, ICANS of any grade, or cytokine release syndrome of grade 3 or higher occurred in the 12 patients who received doses of 25×10^6 to 150×10^6 cells. A response was reported in 71% of the patients in the entire cohort and in 58% of those who received doses of 25×10^6 to 150×10^6 cells. The patients who had a response included those who had received previous BCMA therapies; responses were observed in 7 of 10 such patients in the entire cohort and in 3 of 6 such patients who received 25×10^6 to 150×10^6 cells.

CONCLUSIONS

The results of this study of a GPRC5D-targeted CAR T-cell therapy (MCARH109) confirm that GPRC5D is an active immunotherapeutic target in multiple myeloma. (Funded by Juno Therapeutics/Bristol Myers Squibb; ClinicalTrials.gov number, NCT04555551.)

The authors' affiliations are listed in the Appendix. Dr. Brentjens can be contacted at renier.brentjens@roswellpark.org or at the Department of Medicine, Roswell Park Comprehensive Cancer Center, Elm and Carlton Sts., Buffalo, NY 14263.

Drs. Brentjens and Smith contributed equally to this article.

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DOI: 10.1056/NEJMoa2209900

Mailankody S et al., ASH 2021; *N Engl J Med* 2022

Clinical activity of BMS-986393 (CC-95266), a G protein-coupled receptor class C group 5 member D (GPRC5D)-targeted chimeric antigen receptor (CAR) T cell therapy, in patients with relapsed and/or refractory (R/R) multiple myeloma (MM): first results from a phase 1, multicenter, open-label study

Susan Bal,[1] M. Hakan Kocoglu,[2] Omar Nadeem,[3] Myo Htut,[4] Tara Gregory,[5] Larry D. Anderson, Jr,[6] Luciano J. Costa,[1] Tonia J. Buchholz,[7] Safiyyah Ziyad,[7] Meng Li,[7] Yanping Chen,[7] Allison J. Kaeding,[7] Michael R. Burgess,[7] Kristen Hege,[7] Jesus Berdeja[8]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Maryland, Baltimore, MD; [3]Dana-Farber Cancer Institute, Boston, MA; [4]City of Hope Comprehensive Cancer Center, Duarte, CA; [5]Colorado Blood Cancer Institute, Sarah Cannon Cancer Network, Denver, CO; [6]Cellular Therapy and Hematologic Malignancies Program, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [7]Bristol Myers Squibb, Princeton, NJ; [8]Sarah Cannon Research Institute, Nashville, TN

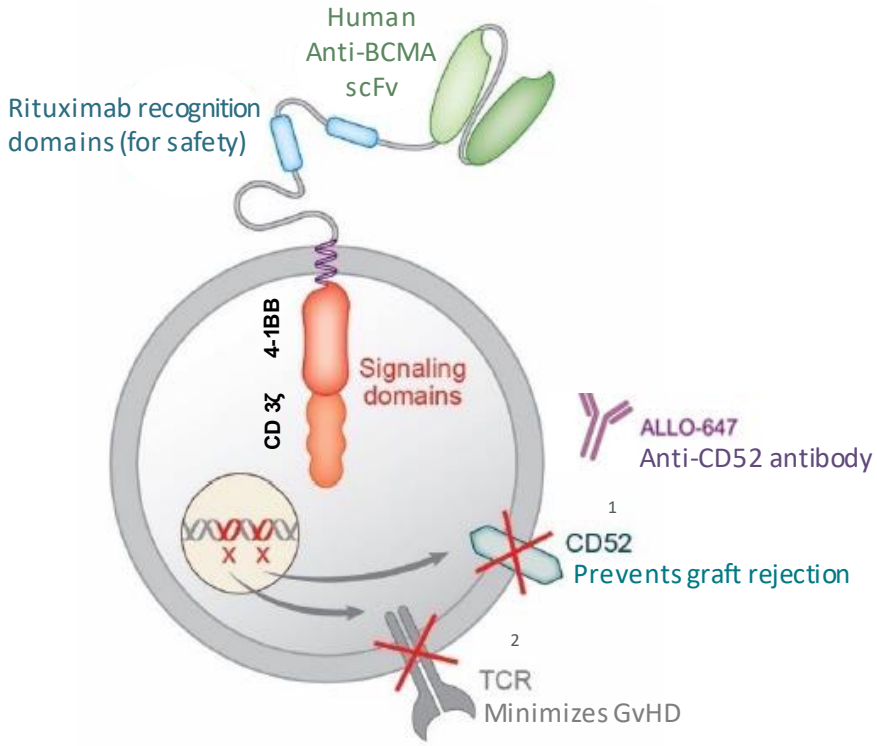
ASH 2022, Presentation number 364

N = 33 (evaluated at doses from 25-300 × 10^6 cells)

N = 17 phase 1 study (based on preclinical data presented at ASH 2018)
MTD 150 × 10^6 cells
Dose limiting toxicity at 450 × 10^6 cells, two patients had grade 3 cerebellar toxicity at 6.5 and 8.4 months
GPRC5D expression enriched in inferior olivary nucleus, structure in medulla that regulates coordination

The First Allogeneic anti-BCMA CAR T Study for R/R Multiple Myeloma

- BCMA cell therapy has demonstrated unprecedented efficacy, but is not readily available to all patients
- Allogeneic chimeric antigen receptor (CAR) T cell therapy has the potential for all eligible patients to receive therapy on demand and supports re-dosing
- ALLO-715 (anti-BCMA) is an allogeneic CAR T cell product utilizing TALEN®* gene editing specifically designed to
  - Disrupt TCRα constant gene – to reduce the risk graft-versus-host disease (GvHD)
  - Edit CD52 gene – permits use of ALLO-647 (a humanized anti-CD5 mAb) to selectively deplete host T cells while protecting donor cell



*TALEN® gene editing is a technology pioneered and controlled by Cellectis.

1. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647
2. TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD

Current Understanding and Future Directions

- BCMA is a validated target with deep and durable responses with CAR T cells
- Other novel targets already under investigation
- Understanding the mechanism of resistance is key to future development of CAR T cells
- Incorporating bispecific T-cell engagers with cellular products may be critical to improving duration of response
- Next generation approaches will focus on improving efficacy and DOR

Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Richardson

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) MM — Dr Lonial

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies in the Treatment of MM — Dr Krishnan

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Orlowski

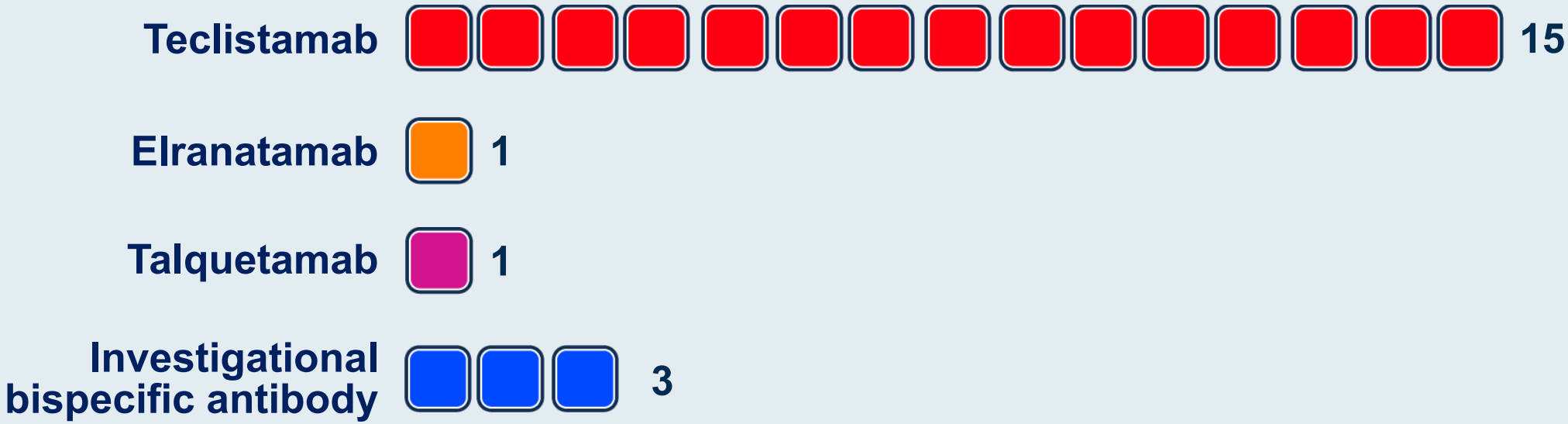
What is the age of the oldest patient to whom you have administered or whom you have referred for therapy with a bispecific antibody?

Patient age: 83 (median; range 75-92)

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Bispecific antibody the patient received:



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe the oldest patient to whom you have administered or whom you have referred for therapy with a bispecific antibody.

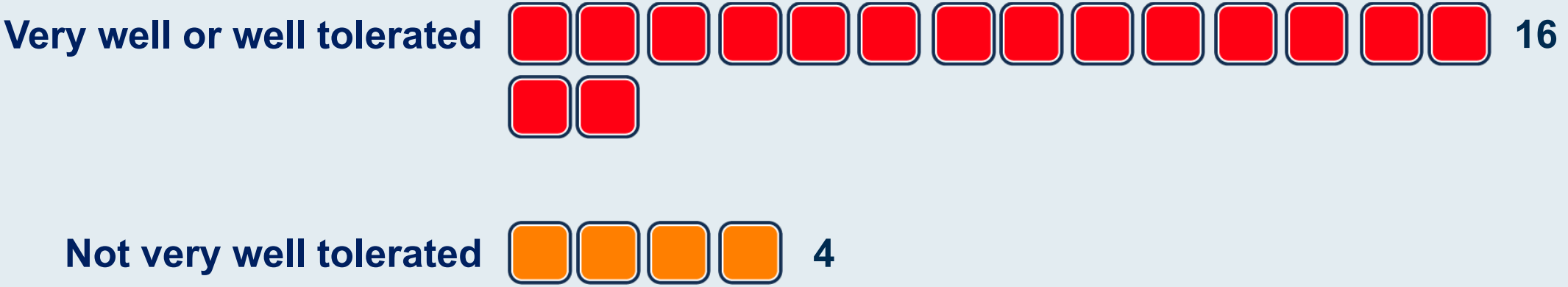
Patient's response to therapy:

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe the oldest patient to whom you have administered or whom you have referred for therapy with a bispecific antibody.

Patient's tolerance of therapy:



Survey of 20 US-based clinical investigators November 2023

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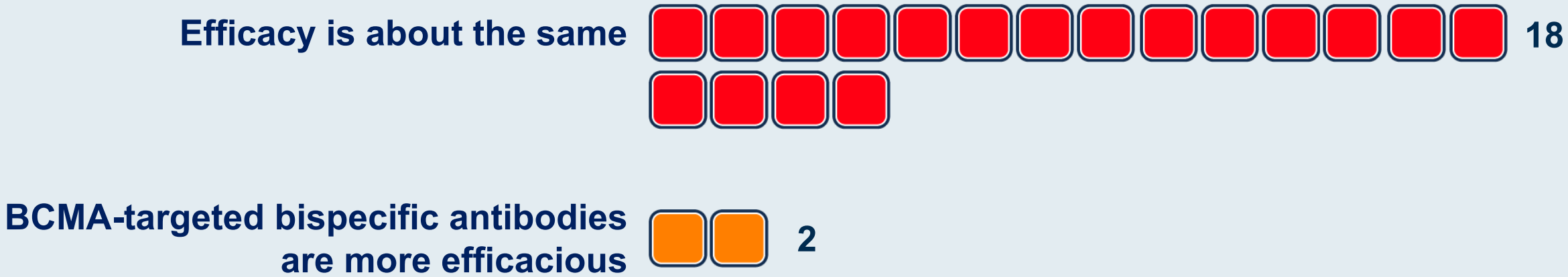
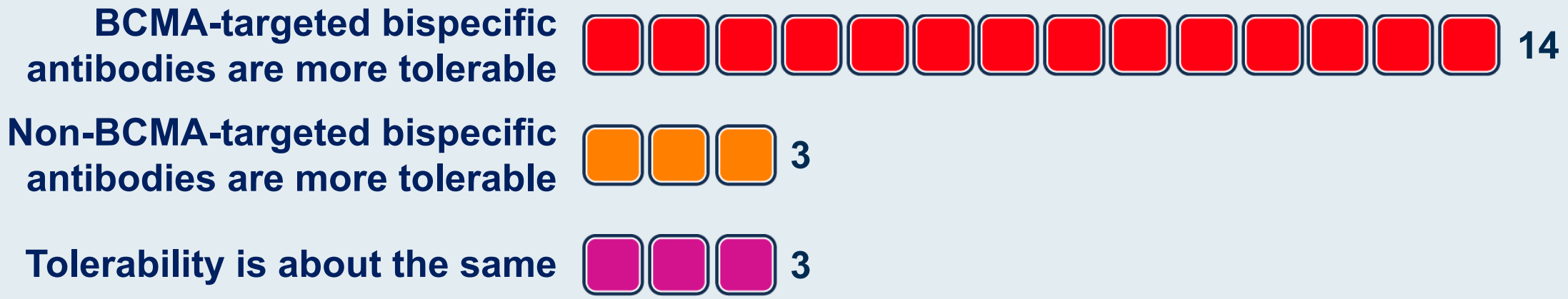
Based on your personal clinical experience and knowledge of available data, how would you compare the global efficacy of BCMA-targeted bispecific antibodies (eg, teclistamab, elranatamab) to that of non-BCMA-targeted bispecific antibodies (eg, talquetamab) for R/R MM?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

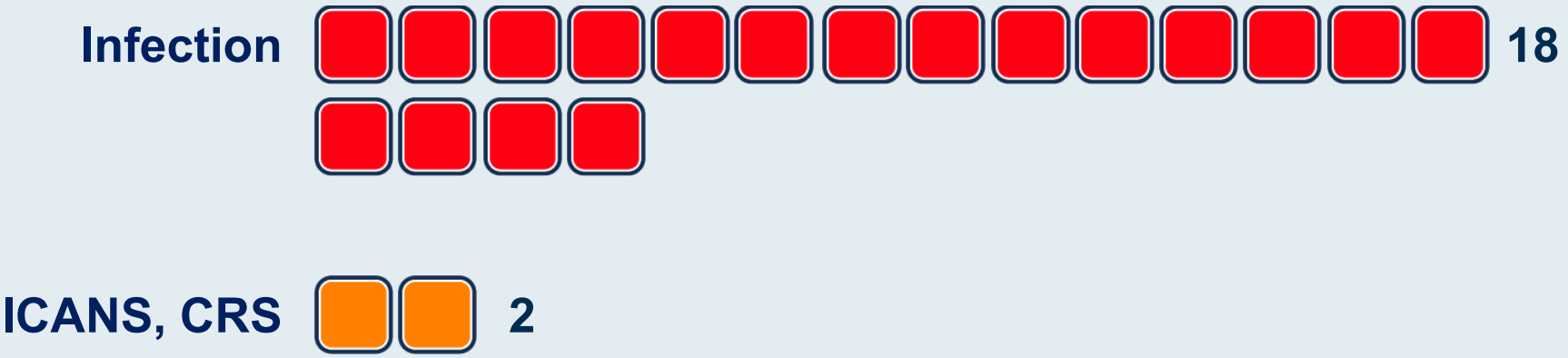
Based on your personal clinical experience and knowledge of available data, how would you compare the tolerability of BCMA-targeted bispecific antibodies (eg, teclistamab, elranatamab) to that of non-BCMA-targeted bispecific antibodies (eg, talquetamab) for patients with R/R MM?



Survey of 20 US-based clinical investigators November 2023

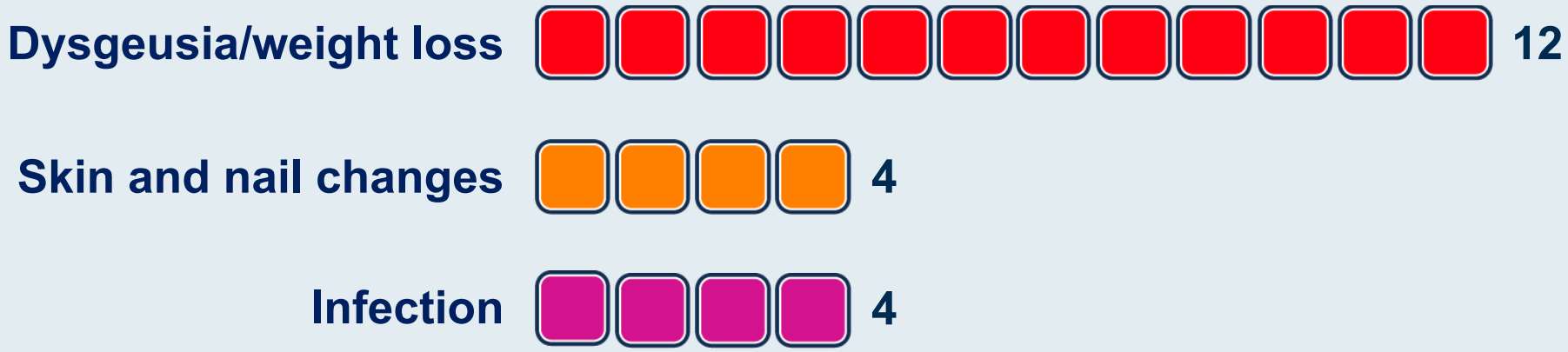
RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, what are the most common tolerability issues that result in therapy being held or discontinued among patients receiving teclistamab?



Survey of 20 US-based clinical investigators November 2023

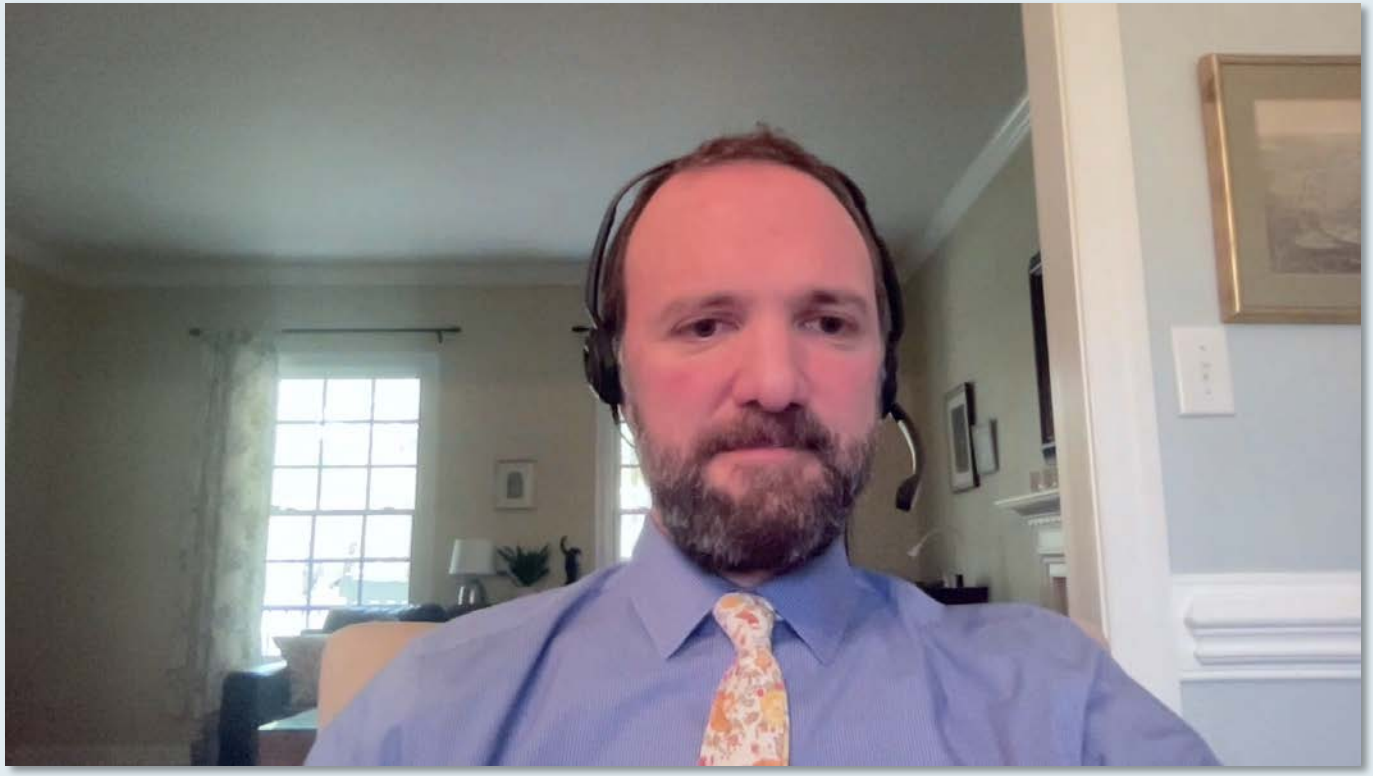
Based on your personal clinical experience and knowledge of available data, what are the most common tolerability issues that result in therapy being held or discontinued among patients receiving talquetamab?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Management of bispecific antibody-associated cytokine release syndrome and neurological toxicity



Sascha A Tuchman, MD, MHS

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RESEARCH
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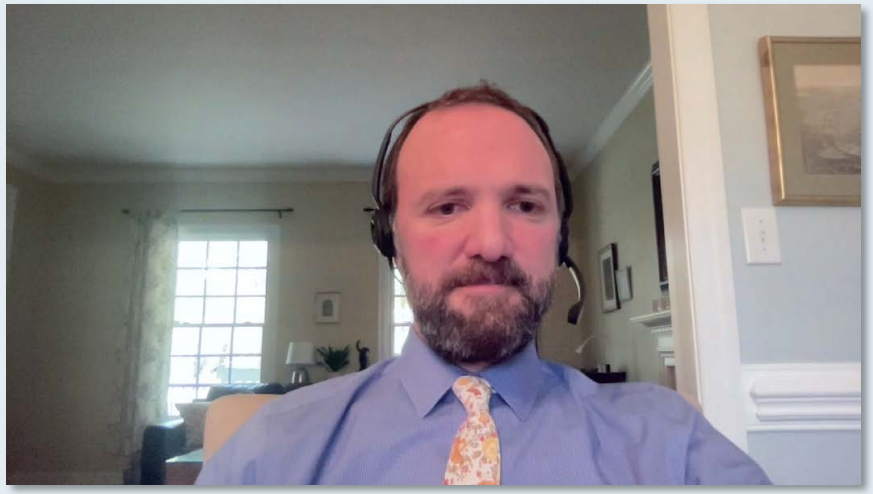
Risk of infections associated with the use of bispecific antibodies for MM

Melissa Alsina, MD



Sascha A Tuchman, MD, MHS

RTP RESEARCH TO PRACTICE

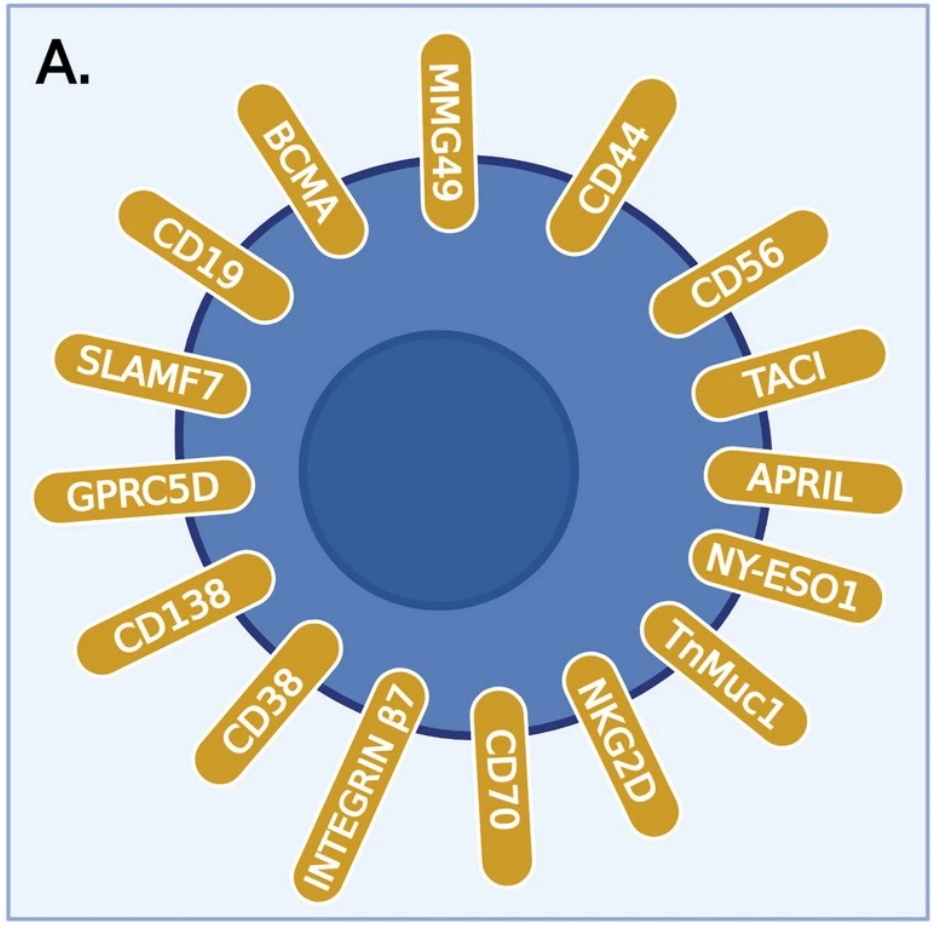
Bispecific Therapy for Multiple Myeloma

Amrita Krishnan, MD, FACP
Director of the Judy and Bernard Briskin Center for Myeloma
Professor of Hematology HCT

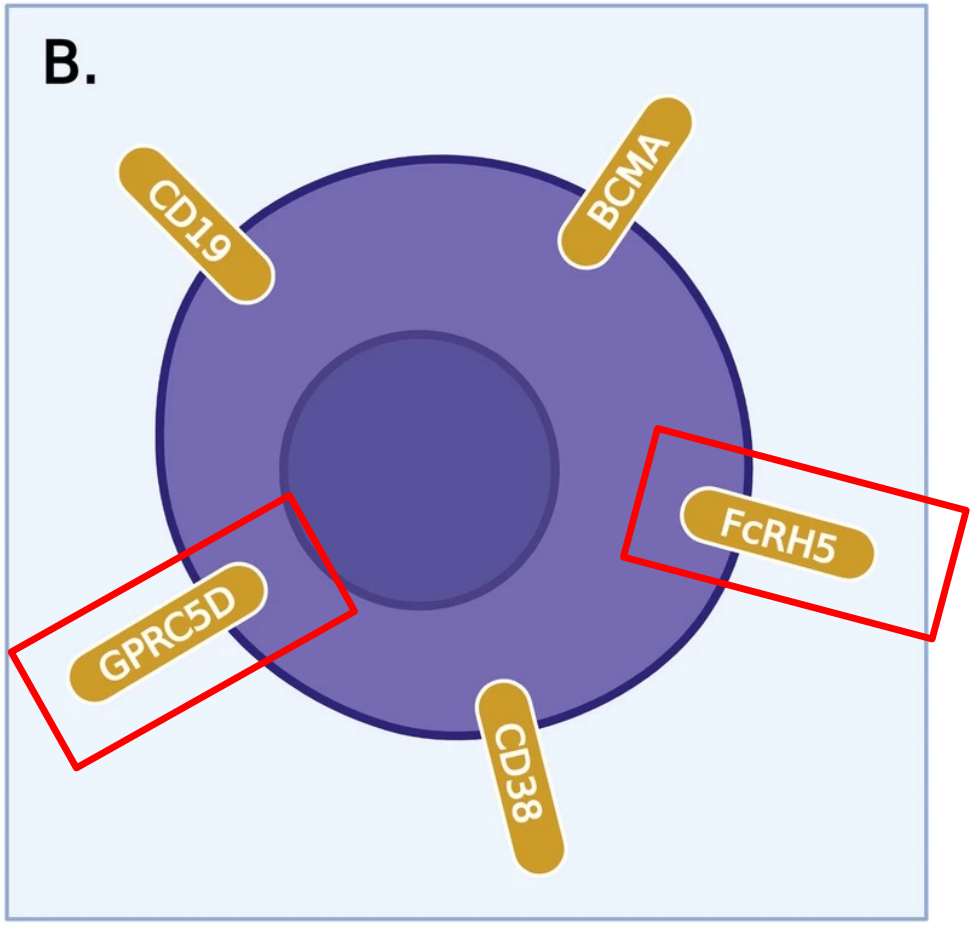
Executive Director Hematology COH OC
City of Hope Cancer Center

Bispecifics; many targets

CAR/TCR T cell trials



BsAb trials



Kegyes et al, J Hematol Oncol 2022

MajesTEC-1 Update: Teclistamab

Patients with R/R MM; triple-class exposed (IMiD, PI, and anti-CD38 mAb); no prior BCMA therapy; ECOG PS 0–1 (N = 165)

Phase I

Teclistamab
IV and SC escalation dosing
RP2D: 1.5 mg/kg SC QW*

Phase II: Cohort A

Teclistamab
1.5 mg/kg SC QW*

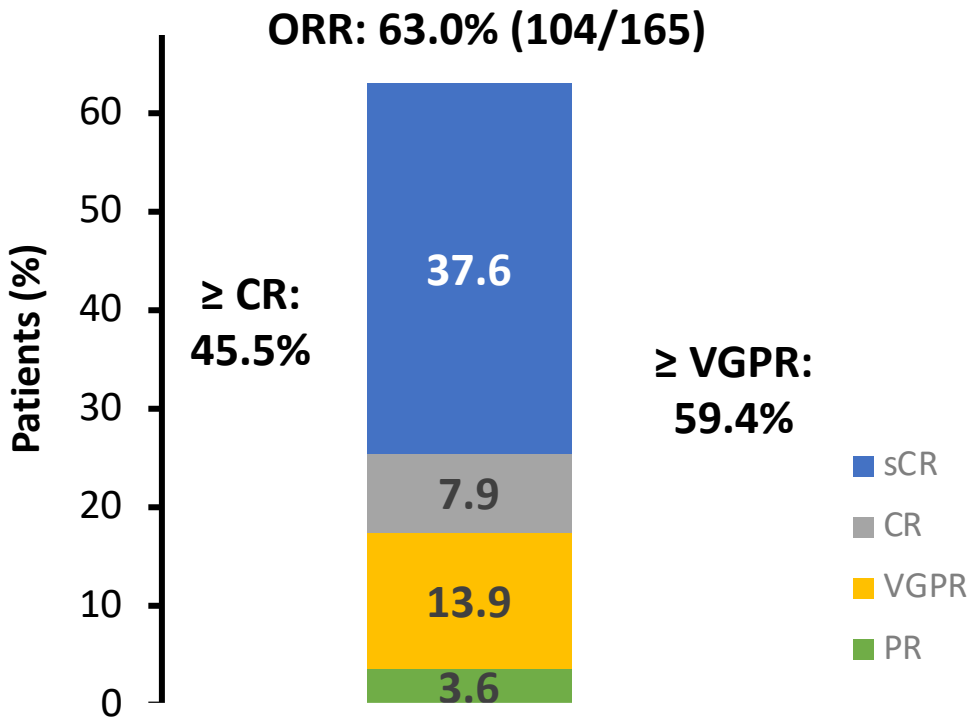
Option for responders to switch to Q2W/Q4W dosing[†]

*Step-up dosing: 0.06 and 0.3 mg/kg, 2–4 days between each dose.
Hospitalization and premedication with dexamethasone 16 mg, acetaminophen, and diphenhydramine.
[†]Q2W option if ≥ PR after ≥4 cycles (phase I) or ≥ CR for ≥6 mo (phase II); Q4W option if continued response on Q2W schedule.

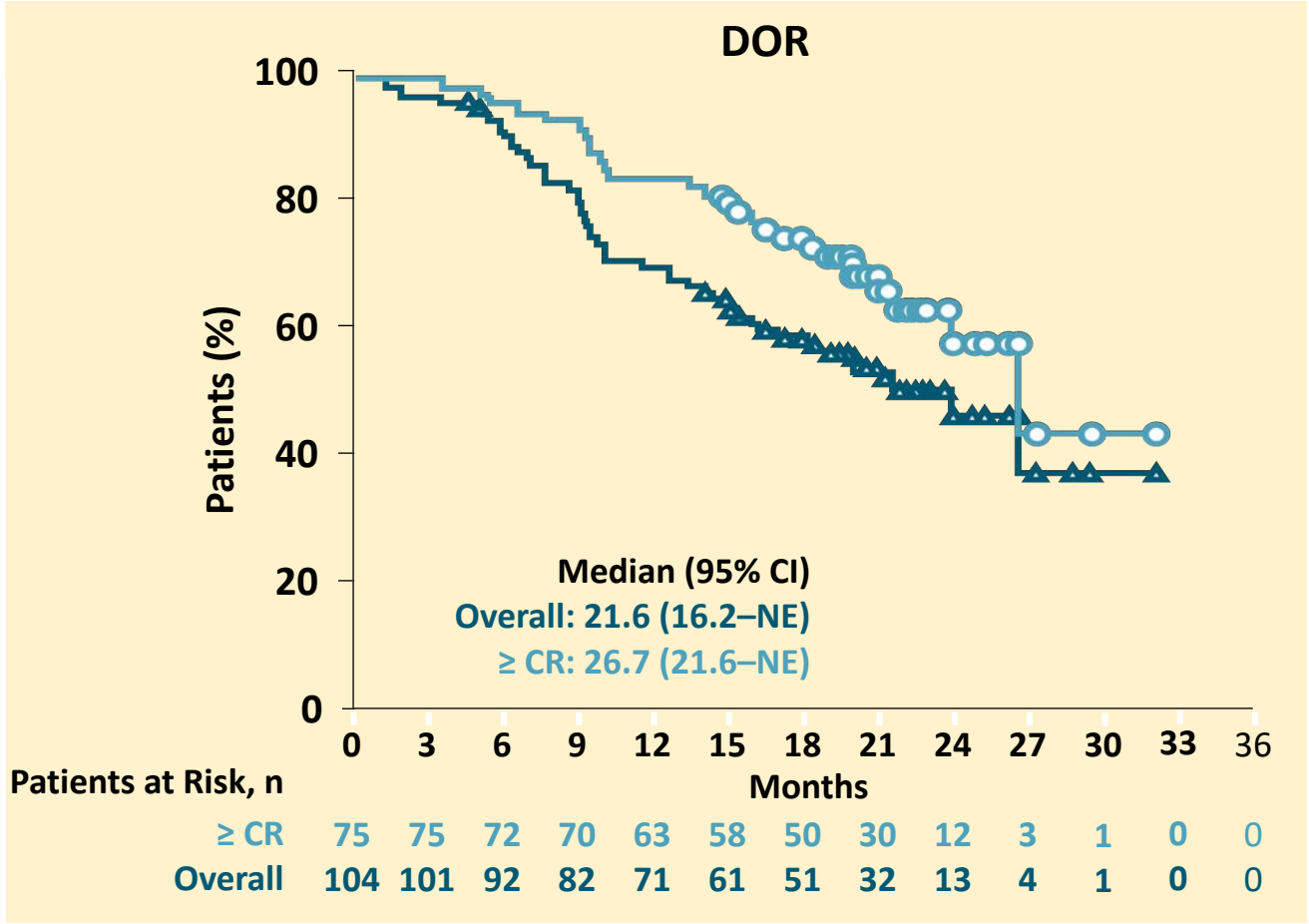
- **Primary endpoint:** ORR
- **Key secondary endpoints:** PK/PD, DOR, PFS, OS, undetectable MRD, safety, and HRQOL
- **Open-label,** dose-escalation/dose-expansion phase I/II trial (data cutoff: Jan 4, 2023)

van de Donk N, et al. ASCO 2023. Abstract 8011.

MajesTEC-1 Update: Response and Duration of Response



Patient Subgroup	ORR, % (n/N)
≤3 prior lines of treatment	74.4 (32/43)
>3 prior lines of treatment	59.0 (72/122)
High-risk cytogenetics and/or EMD	53.3 (32/60)



- **Median time to ≥ CR: 4.6 mo (range: 1.6–18.5)**

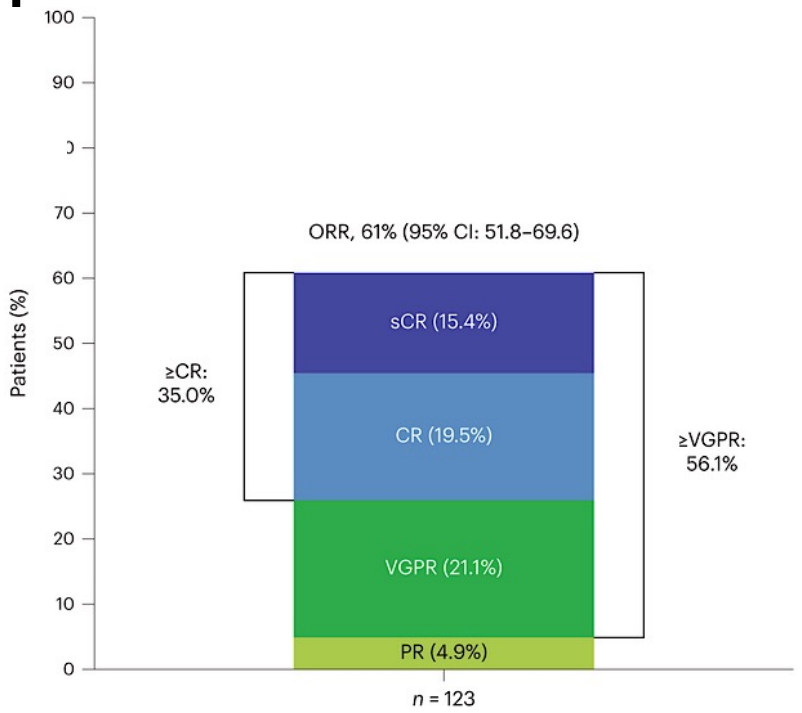
City of Hope.

van de Donk N, et al. ASCO 2023. Abstract 8011.

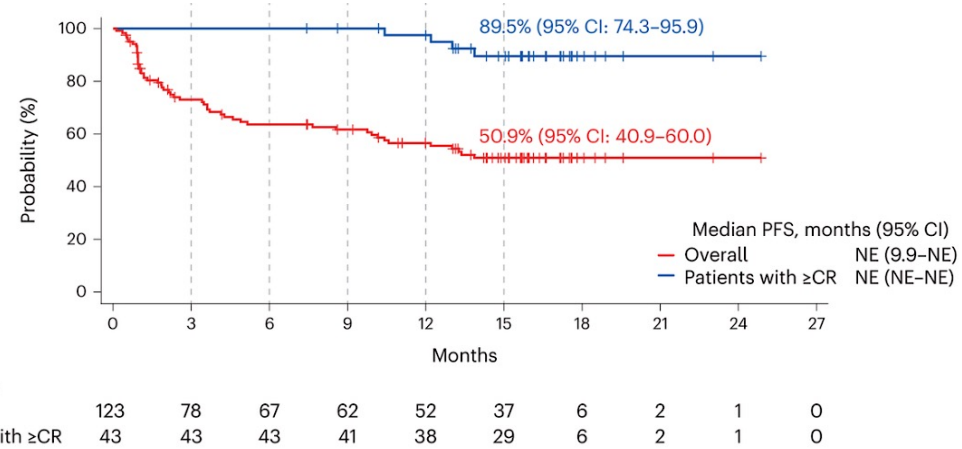
MagnetisMM-3: Elranatamab Phase I

- **Cohort A: no prior BCMA (n = 123)**
  - 2 step-up priming doses (12 mg, 32 mg) → weekly (76 mg)
  - After 6 cycles, responders → q2 weeks
- **Median prior lines 5 (2–22)**
  - 96.7% TCR, 42.3% PCR
- **25% hrFISH, 31.7% EMD**
- **ORR 61, 35% CR or better**
- **At a median follow-up of 14.7 months**
  - mDOR: NR (15-month rate 71.5%)
  - PFS: NR (15-month rate 50.9%)
  - OS: NR (15-month rate 56.7%)
- CRS 57.7% (no G3/4), ICANS 3.4% (no G3/4)
- Motor (17.1%) and sensory (13.8%) neuropathy
- All-grade infections 69.9% (39.8% G3/4); 43% received IVIG

ORR



PFS



No. at risk

Overall	123	78	67	62	52	37	6	2	1	0
Patients with ≥CR	43	43	43	41	38	29	6	2	1	0

City of Hope.

Lesokhin AM, et al. *Nat Med*. 2023;10.1038/s41591-023-02528-9.

ASCO 2023: Efficacy and Safety of Teclistamab or Elranatamab After Prior BCMA Therapies

Bispecific Evaluated	Patients, N	Baseline Characteristics	Prior BCMA	Follow-up Duration	ORR	AEs
Commercial Teclistamab	24 treated 15 evaluable	Median age: 66 (51-80) Prior lines: 7 (4-13) High-risk cytogenetics: 53% Triple-refractory: 100% Penta-refractory: 80%	Belamaf:7 BCMA CART: 8 BCMA BsAb:1 ≥2 anti-BCMA: 5	Median: 1.3 mo	All: 60% 1 prior BCMA: 50% ≥2 prior BCMA: 40%	CRS: 41% (G1, 5/7; G2, 2/7) Neurotox: 13%
Elranatamab	86 from pooled analysis of MM-1, MM-3 and MM-9	Median age: 66 (40-84) Prior lines: 7 (3-19) High-risk cytogenetics: 24% Triple-refractory: 97% Penta-refractory: 55%	Belamaf:67% BCMA CART: 42% ≥2 anti-BCMA: 9%	10.3 mo (0.3–32.3)	All: 45% Prior BCMA ADC: 41% Prior BCMA CAR-T: 53%	CRS: 65% (G3, 1.2%) Neurotox: 6% (G3, 2%)

Firestone R et al. ASCO 2023: Abstract 8049; Nooka AK et al. ASCO 2023: Abstract 8008.

2023 ASCO ANNUAL MEETING

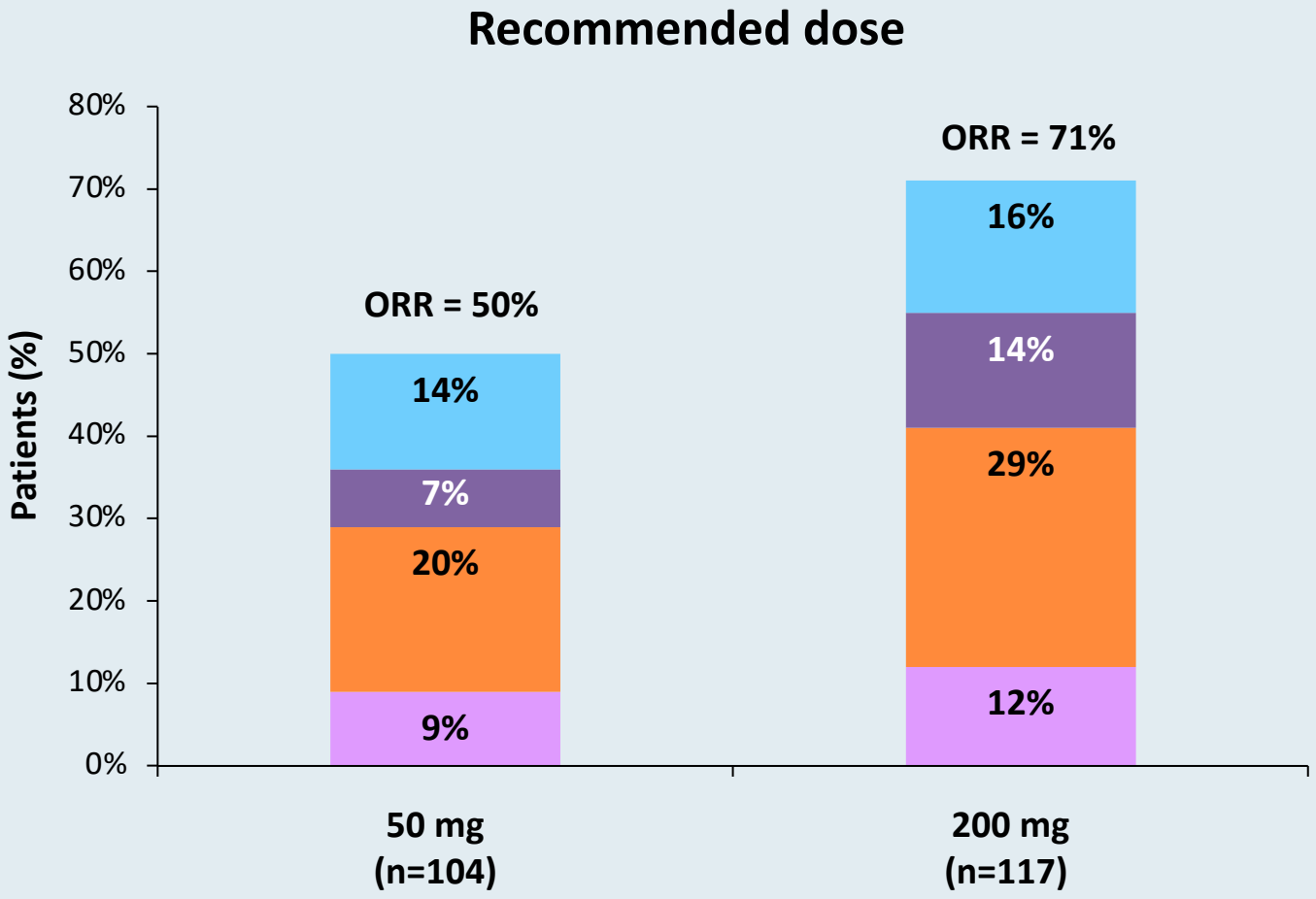
Abstract 8006

LINKER-MM1 Study: Linvoseltamab (REGN5458) in Patients with Relapsed/Refractory Multiple Myeloma

Hans C. Lee[1], Naresh Bumma[2], Joshua Richter[3], Madhav V. Dhodapkar[4], James E. Hoffman[5], Attaya Suvannasankha[6], Jeffrey A. Zonder[7], Mansi R. Shah[8], Suzanne Lentzsch[9], Rachid Baz[10], Joseph J. Maly[11], Jing Christine Ye[12], Ka Lung Wu[13], Swathi Namburi[14], Rebecca Silbermann[15], Chang-Ki Min[16], Marie-Christiane Vekemans[17], Markus Munder[18], Ja Min Byun[19], Michelle DeVeaux[20], Dhruti Chokshi[20], Anita Boyapati[20], Anasuya Hazra[20], Karen Rodriguez Lorenc[20], Glenn S. Kroog[20], Yariv Houvras[20], Sundar Jagannath[3]

RTP RESEARCH TO PRACTICE

LINKER-MM1 Study: Linvoseltamab in Patients with Relapsed/Refractory Multiple Myeloma



ORR = objective response rate

- **Median duration of follow-up:**
  - 50 mg – 7.7 months (range 0.3-31.3)
  - 200 mg – 5.6 months (range 0.2-28.2)
- **At the recommended dose (200 mg):**
  - ORR 71%
  - VGPR or better in 59%
  - 77 (66%) patients on the 200 mg dose remain on study
- **Based on earlier results, responses may deepen over time**
- **Among patients with complete response or stringent complete response with available minimum residual disease data (N = 46), 54.3% were MRD-negative at 10^{-5}**

Lee HC et al. ASCO 2023;Abstract 8006.

RTP RESEARCH TO PRACTICE

BCMAxCD3

Bispecific Antibody	Teclistamab (JNJ-64007957)	Elranatamab (PF-06863135)	Linvoseltamab (REGN5458)	ABBV-383	Alnuctamab (BMS-93269)	HPN217
Structure/Function	Humanized antibody	Humanized antibody	Veloci-Bi® platform fully human antibody	Low CD3 affinity fully human antibody	Humanized antibody 2 BCMA + 1 CD3	Trispecific 50kDa (albumin)
Treatment	Weekly SC	Weekly SC	Weekly IV	IV q3w	Qwk -> Q4wk SQ	Q2wk IV
Patients	n= 165	n= 123	n= 252	n= 174	n= 68	n= 62
Median prior lines	5	5	5	5	4	6
Triple-class refractory	78%	97%	81%	80%	63%	76%
ORR at RP2d RP2D (n)	63% 1.5 mg/kg SC (n=165)	61% 76 mg SQ (n=123)	64% 200 mg IV (n=58)	58-61% 40 to 60 mg IV (n=52; n=59)	65% 30 mg SQ (n=26)	73% ?12 or 24 mg (n=13)
PFS	11.3 mos (8.8-17.1)	NE @ 12 mos	NR	13.7 or 11.2 mos	NR	NR
DOR	18.4 mos (14.9-NE)	NE @12 mos	89% @ 6 mos	NE	NE	NR
Median f/u	14.1 mos	10.4 mos	3.2 mos	6.8	4.6 mos	
AEs, (All/(Gr 3+);						
CRS	72% (0.6%)	58% (0%)	44% (1%)	60% (1%)	53% (0%)	27 (0%)
Infections	76% (45%)	67% (35%)	54% (29%)	(22%)	34% (9%)	45% (16%)
Neutropenia	71% (64%)	48% (48%)	25% (23%)	34% (26%)	37%(32%)	16% (13%)
Anemia	52% (37%)	48% (37%)	36% (31%)	37% (16%)	38%(25%)	44% (34%)
Thrombocytopenia	40% (21%)	26% (24%)	18% (6%)	29% (11%)	24%(9%)	NR
Neuro	Neurotoxicity 15% (0.1)	NR/ PN?	ICANS 2% (1%)	5% (0.1%)	ICANS 3 (0%)	16% (0%)
# Deaths	68/(41 due to PD)	21 (/11 due to PD)	NR	46	1	NR
Hypogamma/IVIg	75%//39%	75%/40%	NR	NR		

Moreau P et al. *N Engl J Med*. 2022;387(6):495-505. Bahlis NJ et al. 2022 ASH. Abstract 97. Bumma N et al. 2022 ASH. Abstract 1936. Voorhees PM et al. 2022 ASH. Abstract 1919. Wong SW et al. 2022 ASH. Abstract 162. Abdallah AO et al. 2022 ASH. Abstract 3240. D'Souza A et al. *J Clin Oncol*. 2022;40(31):3576-3586.

BCMAxCD3 Combinations

Bispecific Antibody	Teclistamab (JNJ-64007957)	Teclistamab + Daratumumab (TRIMM2)	Teclistamab + Dara + Lenalidomide (MajesTEC-2)	Elranatamab (PF-06863135)	Elranatamab + Daratumumab (MAGNETISMM-5)
Treatment	Weekly 1.5 mg/kg SC	Dara SC 1800 mg Tec SC 1.5–3 mg/kg QW or Q2W	Dara + Len 25 + dex 40 +Tec 0.72 or 1.5 QWK to 3 mg/kg Q2WK C3+	Weekly SC 76 mg SQ	Dara SC 1800 mg + Elra44 or 76 mg QW SC -> Q2W C7+
Patients	n = 165	n = 65	n = 32	n = 123	n = 34
Median prior lines	5	5	2	5	4
Triple-class refractory	78%	59%	N/A	97%	18%
ORR at RP2d	63%	76.5% (n=51)	94%	61%	71%
PFS	11.3 mos (8.8-17.1)	NE	NE	NE @ 12 mos	
DOR	18.4 mos (14.9-NE)	NE	NE	NE @12 mos	
Median f/u	14.1 mos	8.6 mos	8.4 mos	10.4 mos	
AEs, (All/(Gr 3+);					
CRS	72% (0.6%)	67% (0%)	81% (0%)	58% (0%)	41% (0%)
Infections	76% (45%)	68% (28%)	91% (38%)	67% (35%)	
Neutropenia	71% (64%)	49% (41%)	84% (74% incl 13% FN)	48% (48%)	47% (47%)
Anemia	52% (37%)	42% (28%)	22% (13%)	48% (37%)	29% (27%)
Thrombocytopenia	40% (21%)	32% (25%)	25% (16%)	26% (24%)	21% (15%)
Neuro	Neurotoxicity 15% (0.1)	2% (0%)	0% (0%)	NR/ PN?	0%(0%)
# Deaths	68/(41 due to PD)	4	2	21 (/11 due to PD)	15 (6 COVID)
Hypogamma/IVIg	75%//39%	NR	NR	75%/40%	

Accelerated approval

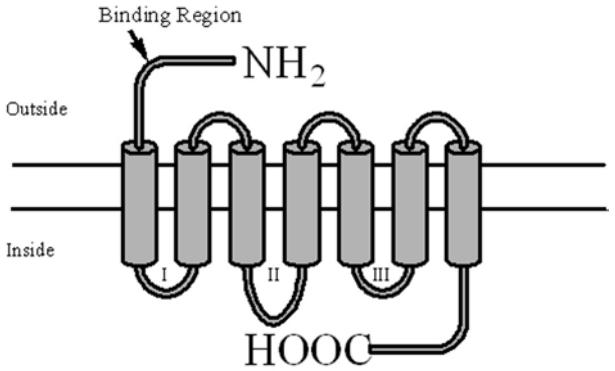
Moreau et al. *N Engl J Med.* Jun 5 2022 Rodriguez-Otero et al ASCO 2022 Searle et al ASH 2022 Bahlis et al ASH 2022 Grosicki et al ASH 2022;

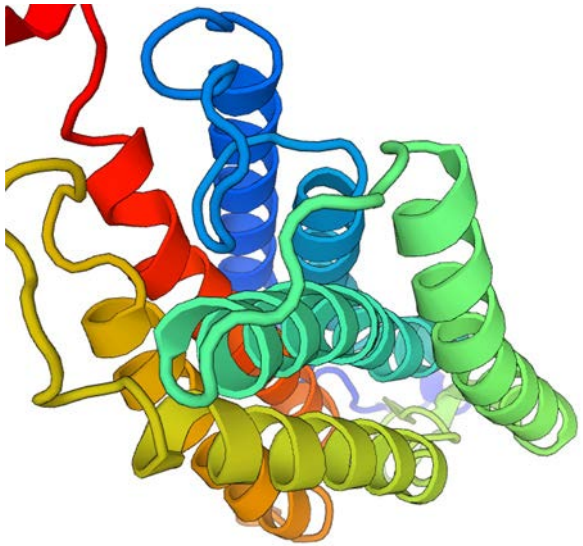
ASH 2023

- **3394 A Phase 2, Single-Arm, Non-Inferiority Study of Limited-Duration Teclistamab for Relapsed and Refractory Multiple Myeloma (LimiTec) (6-9m)**
- (is rate of treatment failure same as historic controls?)
- **4666 Bivalent BCMA Binding and Low Affinity CD3 T-Cell Engagement By Abbv-383 Drives Sustained Activation with Reduced T-Cell Exhaustion in Preclinical Models of Multiple Myeloma**
- **1012 Results from the Completed Dose Escalation Portion of the Phase 1 Study of HPN217, a Half-Life Extended Tri-Specific T Cell Activating Construct (TriTACÂ®) Targeting B Cell Maturation Antigen (BCMA) for Relapsed/Refractory Multiple Myeloma (MM)**
- **455 Longitudinal Correlative Profiles of Responders, Nonresponders, and Those with Relapse on Treatment with Teclistamab in the Phase 1/2 MajesTEC-1 Study of Patients with Relapsed/Refractory Multiple Myeloma**
- (T cell exhaustion)

GPRC5D

- G-protein coupled receptor family C group 5 (GPRC5D) is an orphan receptor with no known ligands or functions in humans (and human cancer)
- GPRC5D has seven transmembrane segments and is expressed in cell membranes
- The GPRC5D gene that is mapped on chromosome12p13.3 contains three exons and spans about 9.6 kb. The large first exon encodes the seven-transmembrane domain
- Biological function in MM not known, but GPRC5D is described to be associated with poor prognosis and high tumour load (plasma cell number) in MM patients[1, 2, 3]
- Talquetamab received accelerated approval for 5L+ RRMM in August 2023
- At least 3 CAR T therapies targeting GPRC5D are in development





[1]Venkateshaiah, Blood 2013; [2]Atamaniuk, ESCI 2012; [3]Cohen, Hematology 2013;

MonumenTAL-1: Study Design

Adults with measurable MM

Phase I: progression on or intolerance to all established therapies; ECOG PS 0–1

Phase II: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody; ECOG PS 0–2

Talquetamab 0.4 mg/kg SC QW*
(n = 143)

Talquetamab 0.8 mg/kg SC Q2W*
(n = 145)

Prior T-Cell Redirection Group: Talquetamab
Either 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W
(n = 51)

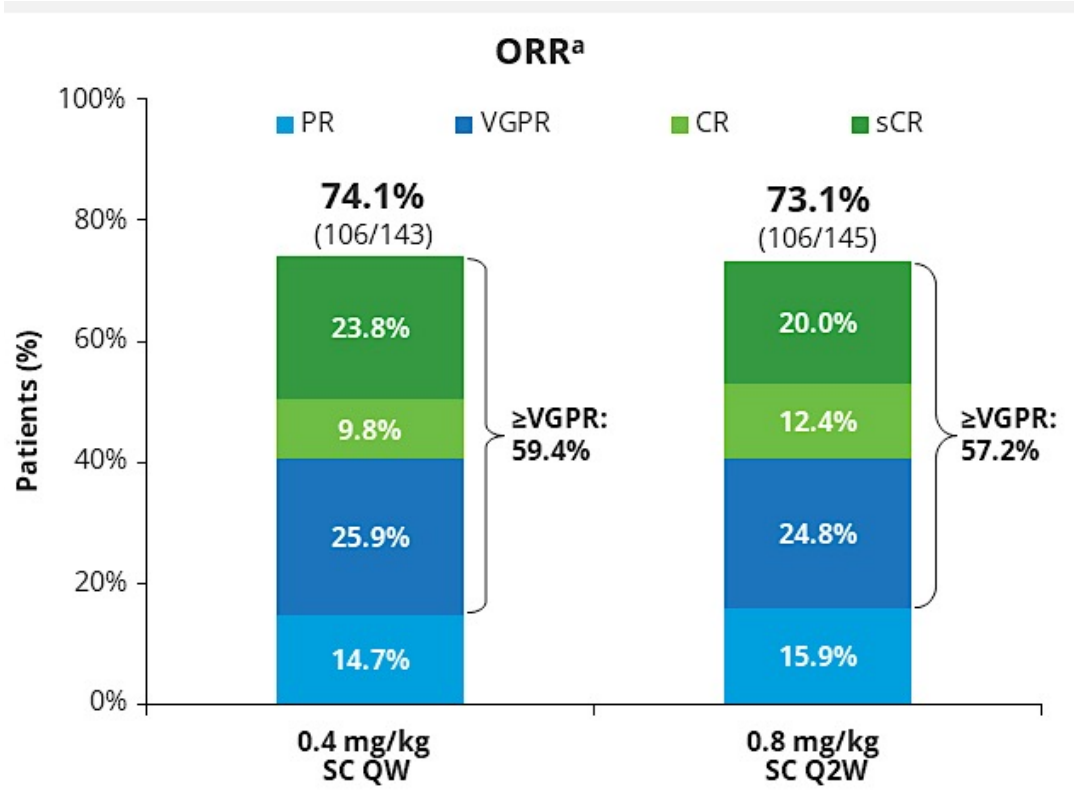
*Previous anti-BCMA therapy allowed; T-cell redirection therapy naive.

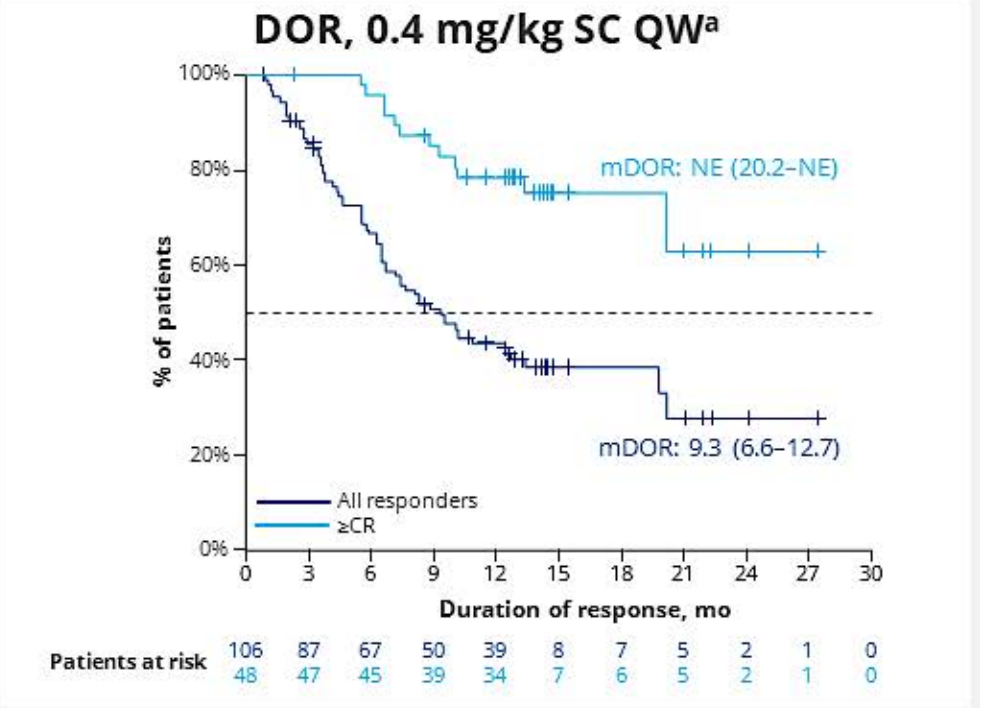
- Multicenter, open-label phase I/II trial
- **Primary endpoint (phase II):** ORR
- **Secondary endpoints (phase II):** DOR, ≥ VGPR rate, ≥ CR, sCR rate, TTR, PFS, OS, MRD, safety

Chari A, et al. ASH 2022. Abstract 157; NCT03399799; NCT04634552.

MonumenTAL-1: phase 2 expansion of talquetamab in RRMM

- Dose: 0.4 mg/kg SQ qwk (n=143) or 0.8 mg/kg SQ q2wks (n=145)
- Med 5 priors, 72% TCR, 25% PDR, 25% EMD. 13% prior belantamab
- Med f/up 14.9 and 8.6 mos





mPFS: 7.5 months (95% CI: 5.7–9.4; 33% censored)

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Chari et al, ASH 2022, #157

MonumenTAL-1: phase 2 expansion of talquetamab in RRMM

AEs (≥20% of any RP2D cohort), n (%)	0.4 mg/kg SC QW[a] (n=143) mFU, 11.0 months[b]		0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anemia	64 (44.8)	45 (31.5)	57 (39.3)	36 (24.8)
Neutropenia	49 (34.3)	44 (30.8)	41 (28.3)	32 (22.1)
Lymphopenia	40 (28.0)	37 (25.9)	38 (26.2)	37 (25.5)
Thrombocytopenia	39 (27.3)	29 (20.3)	39 (26.9)	24 (16.6)
CRS	113 (79.0)	3 (2.1)	105 (72.4)	1 (0.7)
Skin-related AEs[d]	80 (55.9)	0	98 (67.6)	1 (0.7)
Nail-related AEs[e]	74 (51.7)	0	63 (43.4)	0
Dysgeusia[f]	69 (48.3)	NA	67 (46.2)	NA
Rash-related AEs[g]	56 (39.2)	2 (1.4)	39 (26.9)	8 (5.5)
Weight decreased	57 (39.9)	3 (2.1)	47 (32.4)	2 (1.4)
Pyrexia	53 (37.1)	4 (2.8)	35 (24.1)	1 (0.7)
Asthenia	37 (25.9)	3 (2.1)	13 (9.0)	2 (1.4)
Dry mouth	36 (25.2)	0	53 (36.6)	0
Diarrhea	34 (23.8)	3 (2.1)	32 (22.1)	0
Dysphagia	34 (23.8)	0	33 (22.8)	3 (2.1)
Fatigue	32 (22.4)	5 (3.5)	29 (20.0)	1 (0.7)
Decreased appetite	25 (17.5)	2 (1.4)	29 (20.0)	2 (1.4)

ICANS in 10-11% (1-2% grade 3)

Infections

- At 0.4 mg/kg QW and 0.8 mg/kg Q2W:
  - Infections occurred in 57.3% and 50.3%
    - Grade 3/4 in 16.8% and 11.7%
  - 5 (3.5%)[d] and 4 (2.8%)[e] patients had opportunistic infections
  - 13 (9.1%) and 16 (11.0%) patients had COVID-19
    - 2 patients died from COVID-19
- 13.3% and 9.7% of patients received IVIg, respectively

- **Low rates of discontinuation due to AEs** with QW (4.9%) and Q2W (6.2%) schedules
- At time of data cut-off, no patients in these cohorts died due to drug-related AEs

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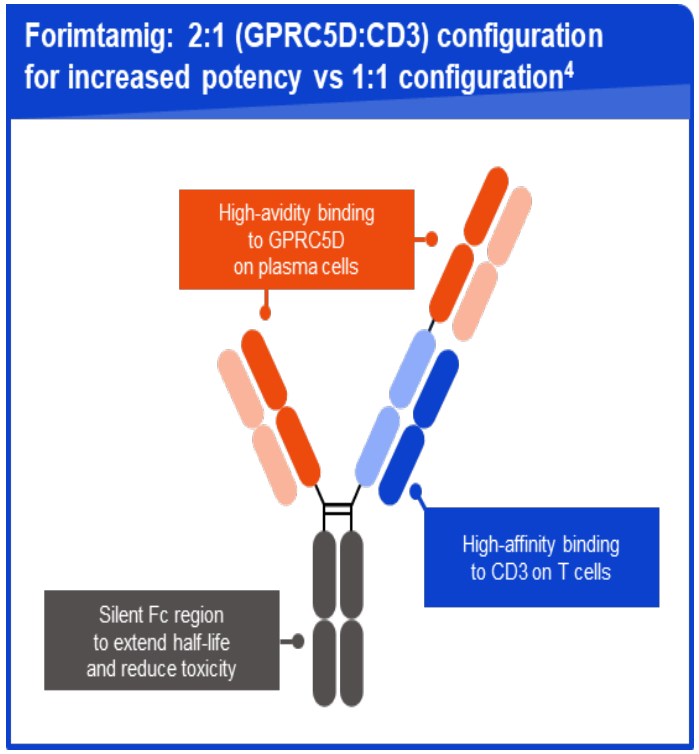
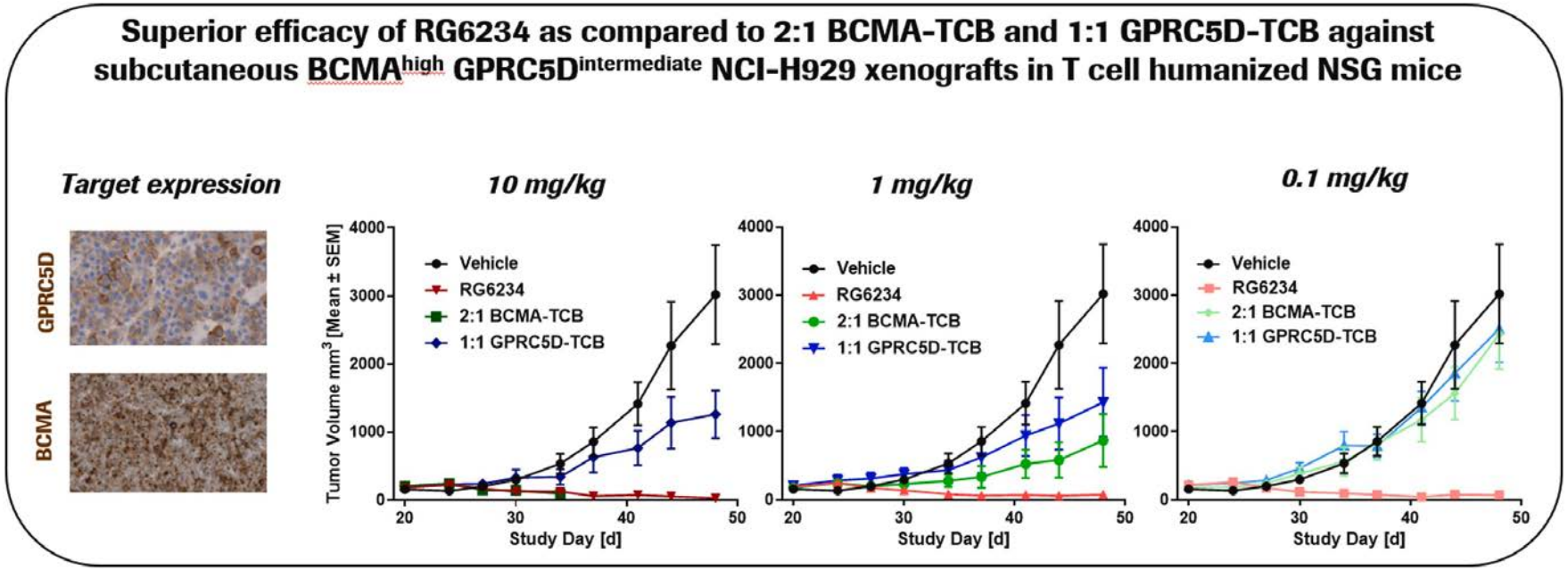
Schinke et al, ASCO 2023, #8036; Chari et al, ASH 2022, #157

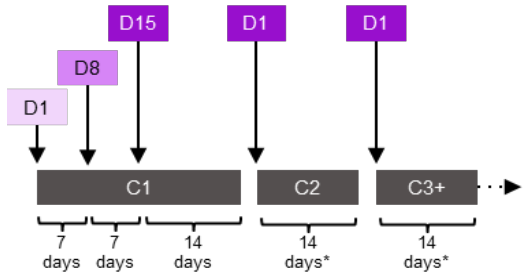
2403 Taste Abnormalities Emerging during Anti-Myeloma Therapies Including GPRC5D x CD3 Bispecific Antibody Talquetamab

Forimtamig (RG6234): GPRC5D x CD3 bsAb



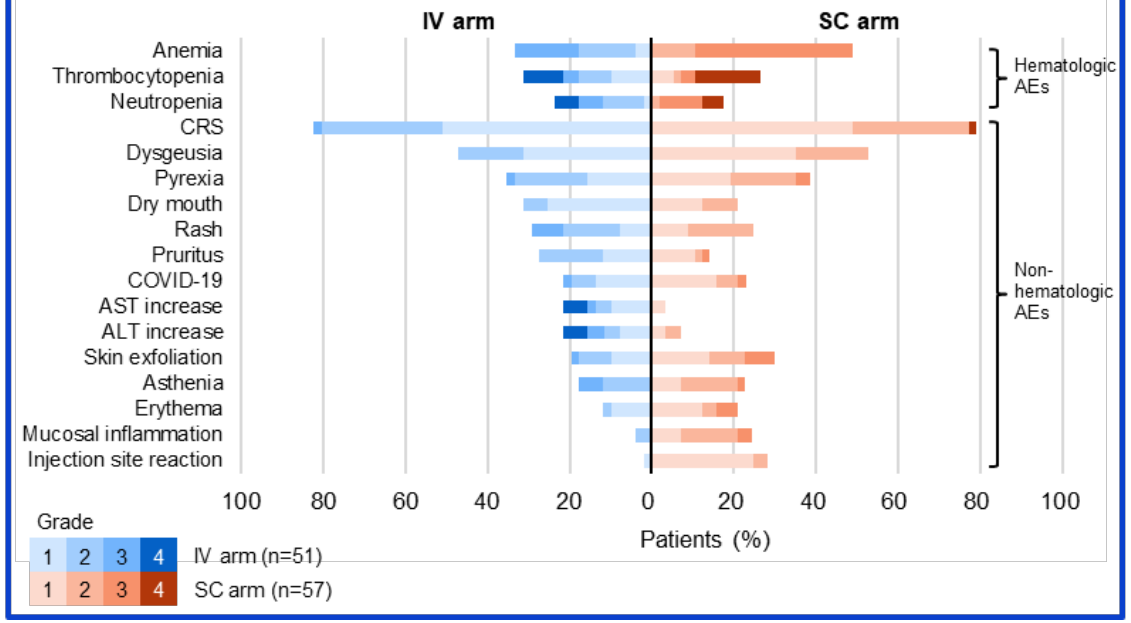


Forimtamig (GPRC5D x CD3 bsAb) phase 1/2 study

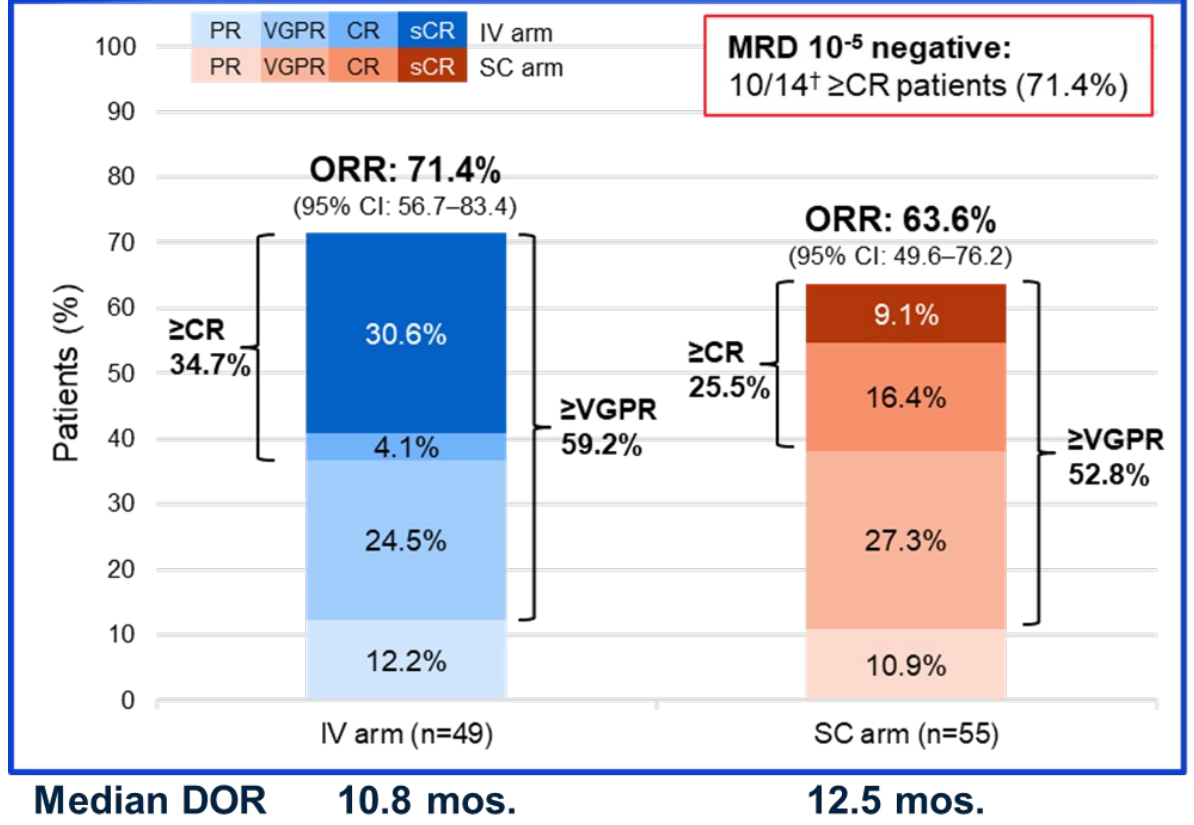


Med 5 prior tx, 70% TCR, 20% BCMA tx, 30% EMD

Common (≥20%) hematologic and non-hematologic AEs by Grade



Response rate across all tested target doses (IV: 18–10,000µg; SC 30–7200µg) in efficacy-evaluable patients*



Median DOR **10.8 mos.** **12.5 mos.**

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Carlo-Stella et al, Blood (2022) 140 (Supplement 1): 2091–2092.

GPRC combination

Bispecific Antibody	Talquetamab Phase 1/2 MonumenTAL-1 Study GPRC x CD3			Tal+ Dara Phase 1b TRIMM 2 Study	Tal + Tec RedirectTT-1
Treatment	0.4 mg/kg SQ QW	0.8 mg/kg SC Q2W	Either dose	Dara + Tal 0.4 or 0.8	Phase 1/RP2D tec 3 mg/kg, tal 0.8
Patients	n=143	n=145	n=51	n=14 **n=51**	**n=93/**n=34
Median LOT	5	5	6	5	4
TCRefr	74%	69%		61% (53% prior BCMA exp)	80%
ORR @RP2D	**74%**	**72%**	**65% (prior CART/bisp 75%/44%)**	**84% (n=50)**	**86%**
PFS	**7.5 mos**	**14.2 mos**	**5.1**	**19.4**	**20.9 mos**
DOR	**9.5 mos**	**NR**	**11.3 mos**	**20.3**	**NE**
Median f/u	18.8 mos	12.7 mos	14. 8 mos	15 mos	13.4 mos
AEs, (All/(Gr 3+)					
CRS	79% (2%)	75% (0.7%)	77% (2.0%)	~80% (0%)	76% (3.2%)
Infections	59% (20%)	66% (15%)	73% (28%)	73% (26%)	84% (53%)
Neutropenia	35% (31%)	28% (22%)	55% (53%)	~39%(28%)	66% (61%)
Anemia	45% (32%)	39% (25%)	39% (25%)	~49% (26%)	51% (34%)
Thrombocytopenia	27% (20%)	30% (19%)	37% (29%)	~37% (20%)	43% (29%)
ICANS	11% (1.6%)	10% (1.8%)	10% (1.8%)	5% (0%)	3% (? 1)
# Deaths	0 due to AEs	0 due to AEs	0 due to AEs	1 due to AE	NR
Hypogamma/IVIg	NR/13%	NR/10%	NR/10%	NR	82%/NR
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%)	Oral 90% (4%) Skin 84% (8%) Nail 67% (2%)	61% (N/A) 54% (0%) 46% (0%)

Accelerated approval

Chari et al ASH 2022; Touzeau et al EHA 2023

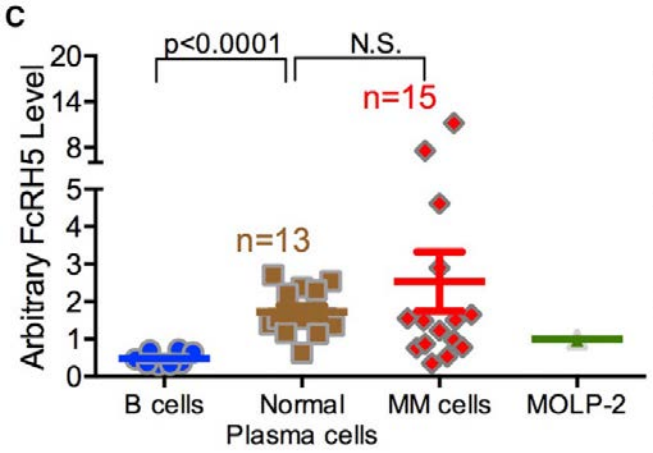
Cohen ASCO 2023

Dholaria ASCO 2023

Fc receptor-homolog 5 (FcRH5) Protein and mRNA expression

- Surface protein in immunoglobulin superfamily, closely related to Fc receptors
- Ligand(s) for FcRH5 are unknown, but implicated in proliferation and isotype expression in the development of antigen-primed B cells
- FcRH5 protein and mRNA over-expressed in malignant plasma cells
- Expressed on 100% of myeloma cells; expression increased in gain(1q)

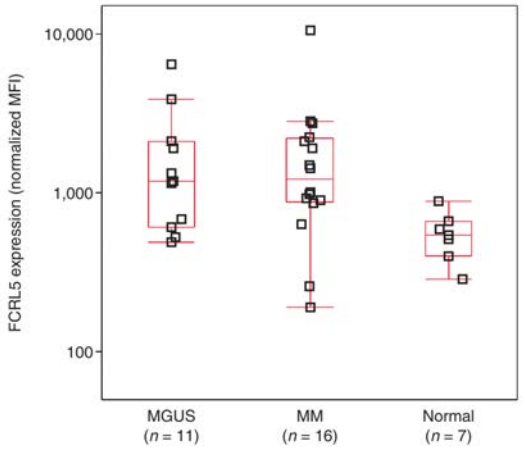
FcRH5 protein expression by flow cytometry



MGUS, monoclonal gammopathy of undetermined significance

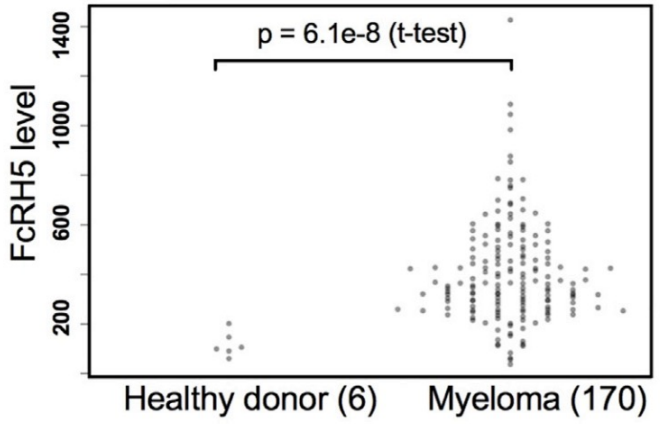
Li J et al. Cancer Cell 2017;31(3):383-395

FcRH5 protein expression by flow cytometry



Elkins K et al. Mol Cancer Ther 2012;11(10):2222-32

FcRH5 mRNA expression in CD138+ plasma cells



Li J et al. Cancer Cell 2017;31(3):383-395

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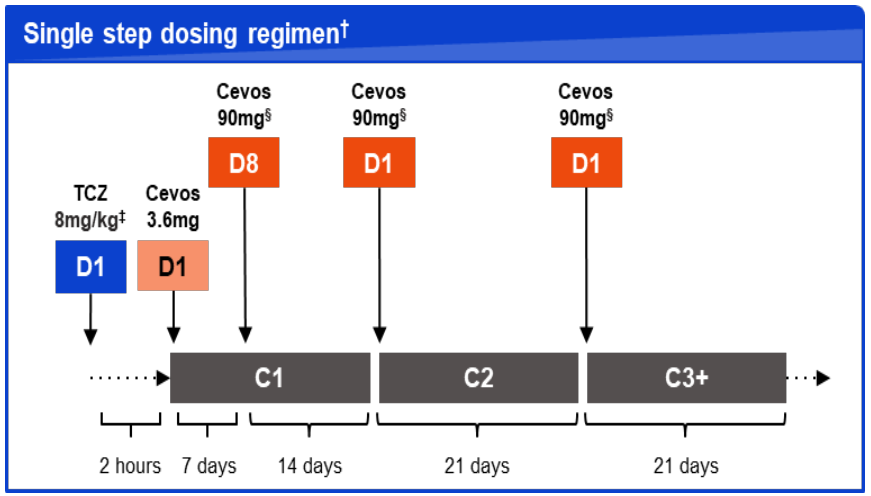
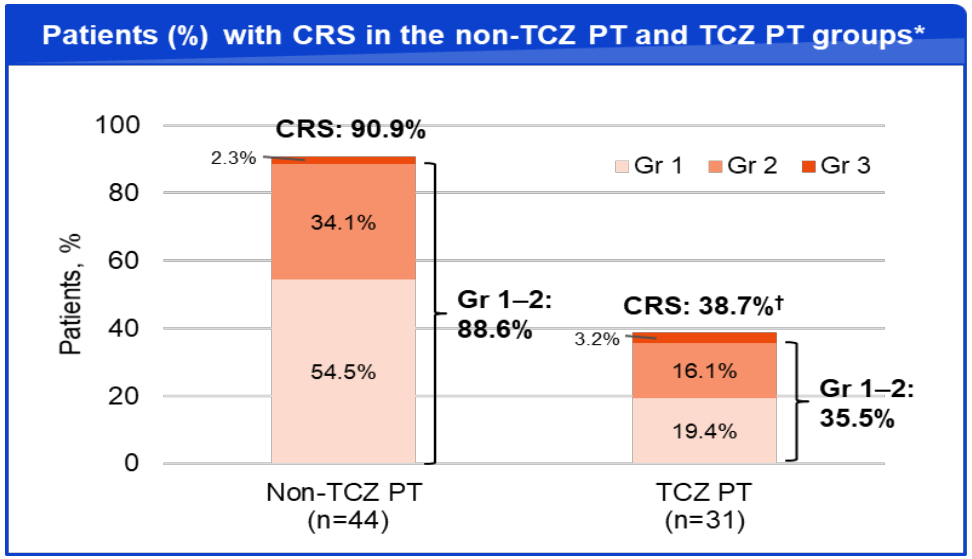
Cevostamab (FcRH5 x CD3 bsAb)

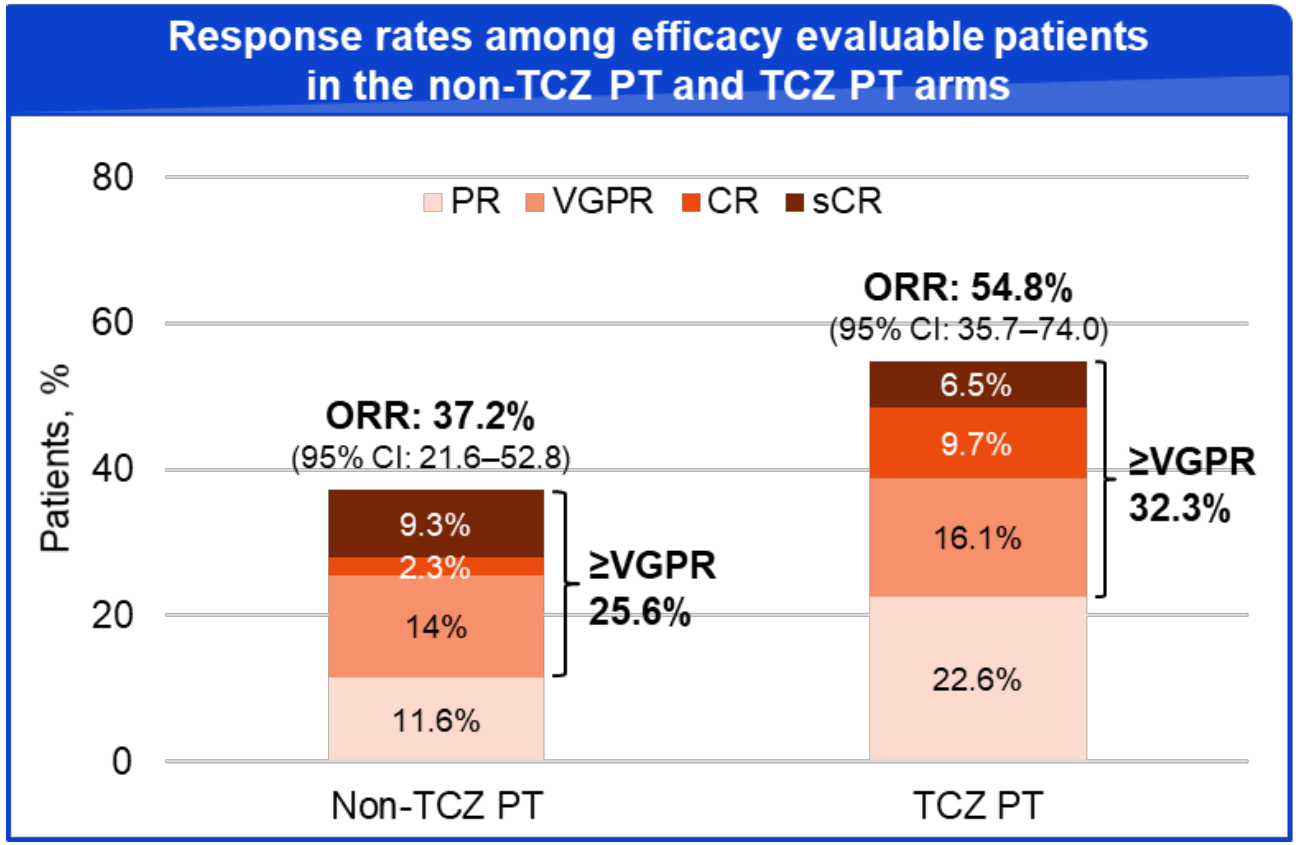




No Toci **Toci**

ICANS: 13.6% vs 6.5%

⬇ANC G3/4: 39% vs 64%



Trudel et al, ASH 2022, #567; Mateos et al., EHA 2023.

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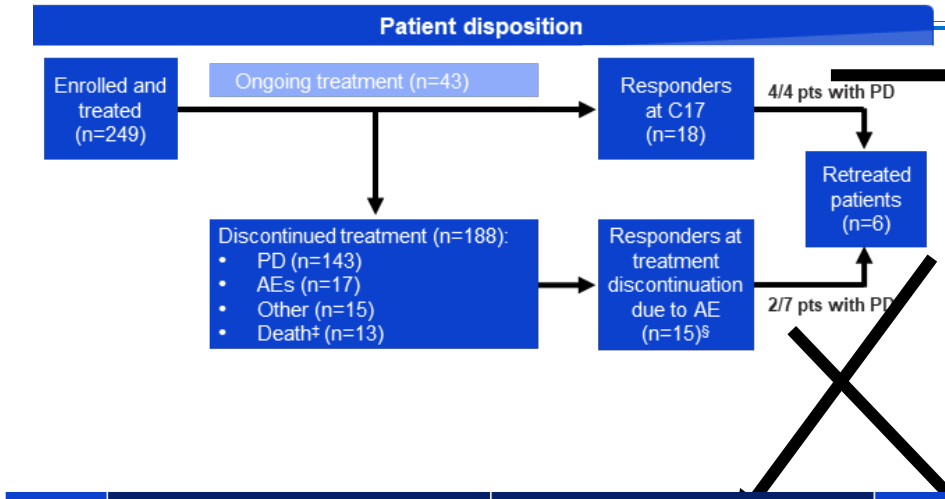
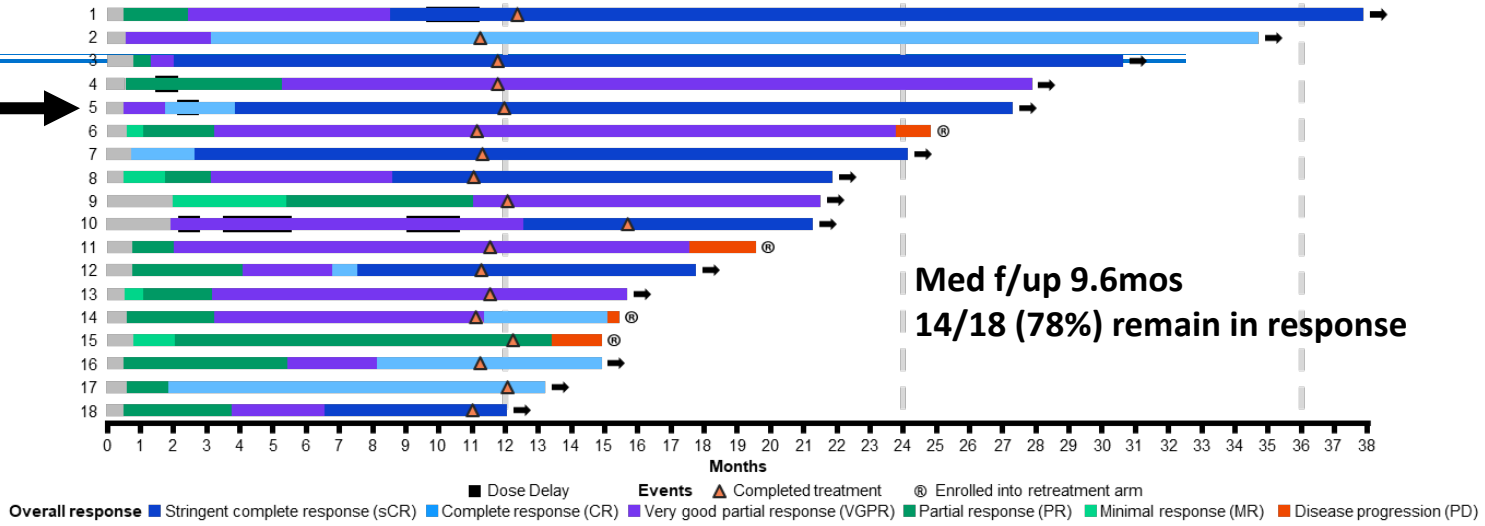
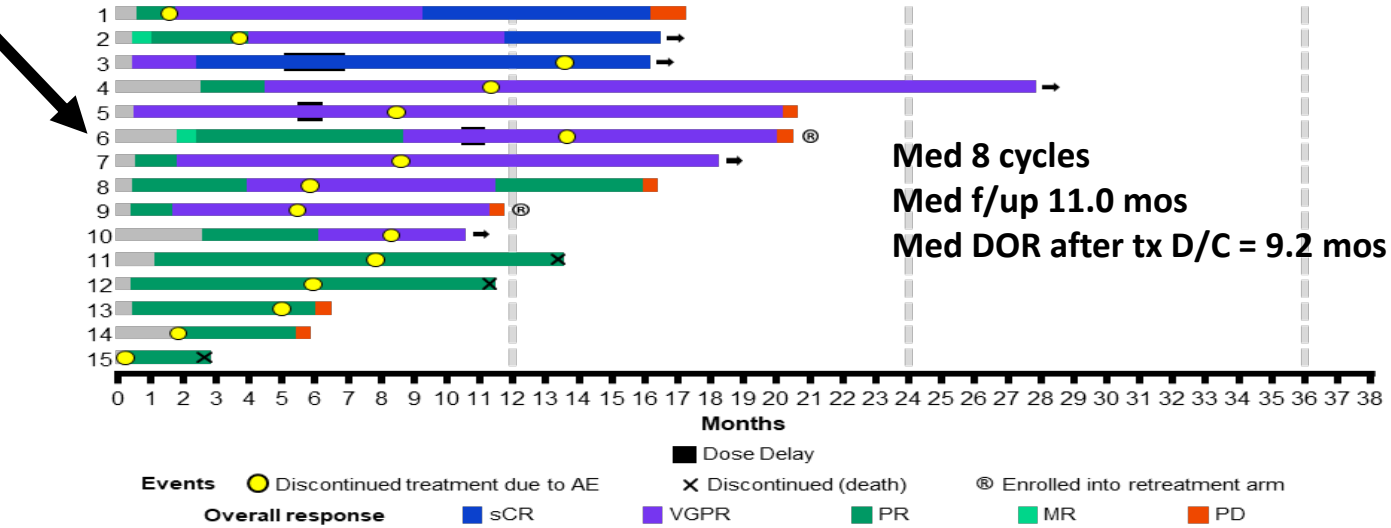
Cevostamab (FcRH5 x CD3 bsAb): Durable responses off therapy



	Initial treatment phase			Retreatment phase			Total time on study (months)
	Time on treatment (months)	Best response	Time from last initial treatment to retreatment (months)	Time on retreatment (months)	Best response	Data cut-off	
Patient 1	12.2	PR	2.5	5.1	MR	Ongoing	19.8
Patient 2	11.1	VGPR	14.0	4.4	SD	Ongoing	29.5
Patient 3	11.1	VGPR	10.1	0.7	SD	Ongoing	21.9
Patient 4	11.5	VGPR	8.5	8.3	PR	PD at 8.3 months	28.3
Patient 5	11.1	CR	4.8	1.0	SD	PD at 1.9 months	16.9
Patient 6	4.8	VGPR	7.1	1.5	PD	PD at 0.7 months	13.4



Med f/up 9.6mos
14/18 (78%) remain in response



Med 8 cycles
Med f/up 11.0 mos
Med DOR after tx D/C = 9.2 mos

Leshokin et al, ASH 2022, #1924; Mateos et al, EHA 2023

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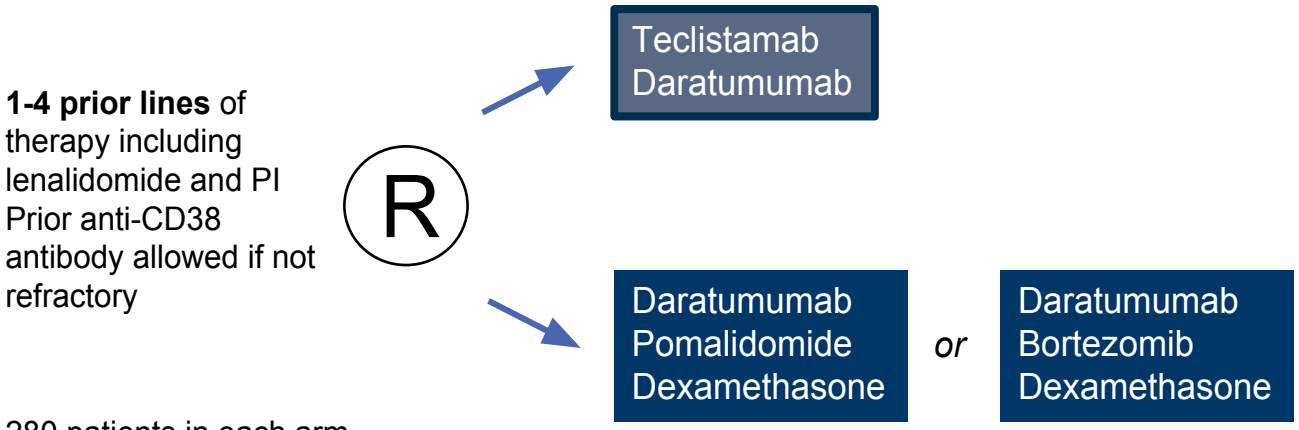
3389 Sequential T-Cell Engagement for Myeloma ("STEM") Trial: A Phase 2 Study of Cevostamab Consolidation Following BCMA CAR T Cell Therapy

Moving BCMA Bispecifics Into Early Relapse

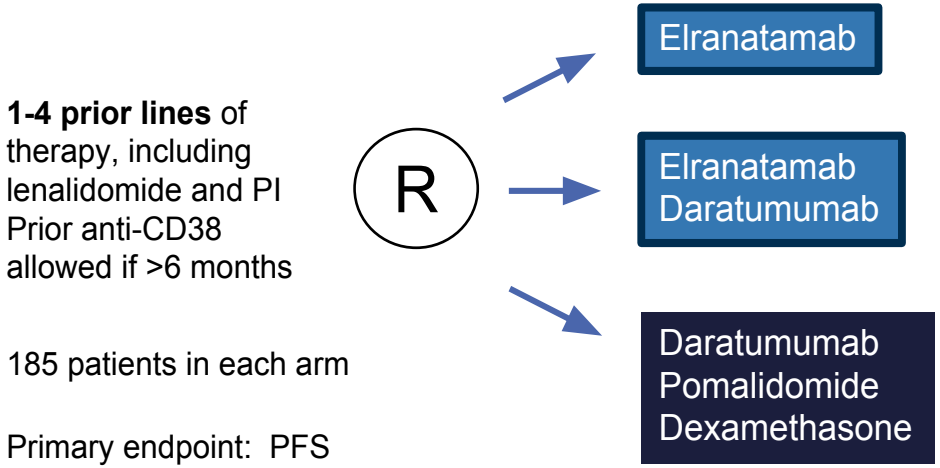
MajesTEC-3. Teclistamab

Adapted from Mateos M-V et al., ASCO 2022

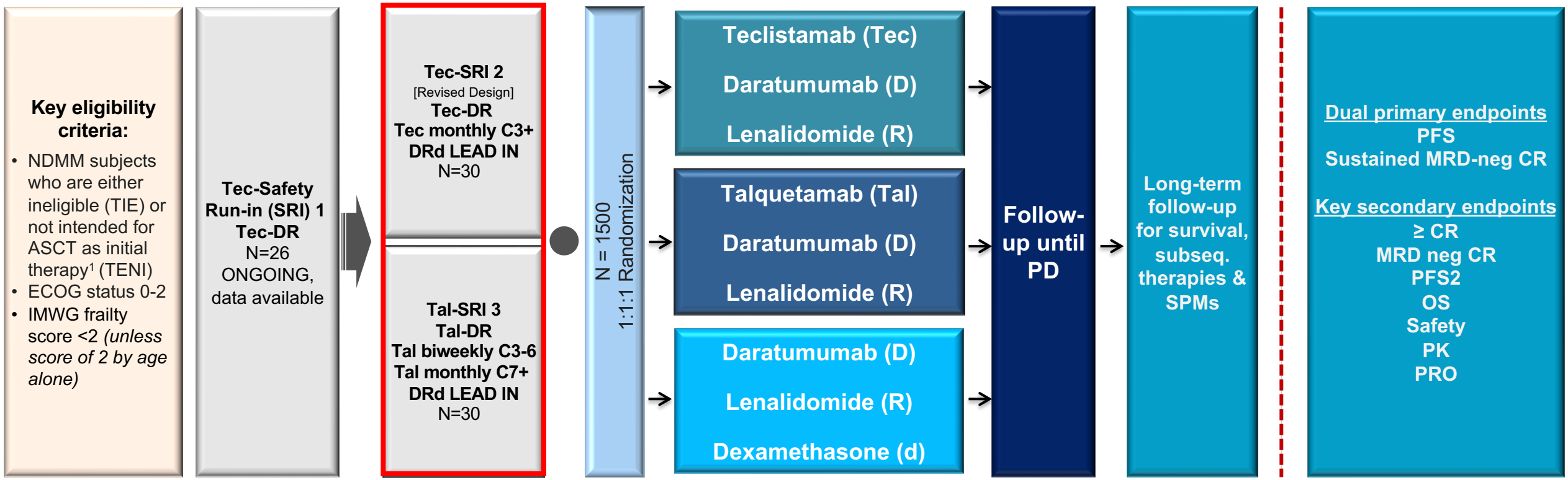


MagnetisMM-5. Elranatamab

Adapted from Grosicki S et al., ASCO 2022



MajesTEC-7: Study Design



Dosing

Cycle	1	2	3	4	5	6	7+ until PD
TEC (SRI1)	TEC Step Up + Dara	1.5 mg/kg TEC Weekly + Dara + Len	Q2W				Q4W
TEC (SRI2)	DRd Lead-in[2]	TEC Step Up + Dara + Len	Q4W				
TAL (SRI3)	DRd Lead-in[2]	TAL Step Up + Dara + Len	Q2W	Q2W	Q2W Change to Q4W if in ≥ VGPR		Q4W

1- Transplant "not intended"/deferred is limited to 15% per protocol to ensure power for truly transplant ineligible (TIE) population

2- Lead-in of 1 cycle of DRd prior to introducing Teclistamab OR Talquetamab in C2

Key changes from original design (SRI1): Addition of Tec-DR arm; monthly dosing of tec (before QW→Q2W C3-6→Q4W C7+); bi-specific free "lead-in cycle" and exclusion of frail patients

Conclusions: Bispecifics

- The future is bright with BCMA

- Non BCMA targets (GPRC5d, FCRH5)
- CD38 (ISB1342, IGM 2644)
- Improving toxicity
  - Prophylaxis for CRS ➔ need outpatient therapy
  - Limiting duration of therapy [MRD guided, risk-adapted de-escalation]
  - Rational combinations: TCE ➔ IMiD/CELMoD maintenance
- Sequencing therapies: CART before bispecific?

Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Richardson

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) MM — Dr Lonial

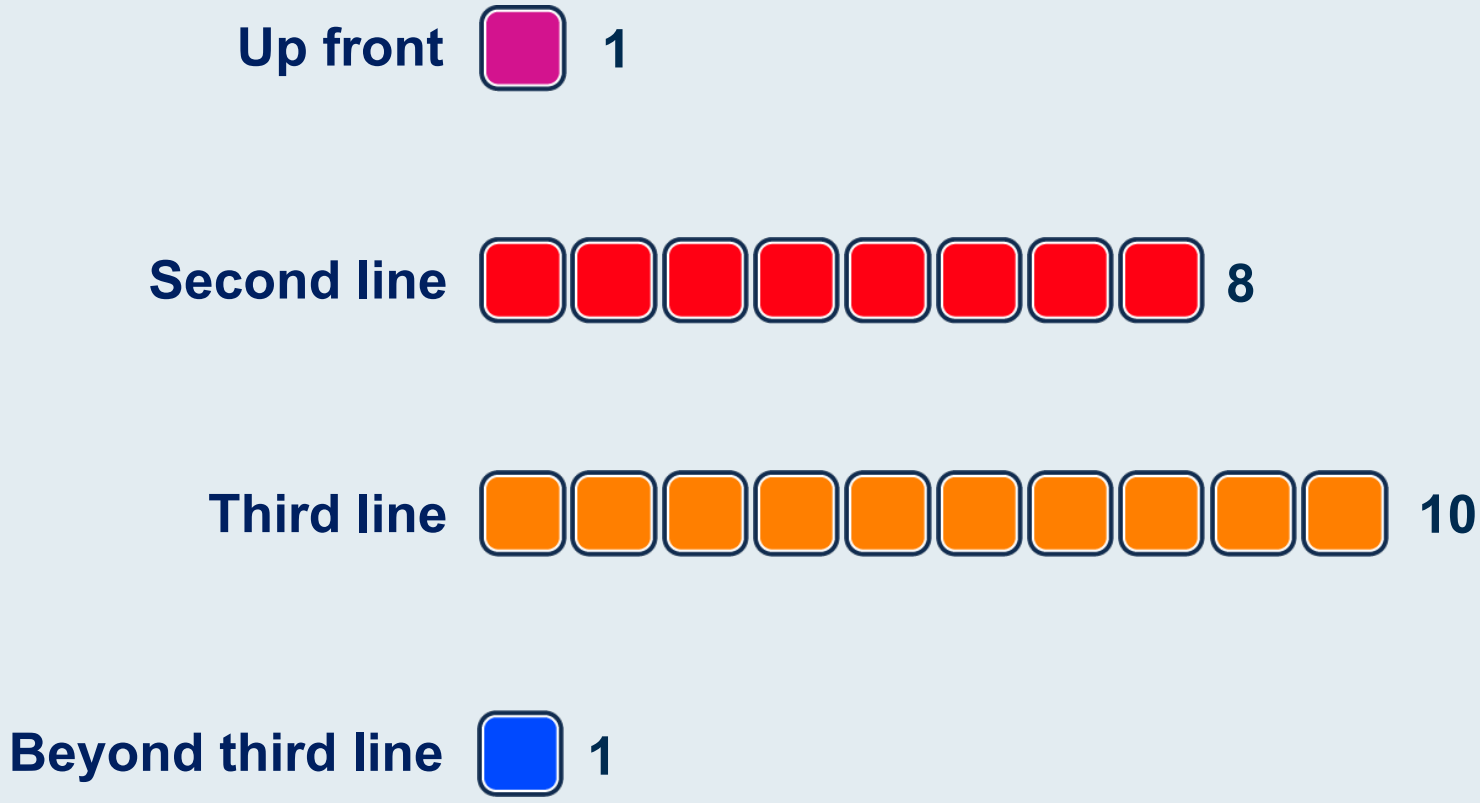
Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies in the Treatment of MM — Dr Krishnan

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Orlowski

RTP RESEARCH TO PRACTICE

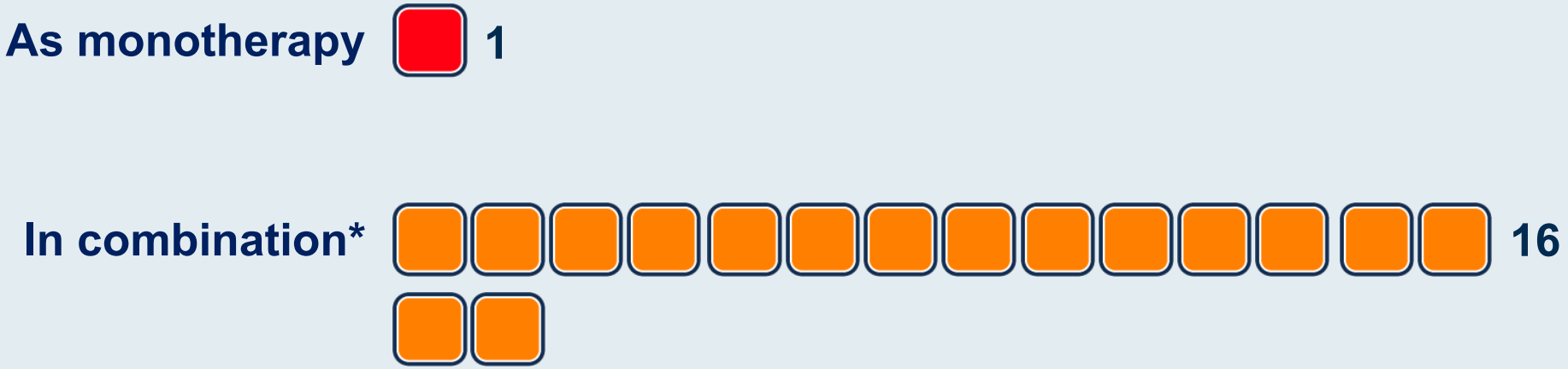
Regulatory and reimbursement issues aside, at what point, if any, would you attempt to access venetoclax for a patient with t(11;14) MM?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which method do you consider optimal for administering venetoclax to a patient with MM?



* Generally with a proteasome inhibitor or daratumumab

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Biological rationale for targeting Bcl-2 in t(11;14)-positive MM; use of venetoclax-based combinations

C Ola Landgren, MD, PhD

RTP
RESEARCH
TO PRACTICE

Clinical experience with venetoclax for t(11;14)-positive R/R MM

Melissa Alsina, MD

RTP
RESEARCH
TO PRACTICE

Other Novel Agents & Strategies Under Investigation in Multiple Myeloma

Robert Z. Orlowski, M.D., Ph.D.

Director, Myeloma Section, & Deputy Chair, Department of Lymphoma/Myeloma

Florence Maude Thomas Cancer Research Professor

Principal Investigator, MD Anderson SCOR in High Risk Plasma Cell Dyscrasias

Chair, SWOG Myeloma Committee

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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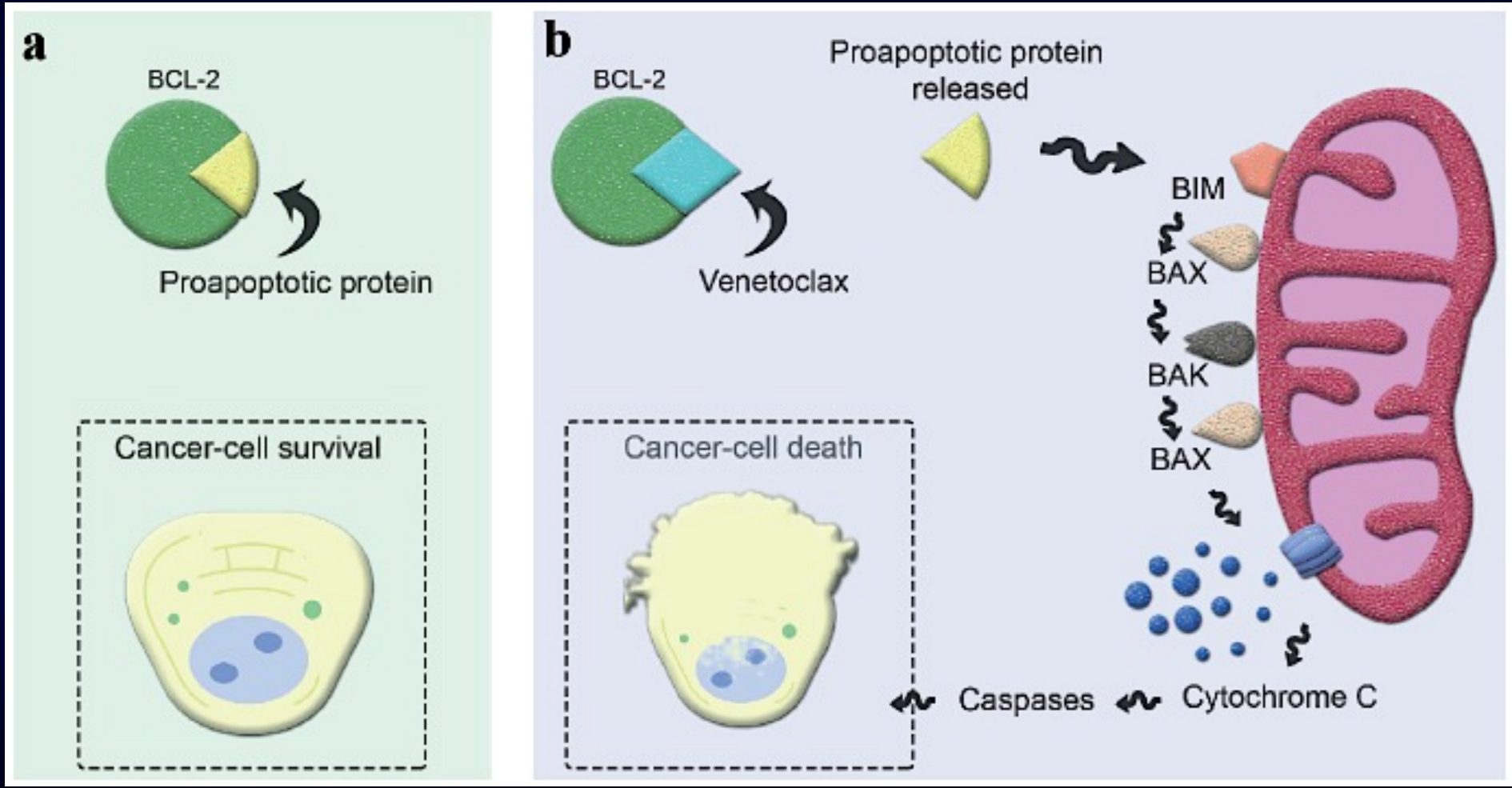
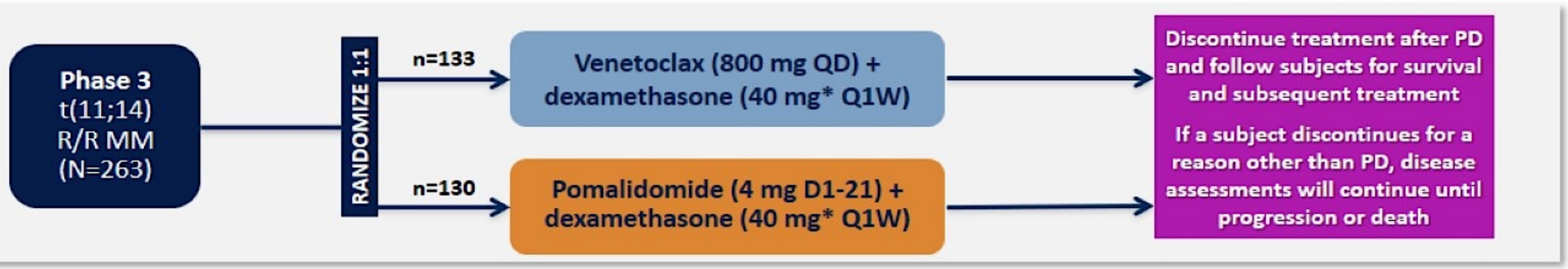
Rationale for Venetoclax in t(11;14)



Ehsan H et al. *J Hematol*. 2021;10(3):89-97.

CANOVA: Venetoclax in t(11;14)



INCLUSION CRITERIA

- t(11;14)-positive multiple myeloma by FISH
- ≥ 2 prior lines of therapy
- ECOG PS ≤2
- Documented disease progression on or within 60 days after completion of their last therapy
- Received at least 2 cycles of both lenalidomide and a proteasome inhibitor, alone or together
- Refractory to lenalidomide

EXCLUSION CRITERIA

- Prior venetoclax or pomalidomide

OBJECTIVES

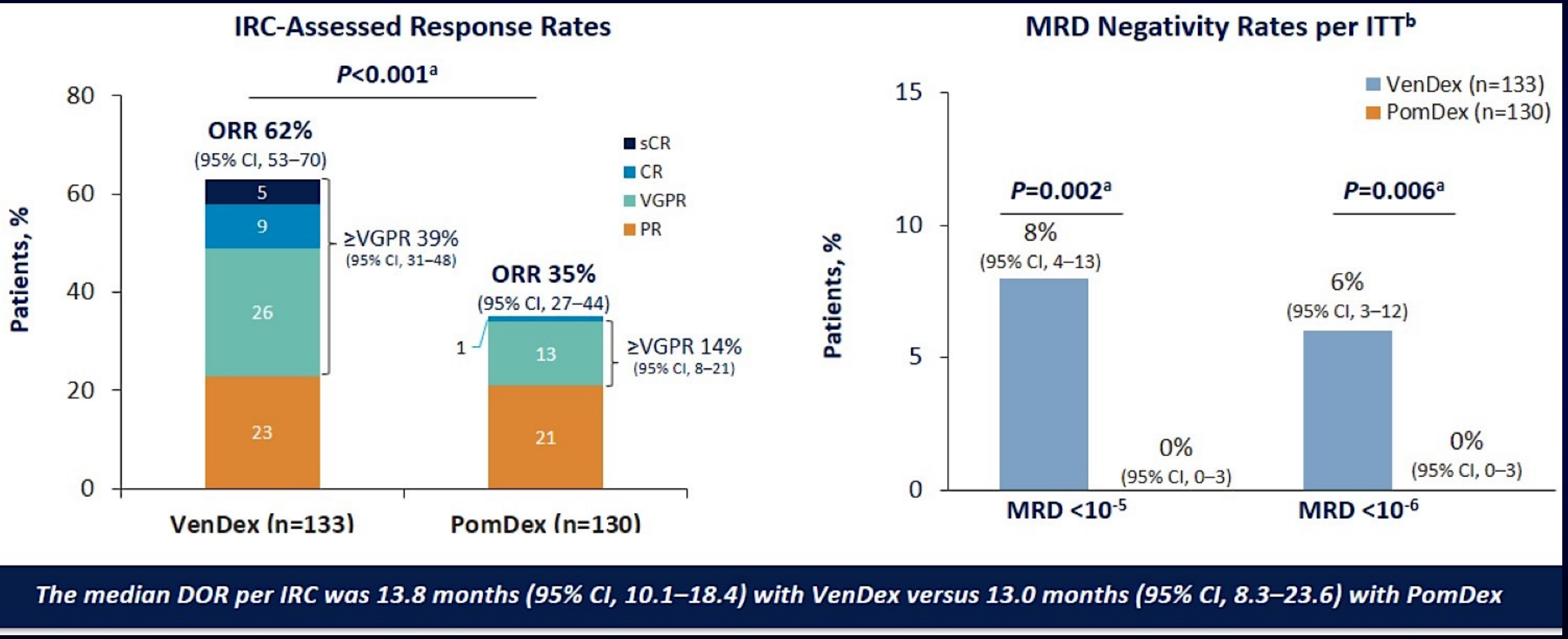
Primary: ***PFS***

Secondary: ***Response rates (ORR, VGPR or better), OS, DOR, TTP, TTR, MRD, PK, Safety, PROs***

Data cutoff date: July 24, 2023.
*Patients aged ≥75 years received dexamethasone 20 mg QW. Dexamethasone could be administered IV when PO was not possible.

OA-52: Results From the Randomized, Open-Label Phase 3 CANOVA Study of Venetoclax Versus Pomalidomide Added to Dexamethasone in Patients With t(11;14)-Positive Relapsed/Refractory Multiple Myeloma — Maria-Victoria Mateos

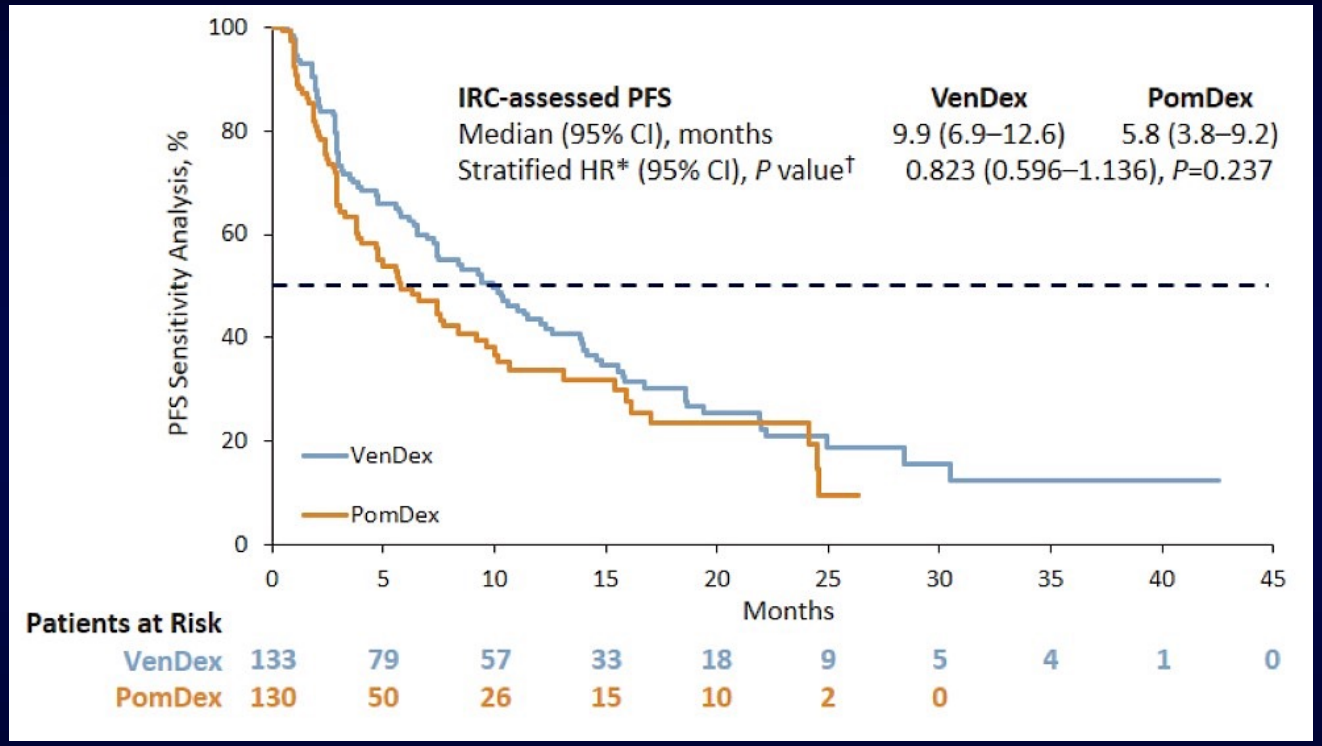
Response Rate and Depth

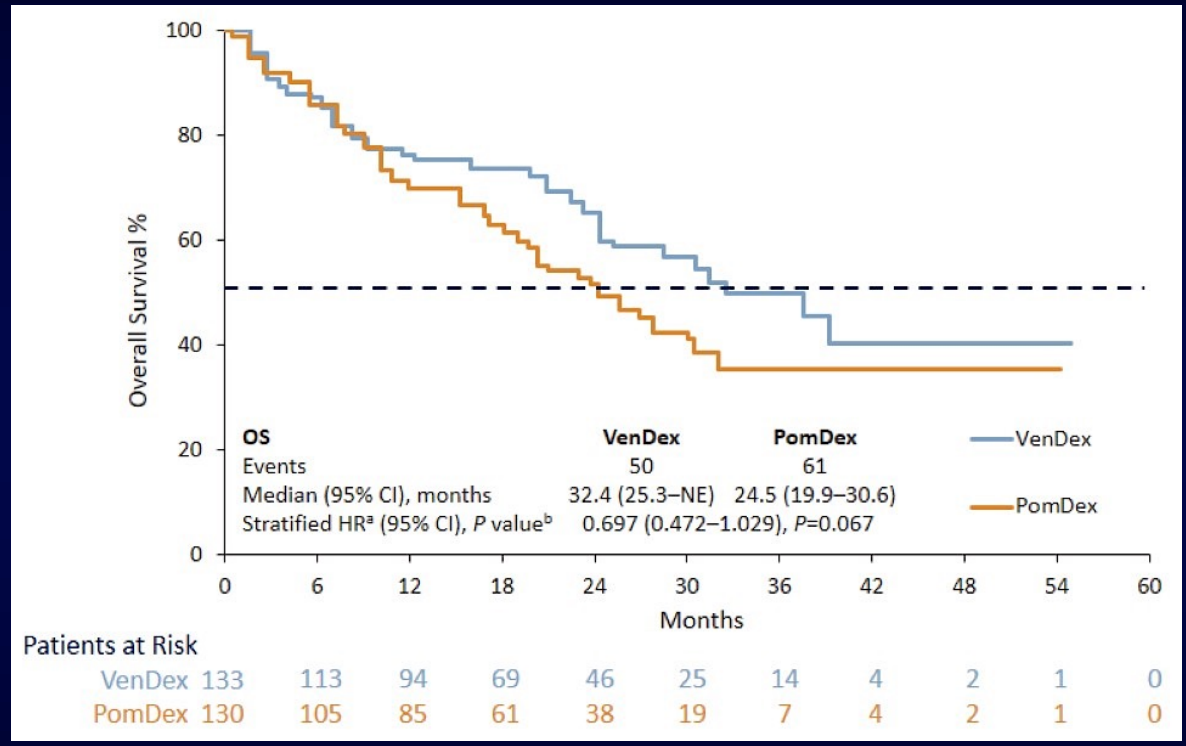


The median DOR per IRC was 13.8 months (95% CI, 10.1–18.4) with VenDex versus 13.0 months (95% CI, 8.3–23.6) with PomDex

Mateos M-V et al. IMS 2023; Abstract OA-52.

Durability (PFS & OS) Data

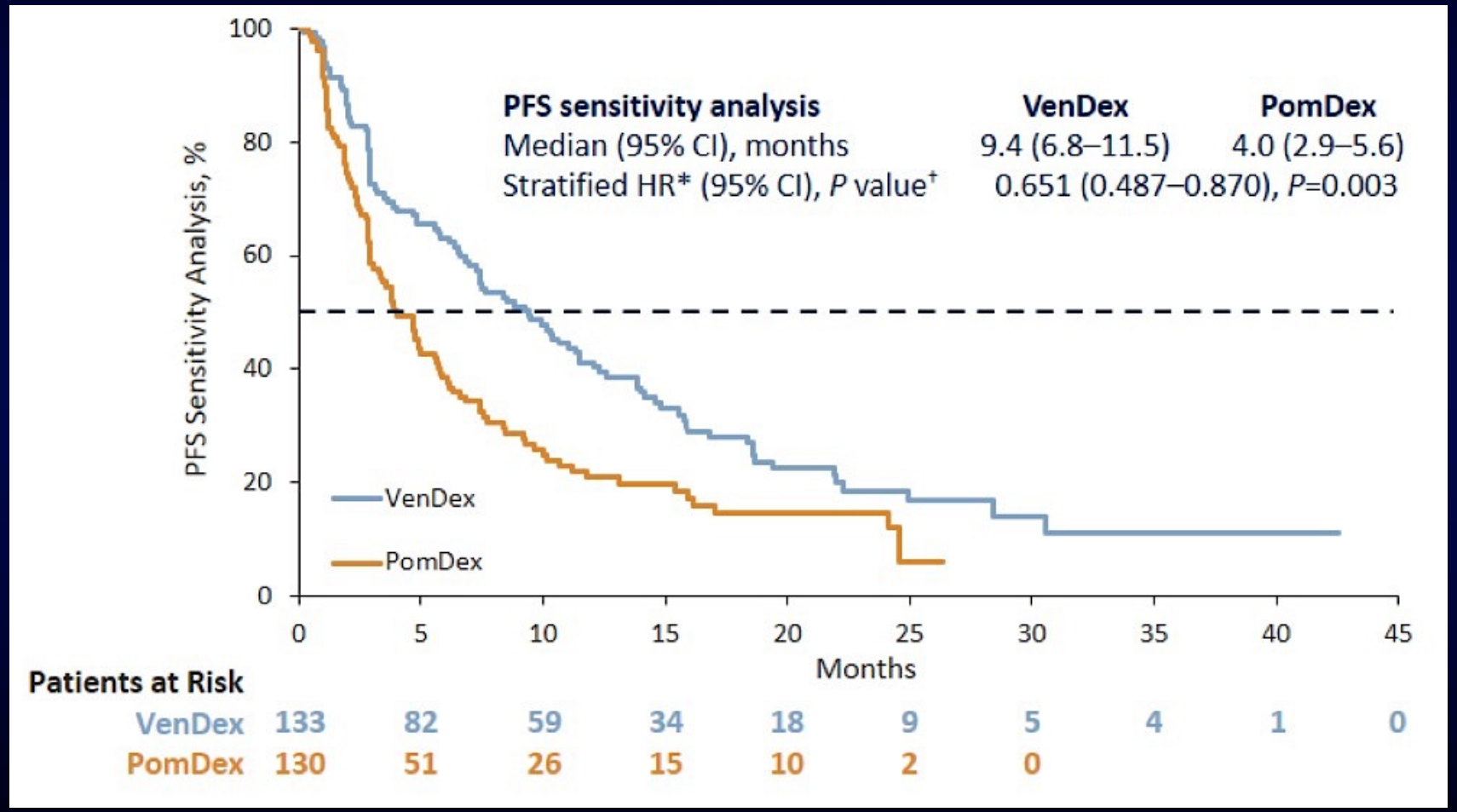




- Nice trends favoring Ven/dex but not reaching statistical significance

Mateos M-V et al. IMS 2023; Abstract OA-52.

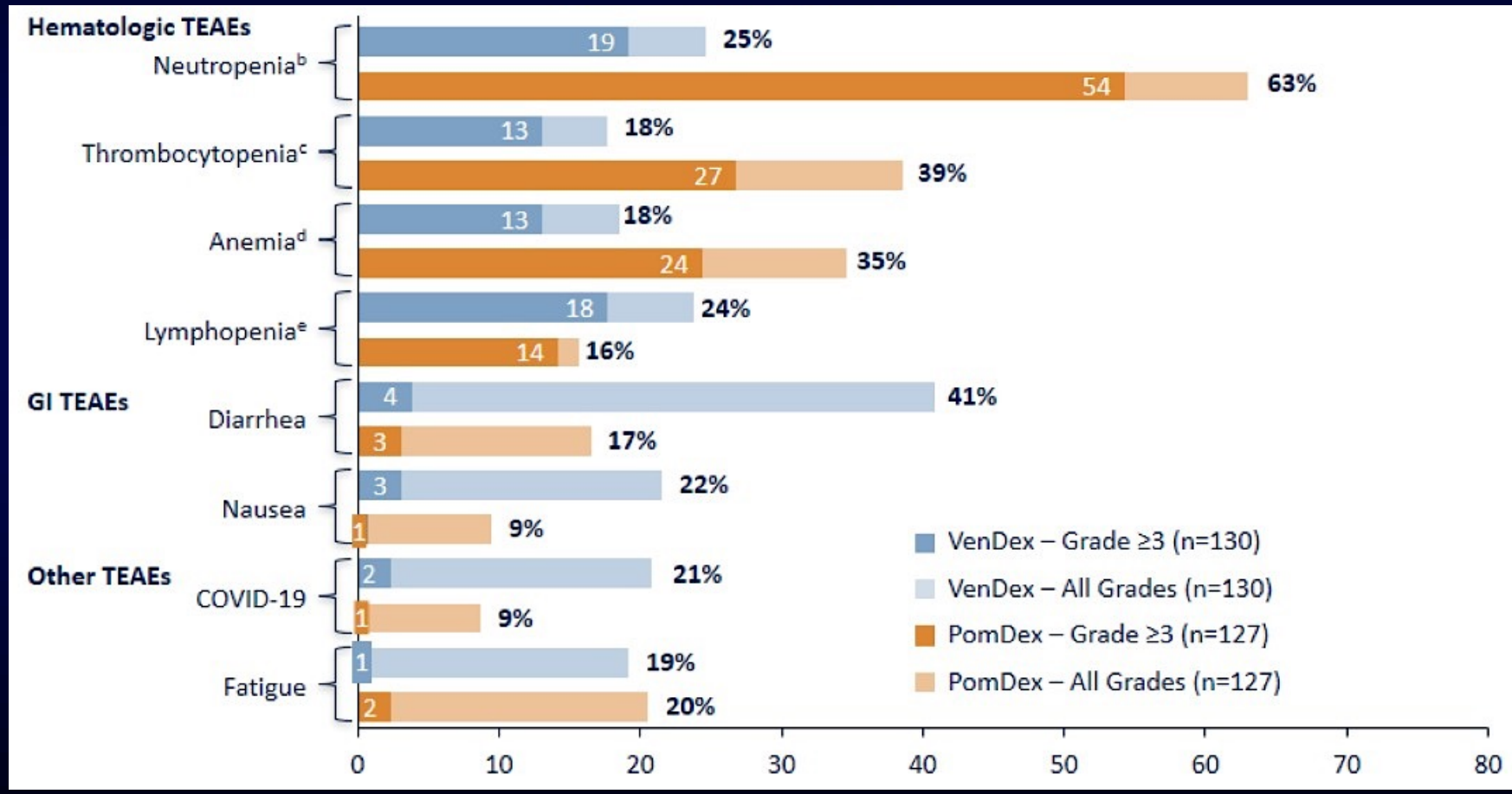
Post hoc Sensitivity Analysis



- Patients without IMWG-defined PD censored
- Also significantly better TTNT

Mateos M-V et al. IMS 2023; Abstract OA-52.

Most Common TEAEs



- Laboratory TLS occurred in 4 patients in the VenDex arm and 2 patients in the PomDex arm; there were no cases of clinical TLS
- **The safety profiles were consistent with the known safety profile of each individual study drug, with no new safety signals observed for venetoclax**

Mateos M-V et al. IMS 2023; Abstract OA-52.

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Response Rate Data

Variable	Dose-Escalation Cohort			Dose-Expansion Cohort		
	All Patients (N=77)	10-Day Schedule, Repeated† (N=10)	21-Day Schedule‡ (N=11)	All Patients (N=101)	Patients with Plasmacytomas§ (N=40)	Patients with Previous Anti-BCMA Therapy (N=30)
	number of patients (percent)					
Overall response¶	19 (25)	4 (40)	6 (55)	41 (41)	12 (30)	15 (50)‖
Stringent complete response	0	0	0	2 (2)	0	0
Complete response	1 (1)	0	1 (9)	3 (3)	2 (5)	1 (3)
Very good partial response	9 (12)	2 (20)	3 (27)	20 (20)	7 (18)	9 (30)
Partial response	9 (12)	2 (20)	2 (18)	16 (16)	3 (8)	5 (17)
Minimal response	4 (5)	1 (10)	1 (9)	6 (6)	0	1 (3)
Stable disease	34 (44)	4 (40)	4 (36)	39 (39)	21 (52)	11 (37)
Progressive disease	17 (22)	1 (10)	0	10 (10)	4 (10)	3 (10)
Response could not be evaluated**	3 (4)	0	0	5 (5)	3 (8)	0

Mateos M-V et al. IMS 2023; Abstract OA-52.

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Other Partners

Clinical Trial > Blood Adv. 2021 Oct 12;5(19):3748-3759.
doi: 10.1182/bloodadvances.2020004146.

Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma

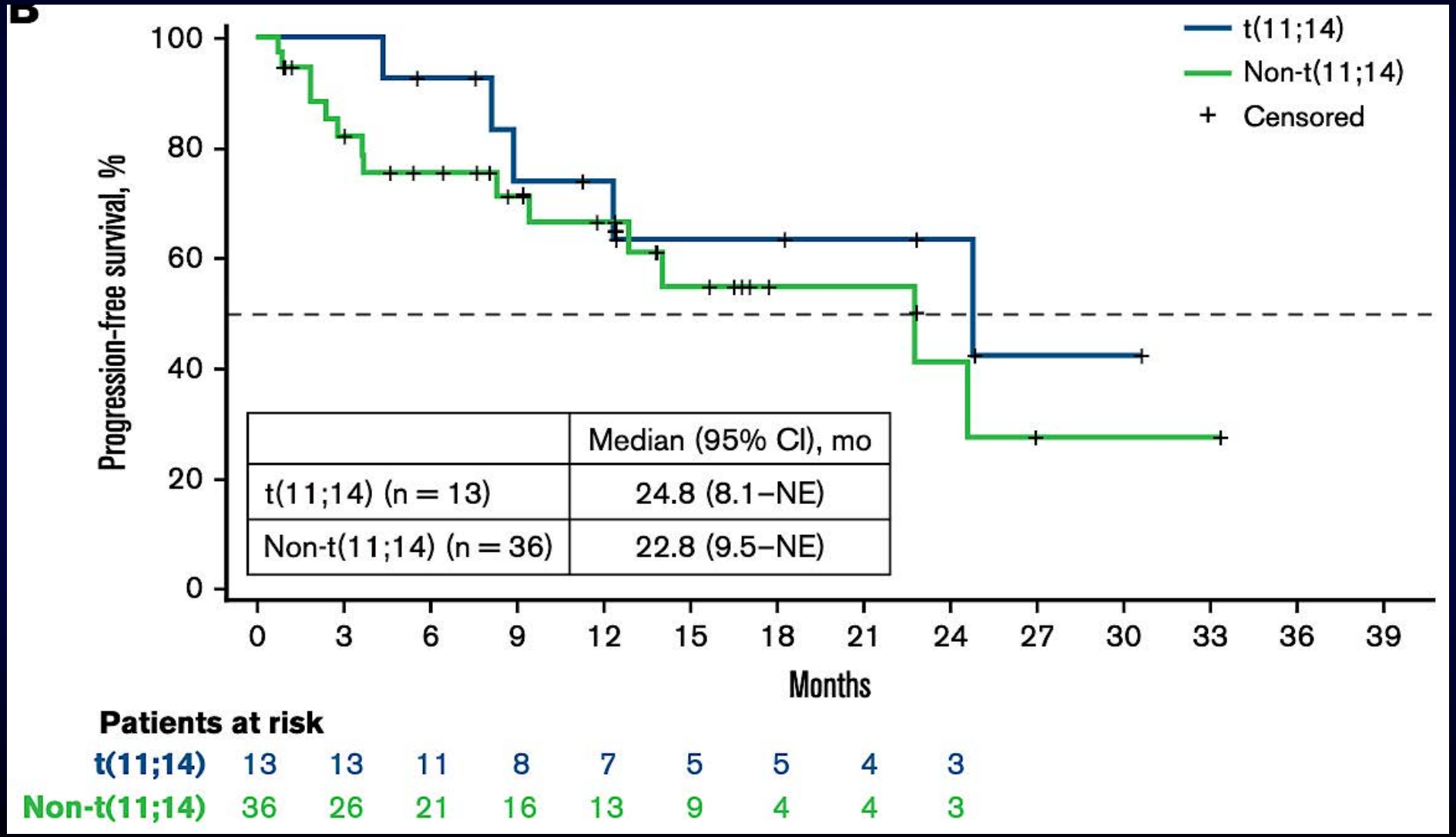
Luciano J Costa [1], Faith E Davies [2], Gregory P Monohan [3], Tibor Kovacsovics [4], Nicholas Burwick [5], Andrzej Jakubowiak [6], Jonathan L Kaufman [7], Wan-Jen Hong [8], Monique Dail [8], Ahmed Hamed Salem [9] [10], Xiaoqing Yang [9], Abdullah A Masud [9], Wijith Munasinghe [9], Jeremy A Ross [9], Orlando F Bueno [9], Shaji K Kumar [11], Edward A Stadtmauer [12]

Affiliations + expand

PMID: 34470049 PMCID: PMC8679663 DOI: 10.1182/bloodadvances.2020004146

Free PMC article

Ven/Car/dex



Costa LJ et al. *Blood Adv*. 2021;5(19):3748-3759.

Other Partners

Clinical Trial > J Clin Oncol. 2021 Nov 10;39(32):3602-3612. doi: 10.1200/JCO.21.00443.
Epub 2021 Aug 13.

Phase I Study of Venetoclax Plus Daratumumab and Dexamethasone, With or Without Bortezomib, in Patients With Relapsed or Refractory Multiple Myeloma With and Without t(11;14)

Nizar J Bahlis [1], Rachid Baz [2], Simon J Harrison [3], Hang Quach [4], Shir-Jing Ho [5], Annette Juul Vangsted [6], Torben Plesner [7], Philippe Moreau [8], Simon D Gibbs [9], Sheryl Coppola [10], Xiaoqing Yang [10], Abdullah Al Masud [10], Jeremy A Ross [10], Orlando Bueno [10], Jonathan L Kaufman [11]

Affiliations + expand

PMID: 34388020 PMCID: PMC8577687 DOI: 10.1200/JCO.21.00443

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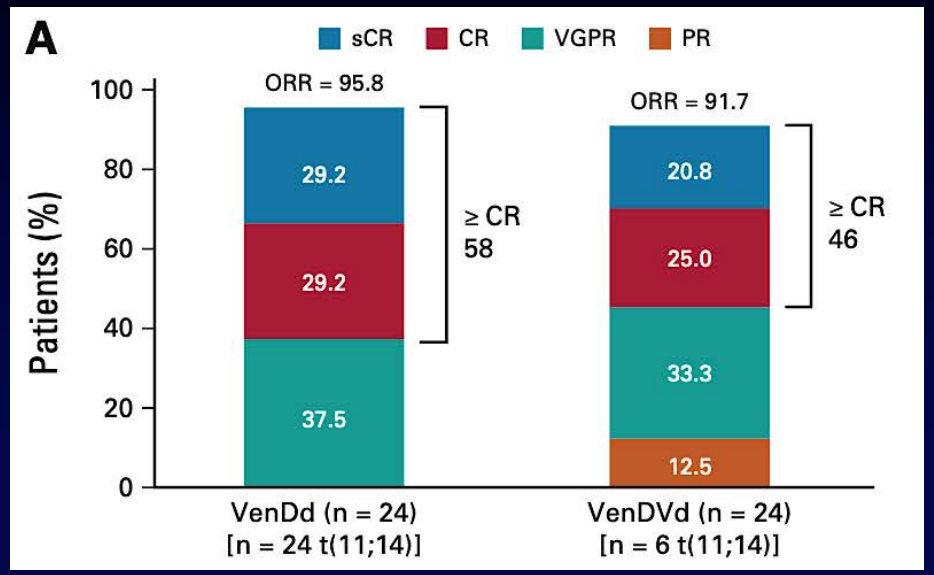
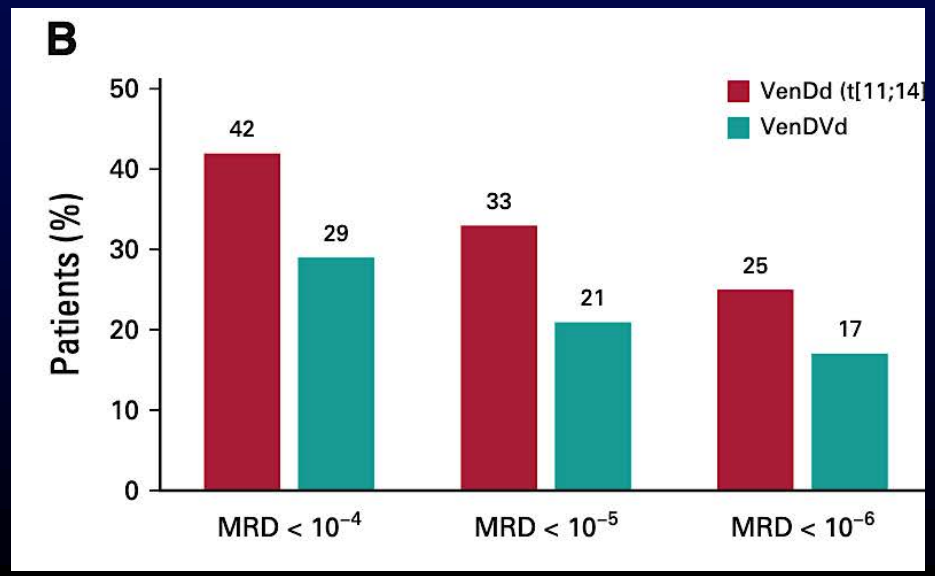
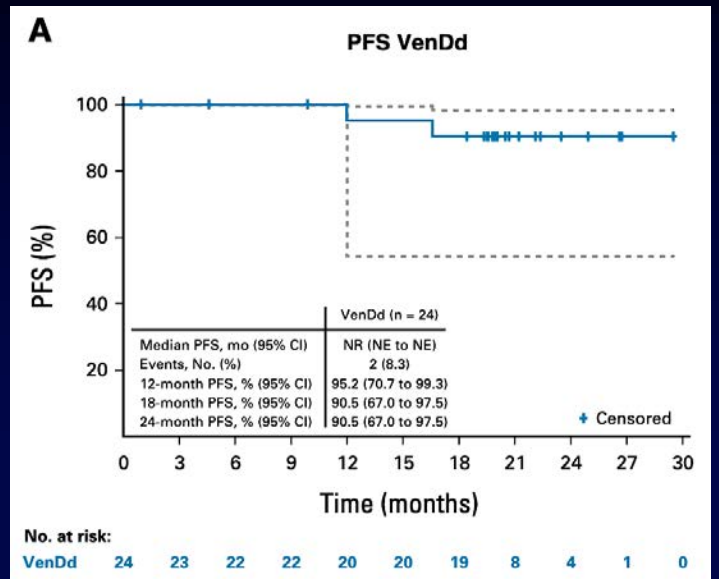
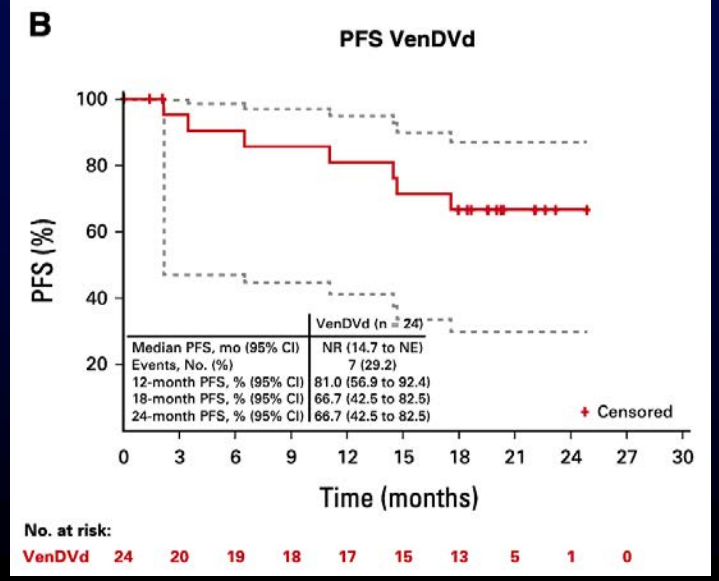
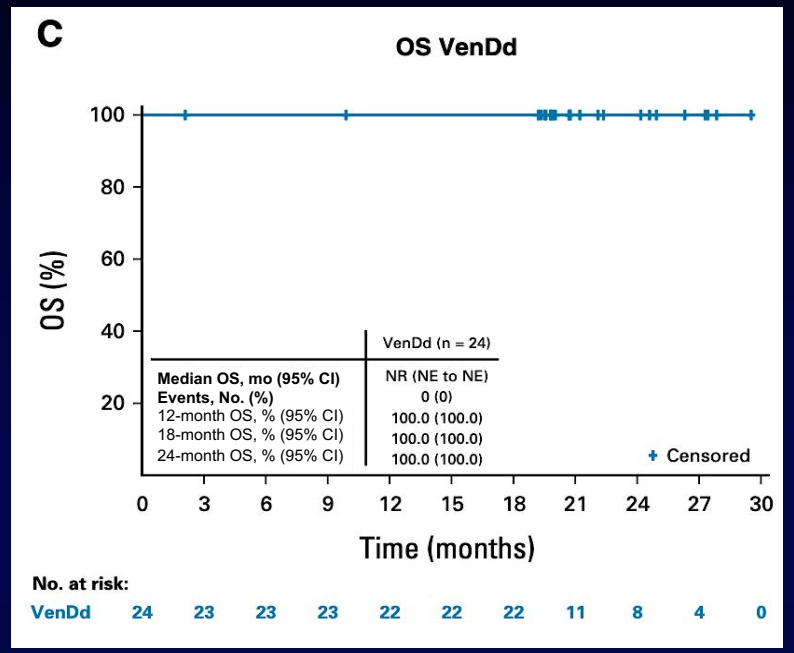
Other Partners





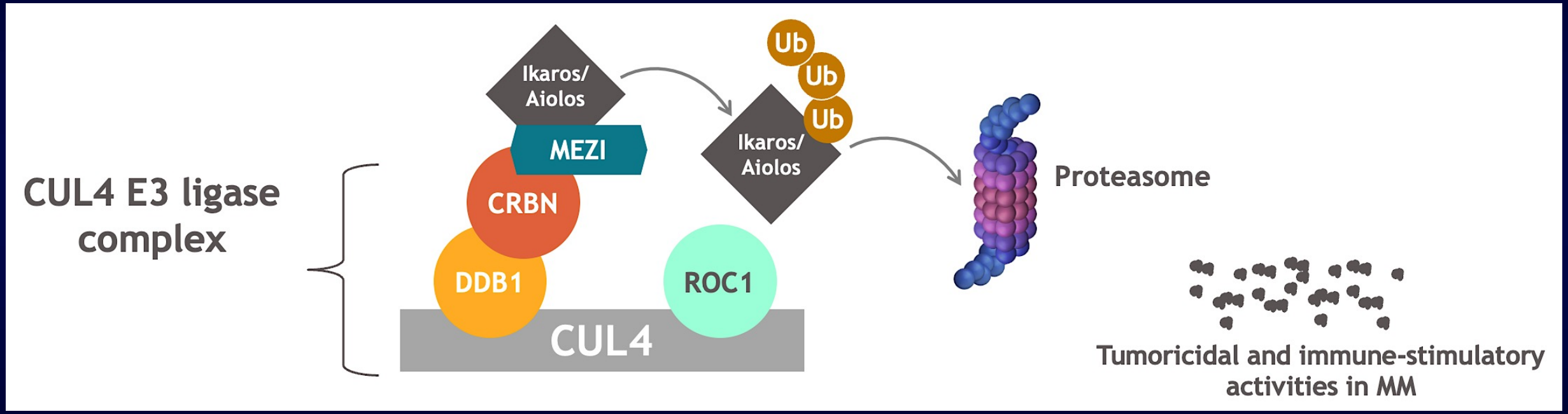






Bahlis NJ et al. *J Clin Oncol*. 2021;39(32):3602-3612.

CELMoDs in Myeloma



Iberdomide: Phase I/II Data

Clinical Trial > Lancet Haematol. 2022 Nov;9(11):e822-e832.
doi: 10.1016/S2352-3026(22)00290-3. Epub 2022 Oct 6.

Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial

Sagar Lonial [1], Rakesh Popat [2], Cyrille Hulin [3], Sundar Jagannath [4], Albert Oriol [5], Paul G Richardson [6], Thierry Facon [7], Katja Weisel [8], Jeremy T Larsen [9], Monique C Minnema [10], Al-Ola Abdallah [11], Ashraf Z Badros [12], Stefan Knop [13], Edward A Stadtmauer [14], Yiming Cheng [15], Michael Amatangelo [15], Min Chen [15], Tuong Vi Nguyen [15], Alpesh Amin [15], Teresa Peluso [16], Niels W C J van de Donk [17]

Affiliations + expand

PMID: 36209764 DOI: 10.1016/S2352-3026(22)00290-3

Patients

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	Dose-escalation cohort (n=90)	Dose-expansion cohort (n=107)
Age, years		
Median (IQR)	65 (58–71)	64 (58–73)
≥75	13 (14%)	18 (17%)
Sex		
Male	43 (48%)	60 (56%)
Female	47 (52%)	47 (44%)
Race		
White	70 (78%)	84 (79%)
Black or African American	12 (13%)	15 (14%)
Other	2 (2%)	3 (3%)
Not reported	6 (7%)	5 (5%)
Ethnicity		
Hispanic or Latino	2 (2%)	3 (3%)
Non-Hispanic or non-Latino	80 (89%)	97 (91%)
Not reported	8 (9%)	6 (6%)
Unknown	0	1 (1%)
ECOG performance status		
0	31 (34%)	42 (39%)
1	50 (56%)	55 (51%)
2	9 (10%)	10 (9%)
Cytogenetic risk category		
High*	14 (16%)	32 (30%)
Standard†	11 (12%)	18 (17%)
Missing‡	65 (72%)	57 (53%)
Time since diagnosis, years	7·5 (5·8–10·0)	6·9 (5·2–10·3)
ISS stage at study entry		
I	43 (48%)	46 (43%)
II	26 (29%)	45 (42%)
III	21 (23%)	16 (15%)
Previous HSCT	74 (82%)§	84 (79%)¶
Number of previous lines of therapy	5 (4–8)	6 (5–8)

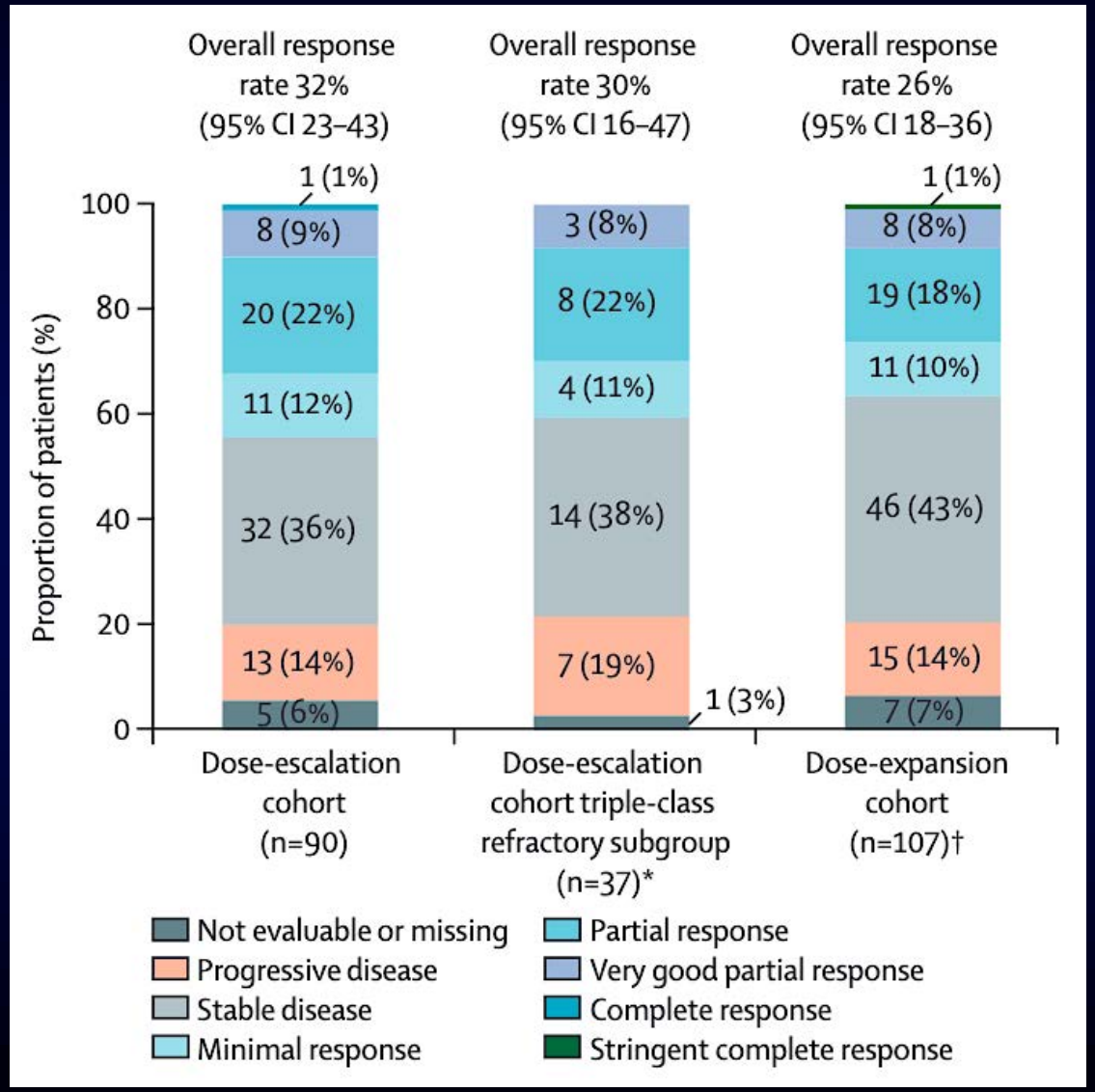
	Dose-escalation cohort (n=90)	Dose-expansion cohort (n=107)
(Continued from previous column)		
Type of previous therapy		
Immunomodulatory drugs	90 (100%)	107 (100%)
Lenalidomide	90 (100%)	107 (100%)
Pomalidomide	63 (70%)	107 (100%)
Proteasome inhibitors	90 (100%)	107 (100%)
Bortezomib	89 (99%)	106 (99%)
Carfilzomib	44 (49%)	73 (68%)
CD38 monoclonal antibodies	68 (76%)	107 (100%)
Alkylating agents	86 (96%)	103 (96%)
Refractory to previous therapy		
Immunomodulatory drugs	86 (96%)	107 (100%)
Lenalidomide	76 (84%)	91 (85%)
Pomalidomide	57 (63%)	102 (95%)
Proteasome inhibitors	70 (78%)	104 (97%)
CD38 monoclonal antibodies	67 (74%)	107 (100%)
Triple-class refractory‖	53 (59%)	104 (97%)
Extramedullary plasmacytomas		
Yes	16 (18%)	27 (25%)
No	74 (82%)	80 (75%)

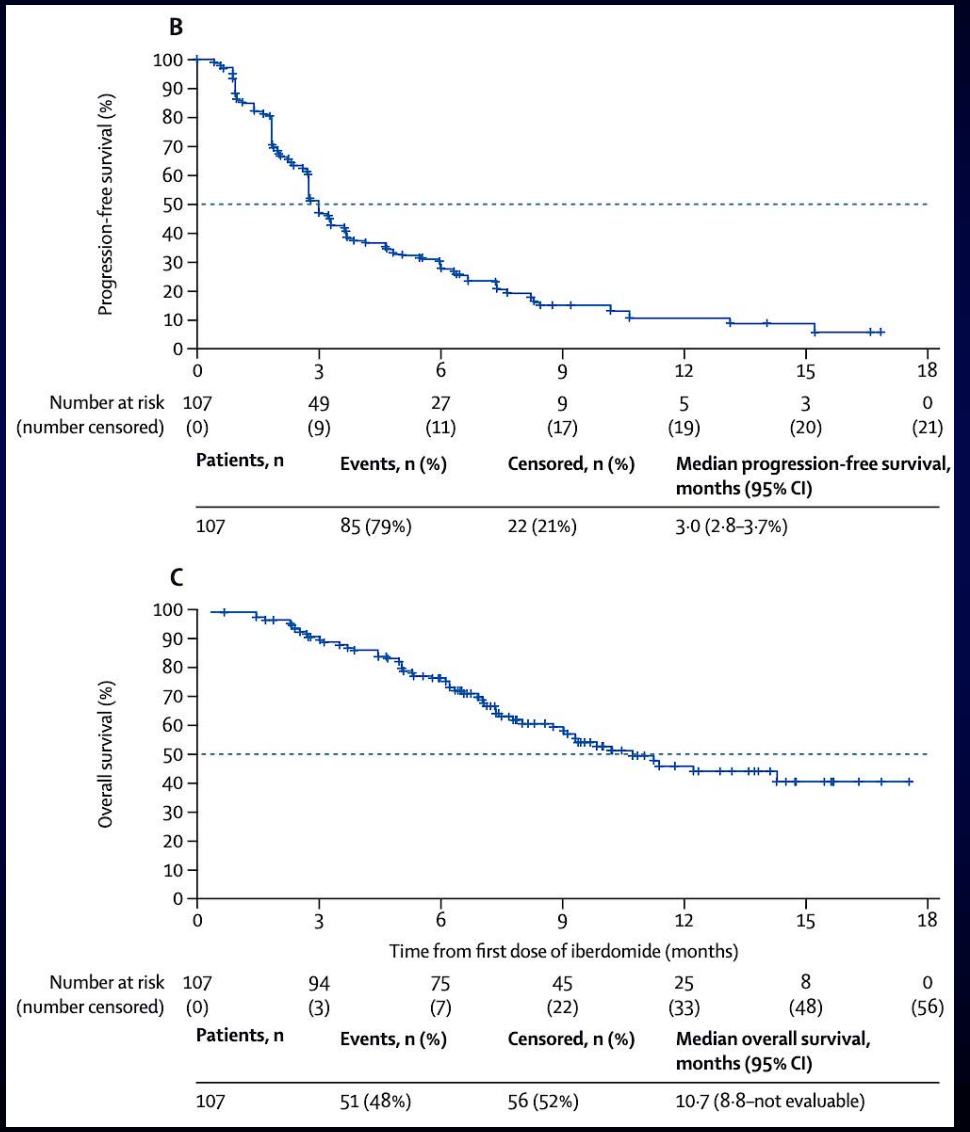
Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. HSCT=haematopoietic stem-cell transplantation. *Defined as presence of any abnormality for del(17p), t(4:14), t(14,16), or amplification 1q21. †Defined as absence of abnormality for all del(17p), t(4:14), t(14,16), and amplification 1q21. ‡Patients were not evaluable because of insufficient bone marrow aspirate material for complete cytogenetic analysis. §67 patients had previous autologous HSCT, one had allogeneic HSCT, and six had both. ¶76 patients had previous autologous HSCT and eight had both autologous and allogeneic HSCT. ‖Defined as refractory to at least one immunomodulatory drug, at least one proteasome inhibitor, and at least one CD38 monoclonal antibody.

Table 1: **Baseline characteristics**

Lonial S et al. *Lancet Haematol*. 2022;9(11):e822-e832.

Response Data





Lonial S et al. *Lancet Haematol*. 2022;9(11):e822-e832.

TEAEs

	Dose-escalation cohort (n=90)				Dose-expansion cohort (n=107)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
All infections	33 (37%)	21 (23%)	2 (2%)	0	33 (31%)	26 (24%)	3 (3%)	0
Fatigue	31 (34%)	1 (1%)	1 (1%)	0	22 (21%)	2 (2%)	1 (1%)	0
Insomnia	28 (31%)	1 (1%)	0	0	14 (13%)	1 (1%)	0	0
Diarrhoea	20 (22%)	1 (1%)	0	0	24 (22%)	1 (1%)	0	0
Muscle spasms	20 (22%)	0	0	0	8 (7%)	0	0	0
Cough	19 (21%)	0	0	0	11 (10%)	0	0	0
Arthralgia	18 (20%)	1 (1%)	0	0	9 (8%)	1 (1%)	0	0
Pyrexia	18 (20%)	2 (2%)	0	0	12 (11%)	1 (1%)	0	0
Rash	17 (19%)*	0*	0	0	18 (17%)†	3 (3%)†	0	0
Dyspnoea	16 (18%)	2 (2%)	1 (1%)	0	17 (16%)	3 (3%)	1 (1%)	0
Pain in extremity	14 (16%)	2 (2%)	0	0	6 (6%)	0	0	0
Musculoskeletal chest pain	14 (16%)	1 (1%)	0	0	7 (7%)	2 (2%)	0	0
Nausea	14 (16%)	0	0	0	15 (14%)	1 (1%)	0	0
Upper respiratory tract infection	13 (14%)	1 (1%)	0	0	10 (9%)	1 (1%)	0	0
Peripheral oedema	13 (14%)	0	0	0	14 (13%)	2 (2%)	0	0
Back pain	12 (13%)	8 (9%)	0	0	16 (15%)	2 (2%)	0	0
Constipation	12 (13%)	1 (1%)	0	0	23 (22%)	0	0	0
Anaemia	11 (12%)	23 (26%)	1 (1%)	0	14 (13%)	30 (28%)	0	0
Vomiting	10 (11%)	0	0	0	6 (6%)	2 (2%)	0	0
Myalgia	10 (11%)	0	0	0	3 (3%)	0	0	0
Bone pain	9 (10%)	2 (2%)	0	0	7 (7%)	7 (7%)	0	0
Headache	9 (10%)	2 (2%)	0	0	10 (9%)	1 (1%)	0	0
Nasopharyngitis	8 (9%)	0	0	0	3 (3%)	0	0	0
Urinary tract infection	8 (9%)	0	0	0	4 (3%)	2 (2%)	0	0
Hypokalaemia	7 (8%)	1 (1%)	1 (1%)	0	10 (9%)	1 (1%)	0	0
Asthenia	7 (8%)	1 (1%)	0	0	14 (13%)	3 (3%)	0	0
Decreased appetite	7 (8%)	1 (1%)	0	0	13 (12%)	1 (1%)	0	0
Neutropenia	5 (6%)	19 (21%)	19 (21%)	0	16 (15%)	27 (25%)	21 (20%)	0
Thrombocytopenia	5 (6%)	6 (7%)	7 (8%)	0	15 (14%)	7 (7%)	16 (15%)	0
Hyperglycaemia	5 (6%)	3 (3%)	0	0	4 (4%)	5 (5%)	0	0
Pneumonia	4 (4%)‡	10 (11%)‡	0	0	6 (6%)§	7 (7%)§	2 (2%)	0
Bronchitis	3 (3%)	1 (1%)	0	0	8 (8%)	0	0	0
Leukopenia	2 (2%)	9 (10%)	3 (3%)	0	8 (8%)	11 (10%)	11 (10%)	0
Lymphopenia	0	8 (9%)	1 (1%)	0	2 (2%)	11 (10%)	6 (6%)	0
Febrile neutropenia	0	3 (3%)	0	0	0	4 (4%)	1 (1%)	0

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Lonial S et al. *Lancet Haematol*. 2022;9(11):e822-e832.

Mezigdomide: Phase I/II Data

Clinical Trial > N Engl J Med. 2023 Sep 14;389(11):1009-1022.
doi: 10.1056/NEJMoa2303194. Epub 2023 Aug 30.

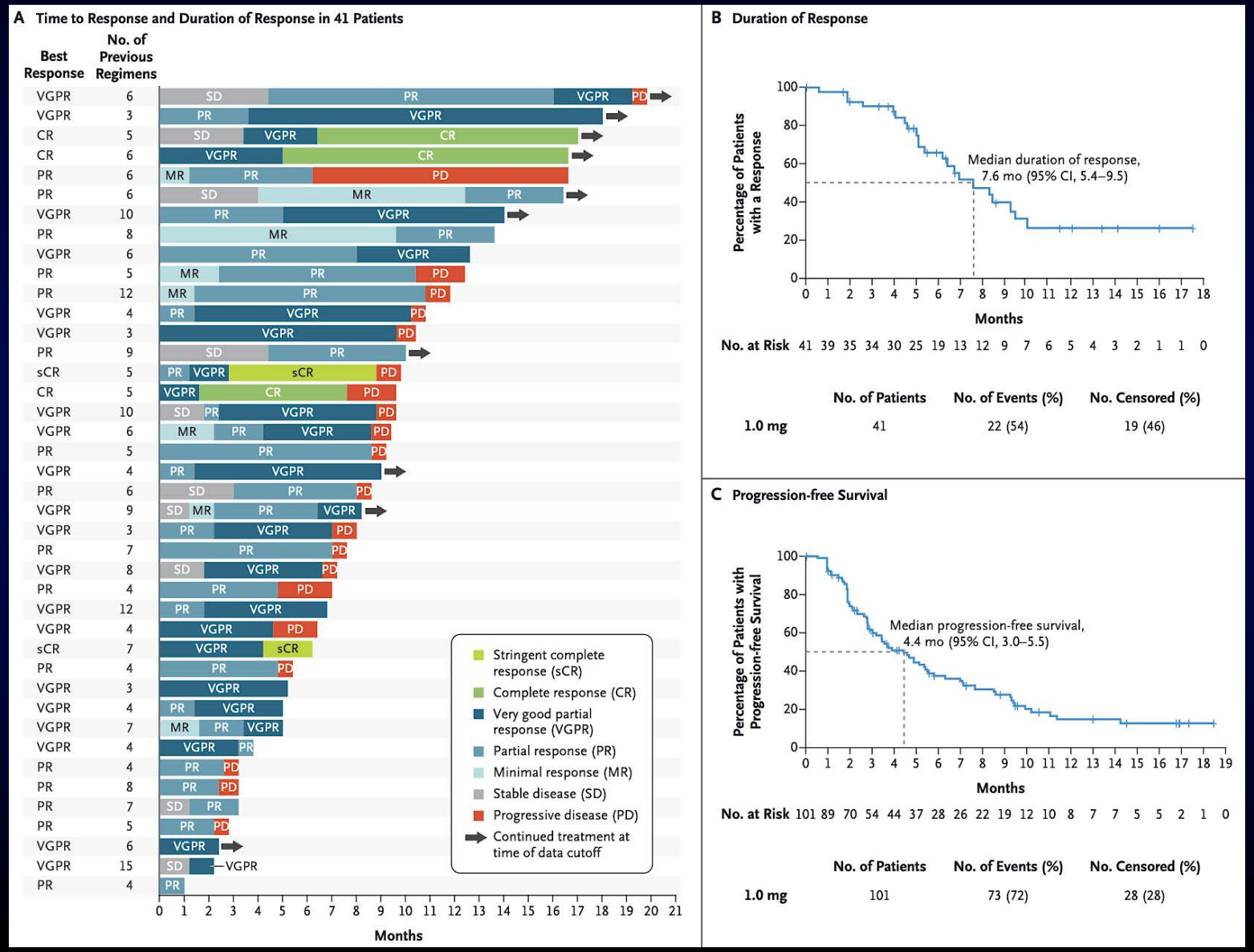
Mezigdomide plus Dexamethasone in Relapsed and Refractory Multiple Myeloma

Paul G Richardson [1], Suzanne Trudel [1], Rakesh Popat [1], María-Victoria Mateos [1], Annette J Vangsted [1], Karthik Ramasamy [1], Joaquín Martinez-Lopez [1], Hang Quach [1], Robert Z Orlowski [1], Mario Arnao [1], Sagar Lonial [1], Chatchada Karanes [1], Charlotte Pawlyn [1], Kihyun Kim [1], Albert Oriol [1], Jesus G Berdeja [1], Paula Rodríguez Otero [1], Ignacio Casas-Avilés [1], Alessia Spirli [1], Jennifer Poon [1], Shaoyi Li [1], Jing Gong [1], Lilly Wong [1], Manisha Lamba [1], Daniel W Pierce [1], Michael Amatangelo [1], Teresa Peluso [1], Paulo Maciag [1], Jessica Katz [1], Michael Pourdehnad [1], Nizar J Bahlis [1];
CC-92480-MM-001 Study Investigators

Collaborators, Affiliations + expand

PMID: 37646702 DOI: 10.1056/NEJMoa2303194

Durability



- PFS of 4.4 months
- DOR of 7.6 months

Richardson PG et al. *N Engl J Med*. 2023;389(11):1009-1022.

Adverse Events

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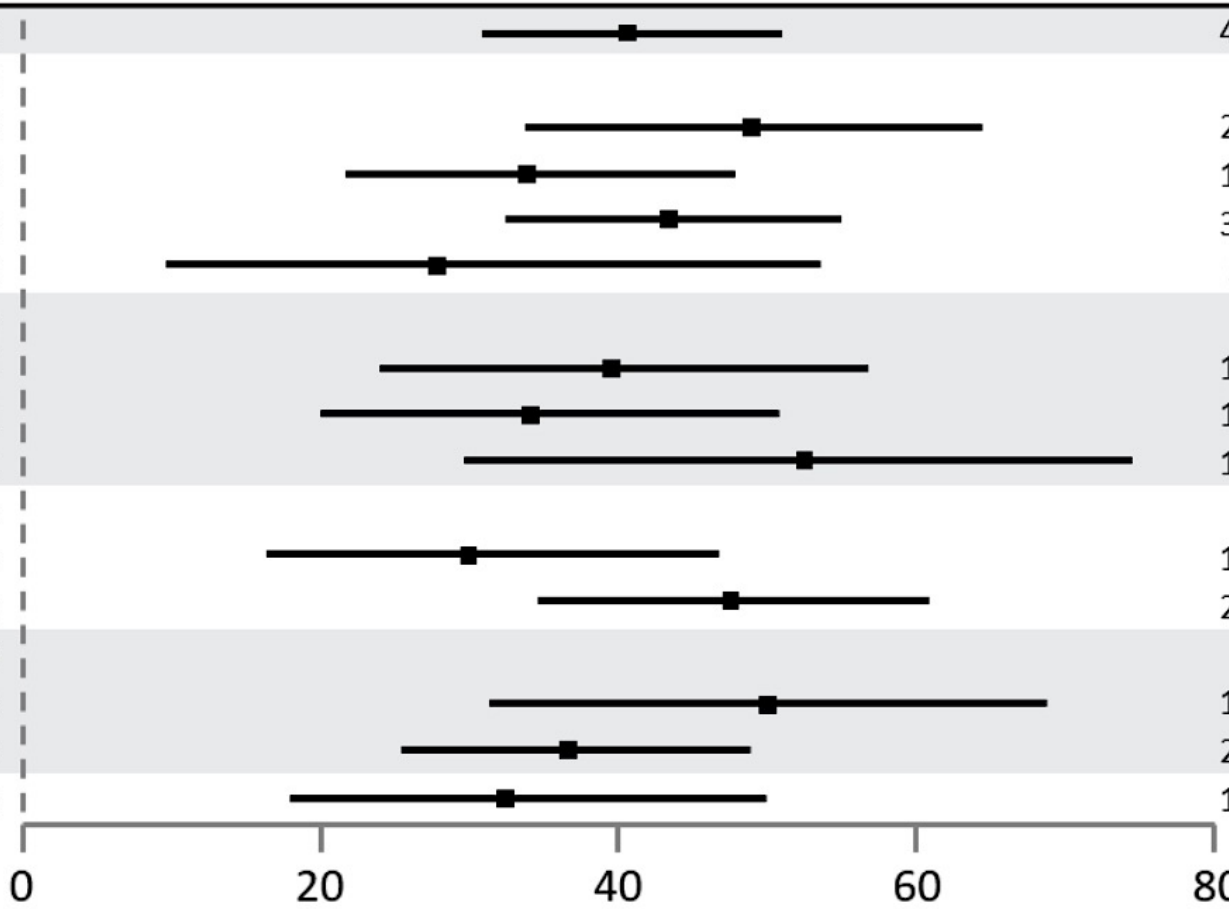
Adverse Event	Dose-Escalation Cohort (N=77)			Dose-Expansion Cohort (N=101)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Hematologic						
Neutropenia	62 (81)	18 (23)	37 (48)	78 (77)	22 (22)	54 (54)
Anemia	47 (61)	29 (38)	0	53 (52)	35 (35)	1 (1)
Thrombocytopenia	39 (51)	9 (12)	9 (12)	43 (43)	14 (14)	14 (14)
Febrile neutropenia	7 (9)	4 (5)	3 (4)	15 (15)	13 (13)	2 (2)
Nonhematologic						
Infections and infestations	57 (74)	28 (36)	3 (4)	66 (65)	29 (29)	6 (6)
Pneumonia†	19 (25)	16 (21)	0	22 (22)	13 (13)	3 (3)
Covid-19	1 (1)	1 (1)	0	17 (17)	7 (7)	0
Fatigue	31 (40)	8 (10)	0	36 (36)	5 (5)	0
Nausea	21 (27)	1 (1)	0	21 (21)	1 (1)	0
Decreased appetite	20 (26)	1 (1)	0	21 (21)	1 (1)	1 (1)
Diarrhea	20 (26)	2 (3)	0	31 (31)	3 (3)	0
Pyrexia	20 (26)	2 (3)	0	15 (15)	3 (3)	0
Peripheral edema	17 (22)	1 (1)	0	8 (8)	0	0
Arthralgia	12 (16)	2 (3)	0	21 (21)	2 (2)	0
Insomnia	12 (16)	0	0	20 (20)	1 (1)	0
Constipation	11 (14)	0	0	24 (24)	0	0
Dyspnea	11 (14)	3 (4)	0	22 (22)	5 (5)	0
Peripheral neuropathy‡	7 (9)	0	0	7 (7)	1 (1)	0
Deep-vein thrombosis	1 (1)	0	0	3 (3)	1 (1)	0

Richardson PG et al. *N Engl J Med*. 2023;389(11):1009-1022.

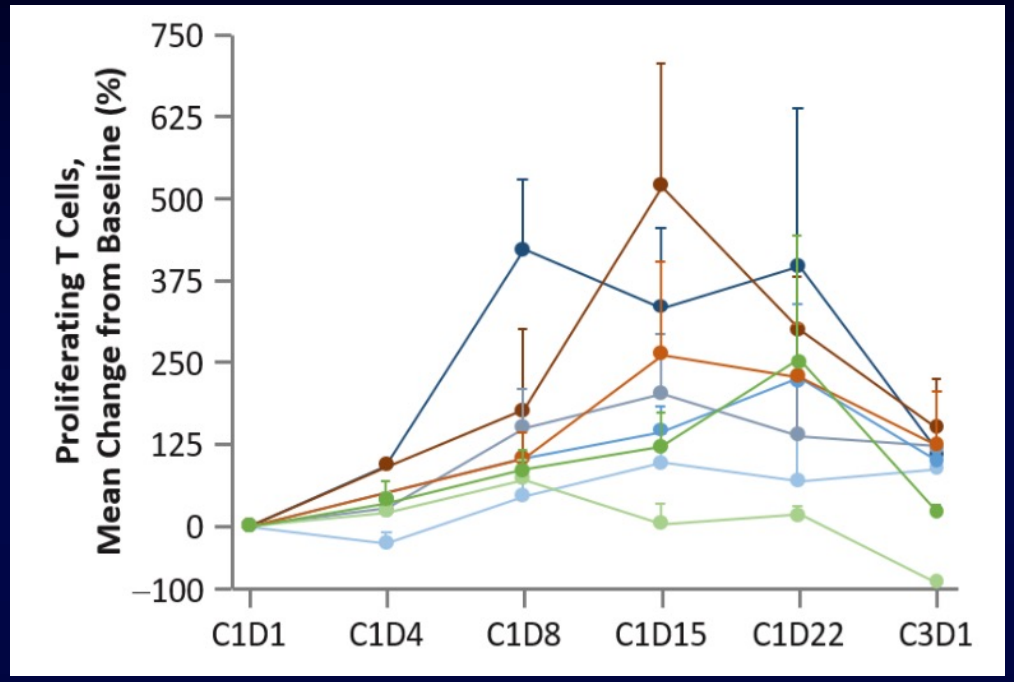
Subgroups

Subgroup	n	N	ORR%	LCL	UCL
All patients	41	101	40.6	30.9	50.8
Age					
< 65	22	45	48.9	33.7	64.2
≥ 65	19	56	33.9	21.8	47.8
< 75	36	83	43.4	32.5	54.7
≥ 75	5	18	27.8	9.7	53.5
ISS stage at study entry					
I	15	38	39.5	24.0	56.6
II	14	41	34.1	20.1	50.6
III	11	21	52.4	29.8	74.3
Presence of plasmacytomas					
Yes	12	40	30.0	16.6	46.5
No	29	61	47.5	34.6	60.7
Prior anti-BCMA therapy					
Yes	15	30	50.0	31.3	68.7
No	26	71	36.6	25.5	48.9
High-risk cytogenetics	12	37	32.4	18.0	49.8

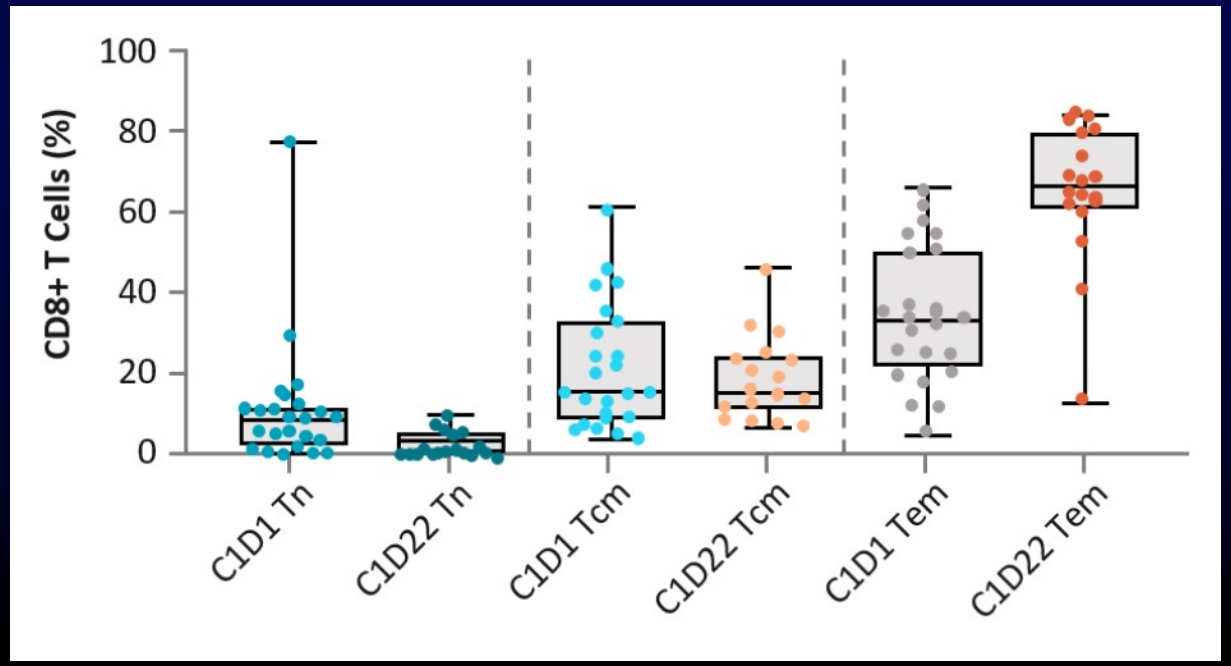


Richardson PG et al. *N Engl J Med*. 2023;389(11):1009-1022.

T-cell Effects



- Enhances T-cell proliferation
- Increased effector memory cells



- Rationale for post-TCEs or CAR-Ts?

Richardson PG et al. *N Engl J Med*. 2023;389(11):1009-1022.

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Other Agents of Interest

456 Characterization of JNJ-79635322, a Novel BCMAxGPRC5DxCD3 T-Cell Redirecting Trispecific Antibody, for the Treatment of Multiple Myeloma

Program: Oral and Poster Abstracts
Type: Oral
Session: 651. Multiple Myeloma and Plasma Cell Dyscrasias: Basic and Translational: Characterizing Response and Resistance to CAR-T and TCEs
Hematology Disease Topics & Pathways:
Research, Diseases, Therapies

Sunday, December 10, 2023: 10:45 AM

1011 Sonrotoclax (BGB-11417) in Combination with Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma with t(11;14): Safety, Efficacy, and Determination of Recommended Phase 2 Dose

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Multiple Myeloma: Prospective Therapeutic Trials: Relapsed and Refractory Myeloma
Hematology Disease Topics & Pathways:
Research, clinical trials, Clinical Research, Plasma Cell Disorders, Combination therapy, Diseases, Therapies, Lymphoid Malignancies

Monday, December 11, 2023: 5:00 PM

1012 Results from the Completed Dose Escalation Portion of the Phase 1 Study of HPN217, a Half-Life Extended Tri-Specific T Cell Activating Construct (TriTAC®) Targeting B Cell Maturation Antigen (BCMA) for Relapsed/Refractory Multiple Myeloma (MM)

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Multiple Myeloma: Prospective Therapeutic Trials: Relapsed and Refractory Myeloma
Hematology Disease Topics & Pathways:
Biological therapies, Antibody Therapy, Research, clinical trials, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Clinical Research, Plasma Cell Disorders, drug development, Diseases, Therapies, Immunotherapy, Infusion, Lymphoid Malignancies

Monday, December 11, 2023: 5:15 PM

1013 Mezigdomide (MEZI) Plus Dexamethasone (DEX) and Daratumumab (DARA) or Elotuzumab (ELO) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Results from the CC-92480-MM-002 Trial

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Multiple Myeloma: Prospective Therapeutic Trials: Relapsed and Refractory Myeloma
Hematology Disease Topics & Pathways:
Research, clinical trials, Clinical Research, Combination therapy, Therapies

Monday, December 11, 2023: 5:30 PM

2005 Tolerability and Clinical Activity of Novel First in Class Oral Agent, Inobrodib (CCS1477), in Combination with Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma

Program: Oral and Poster Abstracts
Session: 653. Multiple Myeloma: Prospective Therapeutic Trials: Poster I
Hematology Disease Topics & Pathways:
Research, clinical trials, Clinical Research, Combination therapy, Therapies

Saturday, December 9, 2023, 5:30 PM-7:30 PM

3334 Hdp-101, an Anti-BCMA Antibody-Drug Conjugate with a Novel Payload Amanitin in Patients with Relapsed Multiple Myeloma, Initial Findings of the First in Human Study

Program: Oral and Poster Abstracts
Session: 652. Multiple Myeloma: Clinical and Epidemiological: Poster II
Hematology Disease Topics & Pathways:
Research, clinical trials, Clinical Research

Sunday, December 10, 2023, 6:00 PM-8:00 PM

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Conclusions

- Venetoclax/BCL2 remains of interest in t(11;14), although optimal combinations unclear
- CELMoDs show good efficacy and may be useful to reactivate T-cells after prior TCEs/CAR-Ts
- Other small molecules and I/O agents are moving forward also, but the bar for success is higher than ever

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. You may also use the iPads available in the meeting room to complete the course evaluation.

Online/Zoom attendees: The CME credit link is posted in the chat room.

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