Year in Review: Multiple Myeloma

A CME/MOC-Accredited Live Webinar

Tuesday, July 9, 2024
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Thomas Martin, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

Jesús G Berdeja, MD
Director of Multiple Myeloma Research
Greco-Hainsworth Centers for Research
Tennessee Oncology
Nashville, Tennessee

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Thomas Martin, MD
Associate Chief, Hematology/Oncology
Director, Hematology, Blood and Marrow Transplantation and Cell Therapy
Helen Diller Family Comprehensive Cancer Center
UCSF Medical Center
San Francisco, California

Commercial Support

This activity is supported by educational grants from Bristol Myers Squibb, Karyopharm Therapeutics, and Sanofi.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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Dr Berdeja — Disclosures

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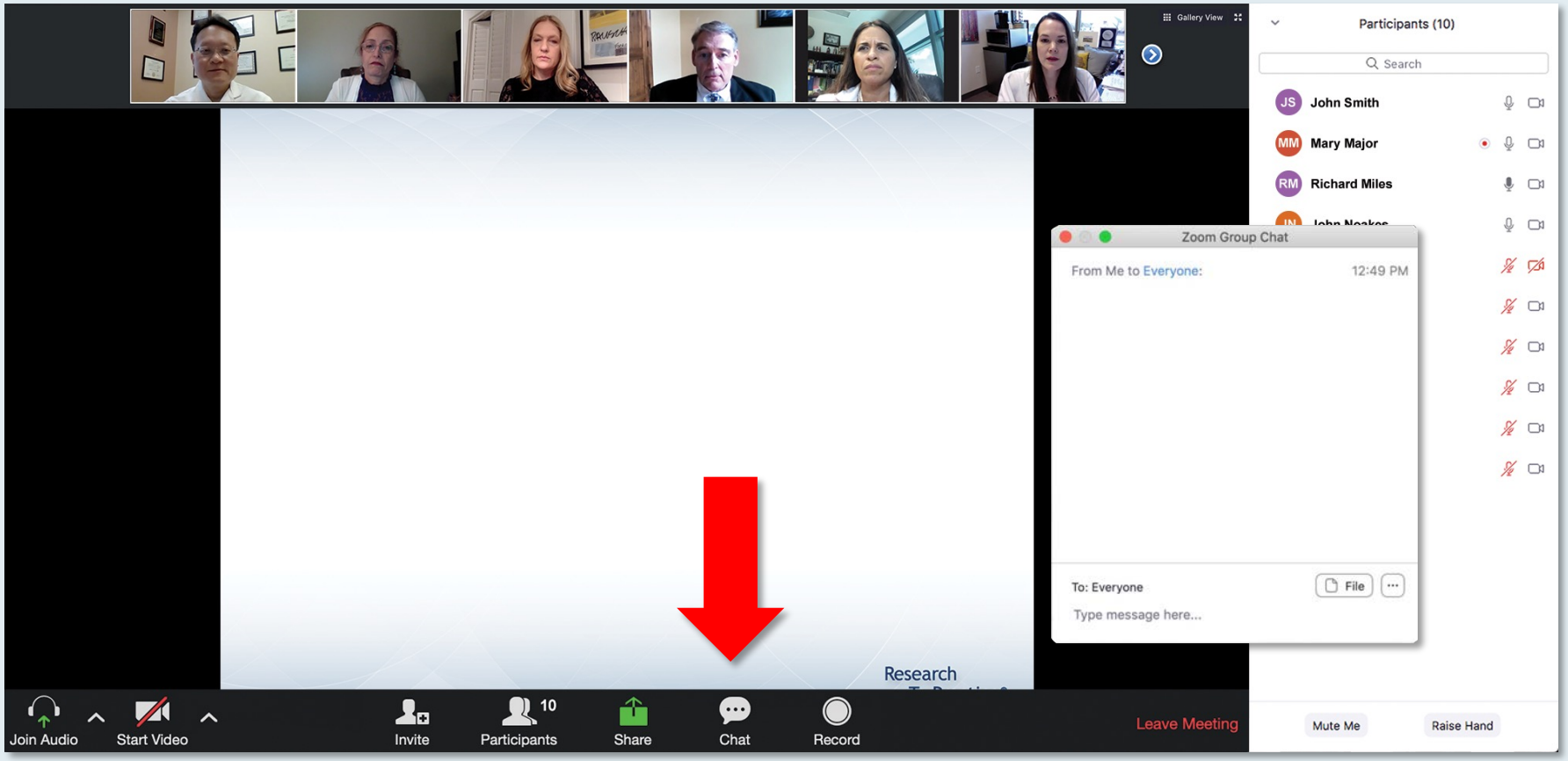
Dr Martin — Disclosures

Consulting Agreements	GSK, Pfizer Inc
Contracted Research	Amgen Inc, Bristol Myers Squibb, Janssen Biotech Inc, Sanofi
Data and Safety Monitoring Boards/Committees	AbbVie Inc, Lilly

We Encourage Clinicians in Practice to Submit Questions



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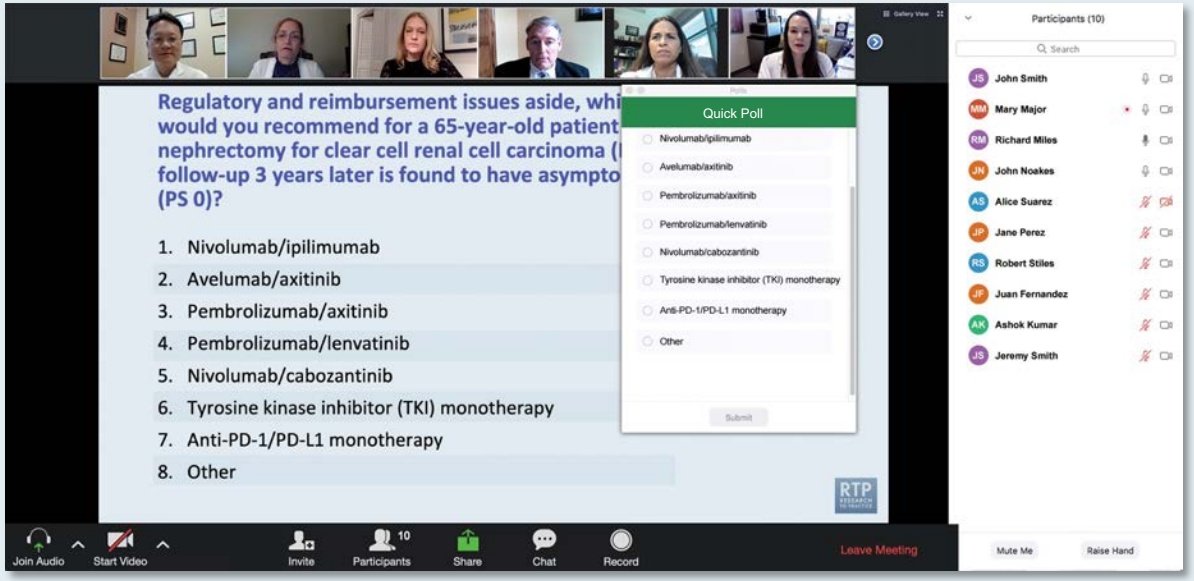
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



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ONCOLOGY TODAY

WITH DR NEIL LOVE

Bispecific Antibodies in the Management of Multiple Myeloma

DR JOSHUA RICHTER

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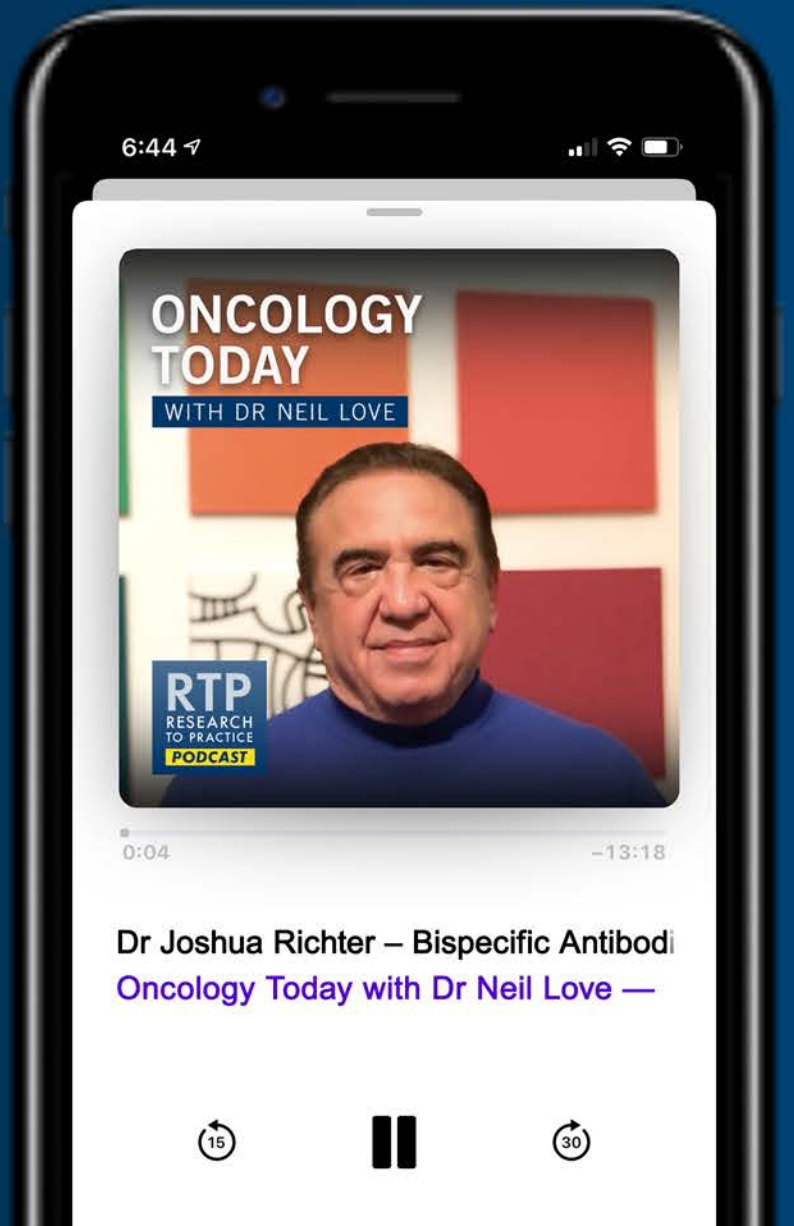

Year in Review: Melanoma and Nonmelanoma Skin Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, July 10, 2024
5:00 PM – 6:00 PM ET

Faculty

Evan J Lipson, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Oncology Today with Dr Neil Love: Novel Agents and Strategies in Lung Cancer

A CME/MOC-Accredited Live Webinar

Thursday, July 11, 2024
5:00 PM – 6:00 PM ET

Faculty

Melissa Johnson, MD
Ticiana Leal, MD
Manish Patel, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Inside the Issue: Integrating Antibody-Drug Conjugates into the Management of HR-Positive and Triple-Negative Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, July 17, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Peter Schmid, FRCP, MD, PhD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Inside the Issue: Integrating ALK-Targeted Therapy into the Management of Localized Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Thursday, July 18, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Professor Ben Solomon, MBBS, PhD

Moderator

Neil Love, MD

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Inside the Issue: Integrating HER2-Targeted Strategies into the Management of Gastrointestinal Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, August 21, 2024
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
John Strickler, MD

Moderator

Neil Love, MD

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TO PRACTICE

Inside the Issue: Optimizing the Diagnosis and Treatment of Neuroendocrine Tumors

A CME/MOC-Accredited Live Webinar

Thursday, August 29, 2024
5:00 PM – 6:00 PM ET

Faculty

Pamela Kunz, MD
Simron Singh, MD, MPH

Moderator

Neil Love, MD

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RESEARCH
TO PRACTICE

Agenda

INTRODUCTION: Real-World Regulatory Issues in Multiple Myeloma (MM)

MODULE 1: Newly Diagnosed MM

MODULE 2: Novel Agents for Relapsed/Refractory MM

MODULE 3: Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2024

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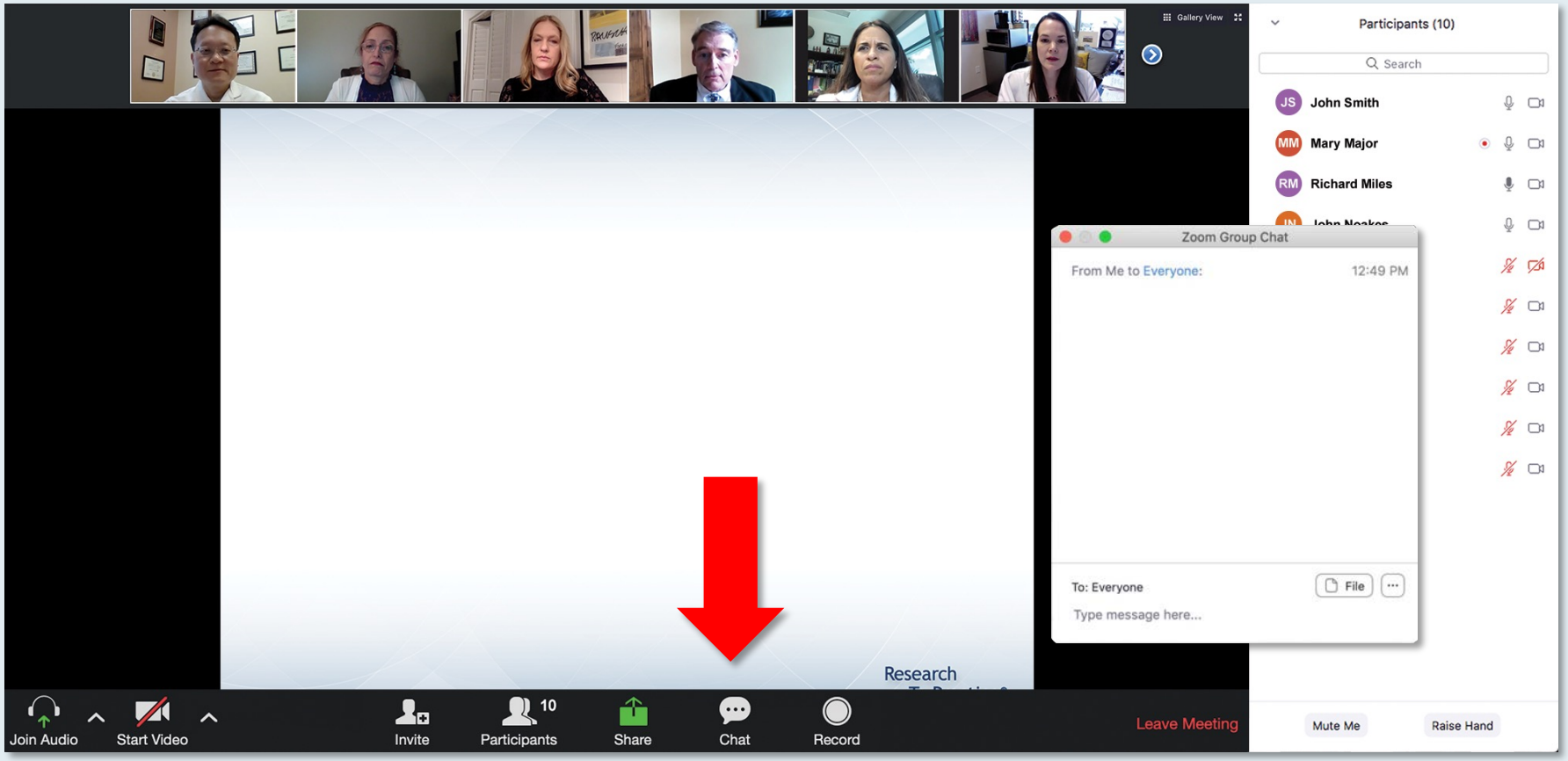

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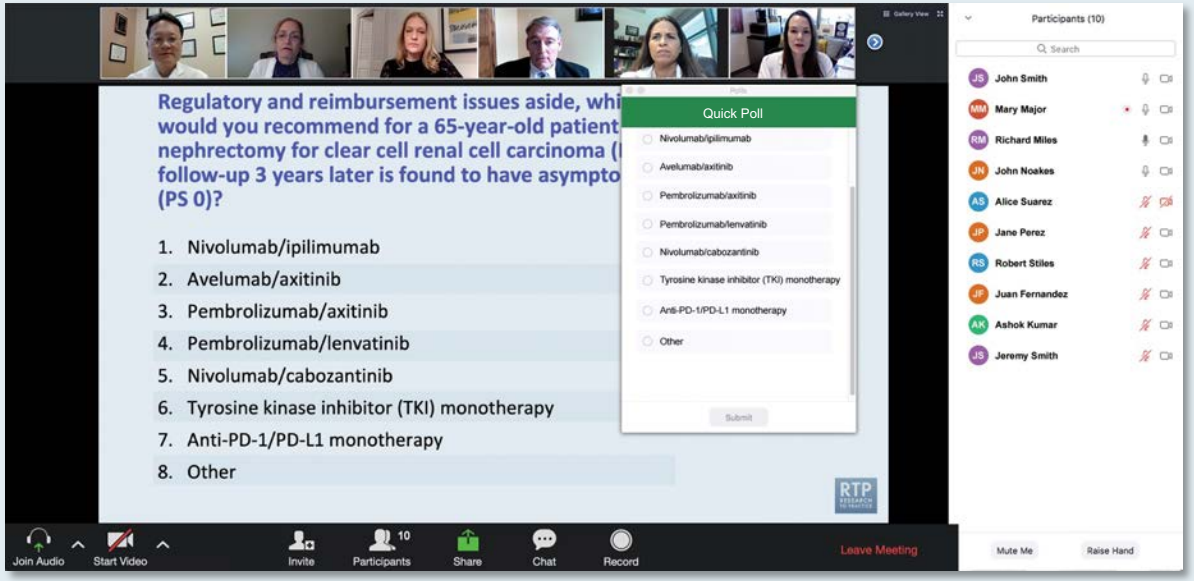

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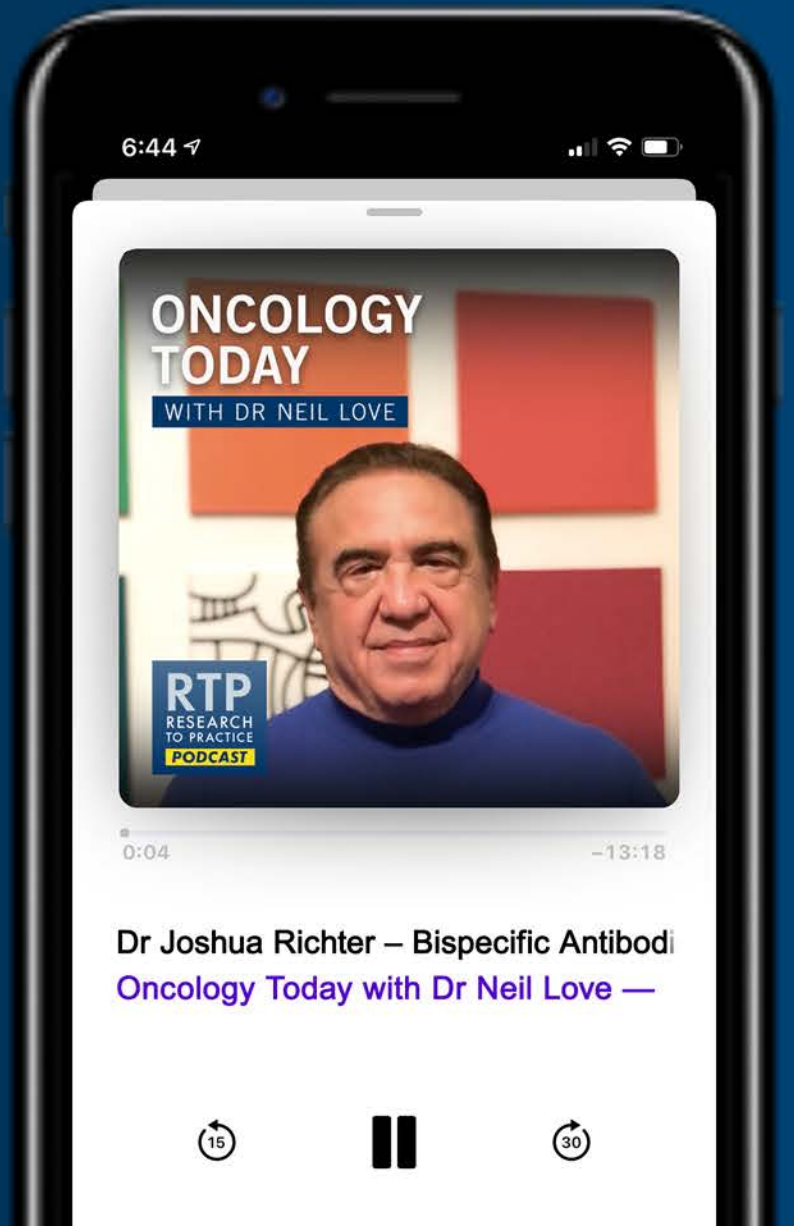

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Dr Berdeja — Disclosures

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Contracted Research	2seventy bio, AbbVie Inc, Amgen Inc, Bristol Myers Squibb, C4 Therapeutics, Caribou Biosciences Inc, CARsgen Therapeutics, Cartesian Therapeutics, Celularity, CRISPR Therapeutics, Fate Therapeutics, Genentech, a member of the Roche Group, GSK, Ichnos Sciences, Incyte Corporation, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, K36 Therapeutics, Karyopharm Therapeutics, Lilly, Novartis, Poseida Therapeutics, Roche Laboratories Inc, Sanofi, Takeda Pharmaceuticals USA Inc

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

Current and Emerging Therapeutic Approaches

Thomas Martin, MD
Helen Diller Family Comprehensive Cancer Center
UCSF Medical Center
San Francisco, California

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Year in Review: Multiple Myeloma Edition

Jesús G. Berdeja, M.D.
Director of Multiple Myeloma Research

RTP Year in Review 2024

Key Data Sets

Thomas Martin, MD

- Rodriguez-Otero P et al. **Daratumumab (DARA) + bortezomib/lenalidomide/dexamethasone (VRd)** with **DARA-R maintenance** in **transplant-eligible** patients with **newly diagnosed** multiple myeloma (NDMM): **Minimal residual disease (MRD) analysis** in the **PERSEUS** trial. ASCO 2024;Abstract 7502.
- Sonneveld P et al. **Daratumumab, bortezomib, lenalidomide, and dexamethasone** for multiple myeloma. *N Engl J Med* 2024;390(4):301-13.
- Facon T et al. **Final survival analysis** of **daratumumab plus lenalidomide and dexamethasone** versus lenalidomide and dexamethasone **in transplant-ineligible** patients with **newly diagnosed** multiple myeloma: **MAIA study**. EHA 2024;Abstract P968.
- Raab MS et al. **Isatuximab, lenalidomide, bortezomib and dexamethasone** for **newly-diagnosed, transplant-eligible** multiple myeloma: **Post transplantation interim analysis** of the randomized phase III **GMMG-HD7 trial**. EHA 2024;Abstract S202.
- Gay F et al. Results of the phase III randomized **Iskia trial**: **Isatuximab-carfilzomib-lenalidomide-dexamethasone** vs carfilzomib-lenalidomide-dexamethasone as **pre-transplant induction and post-transplant consolidation** in **newly diagnosed** multiple myeloma patients. ASH 2023;Abstract 4.

Key Data Sets

Thomas Martin, MD (continued)

- Facon T et al. Phase 3 study results of **isatuximab, bortezomib, lenalidomide, and dexamethasone** (Isa-VRd) versus VRd for **transplant-ineligible** patients with newly diagnosed multiple myeloma **(IMROZ)**. ASCO 2024;Abstract 7500.
- Leleu XP et al. Phase 3 randomized study of **isatuximab (Isa) plus lenalidomide and dexamethasone (Rd) with bortezomib** versus IsaRd in patients with **newly diagnosed transplant ineligible** multiple myeloma (NDMM TI). ASCO 2024;Abstract 7501.
- Zonder JA et al. **Treatment outcomes and prognostic factors** with **lenalidomide, bortezomib, and dexamethasone (RVd)** alone versus Rvd **plus autologous stem cell transplantation (ASCT)** in **African American** (AA) patients (pts) with **newly diagnosed** multiple myeloma (NDMM) in the **Determination phase 3 trial**. ASH 2023;Abstract 4762.
- Martin T et al. **Isatuximab, carfilzomib, and dexamethasone** in patients with **relapsed** multiple myeloma: **Updated results from IKEMA**, a randomized phase 3 study. *Blood Cancer J* 2023;13(1):72.
- Richardson PG et al. **Isatuximab-pomalidomide-dexamethasone** versus pomalidomide-dexamethasone in patients with **relapsed and refractory** multiple myeloma: **Final overall survival analysis**. *Haematologica* 2024;[Online ahead of print].

Key Data Sets

Thomas Martin, MD (continued)

- Mateos MV et al. **Impact of prior treatment** on **selinexor, bortezomib, dexamethasone outcomes** in patients with **relapsed/refractory** multiple myeloma: **Extended follow-up subgroup analysis** of the **BOSTON trial**. *Eur J Haematol* 2024;[Online ahead of print].
- Jagannath S et al. Association of **selinexor dose reductions** with **clinical outcomes** in the **BOSTON study**. *Clin Lymphoma Myeloma Leuk* 2023;23(12):917-23.e3.
- Madan S et al. **Novel selinexor triplet and quadruplet regimens** (SND, SPED, SBD, SDPD): Results from the **phase 1b/2 STOMP** multiple myeloma trial. EHA 2024;Abstract P999.
- Amatangelo M et al. **Iberdomide** is immune stimulatory and induces deep anti-myeloma activity across doses **in combination with daratumumab** in patients with **TNE NDMM** from the **CC-220-MM-001 study**. EHA 2024;Abstract P847.
- Richardson PG et al. **Mezigdomide plus dexamethasone** in **relapsed and refractory** multiple myeloma. *N Engl J Med* 2023;389(11):1009-22.
- Richardson PG et al. **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**. ASH 2023;Abstract 1013.

Key Data Sets

Jesús G Berdeja, MD

- Rodríguez Otero P et al. **Idecabtagene vicleucel (ide-cel)** versus standard (std) regimens in patients (pts) with **triple-class–exposed (TCE) relapsed and refractory** multiple myeloma (RRMM): Updated analysis from **KarMMa-3**. ASH 2023;Abstract 1028.
- Delforge M et al. **Health-related quality of life** in patients with triple-class exposed relapsed and refractory multiple myeloma treated with **idecabtagene vicleucel** or standard regimens: Patient-reported outcomes from the phase 3, randomised, open-label **KarMMa-3** clinical trial. *Lancet Haematol* 2024;11(3):e216-27.
- San-Miguel J et al. **Cilta-cel** or standard care in **lenalidomide-refractory** multiple myeloma. *N Engl J Med* 2023;389(4):335-47.
- Hilengrass J et al. The phase 2 **CARTITUDE-2** trial: **Updated efficacy and safety** of **ciltacabtagene autoleucel** in patients with multiple myeloma and **1–3 prior lines of therapy (cohort A)** and with **early relapse after first line treatment (cohort B)**. ASH 2023;Abstract 1021.
- Leleu X et al. **Idecabtagene vicleucel (ide-cel)** in patients (pts) with **clinical high-risk early relapse** multiple myeloma (MM) **without front-line (1L) autologous stem cell transplantation (ASCT)**: **KarMMa-2 cohort 2b**. EHA 2024;Abstract S208.

Key Data Sets

Jesús G Berdeja, MD (continued)

- Dhodapkar M et al. Efficacy and safety of **idecabtagene vicleucel (ide-cel)** in patients with **clinical high-risk newly diagnosed** multiple myeloma (NDMM) with an **inadequate response to frontline autologous stem cell transplantation (ASCT)**: **KarMMa-2 cohort 2c** extended follow-up. ASH 2023;Abstract 2101.
- Arnulf B et al. Efficacy and safety of **ciltacabtagene autoleucel ± lenalidomide maintenance** in **newly diagnosed** multiple myeloma with **suboptimal response to frontline autologous stem cell transplant: CARTITUDE-2 cohort D**. ASCO 2024;Abstract 7505.
- Dhakal B et al. Phase 1 study of **anitocabtagene autoleucel** for the treatment of patients with **relapsed and/or refractory** multiple myeloma: **Results from at least 1-year follow-up** in all patients. EHA 2024;Abstract S207.
- Bal S et al. **BMS-986393 (CC-95266)**, a G protein-coupled receptor class C group 5 member D **(GPRC5D)-targeted chimeric antigen receptor** (CAR) T-Cell Therapy for **relapsed/refractory** multiple myeloma (RRMM): **Updated results** from a **phase 1** study. ASH 2023;Abstract 219.
- Nadeem O et al. Safety and preliminary efficacy of **BMS-986393, a GPRC5D CAR T cell therapy**, in patients with **relapsed/refractory** (RR) multiple myeloma (MM) and **1-3 prior regimens**: First results from a phase 1 study. EHA 2024;Abstract P951.

Key Data Sets

Jesús G Berdeja, MD (continued)

- Garfall AL et al. **Long-term follow-up** from the phase 1/2 **MajesTEC-1** trial of **teclistamab** in patients with **relapsed/refractory** multiple myeloma. ASCO 2024;Abstract 7540.
- Lesokhin AM et al. **Elranatamab** in **relapsed or refractory** multiple myeloma: Phase 2 **MagnetisMM-3** trial results. *Nat Med* 2023;29(9):2259-67.
- Mohty M et al. **Long-term survival after elranatamab monotherapy** in patients with **relapsed or refractory** multiple myeloma**: MagnetisMM-3**. EHA 2024;Abstract 932.
- Lentzsch S et al. **Linvoseltamab** in patients with **relapsed/refractory** multiple myeloma in the **LINKER-MM1 study**: Depth and durability of response at 14-month median follow-up. EHA 2024;Abstract S212.
- Weisel K et al. Efficacy, safety, and determination of **RP2D** of **ABBV-383**, a **BCMA bispecific antibody**, in patients with **relapsed/refractory** multiple myeloma (RRMM). EHA 2024;Abstract S211.
- Rasche L et al. Long-term efficacy and safety results from the phase 1/2 **MonumenTAL-1** study of **talquetamab**, a GPRC5D×CD3 bispecific antibody, in patients with **relapsed/refractory** multiple myeloma. EHA 2024;Abstract P915.

Key Data Sets

Jesús G Berdeja, MD (continued)

- Hungria V et al. **Belantamab mafodotin, bortezomib, and dexamethasone** for multiple myeloma. *N Engl J Med* 2024;[Online ahead of print].
- Dimopoulos MA et al. **Belantamab mafodotin, pomalidomide, and dexamethasone** in multiple myeloma. *N Engl J Med* 2024;[Online ahead of print].

Agenda

INTRODUCTION: Real-World Regulatory Issues in Multiple Myeloma (MM)

MODULE 1: Newly Diagnosed MM

MODULE 2: Novel Agents for Relapsed/Refractory MM

MODULE 3: Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies

Agenda

INTRODUCTION: Real-World Regulatory Issues in Multiple Myeloma (MM)

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Ciltacabtagene Autoleucel Achieved Statistically Significant Improvement in Overall Survival in Landmark CARTITUDE-4 Study

Press Release: July 2, 2024

Positive results were announced from a prespecified second interim analysis of the Phase III CARTITUDE-4 study evaluating ciltacabtagene autoleucel (cilta-cel) compared to standard therapies of pomalidomide, bortezomib and dexamethasone (PVd) or daratumumab, pomalidomide and dexamethasone (DPd) for the treatment of relapsed or lenalidomide-refractory multiple myeloma after one prior line of therapy. The interim analysis showed a statistically significant and clinically meaningful improvement in overall survival for patients receiving cilta-cel versus standard therapies. Safety data were consistent with the approved label.

Updated results will be presented at an upcoming medical meeting and submitted to regulatory authorities worldwide.

https://www.prnewswire.com/news-releases/carvykti-ciltacabtagene-autoleucel-achieved-statistically-significant-and-clinically-meaningful-improvement-in-overall-survival-in-landmark-cartitude-4-study-302187545.html

Dr Jesús Berdeja
Nashville, Tennessee

Administration of bispecific antibodies in the community setting

75-year-old man on a clinical trial of the anti-BCMA bispecific antibody teclistamab

Clinical trial participation; experience with a bispecific antibody

Video interviews, September 2022

RTP RESEARCH TO PRACTICE

Dr Natalie Callander
Madison, Wisconsin

62-year-old woman with multiregimen-refractory MM who began treatment with belantamab mafodotin on the DREAMM-2 trial in 2018 remains on therapy

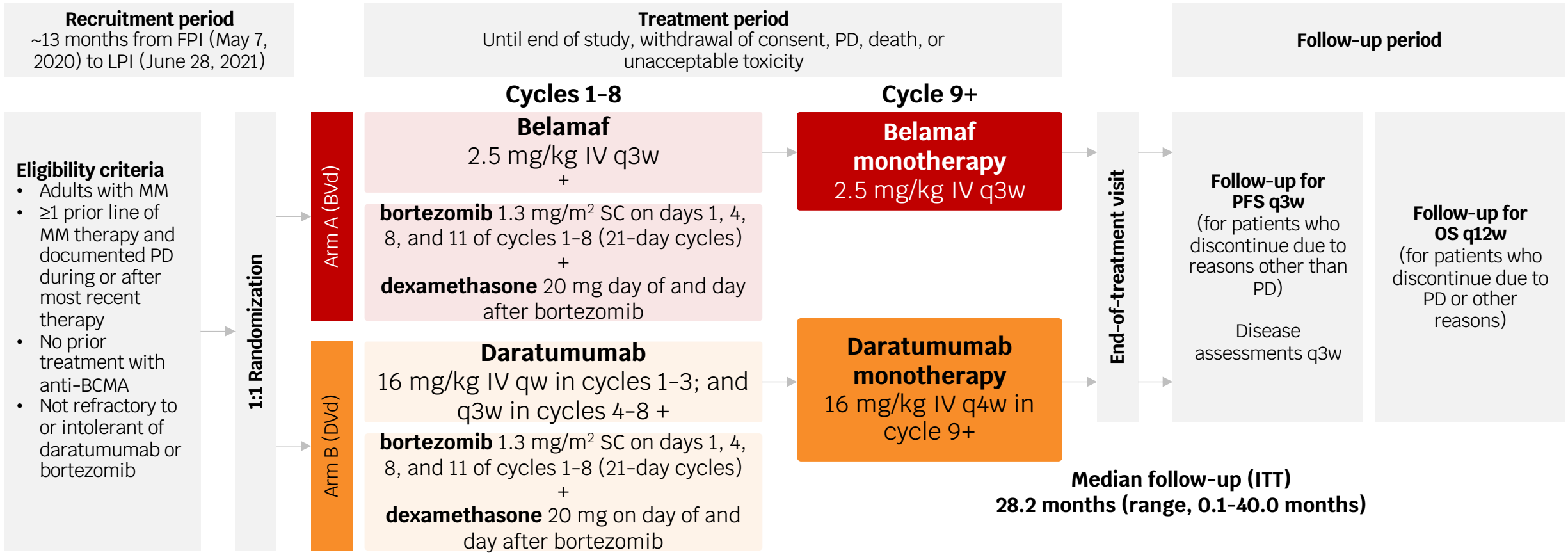
62-year-old woman enrolled on the DREAMM-2 trial in 2018

Experiences with belantamab mafodotin

Video interviews, September 2022

RTP
RESEARCH TO PRACTICE

DREAMM-7: study design



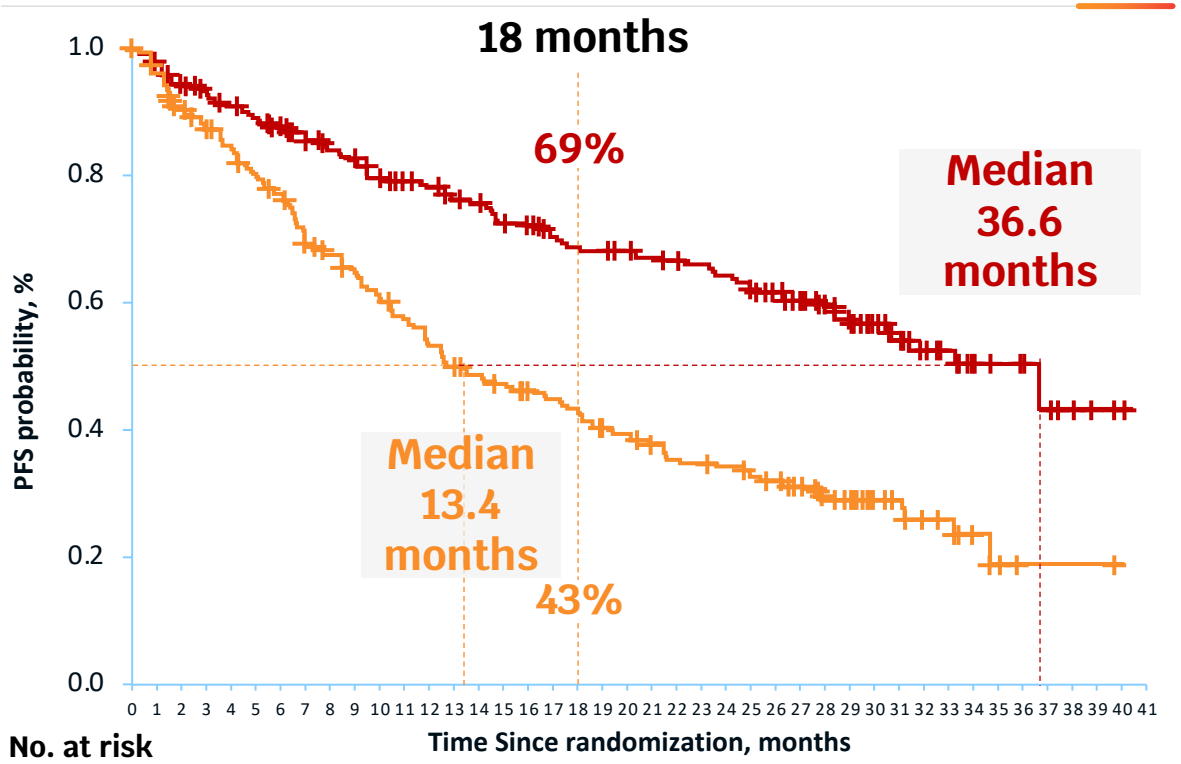
Hungria et. al. NEJM 2024;[Online ahead of print]

Courtesy of Jesús G Berdeja, MD

DREAMM-7: PFS and OS in the ITT

BVd DVd

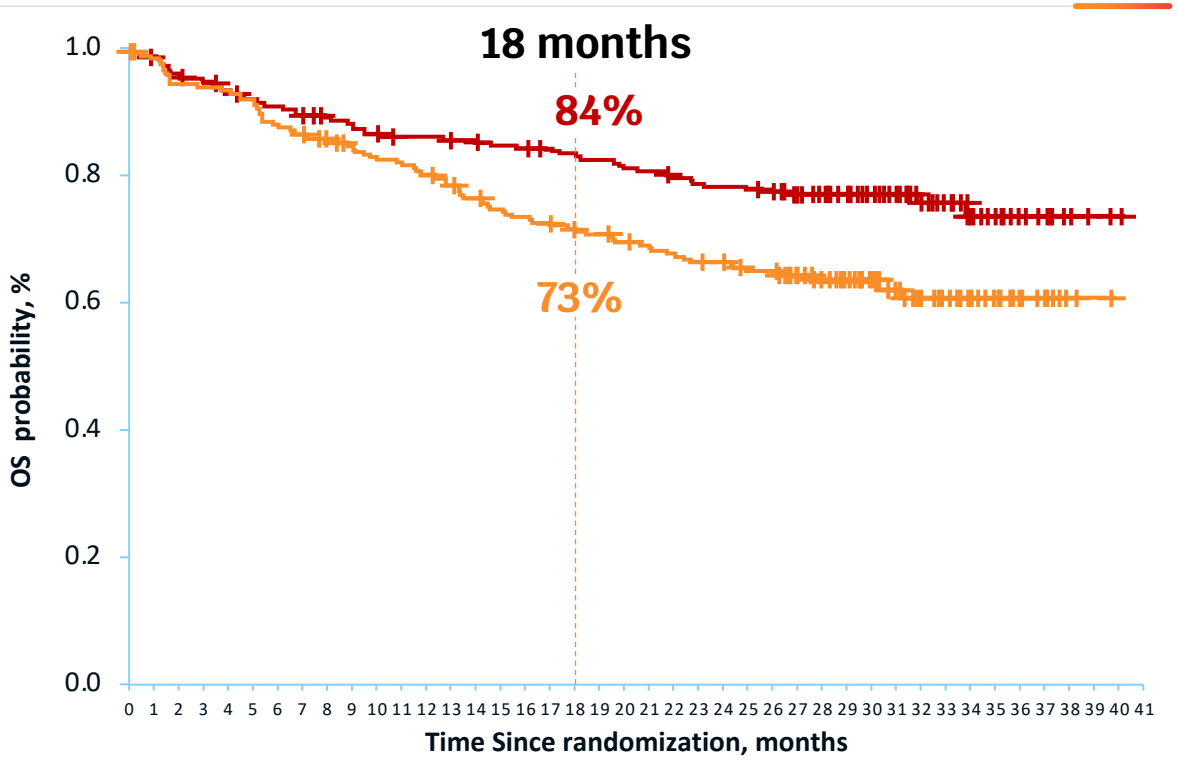
PFS



No. at risk

PFS[a]	BVd (N=243)	DVd (N=251)
Events, n(%)	91 (37)	158 (63)
PFS, median (95% CI), mo[b]	**36.6 (28.4-NR)**	**13.4 (11.1-17.5)**
HR (95% CI)[c]	0.41 (0.31-0.53)	
P value[d]	<.00001	

OS



OS[a]	BVd (N=243)	DVd (N=251)
Events, n(%)	54 (22)	87 (35)
OS, median (95% CI), mo[b]	NR	NR
HR (95% CI)[c]	0.57 (0.4-0.8)	
P value[d]	.00049[e]	

Hungria et. al. NEJM 2024;[Online ahead of print]

Courtesy of Jesús G Berdeja, MD

DREAMM-8: Study Design

Recruitment period
October 2020 to December 2022

Treatment period
Until PD, death, unacceptable toxicity, end of study, or withdrawal of consent

Eligibility criteria
- Adults with MM
- ≥1 prior line of MM therapy including LEN
- Documented PD during or after their most recent therapy
- No prior treatment with anti-BCMA or pomalidomide; not refractory/ intolerant to bortezomib

N=302

1:1 Randomization

BPd (Q4W)

Belantamab mafodotin
2.5 mg/kg IV (cycle 1) then 1.9 mg/kg IV Q4W from cycle 2 onward
+
Pomalidomide 4 mg orally on days 1-21 (28-day cycles)
+
Dexamethasone 40 mg on days 1, 8, 15, and 22

PVd (Q3W)

Bortezomib
1.3 mg/m^2 SC on days 1, 4, 8, and 11 of cycles 1-8 then days 1 and 8 (21-day cycles)
+
Pomalidomide 4 mg orally on days 1-14 (21-day cycles)
+
Dexamethasone 20 mg[a] on the day of and day after bortezomib

End-of-treatment visit

Primary endpoint:
PFS (IRC assessed per IMWG)

Key secondary endpoints:
OS, MRD negativity, DOR

Additional secondary endpoints include:
ORR, CRR, ≥VGPR, TTBR, TTR, TTP, PFS2, AEs, ocular findings, HRQOL, and PROs

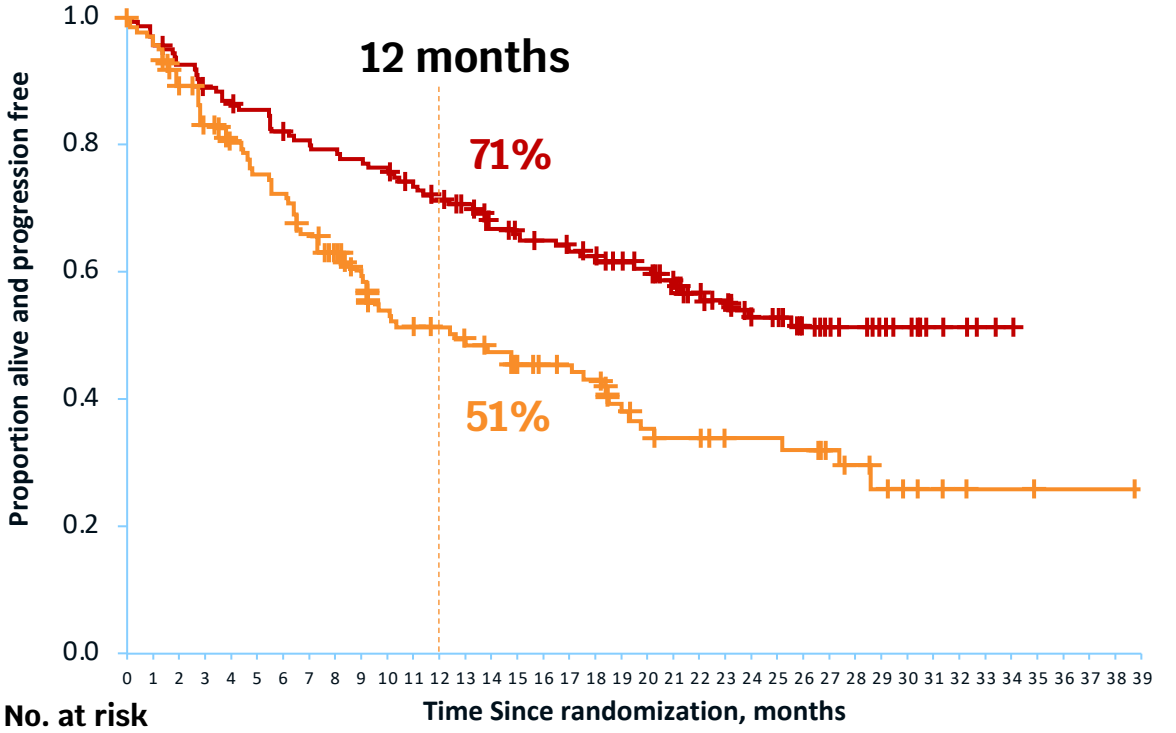
Stratification[b]:
- Prior lines of treatment (1 vs 2 or 3 vs ≥4)
- Prior bortezomib (yes vs no)
- Prior anti-CD38 therapy (yes vs no)

Dimopoulos et. al. NEJM 2024;[Online ahead of print]

Courtesy of Jesús G Berdeja, MD

DREAMM-8: Efficacy

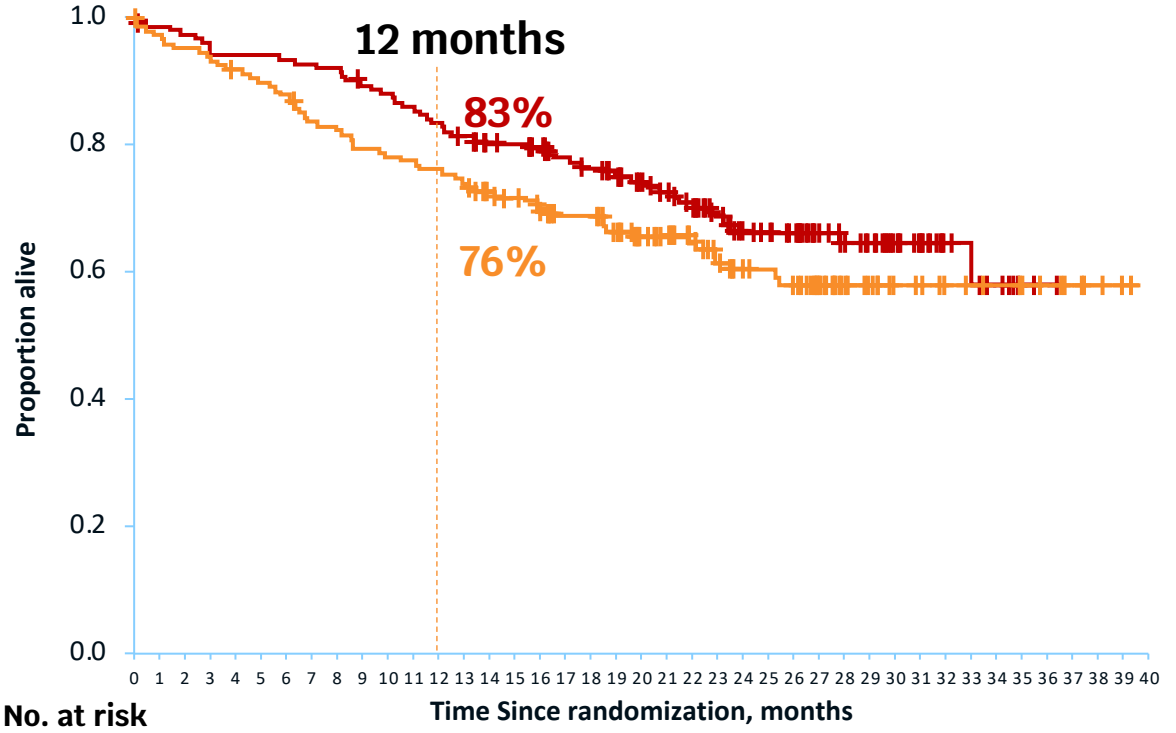
PFS



No. at risk

PFS[a]	BPd (N=155)	PVd (N=147)
Events, n(%)	62 (40)	80 (54)
Median PFS (95% CI), months	NR (20.6-NR)	12.7 (9.1-18.5)
HR (95% CI); *P* value	**0.52** (0.37-0.73); **<.001**	

Positive OS Trend Favoring BPd vs PVd



No. at risk

Interim OS	BPd (N=155)	PVd (N=147)
Events, n(%)[a]	49 (32)	56 (38)
Median OS (95% CI), months	**NR** (33.0-NR)	**NR** (25.2-NR)
HR (95% CI)[b]	**0.77** (0.53-1.14)	

Dimopoulos et. al. NEJM 2024;[Online ahead of print]

Courtesy of Jesús G Berdeja, MD

Conclusions on DREAMM-7 and DREAMM-8

- Belantamab mafodotin was the first FDA-approved ADC in MM based on the DREAMM-2 study
- Withdrawn after the negative confirmatory DREAMM-3

- The impressive results of both the DREAMM-7 and DREAMM-8 studies should get this drug approved in combination
  - DREAMM-7 first trial to beat a dara-based triplet combination

- Ocular toxicity remains an issue but appears improved with less frequent dosing in combination

- If approved as early as 2nd line, it will make sequencing of BCMA-directed drugs much more complicated

Courtesy of Jesús G Berdeja, MD

Agenda

INTRODUCTION: Real-World Regulatory Issues in Multiple Myeloma (MM)

MODULE 1: Newly Diagnosed MM

MODULE 2: Novel Agents for Relapsed/Refractory MM

MODULE 3: Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies

Anti-CD38 Antibody-Based Treatment Approaches for Newly Diagnosed Multiple Myeloma (MM)

- Rodriguez-Otero P et al. **Daratumumab (DARA) + bortezomib/lenalidomide/dexamethasone (VRd)** with **DARA-R maintenance** in **transplant-eligible** patients with **newly diagnosed** multiple myeloma (NDMM): **Minimal residual disease (MRD) analysis** in the **PERSEUS** trial. ASCO 2024;Abstract 7502.
- Sonneveld P et al. **Daratumumab, bortezomib, lenalidomide, and dexamethasone** for multiple myeloma. *N Engl J Med* 2024;390(4):301-13.
- Facon T et al. **Final survival analysis** of **daratumumab plus lenalidomide and dexamethasone** versus lenalidomide and dexamethasone **in transplant-ineligible** patients with **newly diagnosed** multiple myeloma: **MAIA study**. EHA 2024;Abstract P968.
- Raab MS et al. **Isatuximab, lenalidomide, bortezomib and dexamethasone** for **newly-diagnosed, transplant-eligible** multiple myeloma: **Post transplantation interim analysis** of the randomized phase III **GMMG-HD7 trial**. EHA 2024;Abstract S202.
- Gay F et al. Results of the phase III randomized **Iskia trial**: **Isatuximab-carfilzomib-lenalidomide-dexamethasone** vs carfilzomib-lenalidomide-dexamethasone as **pre-transplant induction and post-transplant consolidation** in **newly diagnosed** multiple myeloma patients. ASH 2023;Abstract 4.

Anti-CD38 Antibody-Based Treatment Approaches for Newly Diagnosed MM (continued)

- Facon T et al. Phase 3 study results of **isatuximab, bortezomib, lenalidomide, and dexamethasone** (Isa-VRd) versus VRd for **transplant-ineligible** patients with newly diagnosed multiple myeloma **(IMROZ)**. ASCO 2024;Abstract 7500.
- Leleu XP et al. Phase 3 randomized study of **isatuximab (Isa) plus lenalidomide and dexamethasone (Rd) with bortezomib** versus IsaRd in patients with **newly diagnosed transplant ineligible** multiple myeloma (NDMM TI). ASCO 2024;Abstract 7501.

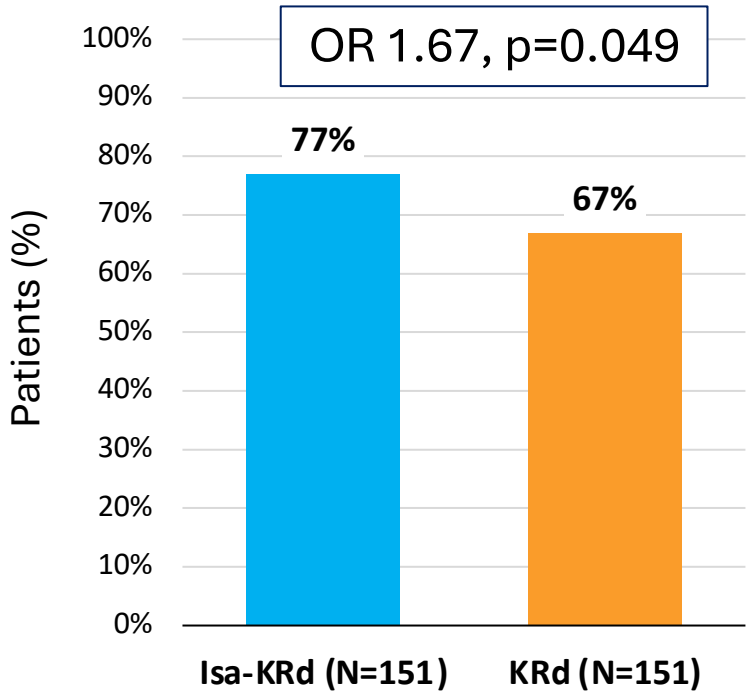
NDMM

- PERSEUS
- GMMG-HD7
- IsKia
- GMMG-CONCEPT Trial
- IMROZ
- BENEFIT Trial
- MAIA Update
- DETERMINATION Diversity

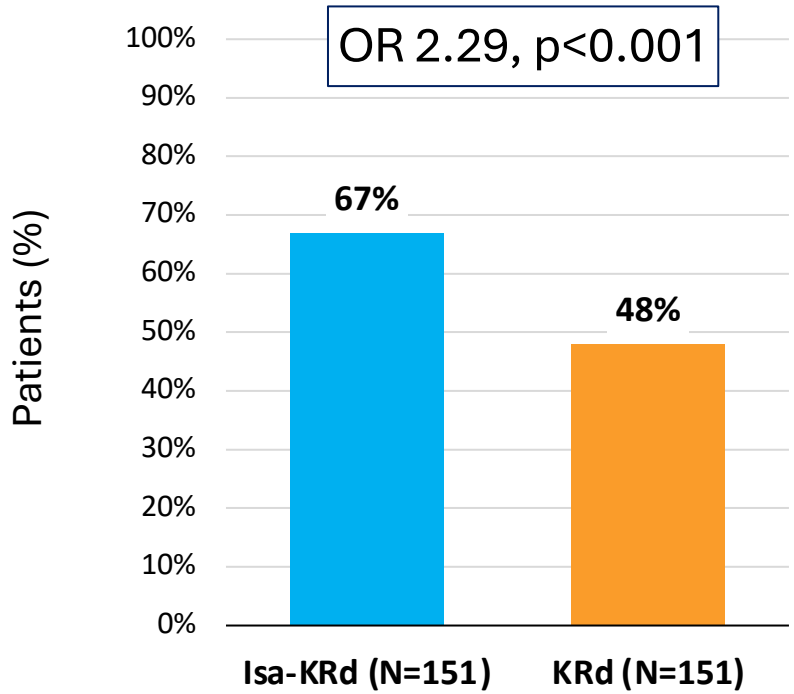
Courtesy of Thomas Martin, MD

IsKia - Primary Endpoint: Post-consolidation MRD negativity (ITT analysis)

NGS, 10^{-5}



NGS, 10^{-6}



≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.

High MRD compliance and sample quality (97-100% of sample evaluable at 10^{-5} and 10^{-6} cut off.

Consistent MRD results were detected by next-generation flow

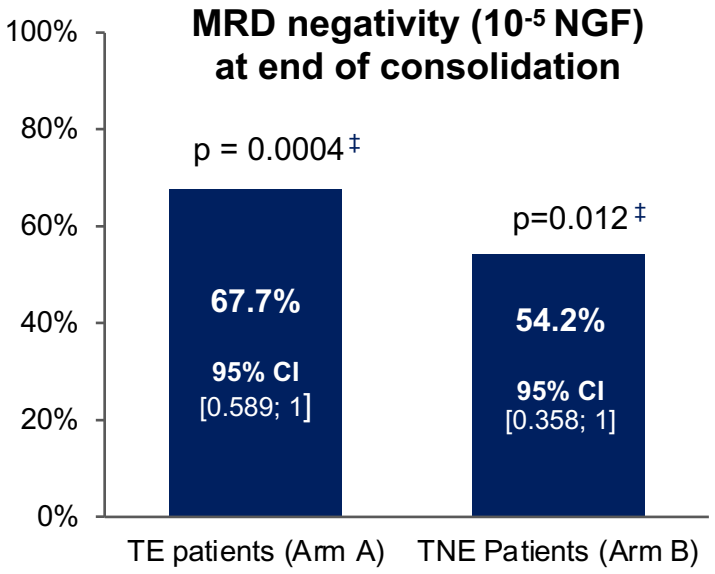
In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

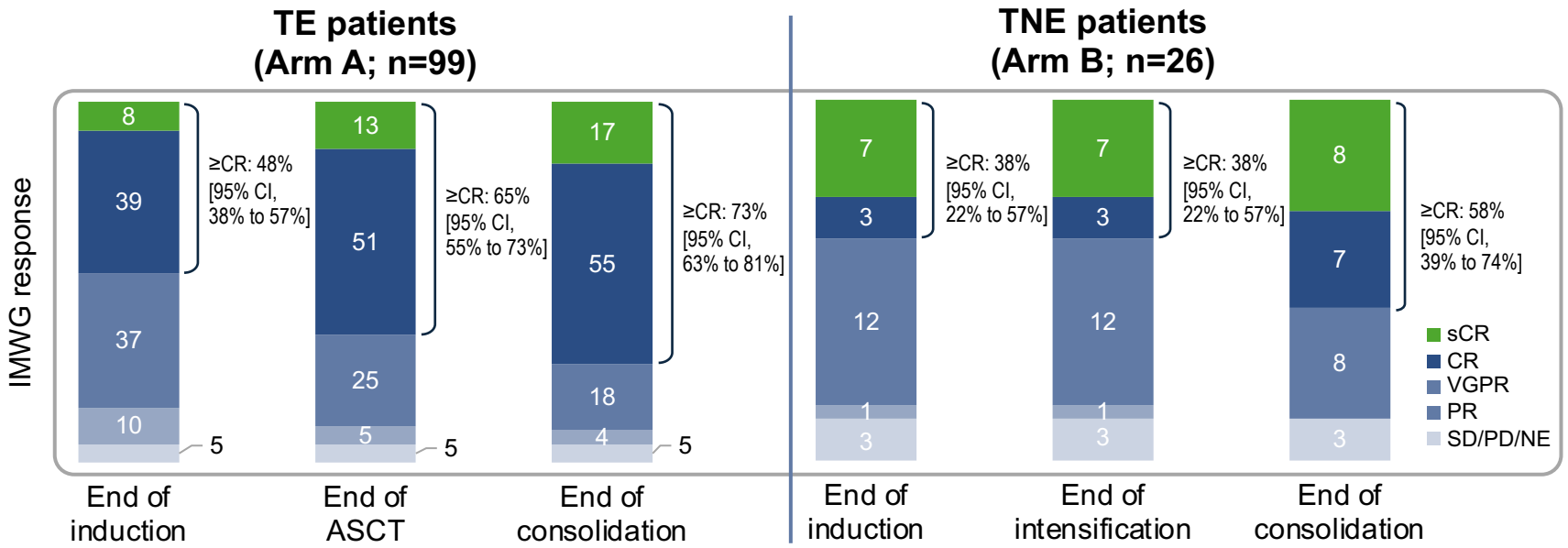
Gay F, et al ASH 2023

Courtesy of Thomas Martin, MD

MRD, minimal residual disease; ITT, intention to treat; NGS, next-generation sequencing; OR, odds ratio; p, p-value; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; CI, confidence interval.

CONCEPT Trial: MRD Negativity and IMWG Response





MRD status, n (%)	TE patients (Arm A) (n=93*)	TNE patients (Arm B) (n=24†)
Negative	**63 (67.7)**	**13 (54.2)**
Positive	3 (3.2)	0 (0)
Not done/missing	2 (2.2)	0 (0)
Time point not reached	25 (27.0)	11 (45.8)

6 TE and 2 TNE patients were not assessable

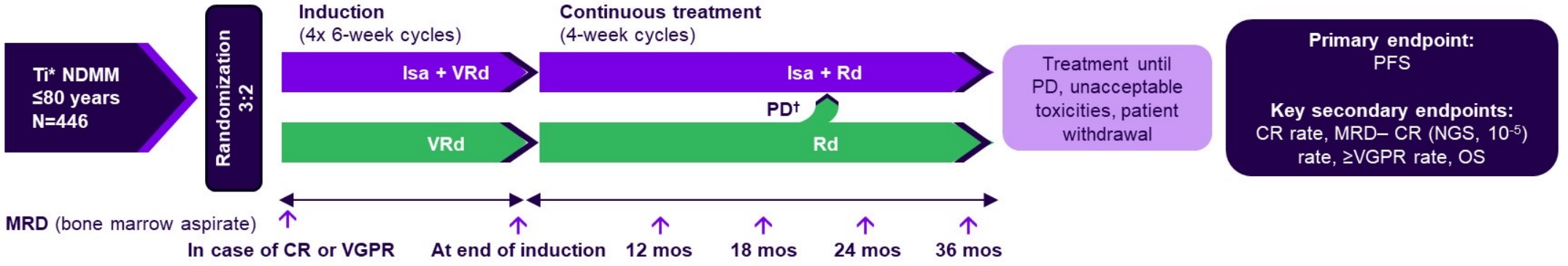
- **The trial met its primary endpoint with MRD negativity rates of 67.7% (TE) and 54.2% (TNE) at the end of consolidation**
- Responses deepened over time with ≥CR-rates of 72.7% (TE) and 57.7% (TNE) as best response

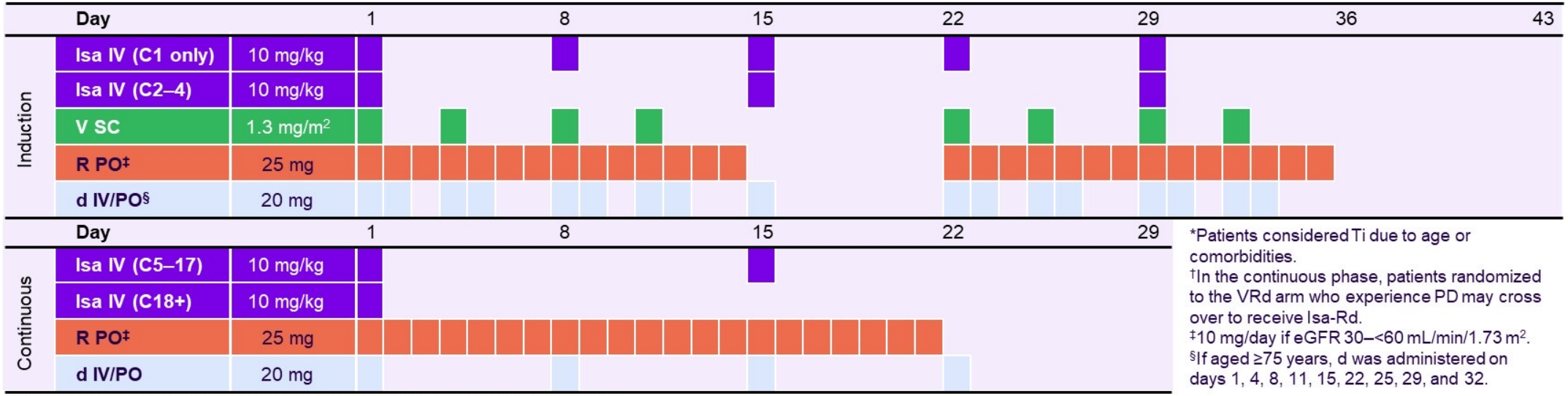
Leypoldt LB, et al, IMS 2023

Courtesy of Thomas Martin, MD

Study design: Isa-VRd vs VRd in transplant-ineligible NDMM

IMROZ



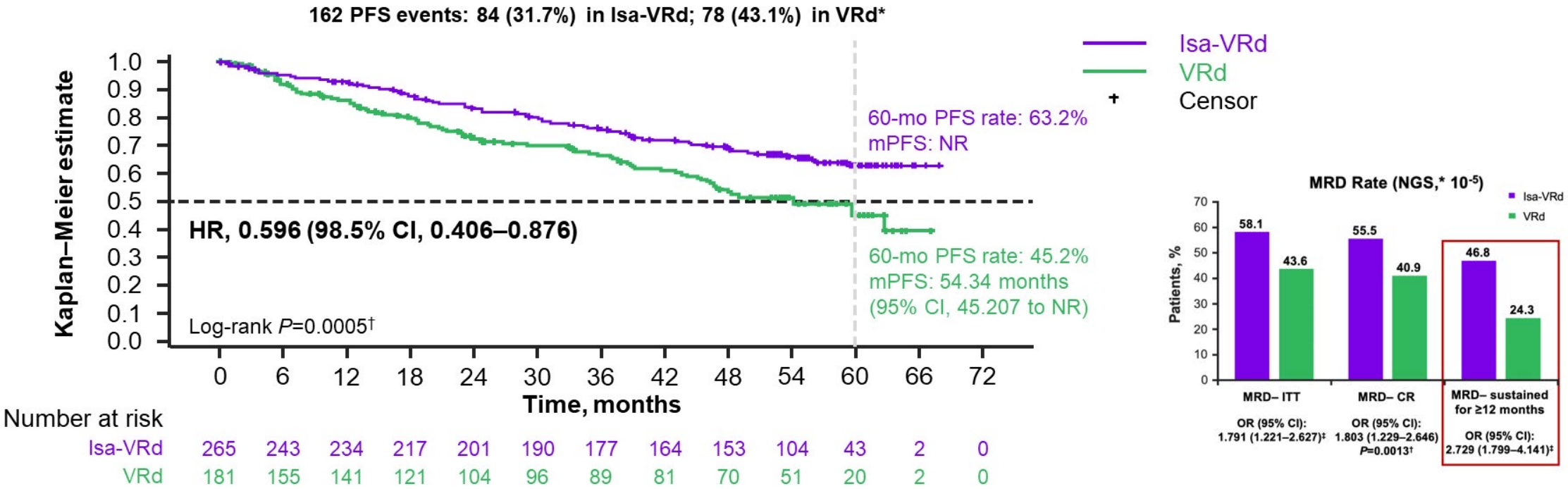


*Patients considered Ti due to age or comorbidities.
†In the continuous phase, patients randomized to the VRd arm who experience PD may cross over to receive Isa-Rd.
‡10 mg/day if eGFR 30–<60 mL/min/1.73 m^2.
§If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

C, cycle; d, dexamethasone; Isa, isatuximab; R, lenalidomide; SC, subcutaneous; V, bortezomib.
Orlowski RZ, et al. ASCO 2018.

Courtesy of Thomas Martin, MD

Primary endpoint met: Interim PFS analysis–IRC assessment in ITT population



At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

*Cutoff date for PFS analysis: September 26, 2023 (median follow-up, ~5 years). †Nominal one-sided *P* value.
NR, not reached.

Courtesy of Thomas Martin, MD

Individualizing Treatment Approaches for Newly Diagnosed MM

- Zonder JA et al. **Treatment outcomes and prognostic factors** with **lenalidomide, bortezomib, and dexamethasone (RVd)** alone versus Rvd **plus autologous stem cell transplantation (ASCT)** in **African American** (AA) patients (pts) with **newly diagnosed** multiple myeloma (NDMM) in the **Determination phase 3 trial**. ASH 2023;Abstract 4762.

Conclusions for NDMM

- CD38 + VRd (QUAD therapy) – appears to be new SOC for TE and TI NDMM
- Results appear durable both in TE and TI – projected PFS >80-90 months
- In TI, (BENEFIT) – QWk bortezomib appears well-tolerated and effective
  - Unclear in TE
- High-risk NDMM appears to benefit from QUAD therapy
  - Dara-VRd subgroup looks good
  - Isa-KRd shows improved MRD- rates, especially in double hit subgroup
- Future results from GMMG-HD7 and PERSEUS will assess the value of doublet maintenance and whether using MRD to guide maintenance duration makes sense
- MRD(–) CR will be the new “early” response metric for future trials
- More treatment adapted trials based on MRD, will be needed to help guide treatment choice and duration in the future
- NDMM trials should further assess differences based on diversity

Courtesy of Thomas Martin, MD

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Isatuximab Combination Regimens for Relapsed/Refractory MM

- Martin T et al. **Isatuximab, carfilzomib, and dexamethasone** in patients with **relapsed** multiple myeloma: **Updated results from IKEMA**, a randomized phase 3 study. *Blood Cancer J* 2023;13(1):72.
- Richardson PG et al. **Isatuximab-pomalidomide-dexamethasone** versus pomalidomide-dexamethasone in patients with **relapsed and refractory** multiple myeloma: **Final overall survival analysis**. *Haematologica* 2024;[Online ahead of print].

Relapsed/Refractory Multiple Myeloma

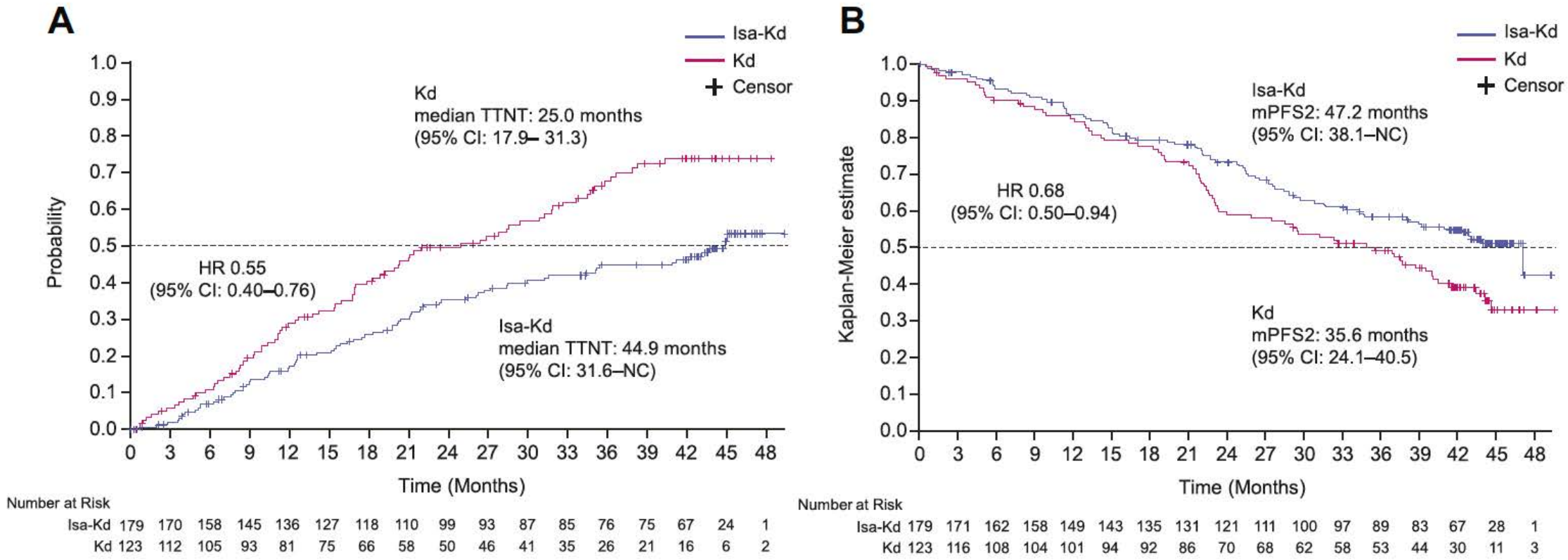
- IKEMA
- ICARIA
- BOSTON Trial
- Mezigdomide +Dex
- Mezigdomide + Dara + Dex

Courtesy of Thomas Martin, MD

Updated Results from IKEMA (Isa-Kd vs. Kd)

A. Time to next therapy (TTNT)

B. Progression free survival-2



Courtesy of Thomas Martin, MD

Martin T, et al; Blood Cancer Journal (2023) 13:72

ICARIA (Isa-Pd vs. Pd): FINAL Results

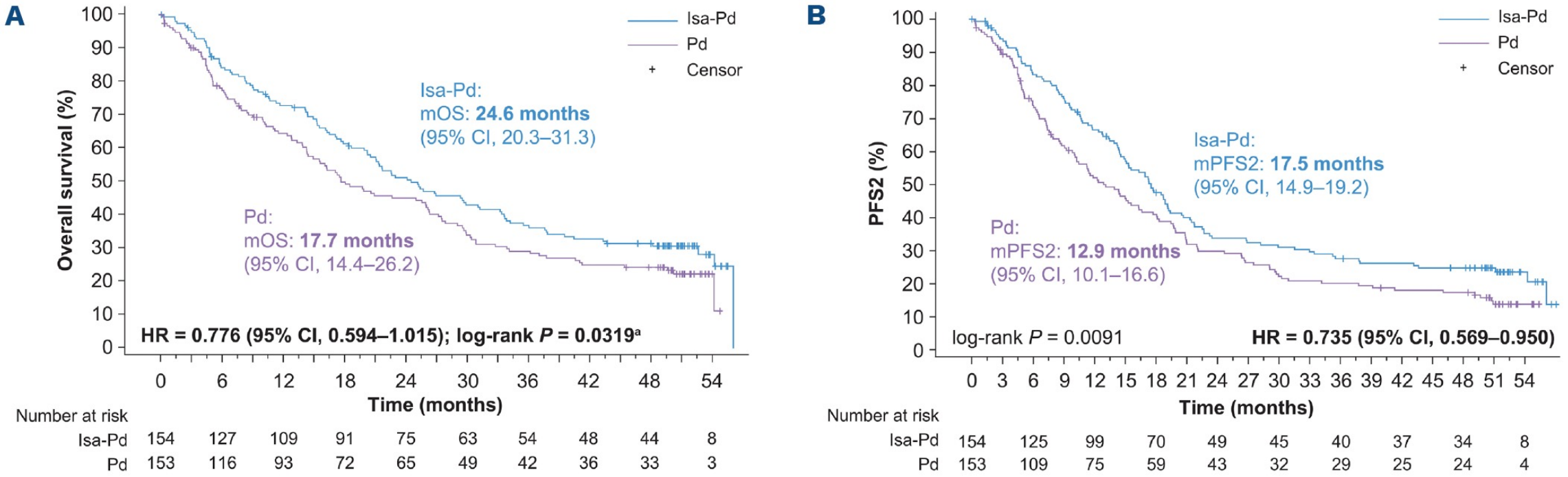


Figure 2. Overall survival and progression-free survival on subsequent therapy or death in the intention-to-treat population. (A)

Richardson P, et al; Haematologica 2024

Courtesy of Thomas Martin, MD

Treatment of Relapsed/Refractory MM with Selinexor

- Mateos MV et al. **Impact of prior treatment** on **selinexor, bortezomib, dexamethasone outcomes** in patients with **relapsed/refractory** multiple myeloma: **Extended follow-up subgroup analysis** of the **BOSTON trial**. *Eur J Haematol* 2024;[Online ahead of print].
- Jagannath S et al. Association of **selinexor dose reductions** with **clinical outcomes** in the **BOSTON study**. *Clin Lymphoma Myeloma Leuk* 2023;23(12):917-23.e3.
- Madan S et al. **Novel selinexor triplet and quadruplet regimens** (SND, SPED, SBD, SDPD): Results from the **phase 1b/2 STOMP** multiple myeloma trial. EHA 2024;Abstract P999.

BOSTON Trial:

Results

- Median F/U >28 mos
- PFS
  - Len-Refr: 10.2 vs 7.1 mos
  - PI-naïve: 29.5 vs 9.7 mos
  - 1 PLOT: 21.0 vs 10.7 mos

- In all subgroups
  - ORR and ≥VGPR favored SVd

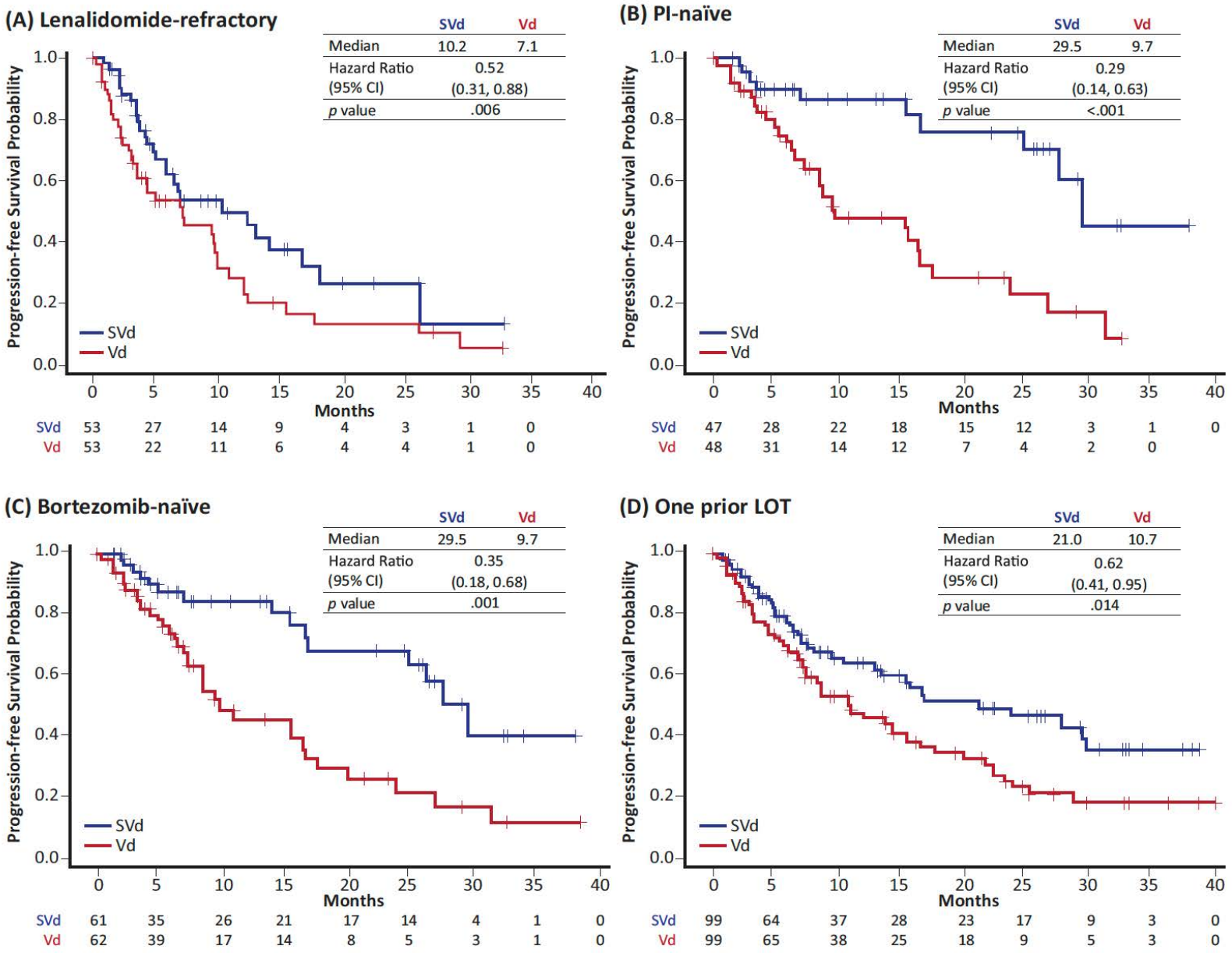


FIGURE 1 Progression-free survival with (A) lenalidomide-refractory, (B) PI-naïve, (C) bortezomib-naïve, and (D) one prior LOT subgroups. CI, confidence interval; LOT, line of therapy; PI, proteasome inhibitor; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone. *p* values are 1-sided.

Mateos MV, et al; Eur J Haematol. 2024;1–11

Courtesy of Thomas Martin, MD

BOSTON Trial: Importance of Dose Adjustments

- 195 Patients
  - Seli-Qwk + Vd
  - 126 (65%) – required dose Adj
  - Median Seli dose 71.4 mg/wk
- PFS –
  - Pts with dose adj ➔ 16.6 mos
  - Pts w/o dose adj ➔ 9.2 mos
- ORR
  - W= 81.7% vs. w/o= 66.7%

Effect of Selinexor Dose Reductions on Clinical Outcomes

Table 2 Comparison of Efficacy Outcomes Between BOSTON Study Patients With and Without Selinexor Dose Reduction

Outcome	With Selinexor Dose Reduction N = 126	Without Selinexor Dose Reduction N = 69
Progression-free survival, months, median (95% CI)	16.6 (12.9, NE)	9.2 (6.8, 15.5)
Overall response rate, n (%), [95% CI]	103 (81.7) [73.9, 88.1]	46 (66.7) [54.3, 77.6]
Stringent complete response, n (%)	16 (12.7)	3 (4.3)
Complete response, n (%)	11 (8.7)	3 (4.3)
≥Very good partial response, n (%), [95% CI]	65 (51.6) [42.5, 60.6]	22 (31.9) [21.2, 44.2]
Very good partial response, n (%)	38 (30.2)	16 (23.2)
Partial response, n (%)	38 (30.2)	24 (34.8)
Minimal response, n (%)	10 (7.9)	6 (8.7)
Stable disease, n (%)	12 (9.5)	13 (18.8)
Progressive disease, n (%)	0	1 (1.4)
Not evaluable, n (%)	1 (0.8)	3 (4.3)
Duration of response, months, median (95% CI)	NR (13.8, NE)	12.0 (8.3, NE)
Time to next treatment, months, median (95% CI)	22.6 (14.6, NE)	10.5 (6.3, 18.2)

Abbreviations: CI = confidence interval; NE = not evaluable; NR = not reached.

Courtesy of Thomas Martin, MD

Jaganath S, et al; Clinical Lymphoma, Myeloma and Leukemia 2023. Vol. 23, No. 12, 917–923

Novel CELMoDs for Relapsed/Refractory MM

- Amatangelo M et al. **Iberdomide** is immune stimulatory and induces deep anti-myeloma activity across doses **in combination with daratumumab** in patients with **TNE NDMM** from the **CC-220-MM-001 study**. EHA 2024;Abstract P847.
- Richardson PG et al. **Mezigdomide plus dexamethasone** in **relapsed and refractory** multiple myeloma. *N Engl J Med* 2023;389(11):1009-22.
- Richardson PG et al. **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**. ASH 2023;Abstract 1013.

Iberdomide is Immune Stimulatory and Induces Deep Anti-Myeloma Activity Across Doses in Combination with Daratumumab in Patients with TNE NDMM from the CC-220-MM-001 Study

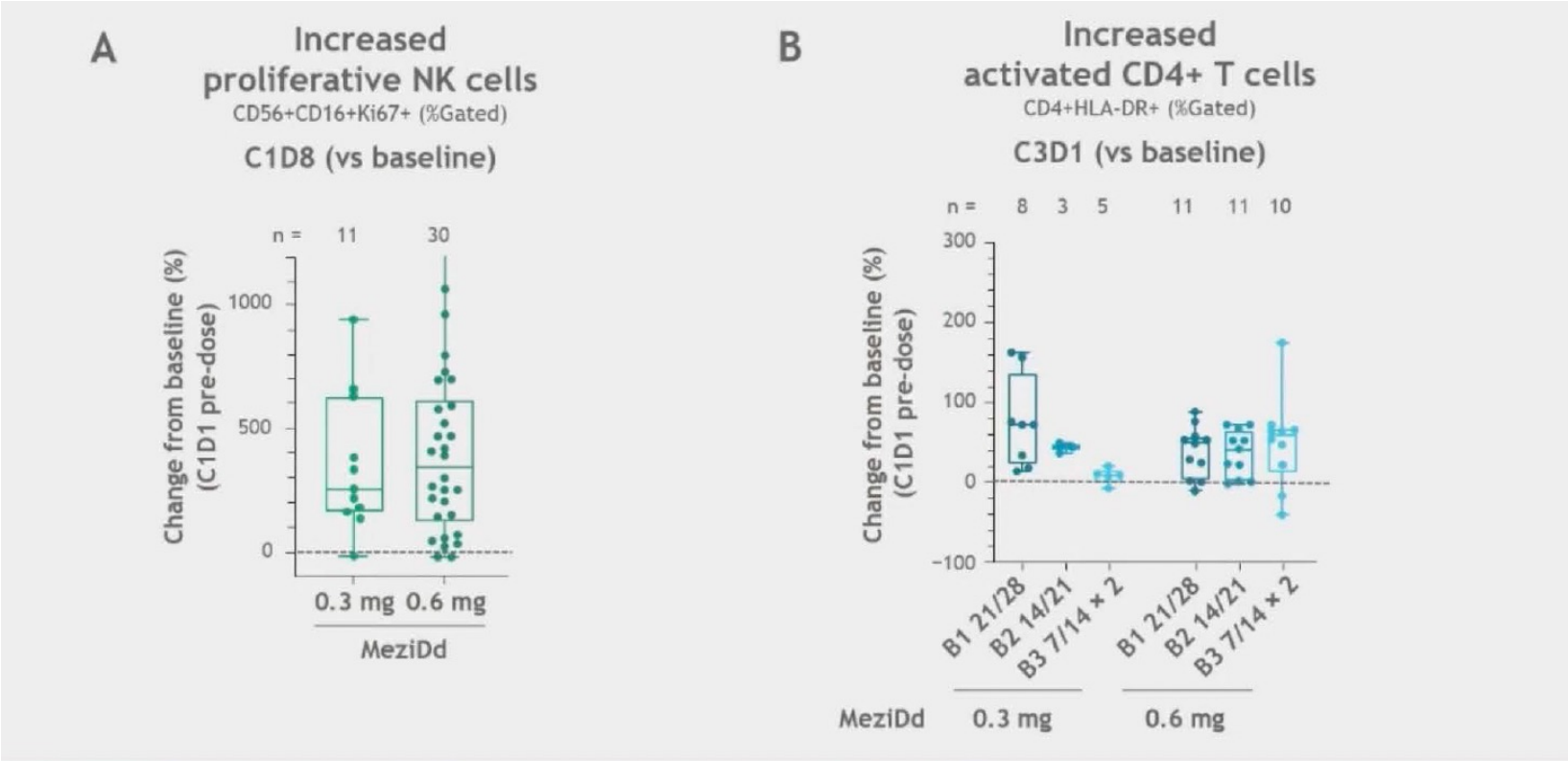
Amatangelo M et al.

EHA 2024;Abstract P847.

Author Conclusions: *IberDd showed pharmacodynamic response across all 3 doses of IBER tested in pts with transplant non-eligible NDMM, including a reduction in substrate protein levels in BM MM cells, induction of proliferation and activation of T and NK cells, deep and sustained decreases in involved serum-free light chains, and induction of MRD negativity. Notably, data showed significant overlap across doses suggesting all 3 doses of IBER tested are biologically active in combination with DARA + DEX. These data support the use of IBER at doses of 1.0 mg or higher in combination with DARA to achieve maximal pharmacodynamic effects.*

Mezigdomide Combinations: Mezi-Dara+Dex

PK/PD with Mezi-Dd:



Richardson P, et al; ASH 2023.

<u>EHA Abstract 2024</u>

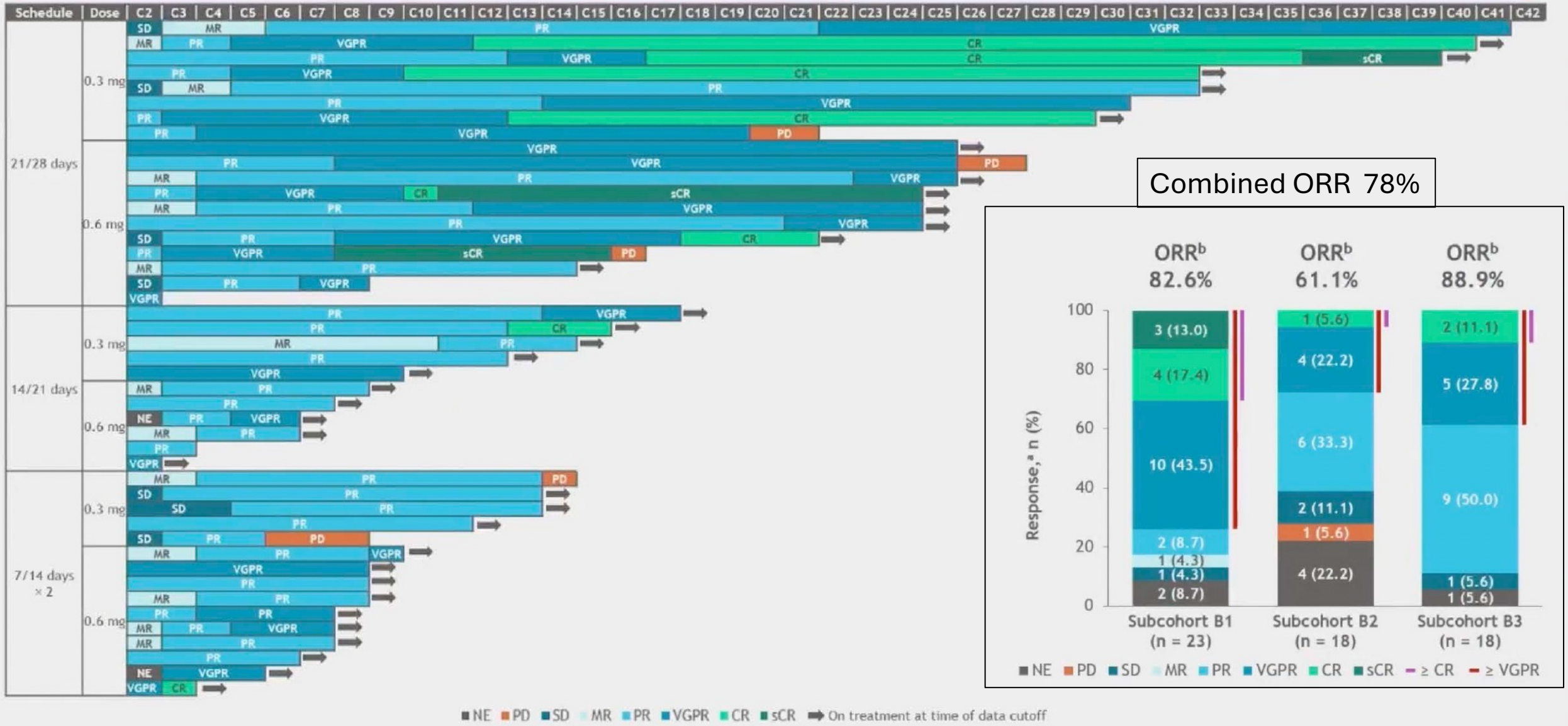
- > 4-fold increase in proliferating T and NK cells,
- > 2-fold increase in activated/ effector memory T cells
- > 75% decrease in median absolute B cells

- MRD(-) response in 23/51

Amantangelo M, et al. EHA 2024

Courtesy of Thomas Martin, MD

Patients' responses over time: Cohort B (MeziDd)



Combined ORR 78%

Data cutoff: July 6, 2023.

Richardson PG, et al. ASH 2023 [Abstract #1013]

Courtesy of Thomas Martin, MD

Conclusions for RRMM

- CD38 + PI (Carfilzomib) – is very active in RRMM with all subgroups showing benefit
- CD38 + pomalidomide – also quite active and more convenient
- Selinexor + Vd in PI naïve has shown impressive results with PFS ~3 years
- Mezigdomide combinations are also showing promise with Mezi-Dara-Dex leading the charge and other combinations under development
- How to incorporate all these combinations as well as early use of CAR T cell therapy will be important questions to answer in the coming years

Courtesy of Thomas Martin, MD

Agenda

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Current Approaches with Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM

- Rodríguez Otero P et al. **Idecabtagene vicleucel (ide-cel)** versus standard (std) regimens in patients (pts) with **triple-class–exposed (TCE) relapsed and refractory** multiple myeloma (RRMM): Updated analysis from **KarMMa-3**. ASH 2023;Abstract 1028.
- Delforge M et al. **Health-related quality of life** in patients with triple-class exposed relapsed and refractory multiple myeloma treated with **idecabtagene vicleucel** or standard regimens: Patient-reported outcomes from the phase 3, randomised, open-label **KarMMa-3** clinical trial. *Lancet Haematol* 2024;11(3):e216-27.

Conclusions on KarMMa-3: Idecabtagene vicleucel

- Previous FDA indication following pivotal KarMMa study
  - Adults with R/R multiple myeloma after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab
- New FDA indication following KarMMa-3 results
  - Adults with R/R multiple myeloma after ≥2 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab

- No new safety signals in an earlier line population

Courtesy of Jesús G Berdeja, MD

CAR T-Cell Therapy in Earlier Lines of Therapy for MM

- San-Miguel J et al. **Cilta-cel** or standard care in **lenalidomide-refractory** multiple myeloma. *N Engl J Med* 2023;389(4):335-47.
- Hilengrass J et al. The phase 2 **CARTITUDE-2** trial: **Updated efficacy and safety** of **ciltacabtagene autoleucel** in patients with multiple myeloma and **1–3 prior lines of therapy (cohort A)** and with **early relapse after first line treatment (cohort B)**. ASH 2023;Abstract 1021.
- Leleu X et al. **Idecabtagene vicleucel (ide-cel)** in patients (pts) with **clinical high-risk early relapse** multiple myeloma (MM) **without front-line (1L) autologous stem cell transplantation (ASCT)**: **KarMMa-2 cohort 2b**. EHA 2024;Abstract S208.
- Dhodapkar M et al. Efficacy and safety of **idecabtagene vicleucel (ide-cel)** in patients with **clinical high-risk newly diagnosed** multiple myeloma (NDMM) with an **inadequate response to frontline autologous stem cell transplantation (ASCT)**: **KarMMa-2 cohort 2c** extended follow-up. ASH 2023;Abstract 2101.
- Arnulf B et al. Efficacy and safety of **ciltacabtagene autoleucel ± lenalidomide maintenance** in **newly diagnosed** multiple myeloma with **suboptimal response to frontline autologous stem cell transplant: CARTITUDE-2 cohort D**. ASCO 2024;Abstract 7505.

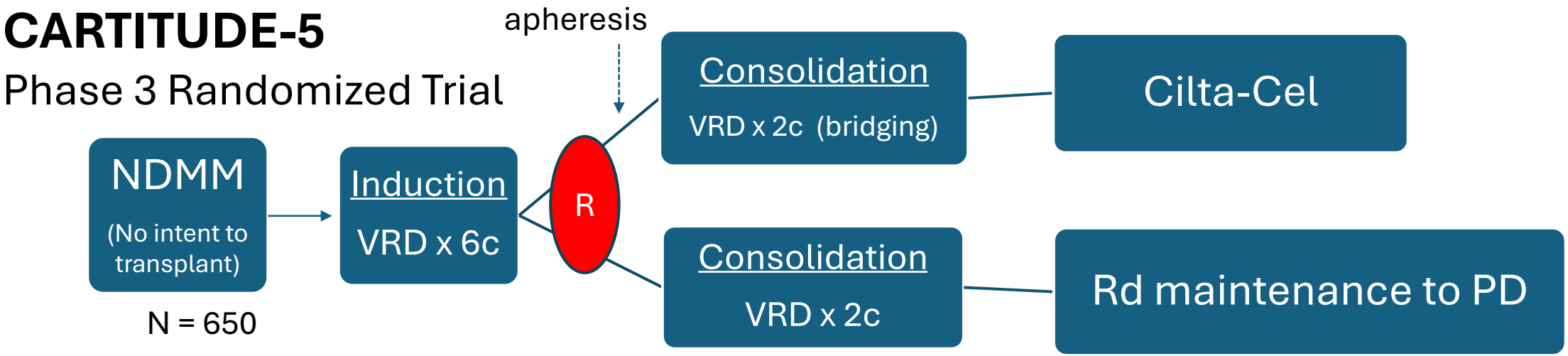
Conclusions on CARTITUDE-4: Ciltacabtagene autoleucel

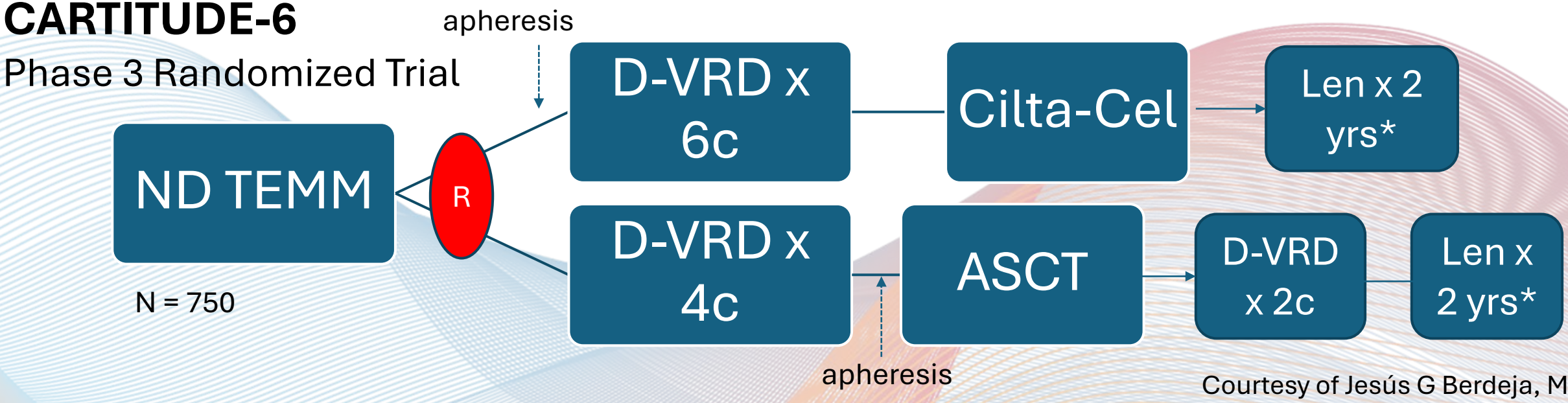
- Previous FDA indication following pivotal CARTITUDE-1 study
  - Adults with R/R multiple myeloma after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab
- New FDA indication following CARTITUDE-4 results
  - Adults with R/R multiple myeloma after ≥1 prior line of therapy, including an immunomodulatory agent, a proteasome inhibitor, and refractory to lenalidomide

- Incidence of delayed MNTs was much less c/w CARTITUDE-1
  - Perhaps due to better bridging therapy – less disease burden
- Incidence of secondary malignancies less c/w CARTITUDE-1
  - Signal for secondary heme malignancies still exists

Courtesy of Jesús G Berdeja, MD

Moving CAR T-Cells to Frontline Treatment





Courtesy of Jesús G Berdeja, MD

Moving CAR T towards the frontline

- Small cohorts with both ide-cel and cilta-cel show that CAR T-cells are feasible as early as consolidation in first line
- CAR T-cells are effective for patients with functional HR MM (relapse within 2 yrs of frontline Tx)
- CAR T-cells expand well even in very low burden of disease (post ASCT)

- As seen with KarMMa-3 and CARTITUDE-4, cytopenias, CRS and neurotoxicity may be less in less heavily pretreated patients and in setting of low burden of disease

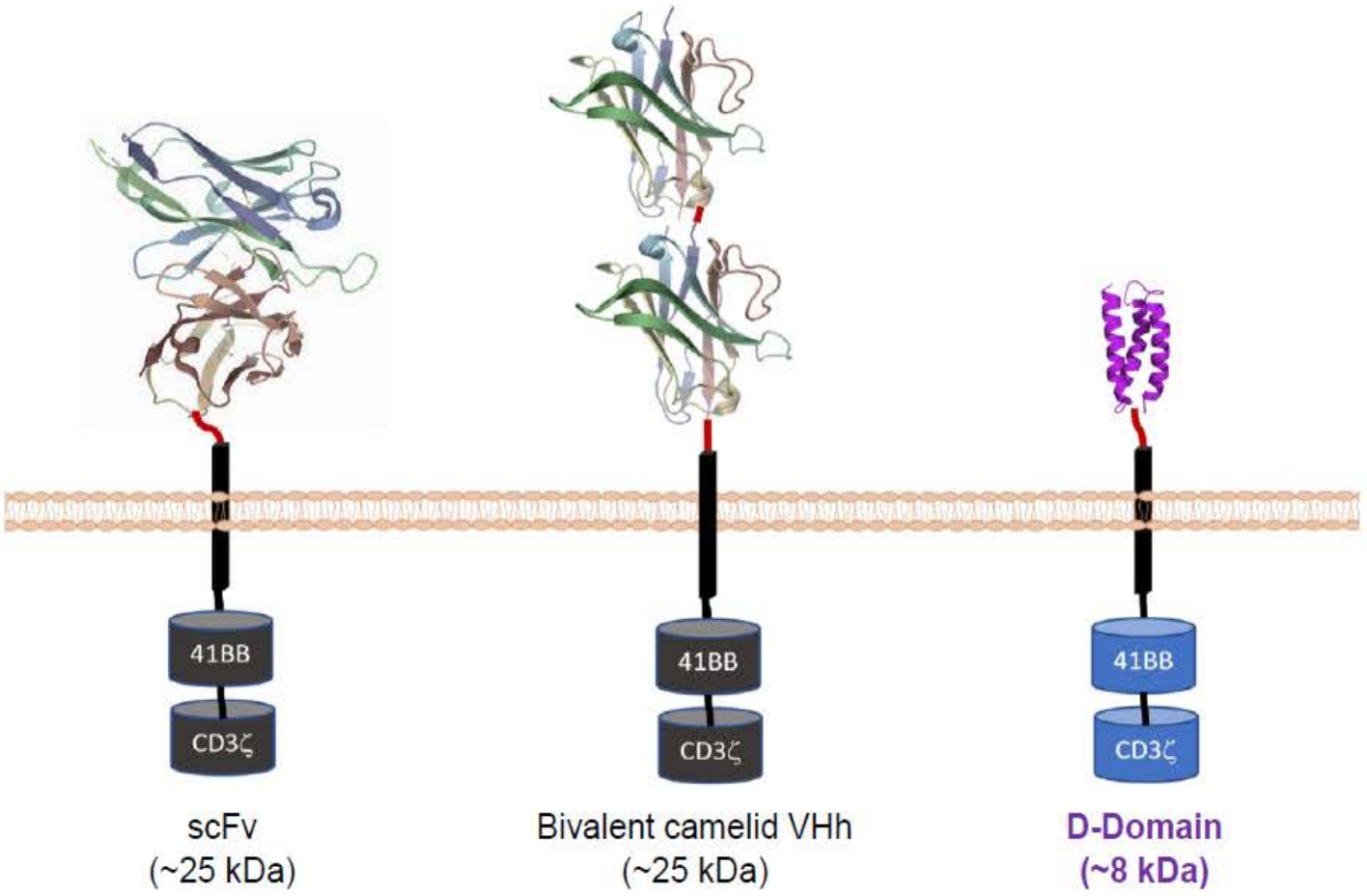
- This data supports planned frontline trials with both ide-cel and cilta-cel

Courtesy of Jesús G Berdeja, MD

Novel CAR T-Cell Therapies Under Development for MM

- Dhakal B et al. Phase 1 study of **anitocabtagene autoleucel** for the treatment of patients with **relapsed and/or refractory** multiple myeloma: **Results from at least 1-year follow-up** in all patients. EHA 2024;Abstract S207.
- Bal S et al. **BMS-986393 (CC-95266)**, a G protein-coupled receptor class C group 5 member D **(GPRC5D)-targeted chimeric antigen receptor** (CAR) T-cell therapy for **relapsed/refractory** multiple myeloma (RRMM): **Updated results** from a **phase 1** study. ASH 2023;Abstract 219.
- Nadeem O et al. Safety and preliminary efficacy of **BMS-986393, a GPRC5D CAR T cell therapy**, in patients with **relapsed/refractory** (RR) multiple myeloma (MM) and **1-3 prior regimens**: First results from a phase 1 study. EHA 2024;Abstract P951.

Anitocabtagene autoleucel (anito-cel/CART-ddbcma)



D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

Size	**Small D-Domain construct facilitates high transduction efficiency, CAR positivity, and CAR density on the T-cell surface[2-4]**
Stability	**Rapid D-Domain folding, lack of disulfide bonds, and a hydrophobic core enables stability at and beyond physiologic conditions[5,6]**
Structure	**Due to small size and compact structure, D-Domain CARs have a low risk of tonic signaling[6] and potentially more efficient Multiple Myeloma cell killing**

[1]Rotte, et al. *Immuno-Oncology Insights* 2022; 3(1), 13–24; [2]Frigault, et al. *Blood Adv.* 2023; 7(5):768-777; [3]Cante-Barrett, et al. *BMC Res. Notes* 2016; 9:13; [4]Buonato, et al. *Mol. Cancer Ther.* 2022; 21(7):1171-1183; [5]Zhu, et al. *Proc. Nat. Acad. Sci.* 2003; 100(26): 15486-15491; [6]Qin, et al. *Mol. Ther.* 2019; 27(7): 1262-1274.

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Conclusions on Anito-cel

- Novel synthetic construct may allow for higher CAR expression, low tonic signaling, improved activity

- Impressive 100% ORR
- Impressive responses in EMD – a difficult to treat population

- Durability of response in all, but especially EMD patients is of great interest

- Toxicity profile seems reasonable with no delayed neurotoxicity

- Pivotal trials ongoing

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Conclusions on BMS-986393

- GPRC5D-directed CAR T-Cells are effective
- Efficacy seen in patients with prior BCMA-directed therapies, implications for sequencing?

- Some toxicity similar to BCMA-directed CARTs (cytopenias, CRS)
- Some toxicity are target specific – GPRC5D
  - Cerebellar neurotox - dose related, reversible?
    - Seen less in cohort C – pts with 1-3 prior LOT
  - On-target, off-tumor tox appears less than same target with bispecifics
    - Less incidence and shorter duration: dysgeusia, nail changes, rash

Courtesy of Jesús G Berdeja, MD

Approved and Investigational Bispecific Antibodies for MM

- Garfall AL et al. **Long-term follow-up** from the phase 1/2 **MajesTEC-1** trial of **teclistamab** in patients with **relapsed/refractory** multiple myeloma. ASCO 2024;Abstract 7540.
- Lesokhin AM et al. **Elranatamab** in **relapsed or refractory** multiple myeloma: Phase 2 **MagnetisMM-3** trial results. *Nat Med* 2023;29(9):2259–67.
- Mohty M et al. **Long-term survival after elranatamab monotherapy** in patients with **relapsed or refractory** multiple myeloma: **MagnetisMM-3**. EHA 2024;Abstract 932.
- Lentzsch S et al. **Linvoseltamab** in patients with **relapsed/refractory** multiple myeloma in the **LINKER-MM1 study**: Depth and durability of response at 14-month median follow-up. EHA 2024;Abstract S212.
- Weisel K et al. Efficacy, safety, and determination of **RP2D** of **ABBV-383**, a **BCMA bispecific antibody**, in patients with **relapsed/refractory** multiple myeloma (RRMM). EHA 2024;Abstract S211.
- Rasche L et al. Long-term efficacy and safety results from the phase 1/2 **MonumenTAL-1** study of **talquetamab**, a GPRC5D×CD3 bispecific antibody, in patients with **relapsed/refractory** multiple myeloma. EHA 2024;Abstract P915.

Conclusions on MajesTEC-1: Teclistamab

- First BCMA:CD3 bispecific approved for MM
  - Indication: Adults with R/R multiple myeloma after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab
- Long-term f/u data >30mos continue to support excellent dz control
  - Patients in CR have not reached median PFS, DOR @ 30 mos
- No new toxicity signals
  - Question if decreased infections with adequate prophy/IVIG replacement and decreased frequency of dosing

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Conclusions MagnetisMM-3: Elranatamab

- 2nd BCMA:CD3 bispecific approved for MM
  - Indication: Adults with R/R multiple myeloma after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab
- Updated data with excellent DOR and PFS
  - Med PFS 17.2 mos
- No new toxicity signals
  - Similar to teclistamab

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Conclusions LINKER-MM1: Linvoseltamab

- FDA Review expected this summer - 3rd BCMA:CD3 bispecific?
- Efficacy similar to teclistamab, elranatamab
- Differences:
  - IV vs SQ
  - 2 1-day hospitalization vs 3-6 days for other products
- Toxicity similar
  - Infections continue to be high as with other BCMA products
  - Decrease with time on therapy, question if true difference or due to less frequent dosing/implementation of better prophy, IVIG use

Courtesy of Jesús G Berdeja, MD

Conclusions on ABBV-383

- Another very active BCMA:CD3 bispecific

- Construct differences
  - Allows for q4wk dosing
  - Less CRS?
  - Less infections?

- Registrational phase 3 trial: CERVINO trial at 60mg Q4wks is ongoing

Courtesy of Jesús G Berdeja, MD

Conclusions on MonumenTAL-1

- First GPRC5D:CD3 bispecific approved for MM
  - Indication: Adults with R/R multiple myeloma after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab

- Longer-term f/u continues to show durable responses
  - Q2wk dosing appears more durable
  - Excellent responses in patients with prior T-cell redirecting Tx, mostly BCMA-directed

- Toxicity
  - Plus – infections though common, appear less frequent/lower grade than BCMA –directed bispecifics
  - Minus – Off tumor, on target effects: dysgeusia, nail dysmorphia, rash, weight loss can be difficult for patient

Courtesy of Jesús G Berdeja, MD

Year in Review: Melanoma and Nonmelanoma Skin Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, July 10, 2024
5:00 PM – 6:00 PM ET

Faculty

Evan J Lipson, MD

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