Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Multiple Myeloma

Thursday, January 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Rafael Fonseca, MD
Jonathan L Kaufman, MD

Moderator

Neil Love, MD

RTP Year in Review 2020

YiR Multiple Myeloma Faculty

Rafael Fonseca, MD
Getz Family Professor of Cancer
Director for Innovation and Transformational Relationships
Interim Executive Director of the Mayo Clinic Comprehensive Cancer Center
Chair, Department of Internal Medicine
Distinguished Mayo Investigator
Mayo Clinic in Arizona
Phoenix, Arizona

Jonathan L Kaufman, MD
Associate Professor of Hematology and Medical Oncology
Winship Cancer Institute of Emory University
Atlanta, Georgia

Commercial Support

This activity is supported by educational grants from Adaptive Biotechnologies Corporation, Bristol-Myers Squibb Company, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Karyopharm Therapeutics, Oncopeptides and Takeda Oncology.

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 commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

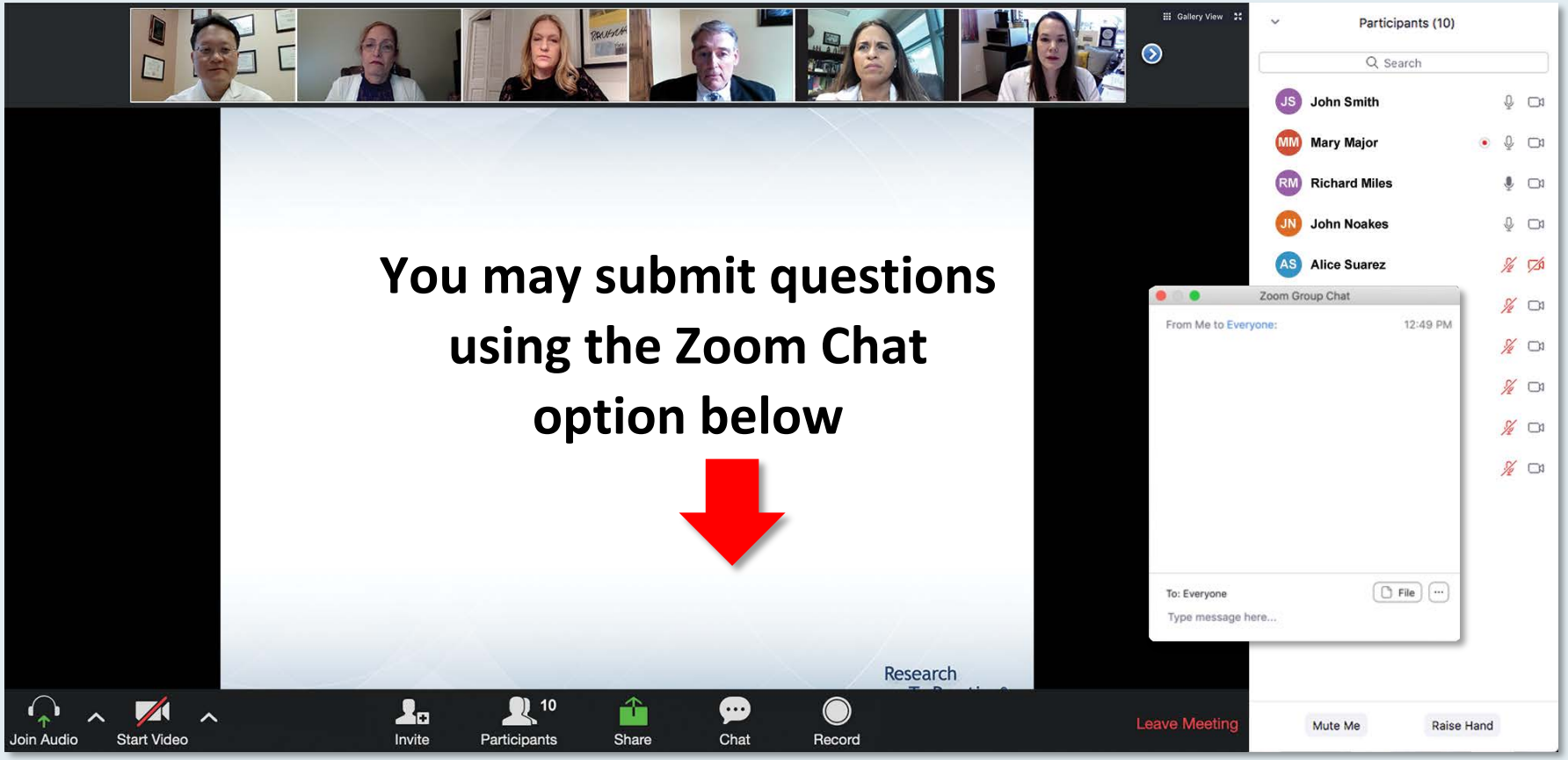
Dr Fonseca — Disclosures

Advisory Committee	Adaptive Biotechnologies Corporation, ONCOtracker Inc
Consulting Agreements	AbbVie Inc, Aduro Biotech, Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Merck, Novartis, ONCOtracker Inc, Pharmacyclics LLC, an AbbVie Company, Sanofi Genzyme, Takeda Oncology

Dr Kaufman — Disclosures

Consulting Agreements	Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Janssen Biotech Inc, Tecnofarma
Contracted Research	Amgen Inc, Bristol-Myers Squibb Company, Fortis Therapeutics, Janssen Biotech Inc, Sutro Biopharma
Data and Safety Monitoring Board/Committee	TG Therapeutics Inc

We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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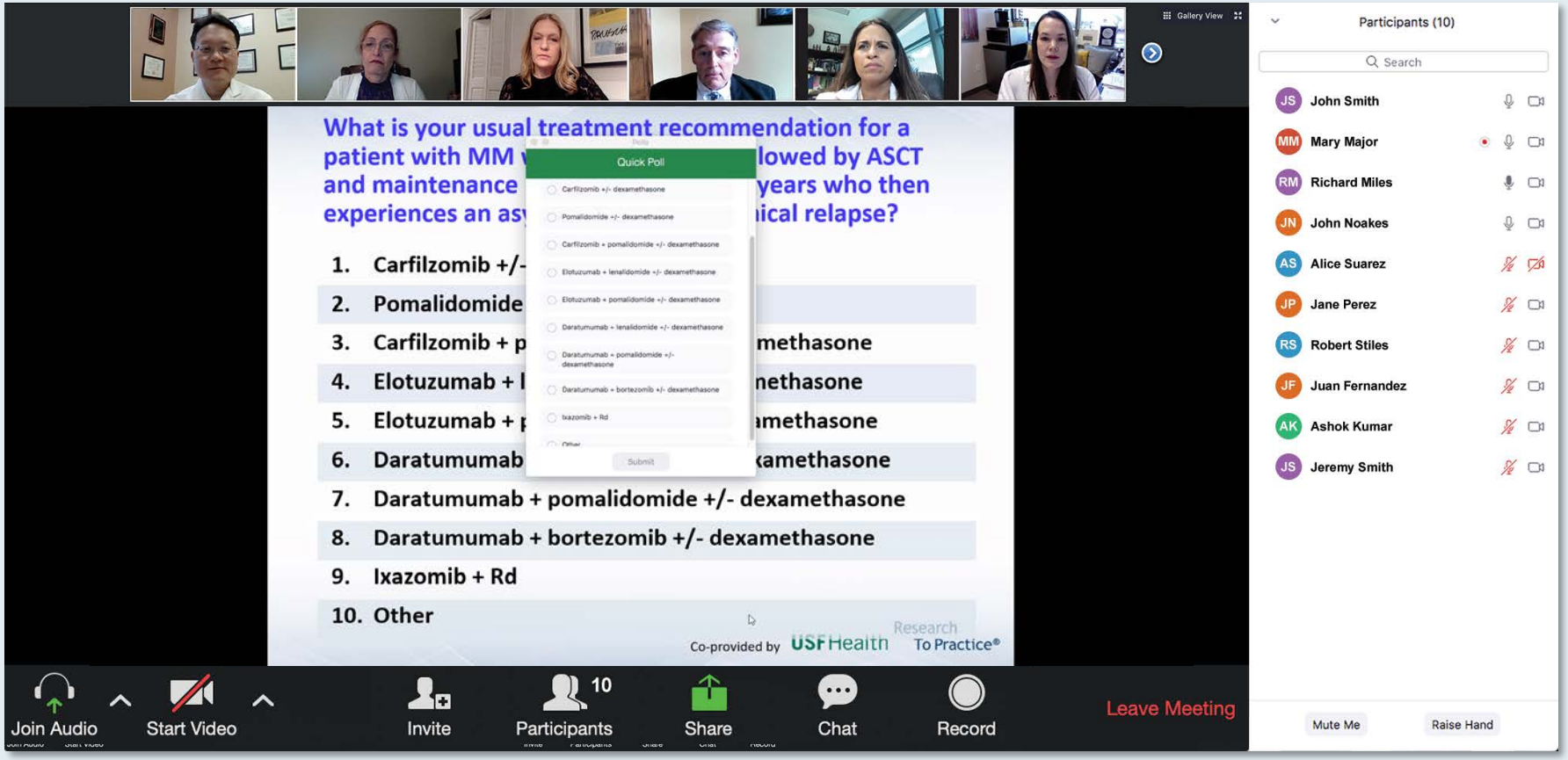
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Presentations on the Treatment of Multiple Myeloma from the 2020 ASH Annual Meeting

DR SAGAR LONIAL

WINSHIP CANCER INSTITUTE

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Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Bladder Cancer and Renal Cell Carcinoma

Tuesday, February 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Sumanta K Pal, MD
David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

RTP Year in Review 2020

Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

Part 2 — Hodgkin and Non-Hodgkin Lymphoma

Wednesday, February 3, 2021
5:00 PM – 6:00 PM ET

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John Kuruvilla, MD
John P Leonard, MD
Michael E Williams, MD, ScM

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, February 4, 2021
5:00 PM – 6:30 PM ET

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Daniel Catenacci, MD
Yelena Y Janjigian, MD
Rutika Mehta, MD, MPH
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Meet The Professor
Management of Lung Cancer

Friday, February 5, 2021
12:00 PM – 1:00 PM ET

Faculty

Joshua Bauml, MD

Moderator

Neil Love, MD

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RESEARCH
TO PRACTICE

Thank you for joining us!

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

RTP Year in Review 2020


Melflufen: A Derivative of the Alkylating Agent Melphalan
Melphalan
Melflufen (JY)
b
a
Melflufen is susceptible to hydrolysis by esterases/amidases that are frequently expressed or overexpressed in tumor tissue, providing the molecule with a target-directed delivery to cells
In vitro studies with melflufen demonstrated it led to a 10- to 20-fold higher intracellular concentration of melphalan in comparison with melphalan alone in various malignant cells
Delforoush M et al. BMC Cancer 2016;16:283.


Have you or would you order an MRD assay to inform the decision regarding autotransplant after induction treatment?
I have
21%
I have not but would for the right patient
47%
I have not and would not
32%
Have you or would you order an MRD assay to inform the decision regarding autotransplant after induction treatment?
I have
21%
I have not but would for the right patient
47%
I have not and would not
32%


nalidomic
ilzomib


Significant Improvement in PFS with Oral Ixazomib Maintenance After ASCT in NDMM: TOURMALINE-MM3 Study Results:
• 39% improvement in PFS
• Median OS not reached in either arm
• Median PFS 26.5 vs. 21.3 months
• HR: 0.72; (0.582–0.890); p=0.
Probability of Progression-Free Survival
Ixazomib
Placebo
Months from Randomization
p=0.0042
Patients with response improvement, %
32%
43%
34%
53%
VGPR to CR
PR to CR or VGPR
• 41% had improvement in response
• 139/302 (46%) on the ixazomib vs 60/187 (32%) on the placebo arm
Dimopoulous MA et al Lancet.


Thomas Iltel, MD


Friday, December 6, 2019
6:30 PM – 9:00 PM
Orlando, Florida
Moderator
Neil Love, MD
Faculty
Jesús G Berdeja, MD
Sagar Lonial, MD
Nikhil C Munshi, MD
Robert Z Orlowski,

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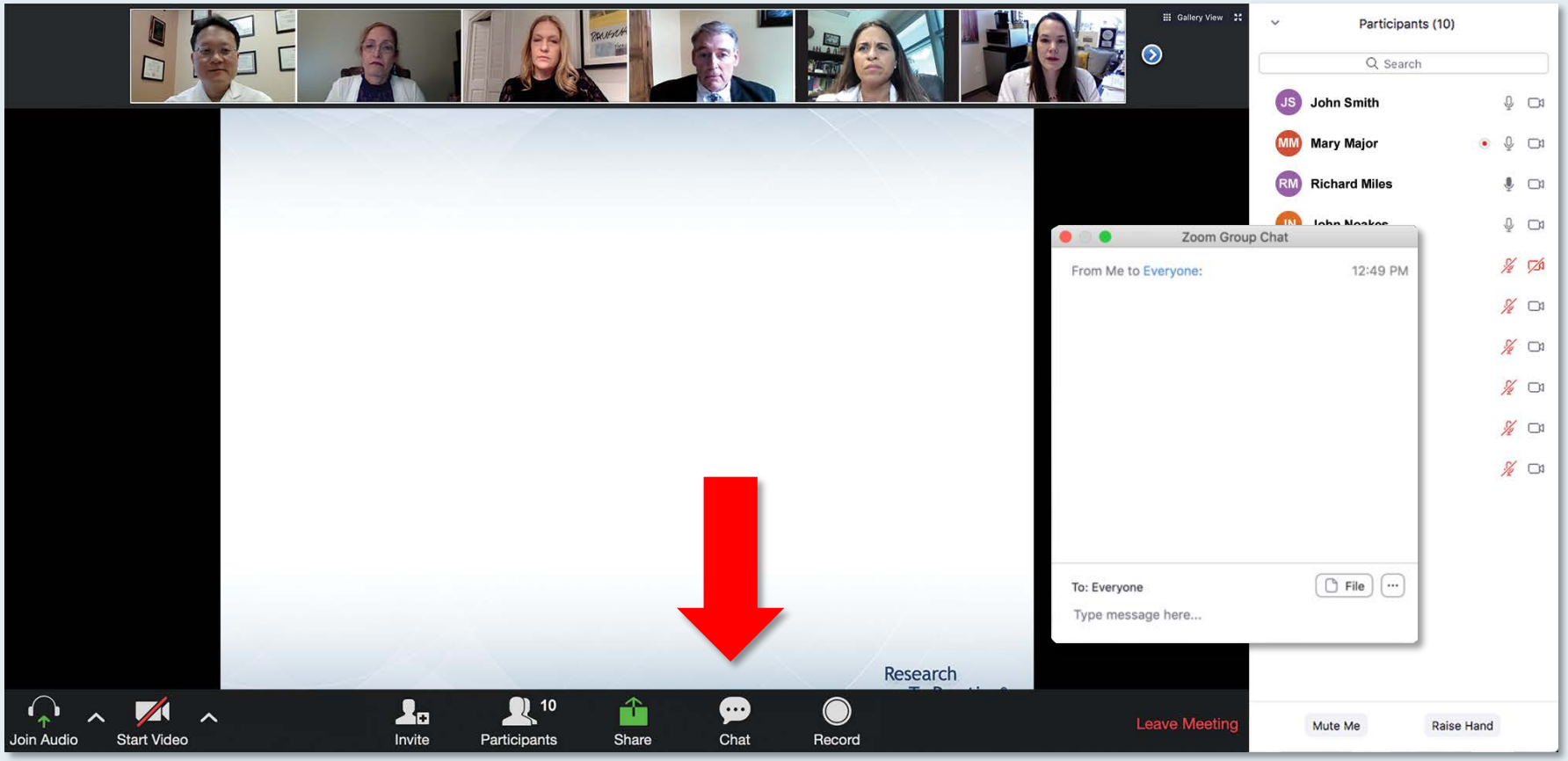

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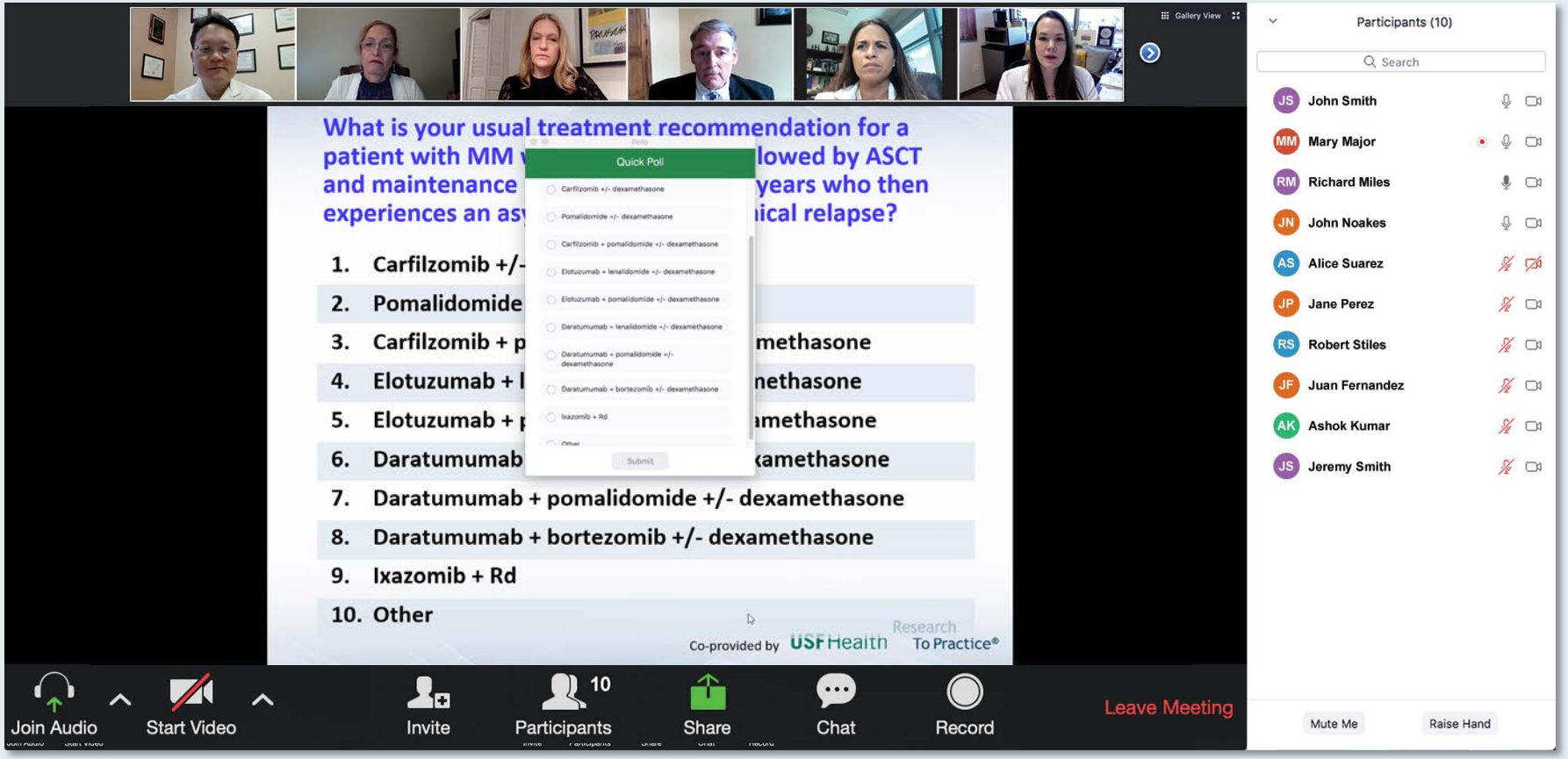

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Module 1: Up-front management

Module 2: Subcutaneous daratumumab

Module 3: Ixazomib

Module 4: Isatuximab

Module 5: Belantamab mafodotin

Module 6: Selinexor

Module 7: BCMA-directed CAR T-cell therapy; bispecifics

Module 8: Melflufen

Module 9: Cereblon E3 ligase modulators (CELMoDs)

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Module 1: Up-front management

- **Key Relevant Data Sets**
  - ENDURANCE: KRd vs RVd
  - GRIFFIN: Daratumumab + RVd
  - MASTER: Daratumumab + KRd induction → MRD-based consolidation

Regulatory and reimbursement issues aside, what is your preferred induction regimen for an 80-year-old patient with MM who is transplant ineligible with normal renal function and no high-risk features?

1. Rd
2. RVd or RVd lite
3. KRd
4. MPV/daratumumab
5. Rd/daratumumab
6. VTd (bortezomib/thalidomide/dexamethasone)/daratumumab
7. MPV, MPR or MPT
8. Other

Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and del(17p)?

1. RVd (lenalidomide/bortezomib/dexamethasone)
2. KRd (carfilzomib/lenalidomide/dexamethasone)
3. CyBorD
4. Rd/daratumumab
5. RVd/daratumumab
6. KRd/daratumumab
7. MPV (melphalan/prednisone/bortezomib)/daratumumab
8. Other

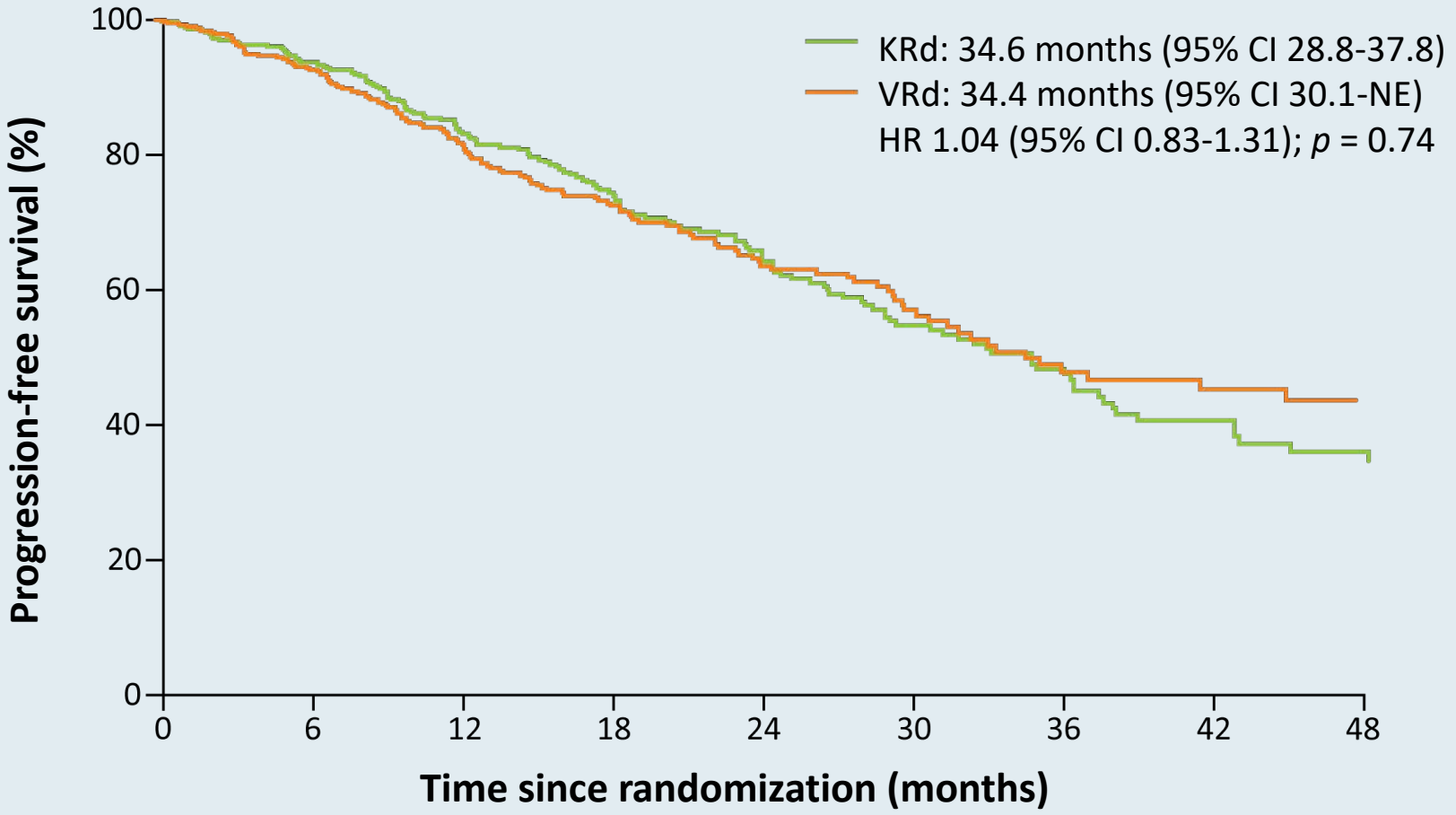
Outside of a clinical trial setting, have you ordered or would you order a minimal residual disease (MRd) assay to inform the decision regarding maintenance therapy?

1. I have
2. I have not but would for the right patient
3. I have not and would not

What is your usual recommendation for post-ASCT maintenance in patients with MM and del(17p) who received RVd induction therapy?

1. I would not use maintenance therapy
2. Lenalidomide +/- dexamethasone
3. Bortezomib +/- dexamethasone
4. Lenalidomide + bortezomib + dexamethasone
5. Ixazomib
6. Ixazomib + dexamethasone
7. Lenalidomide + ixazomib
8. Lenalidomide + ixazomib + dexamethasone
9. Other

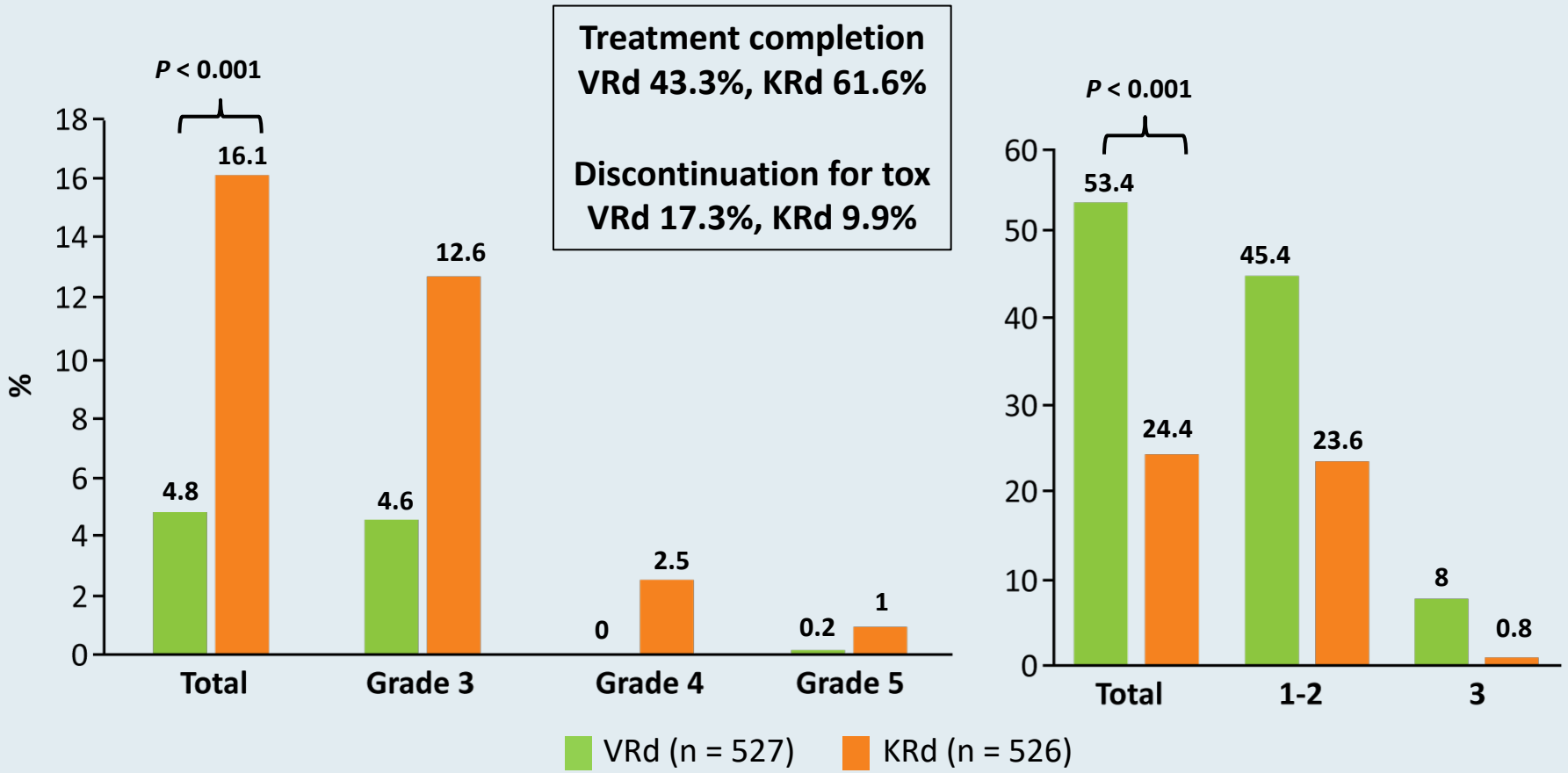
ENDURANCE (E1A11): Primary PFS Endpoint (Second Interim Analysis)



- Median OS has not been reached in either group at median follow-up of 24 months; patients will continue on long-term follow-up for overall survival

Kumar SK et al. *Lancet Oncol* 2020;21(10):1317-30.

ENDURANCE (E1A11): Treatment-Emergent Adverse Events of Interest



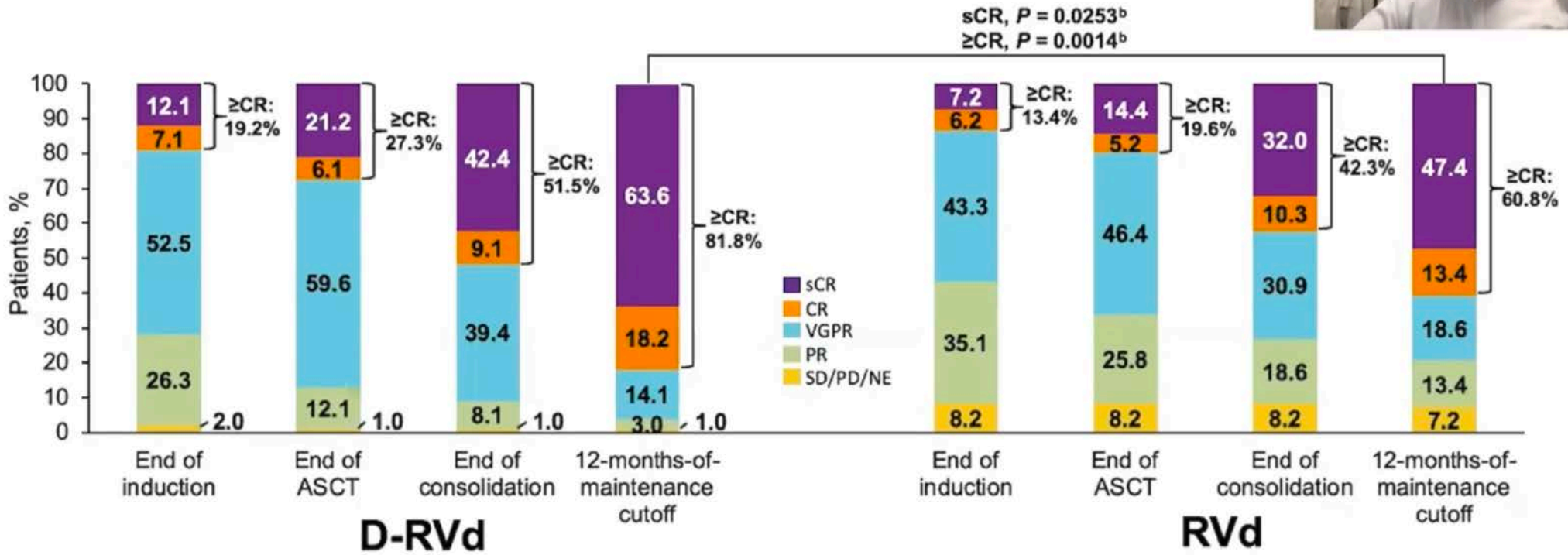
Berdeja JG. ASCO 2020 Discussant.

Daratumumab (DARA) plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin After 12 Months of Maintenance Therapy

Kaufman JL et al.

ASH 2020;Abstract 549.

Responses Deepened over Time[a]



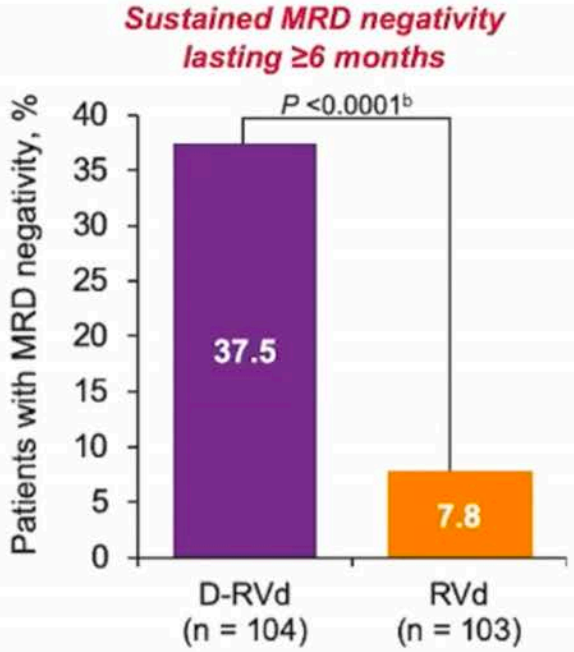
- *Results for end of induction, ASCT, and consolidation are based on a median follow up of 13.5 months at the primary analysis*
- *Median follow up at 12-months-of-maintenance therapy cutoff was 27.4 months*

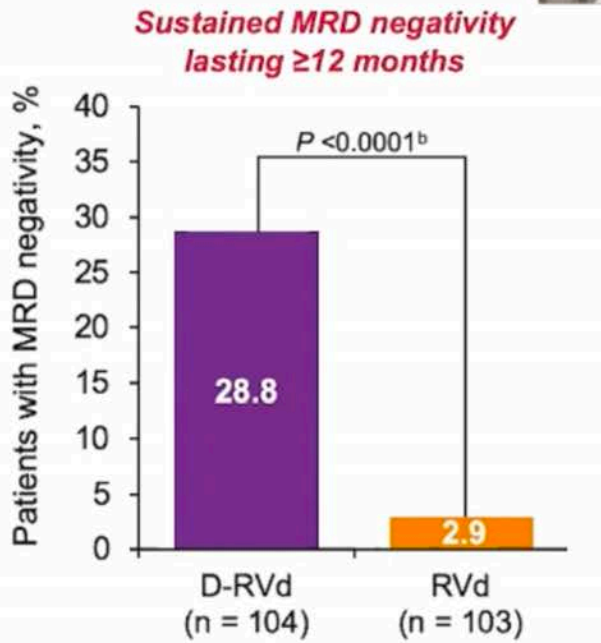
Response rates and depths were greater for D-RVd at all time points

PR, partial response. SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test.

Kaufman JL et al. ASH 2020;Abstract 549.

Durable MRD (10^{-5}) Negativity[a] Lasting ≥6 and ≥12 Months





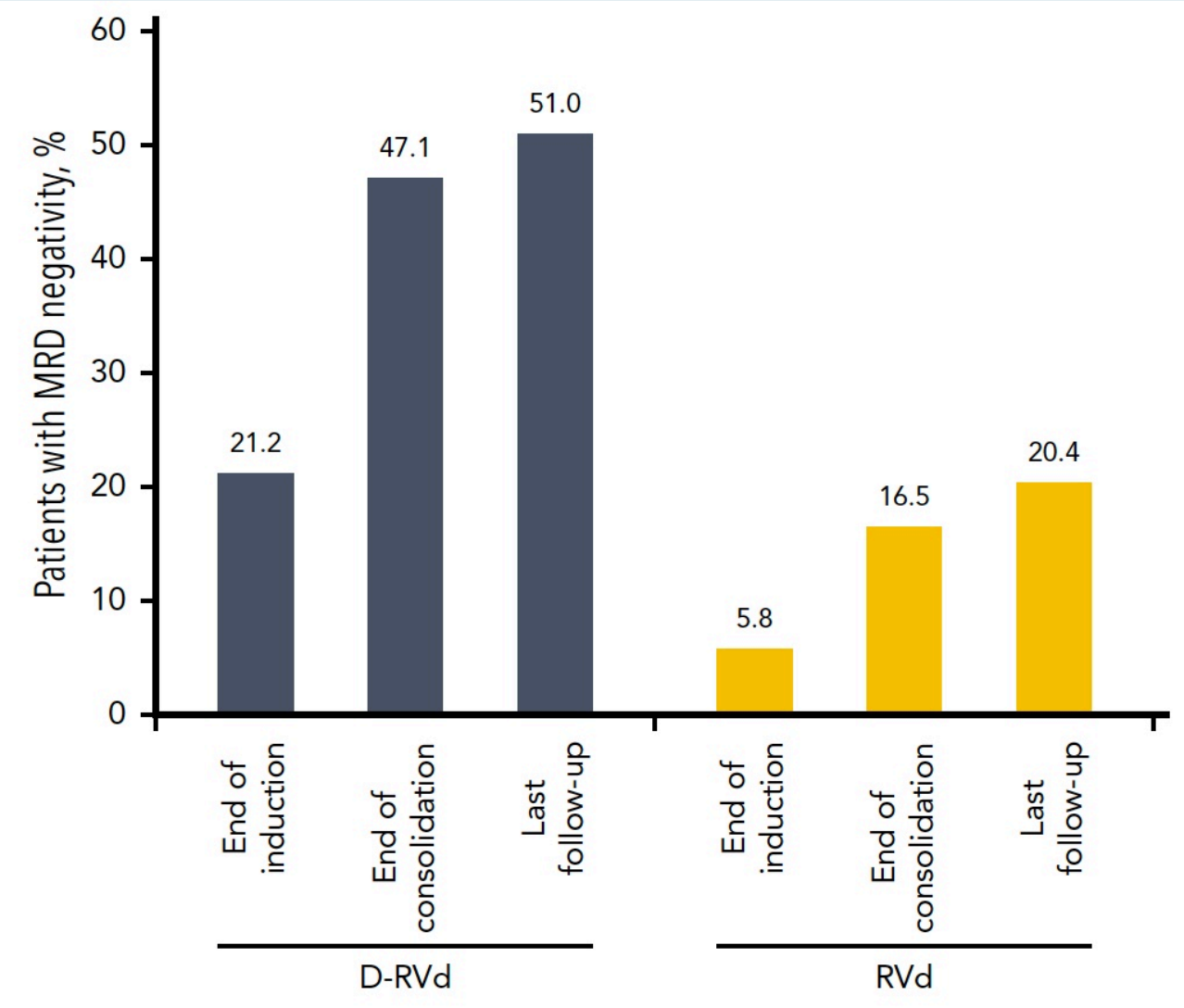
- *Among patients who achieved MRD negative (10^{-5}) status, sustained MRD negativity lasting ≥12 months was noted in 30/65 (46.2%) and 3/28 (10.7%) patients*

D-RVd improved rates of sustained MRD negativity versus RVd

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 27.4 months, and MRD-negativity rates are among the ITT population. [b]*P* values were calculated using the Fisher's exact test.

Kaufman JL et al. ASH 2020;Abstract 549.

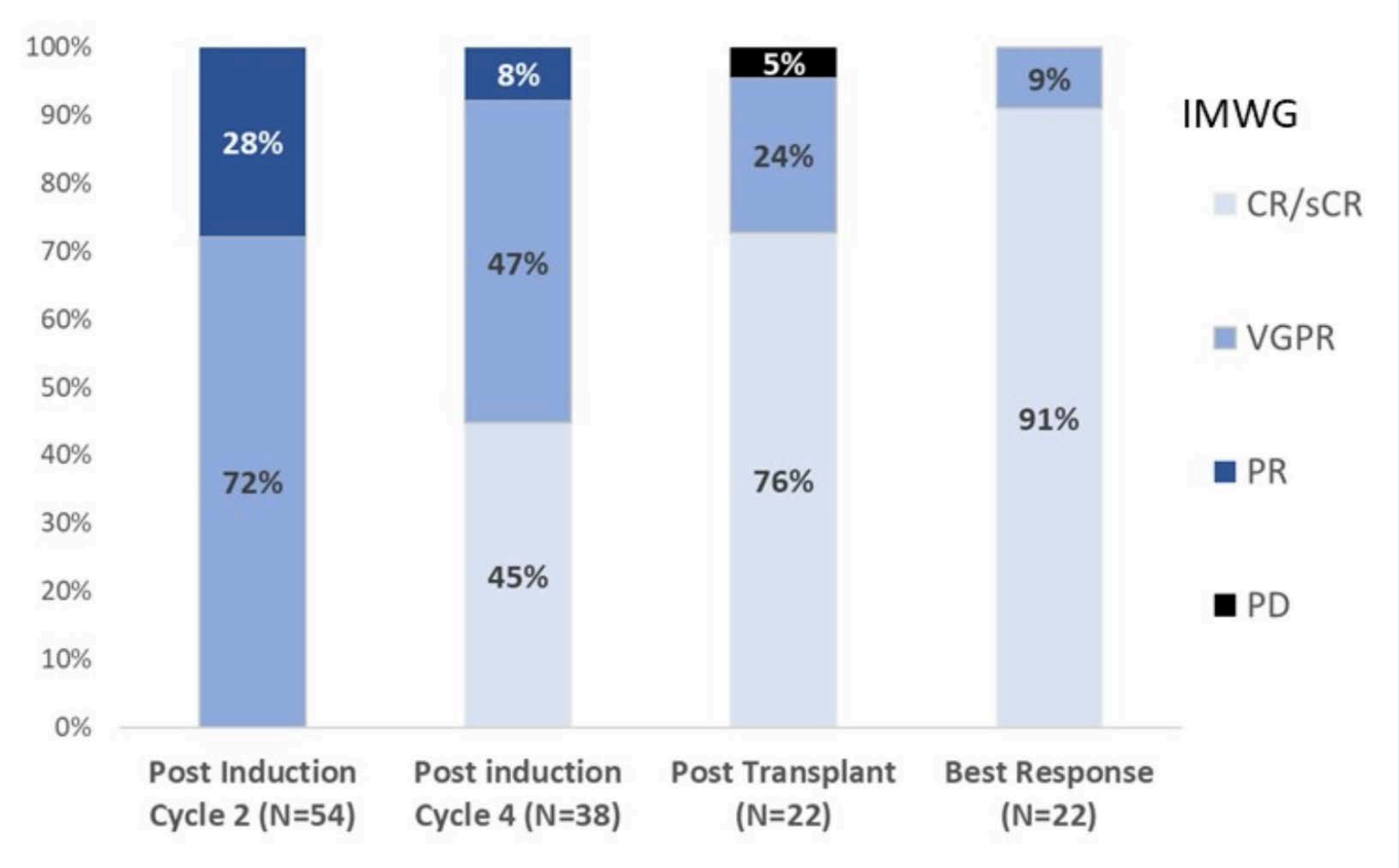
GRIFFIN: Summary of Response Rates and MRD Negativity (10^{-5}) Rates Over Time



- MRD negativity (10^{-5}) rates in the intent-to-treat population by the end of induction therapy, end of consolidation and last follow-up
- All MRD data are from the analysis with a median follow-up of 22.1 months
- MRD was evaluated at baseline, first evidence of suspected CR or sCR, at the end of induction and consolidation, and after 12 and 24 months of maintenance, regardless of response (per protocol amendment 2)

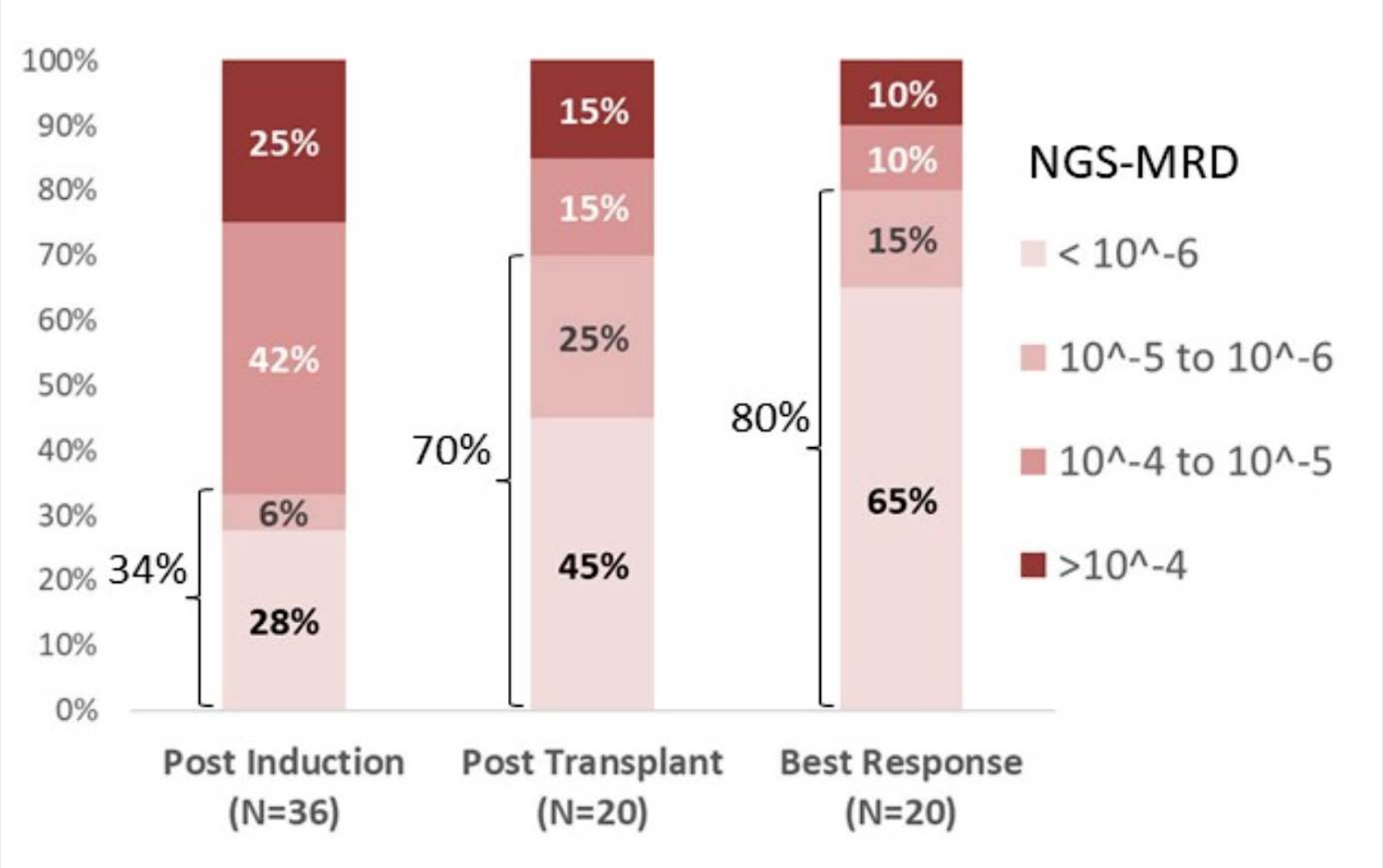
Voorhees PM et al. *Blood* 2020;136(8):936-45.

MASTER — Daratumumab + KRd Induction → MRD-Based Consolidation: Responses Over Time



Costa LJ et al. ASH 2019;Abstract 860.

MASTER: MRD-Negative Remissions



Costa LJ et al. ASH 2019;Abstract 860.

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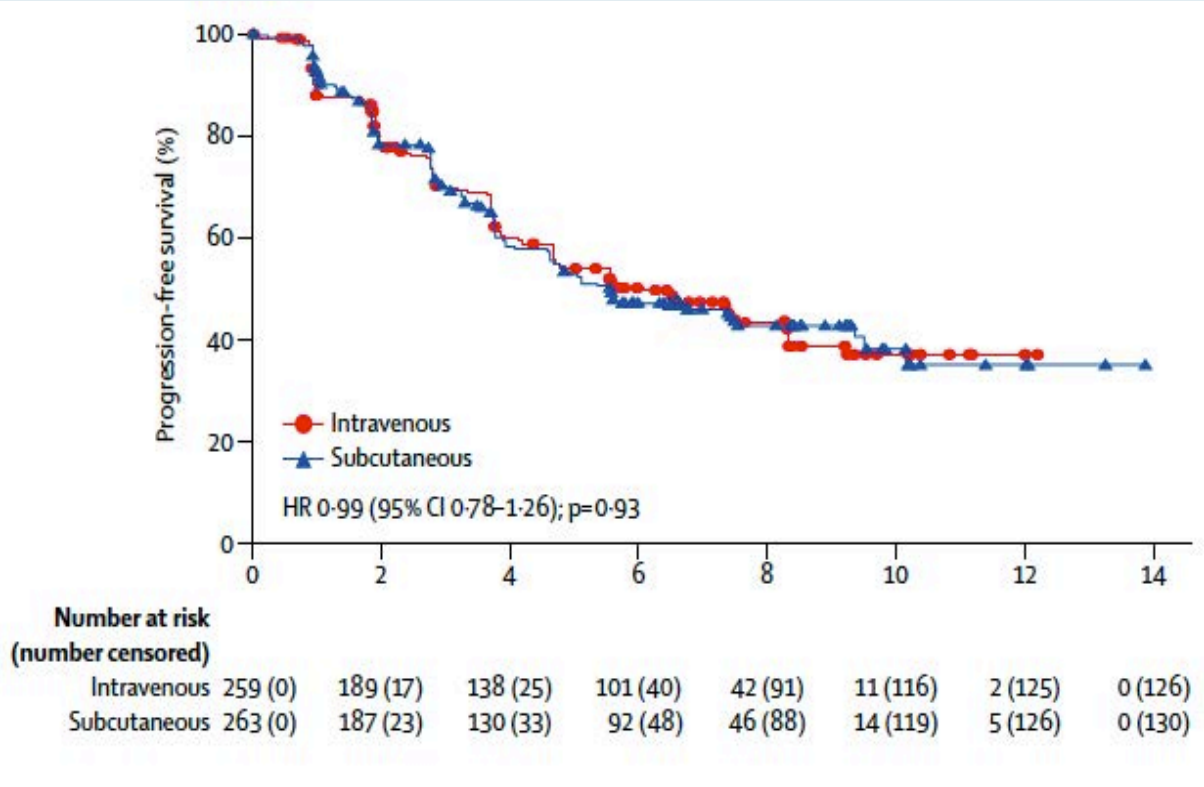
Module 9: Cereblon E3 ligase modulators (CELMoDs)

Module 2: Subcutaneous daratumumab

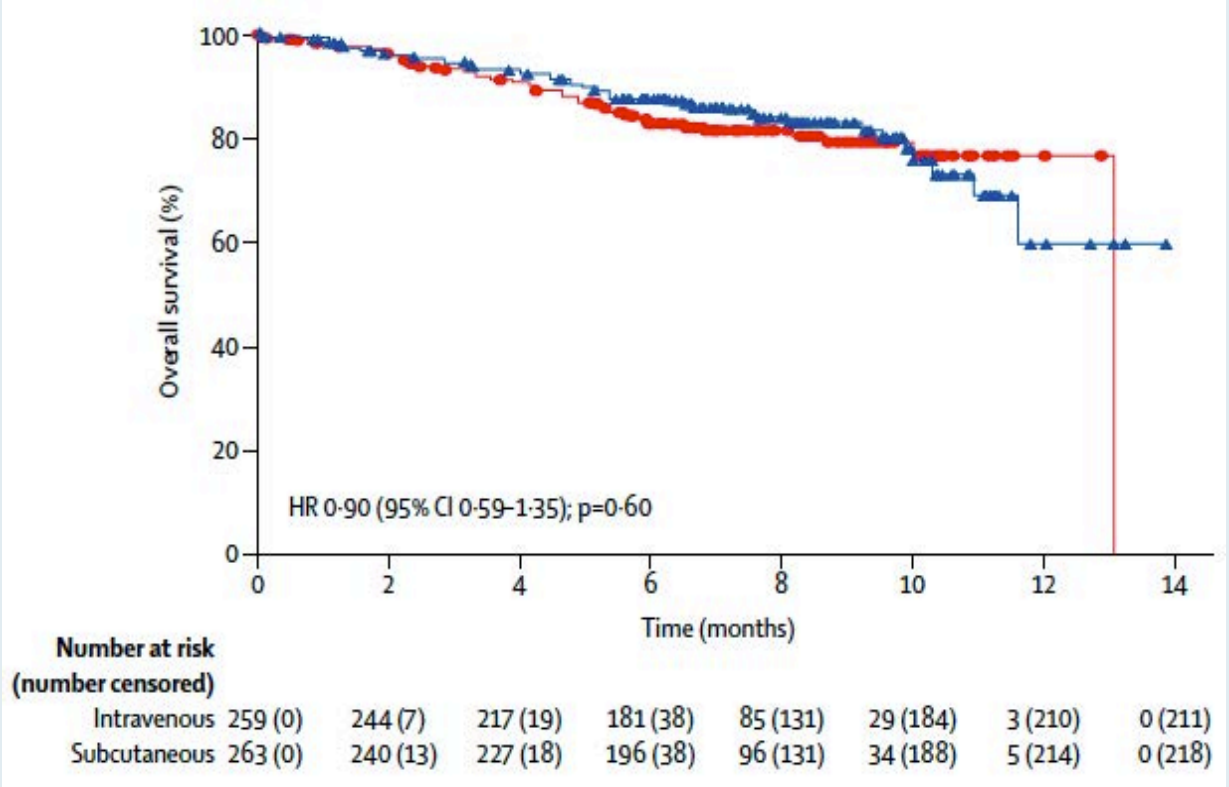
- **Key Relevant Data Sets**
  - COLUMBA: Subcutaneous vs intravenous daratumumab for R/R MM
  - APOLLO: Subcutaneous dara + pomalidomide/dexamethasone (Pd) vs Pd for R/R MM
  - ANDROMEDA: Subcutaneous dara + CyBorD for newly diagnosed amyloidosis

COLUMBA: Subcutaneous versus Intravenous Daratumumab

Progression-Free Survival



Overall Survival



(Median follow-up 7.5 months)

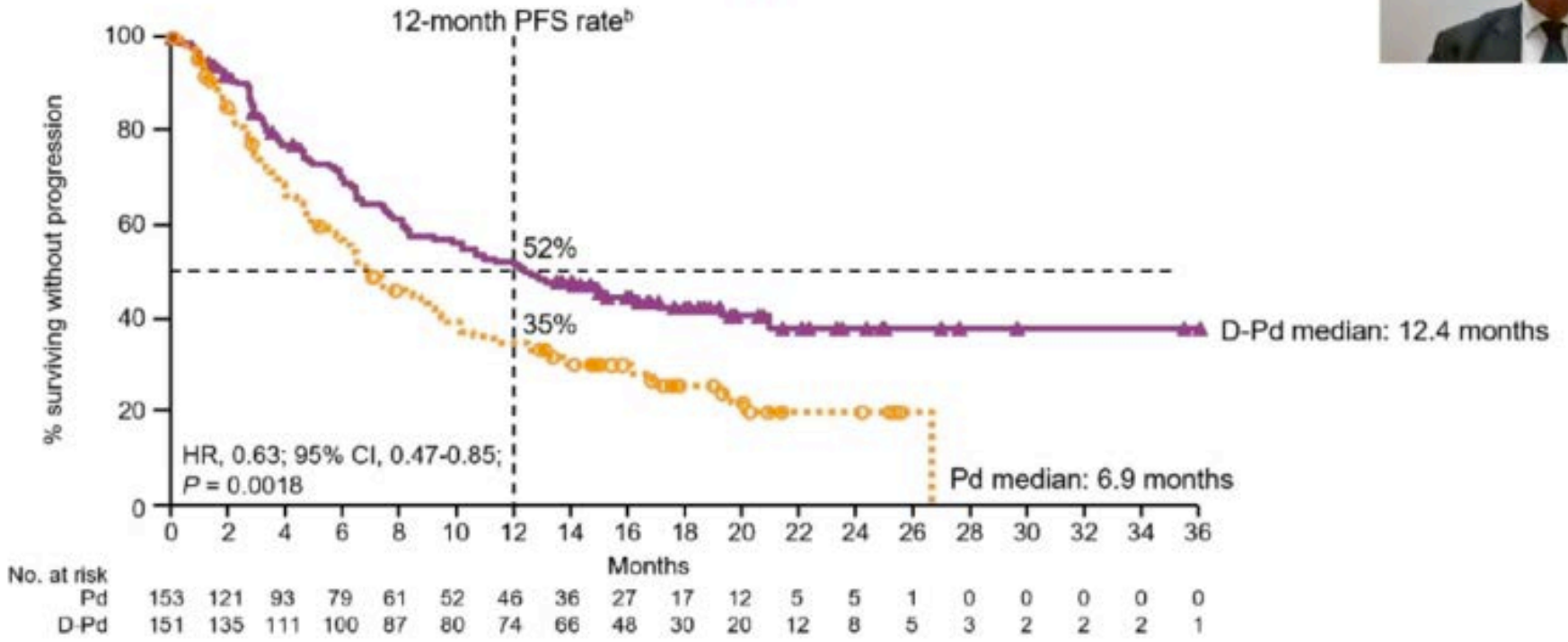
Mateos MV et al. *Lancet Haematol* 2020;7(5):e370-80.

Apollo: Phase 3 Randomized Study of Subcutaneous Daratumumab plus Pomalidomide and Dexamethasone (D-Pd) versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

Dimopoulos MA et al.

ASH 2020;Abstract 412.

PFS at a Median Follow-up of 16.9 Months[a]



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

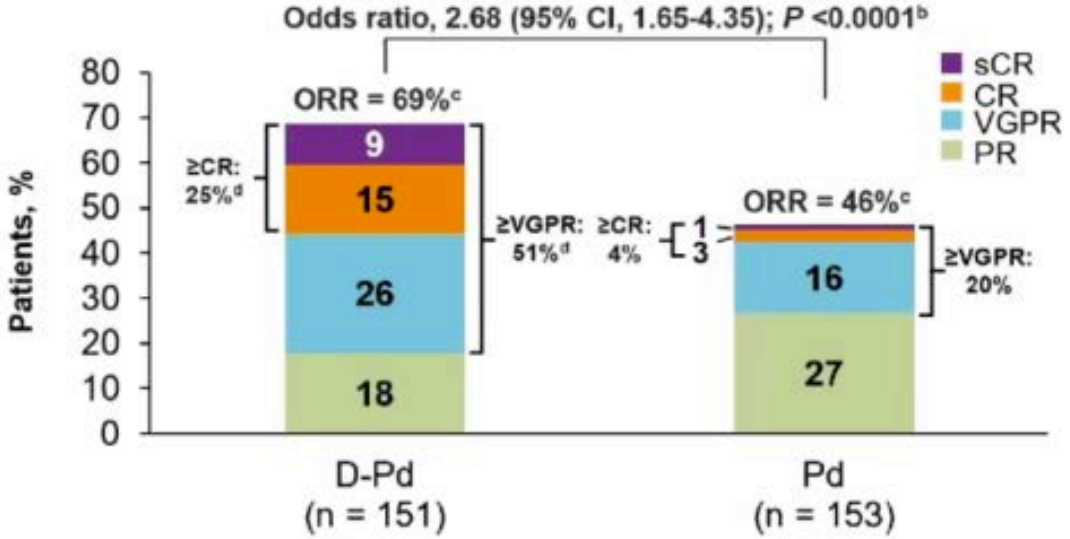
Addition of DARA SC to Pd improved PFS, with a 37% reduction in the risk of progression or death

HR, hazard ratio; CI, confidence interval. [b]Intent-to-treat population. [a]Kaplan–Meier estimate.

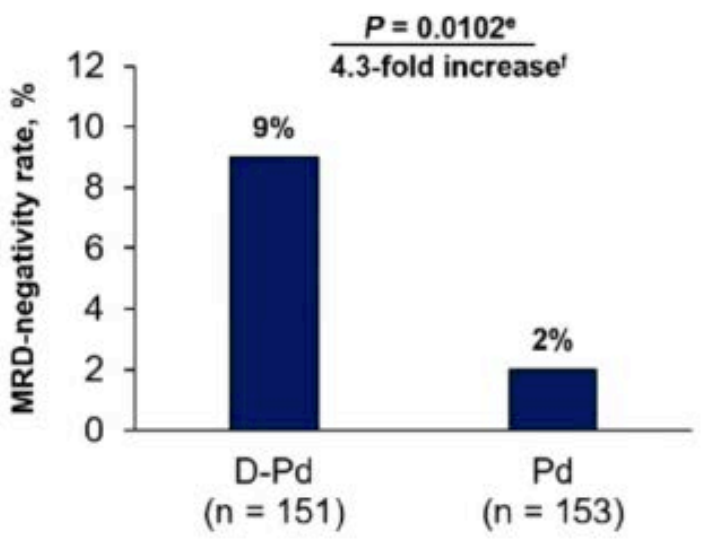
Dimopoulos MA et al. ASH 2020;Abstract 412.

Depth of Response[a]

Hematologic response



MRD negativity



ORR, ≥VGPR rate, ≥CR rate, and MRD-negativity rate were significantly higher with D-Pd versus Pd

PR, partial response; IMWG, International Myeloma Working Group; ITT, intent-to-treat. [a]Responses were assessed by computer algorithm in accordance with IMWG recommendations and included patients in the ITT population. [b]*P* value was calculated from the 2-sided Cochran–Mantel–Haenszel chi-square test, stratified for ISS stage (I, II, III) and number of lines of prior therapy (1, 2-3, ≥4). [c]Values may not add to total due to rounding. [d]*P* <0.0001. [e]*P* value (2-sided) was calculated using the Fisher's exact test. [f]Non-rounded values are 8.6% and 2.0%.

Dimopoulos MA et al. ASH 2020;Abstract 412.

FDA Grants Accelerated Approval for Subcutaneous Daratumumab with Hyaluronidase for Newly Diagnosed Light Chain Amyloidosis

Press Release: January 15, 2021

"The Food and Drug Administration granted accelerated approval to daratumumab plus hyaluronidase in combination with bortezomib, cyclophosphamide and dexamethasone for newly diagnosed light chain (AL) amyloidosis.

Efficacy was evaluated in ANDROMEDA (NCT03201965), an open-label, randomized, active-controlled trial in 388 patients with newly diagnosed AL amyloidosis with measurable disease and at least one affected organ according to consensus criteria. Patients were randomized to receive bortezomib, cyclophosphamide, and dexamethasone (VCd arm) or with daratumumab plus hyaluronidase (D-VCd arm). The hematologic complete response (HemCR) rate based on established consensus response criteria as evaluated by an independent review committee was 42.1% for the D-VCd arm and 13.5% for the VCd arm (odds ratio=4.8; 95% CI: 2.9, 8.1; p<0.0001).

The prescribing information includes a Warnings and Precautions that serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received daratumumab plus hyaluronidase in combination with bortezomib, cyclophosphamide and dexamethasone. Daratumumab plus hyaluronidase is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-darzalex-faspro-newly-diagnosed-light-chain-amyloidosis

ANDROMEDA: Subcutaneous Daratumumab with or without CyBorD for AL Amyloidosis

Efficacy	Daratumumab + CyBorD (n = 195)	CyBorD (n = 193)	Hazard or odds ratio	*p*-value
Overall hematologic response	92%	77%	NR	NR
CR	53%	18%	5.10	<0.0001
≥VGPR	79%	49%	NR	NR

"The addition of DARA to CyBorD was superior to CyBorD alone, resulting in deeper and more rapid hematologic responses and improved clinical outcomes with an acceptable safety profile. DARA-CyBorD therapy resulted in improved MOD-PFS and substantially higher organ responses in newly diagnosed AL amyloidosis pts."

Kastritis E et al. EHA 2020;Abstract LBA2604.

Agenda

Module 1: Up-front management

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Module 3: Ixazomib

Module 4: Isatuximab

Module 5: Belantamab mafodotin

Module 6: Selinexor

Module 7: BCMA-directed CAR T-cell therapy; bispecifics

Module 8: Melflufen

Module 9: Cereblon E3 ligase modulators (CELMoDs)

Module 3: Ixazomib

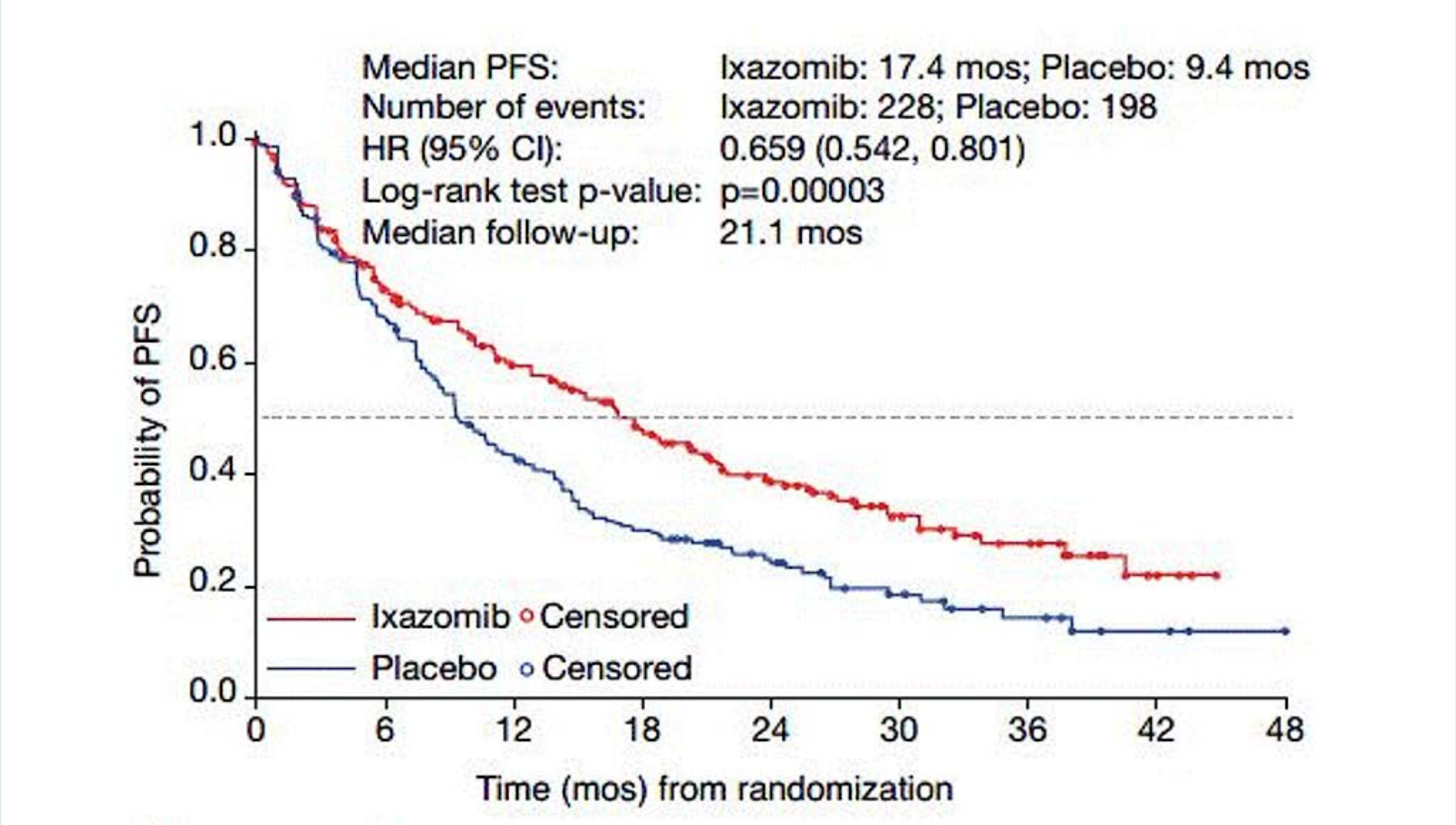
- **Key Relevant Data Set**
  - TOURMALINE-MM4: Ixazomib vs placebo as postinduction maintenance therapy

Ixazomib vs Placebo as Post-induction Maintenance Therapy in Newly Diagnosed Multiple Myeloma (NDMM) Patients (pts) Not Undergoing Autologous Stem Cell Transplant (ASCT): Phase 3 TOURMALINE-MM4 Trial

Dimopoulos MA et al.

EHA 2020;Abstract S200.

TOURMALINE-MM4: Progression-Free Survival



Dimopoulos MA et al. EHA 2020;Abstract S200.

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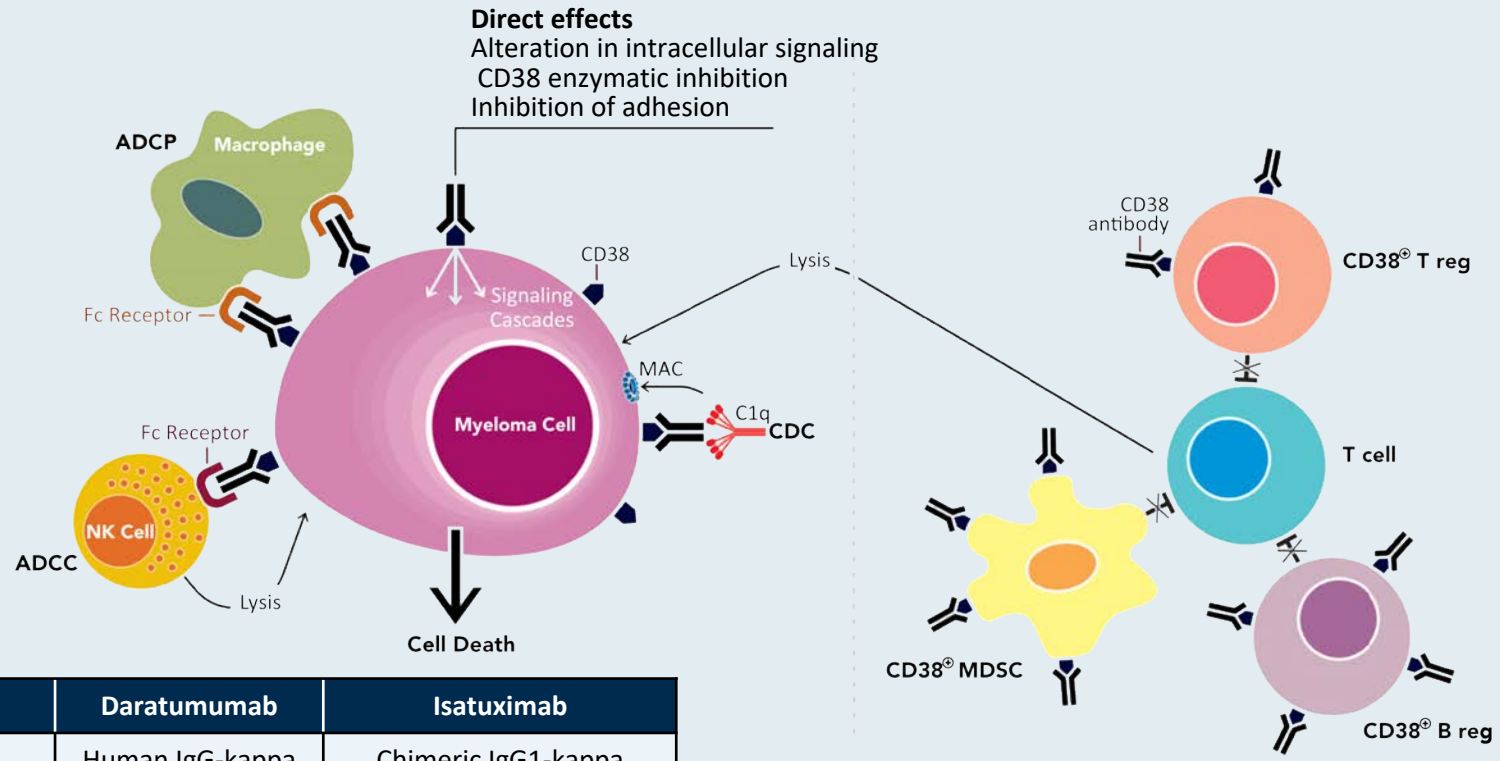
Module 4: Isatuximab

- **Key Relevant Data Sets**
  - ICARIA-MM: Isatuximab + pom/dex for elderly patients with R/R MM
  - IKEMA: Isatuximab + Kd for relapsed MM
  - GMMG-CONCEPT: Isatuximab + KRd as front-line therapy for high-risk MM

Anti-CD38 Antibodies: Mechanism of Action, Structural and Pharmacologic Similarities and Differences

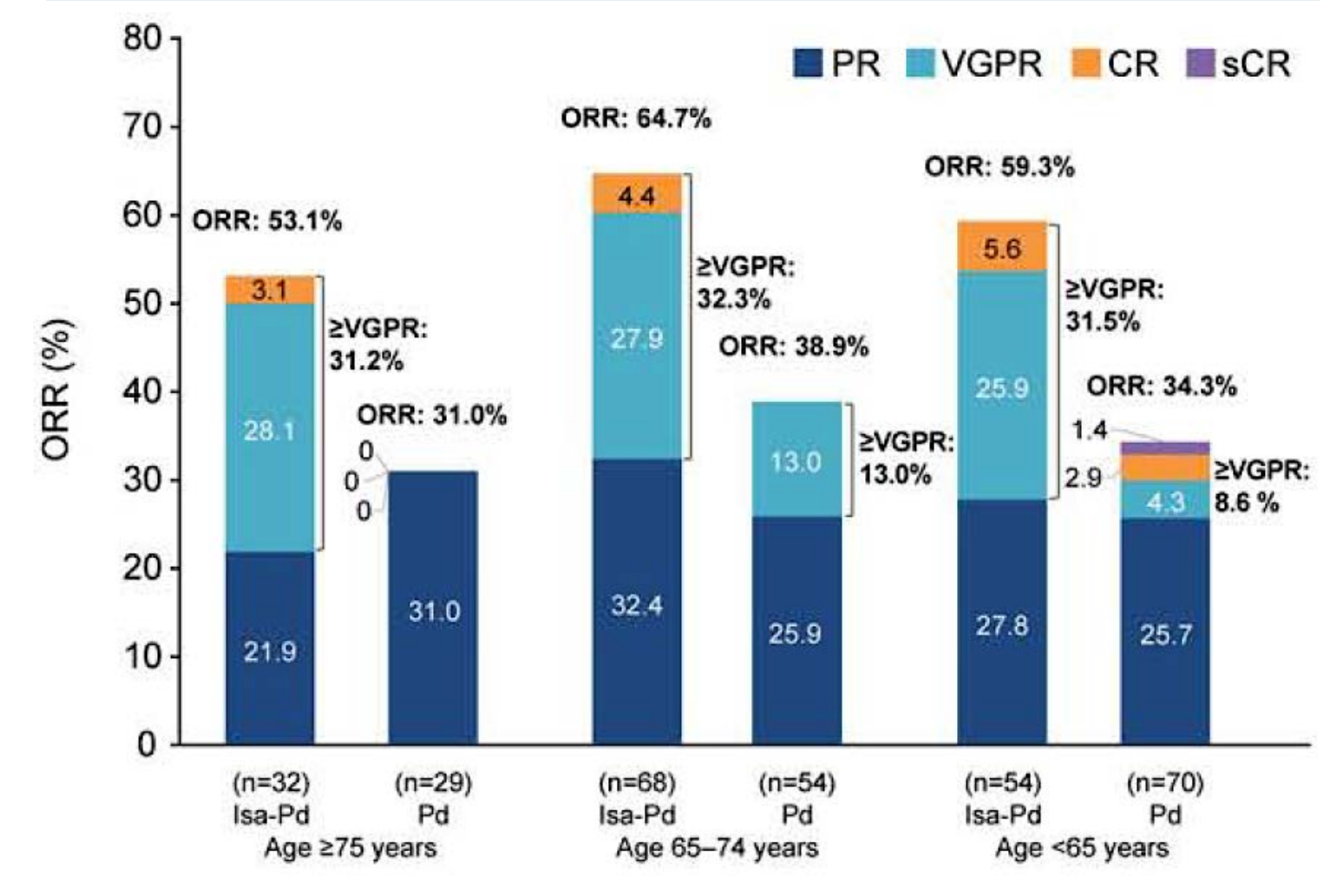
Fc-dependent immune effector mechanisms and direct effects **Immunomodulatory effects**



Mechanism of action	Daratumumab	Isatuximab
Origin, isotype	Human IgG-kappa	Chimeric IgG1-kappa
CDC	+++	+
ADCC	++	++
ADCP	+++	Not determined
PCD direct	—	++
PCD cross linking	+++	+++
Modulation ectoenzyme function	+	+++

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

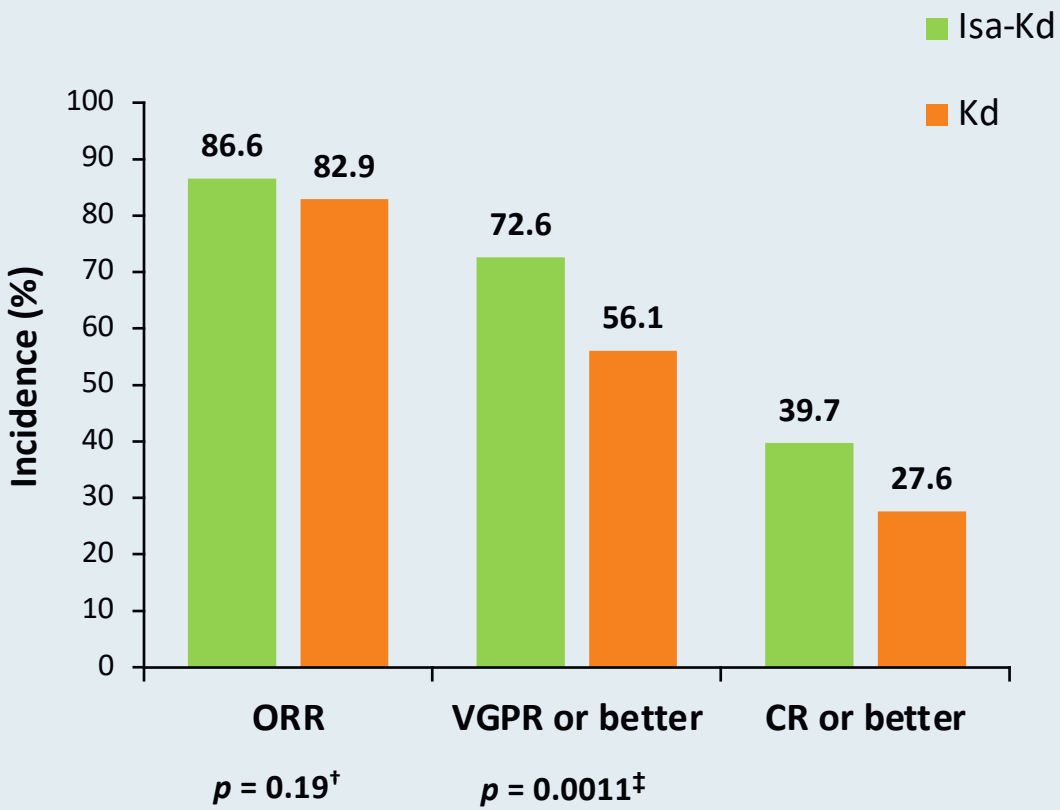
ICARIA-MM – Isatuximab + Pom/Dex: Response to Therapy by Patient Age Group



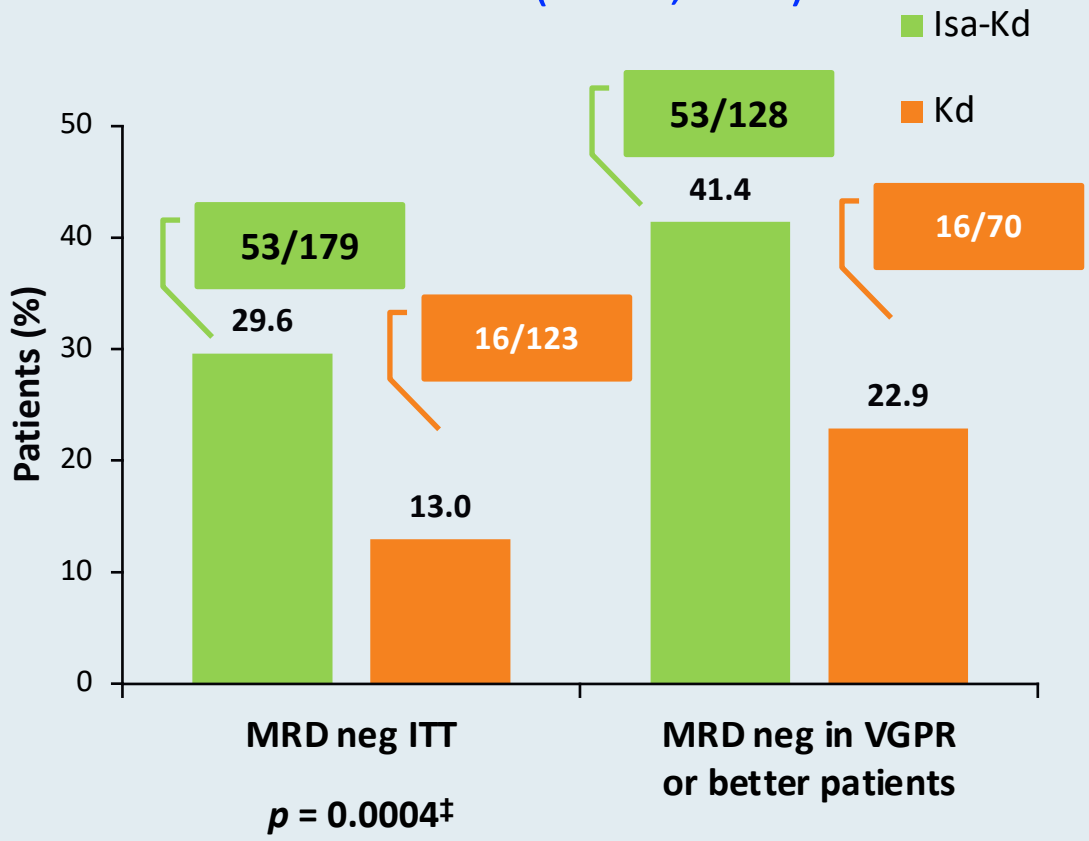
Schjesvold FH et al. *Haematologica* 2020;[Online ahead of print].

IKEMA – Isatuximab + Kd: Depth of Response

Best overall response

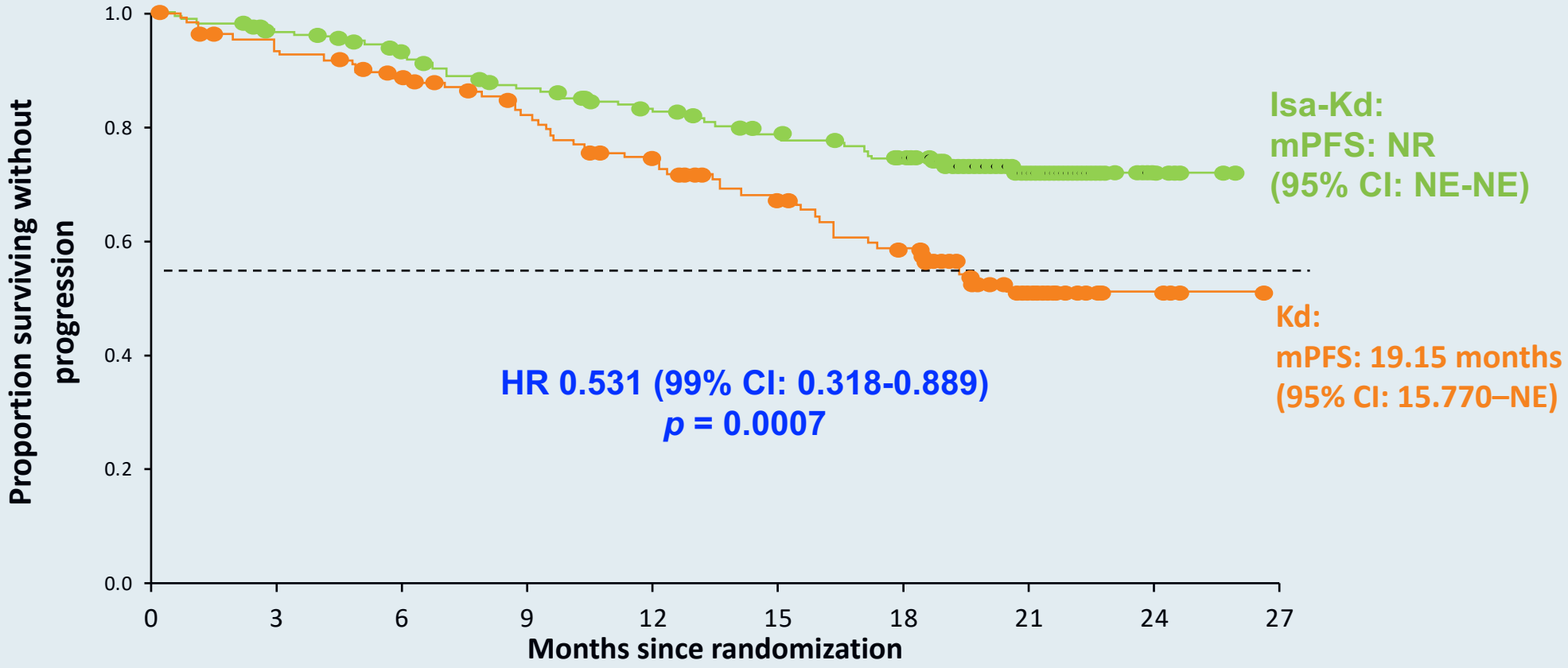


MRD rate (NGS*, 10^{-5})



Moreau P et al. EHA 2020;Abstract LBA2603.

IKEMA: PFS



No. at risk										
Isa-Kd	179	164	151	136	124	110	100	36	5	0
Kd	123	108	99	85	72	61	50	19	6	0

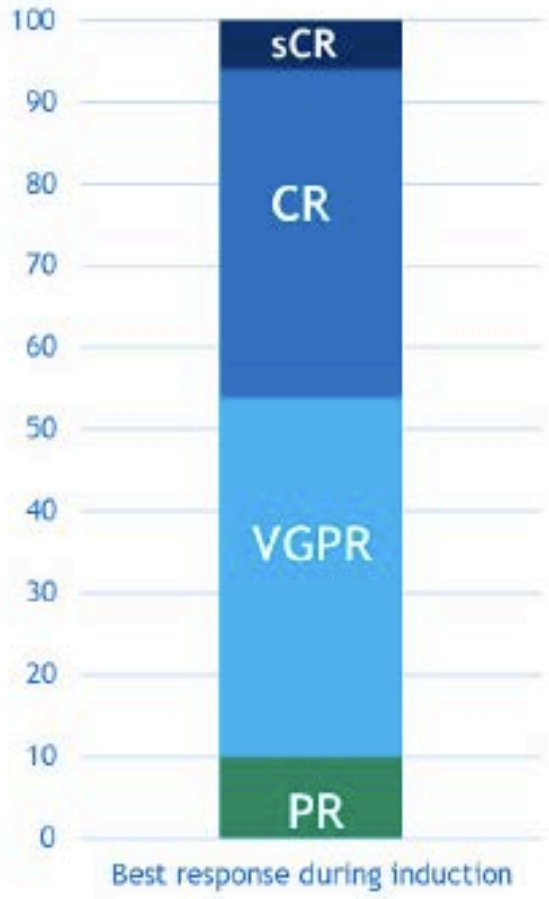
One-sided *p*-value, level of significance <0.005

Moreau P et al. EHA 2020;Abstract LBA2603.

GMMG-CONCEPT – Front-Line Isa-KRd for High-Risk MM: Best Response to Therapy, 6 Induction Cycles

All evaluable patients: n = 50

- Overall response rate (ORR, ≥ PR): 100%
- ≥ VGPR : 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable



Weisel K et al. ASCO 2020;Abstract 8508.

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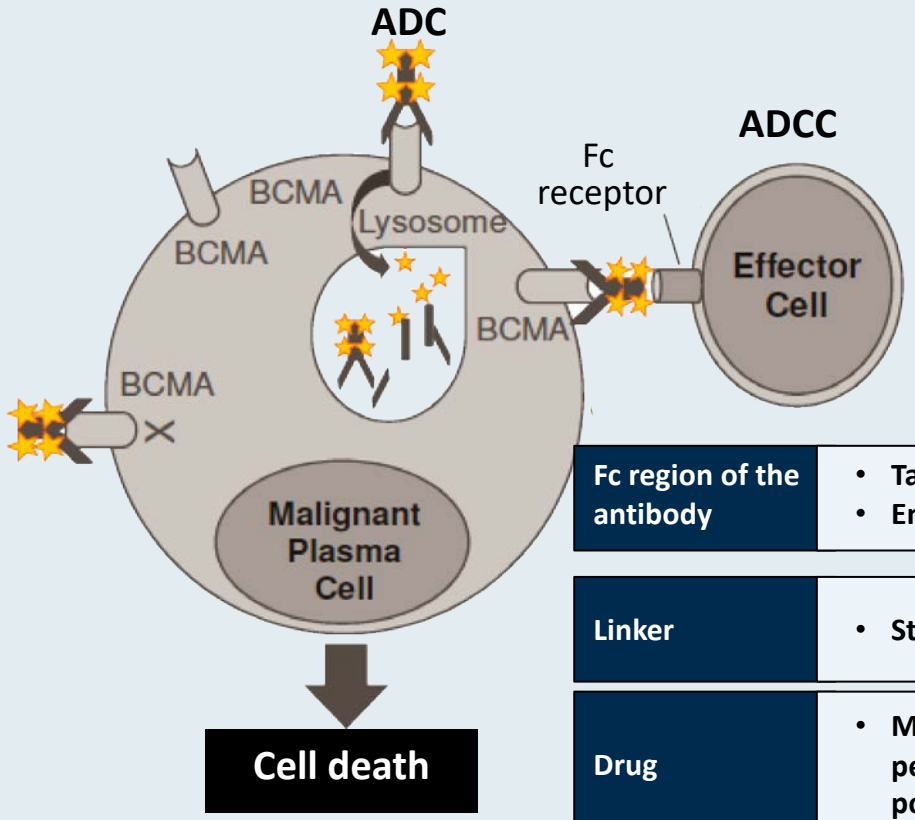
Module 9: Cereblon E3 ligase modulators (CELMoDs)

Module 5: Belantamab mafodotin

- **Key Relevant Data Sets**
  - DREAMM-2: Single-agent belantamab mafodotin (belamaf)
  - DREAMM-6: Belamaf + Vd

Belamaf: Anti-BCMA Antibody-Drug Conjugate

- B-cell maturation factor (BCMA) expression is restricted to B cells at later stages of differentiation and is required for survival of plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker



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

Mechanisms of action:
- ADC mechanism
- ADCC mechanism
- Immunogenic cell death
- BCMA receptor signaling inhibition

Tai YT et al. *Blood* 2014;123(20):3128-38.

DREAMM-2 – Single-Agent Belamaf: Efficacy Outcomes

	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	34 (19.3-51.4)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates), months	2.9 (1.5-5.7)	2.2 (1.2-3.6)
Probability of PFS at 6 months, % (95% CI estimates)	35 (20-50)	30 (17-43)

CI = confidence interval; DoR = duration of response; NR = not reached; ORR = overall response rate; PFS = progression-free survival

Lonial S et al. ASH 2020;Abstract 1417.

DREAMM-6 – Belamaf + Vd: Clinical Activity

- Response was evaluable in all patients:
  - ORR = 78%
  - VGPR = 50%
  - PR = 28%
  - SD = 17%
  - CBR = 83%
- Median DoR = not reached (median 18.2 weeks on treatment)

Popat R et al. ASH 2020;Abstract 1419.

DREAMM-6: Overview of Adverse Events

Patients with AE, n (%)	Belamaf 2.5 mg/kg SINGLE + BorDex (N = 18) [Parts 1 and 2]
AEs related to study treatment	18 (100)
Grade 3/4 AE	16 (89)
AEs leading to permanent discontinuation of a study treatment	5 (28)
AEs leading to permanent discontinuation of belamaf	0
AEs leading to dose reductions	13 (72)
Corneal events	7 (39)
Thrombocytopenia	6 (33)
AEs leading to dose interruption/delay	18 (100)
Corneal events	15 (83)
Thrombocytopenia	7 (39)
Any SAE	12 (67)
Fatal SAE	0
SAEs related to study treatment	5 (28)

Popat R et al. ASH 2020;Abstract 1419.

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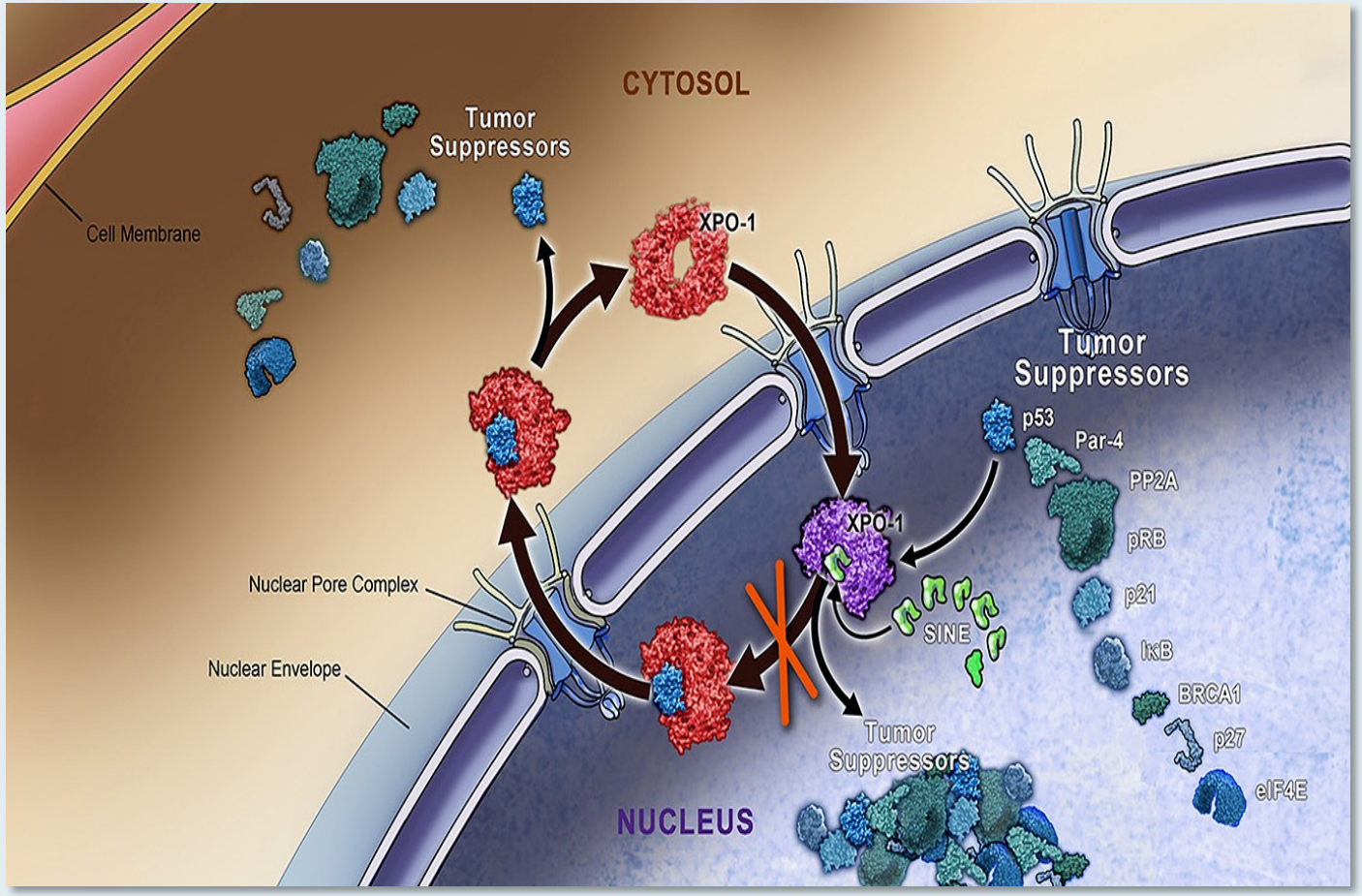
Module 6: Selinexor

- **Key Relevant Data Set**
  - BOSTON: Selinexor + Vd vs Vd after 1 to 3 prior lines of therapy

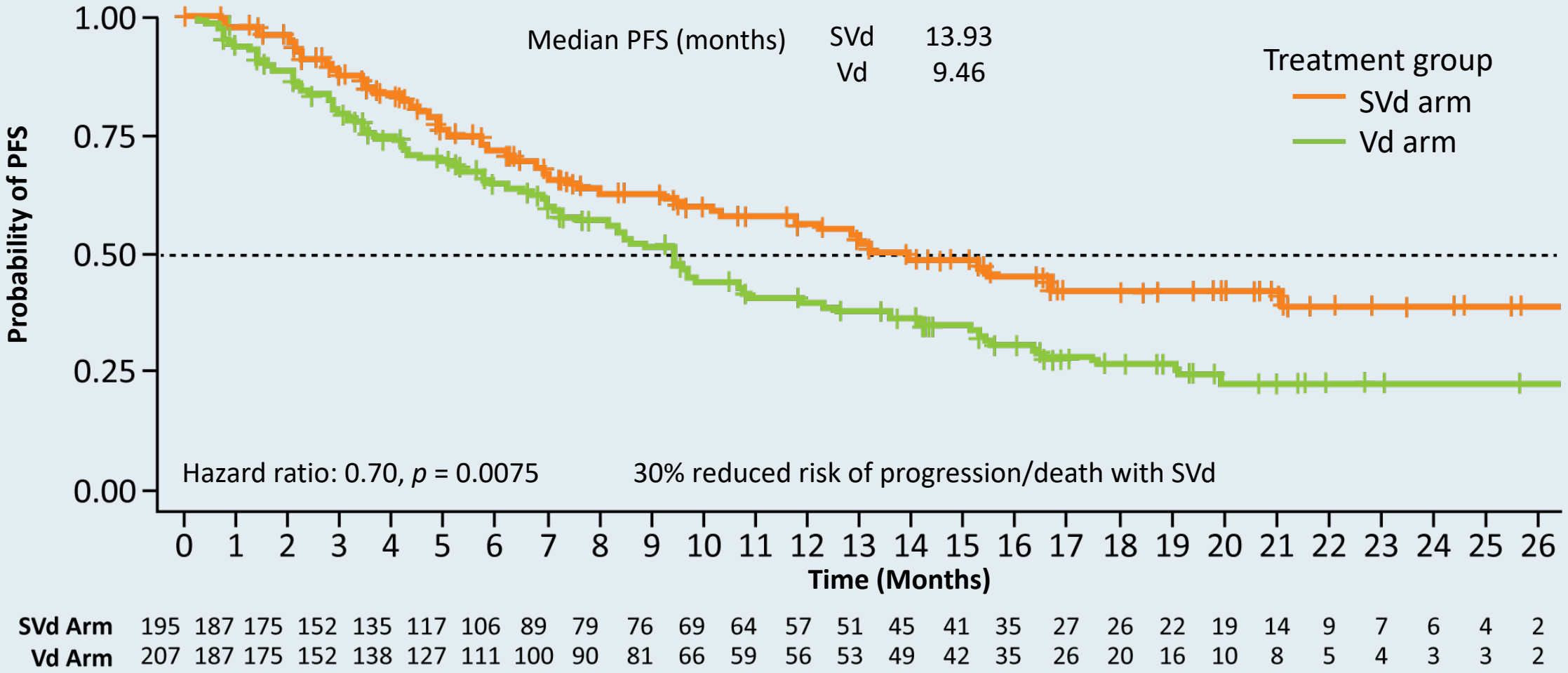
Selinexor: Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR) and eIF4E-bound oncoprotein mRNAs (c-myc, BCL2, BCL-xL and cyclins)
- XPO1 is overexpressed in MM and its levels often correlate with poor prognosis
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression.

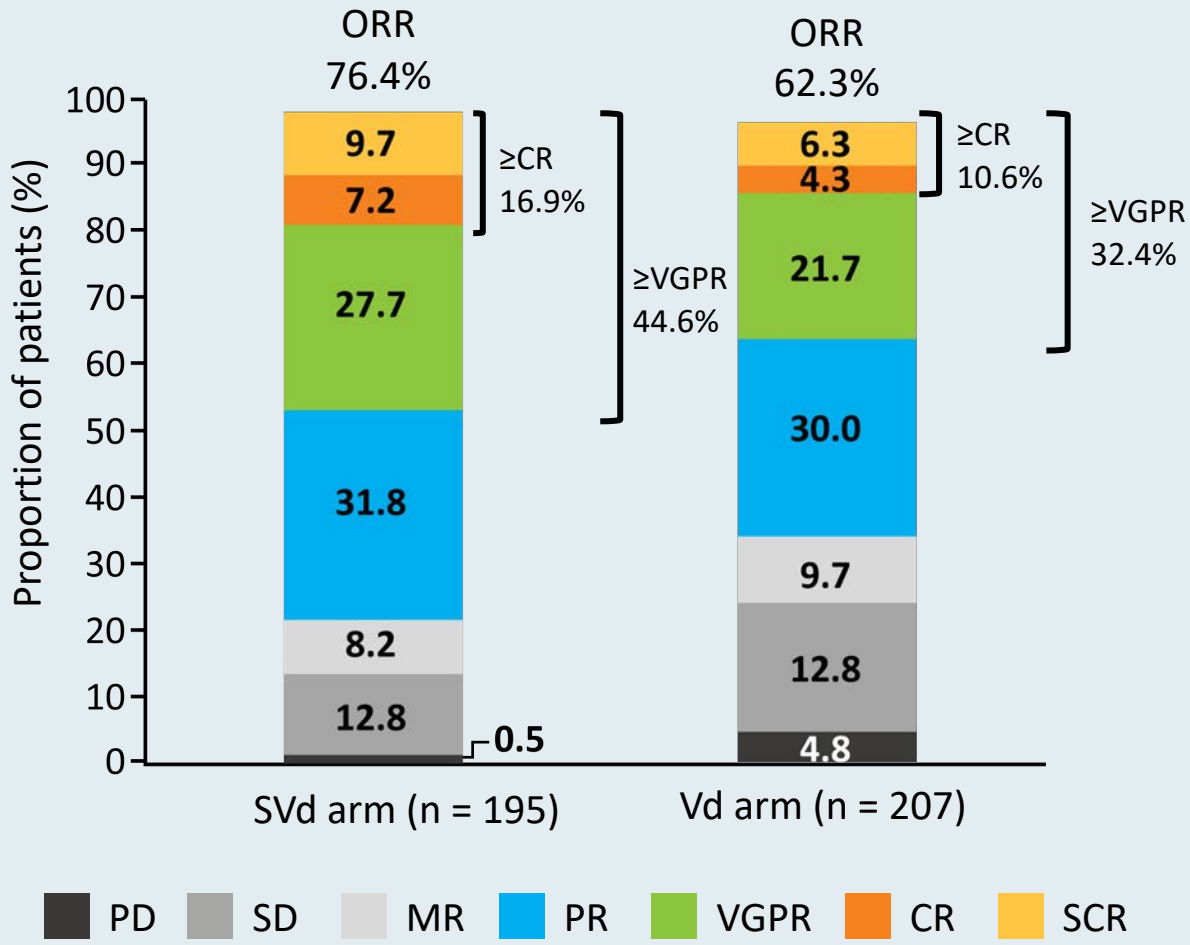
Bahlis N et al. EHA 2016;Abstract P277.

BOSTON Trial – Selinexor + Vd versus Vd: Progression-Free Survival



Dimopoulos M et al. ASCO 2020;Abstract 8501.

BOSTON Trial: Response



Longer duration of response with SVd

	SVd arm (n = 149)	Vd arm (n = 129)
Median time to response (months)	1.1	1.4
Median duration of response (months)	20.3	12.9

Fewer patients with progressive disease:
SVd (n = 1, 0.5%) vs Vd (n = 10, 4.8%)

Dimopoulos M et al. ASCO 2020;Abstract 8501.

Which of the following agents would you generally use first for a patient with relapsed MM?

1. Selinexor
2. Belantamab mafodotin

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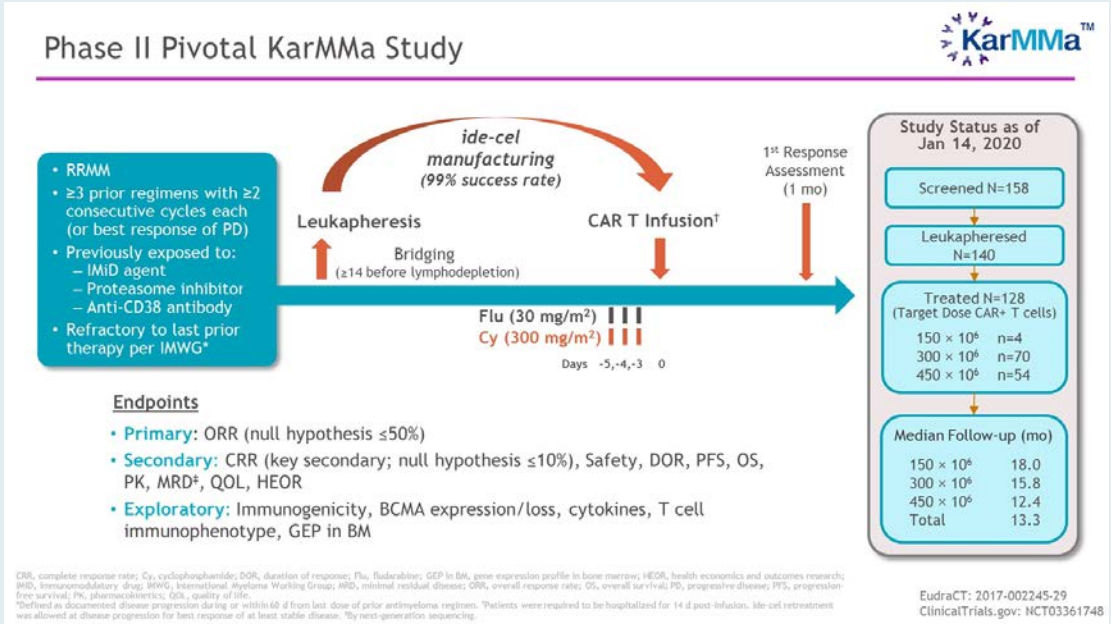
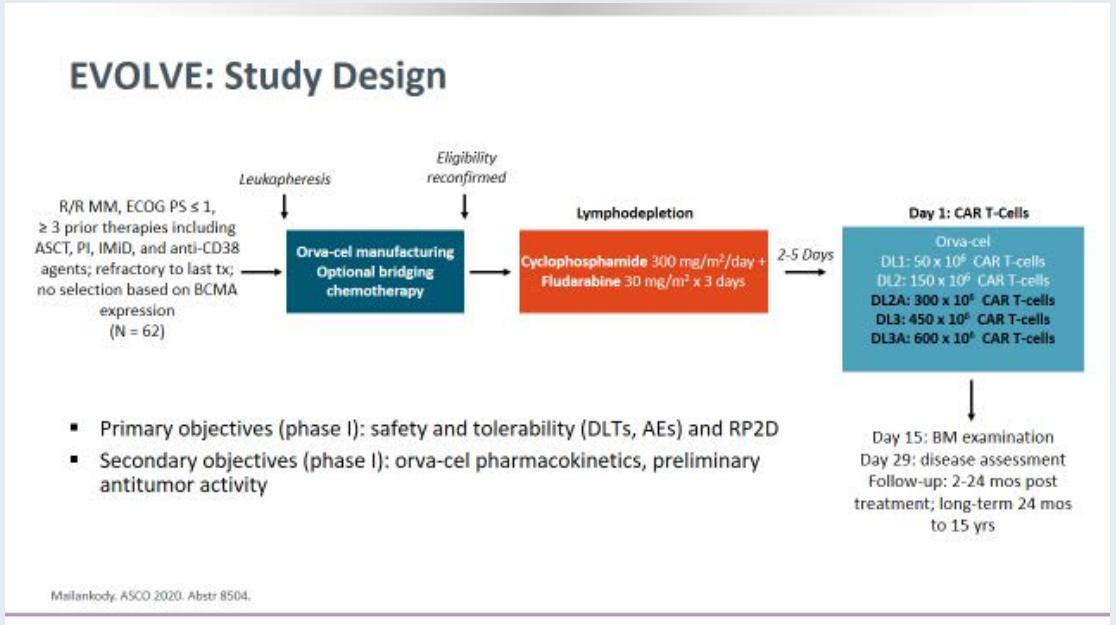
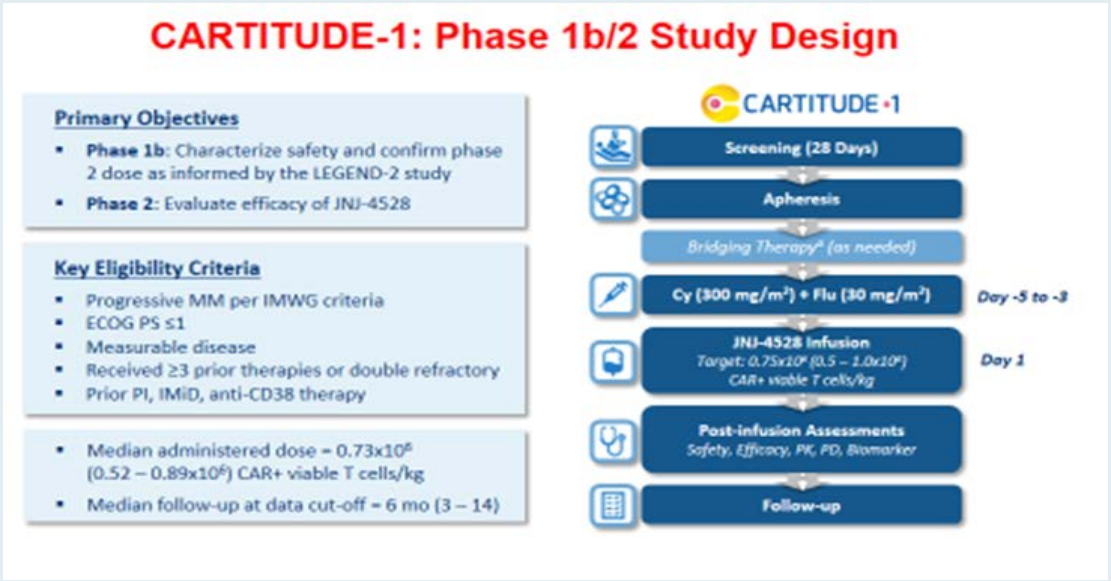
Module 7: BCMA-directed CAR T-cell therapy; bispecifics

- **Key Relevant Data Sets**
  - KarMMa: Idecabtagene vicleucel (ide-cel; bb2121) for elderly patients with R/R MM
  - CRB-402: bb21217 for R/R MM
  - CARTITUDE-1: Ciltacabtagene autoleucel (JNJ-4528) for R/R MM
  - EVOLVE: Orvacabtagene autoleucel (orva-cel) for R/R MM

Key BCMA-Directed CAR-T Study Designs







Similar approach in 3 studies:

R/R MM
Steady state T cell collection
CY/FLU lymphodepletion
Single infusion

Courtesy of Edward A Stadtmauer, MD

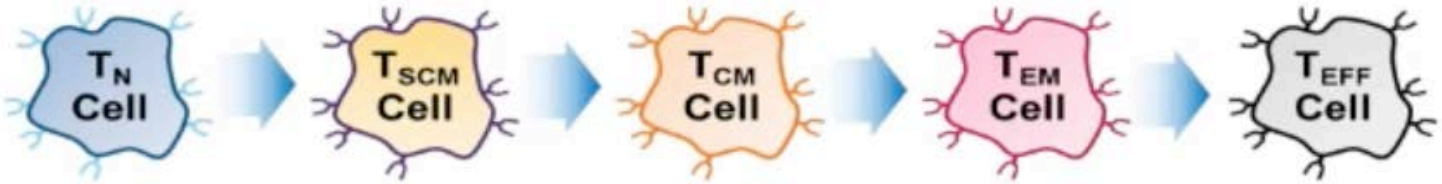
Updated Results from the Phase I CRB-402 Study of Anti-Bcma CAR-T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma: Correlation of Expansion and Duration of Response with T Cell Phenotypes

Alsina M et al.

ASH 2020;Abstract 130.

bb21217: Mechanism of Action

- bb21217 uses the same CAR molecule as bb2121,[1] but is cultured with the PI3K inhibitor, bb007, to enrich for T cells displaying a memory-like phenotype
- CAR T cells enriched for this phenotype may persist and function for longer than non-enriched CAR T cells[2]
- Persistence of functional CAR T cells after infusion may be one determinant of duration of response[3]



- When cultured in the presence of the PI3K inhibitor bb007, donor cells become enriched for memory-like CAR T cells and the percentage of senescent CAR T cells decreases.

Alsina M et al. ASH 2020;Abstract 130.

Updated Phase 1 Results of Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Relapsed and/or Refractory Multiple Myeloma (RRMM)

Garfall AL et al. ASH 2020;Abstract 180.

A Phase 1, First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D (GPRC5D) x CD3 Bispecific Antibody, in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

Chari A et al. ASH 2020;Abstract 290.

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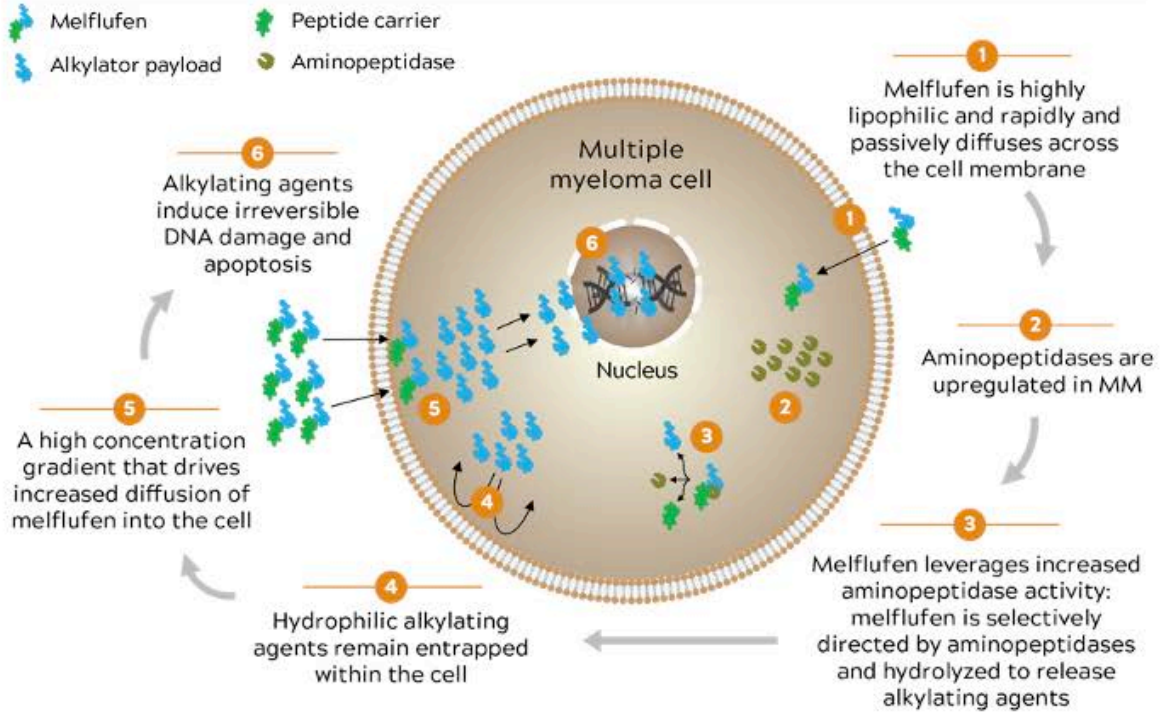
Module 9: Cereblon E3 ligase modulators (CELMoDs)

Module 8: Melflufen

- **Key Relevant Data Set**
  - ANCHOR (OP-104): Melflufen/dexamethasone with daratumumab or bortezomib for multiple regimen-refractory disease

Melphalan Flufenamide (Melflufen): Mechanism of Action

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

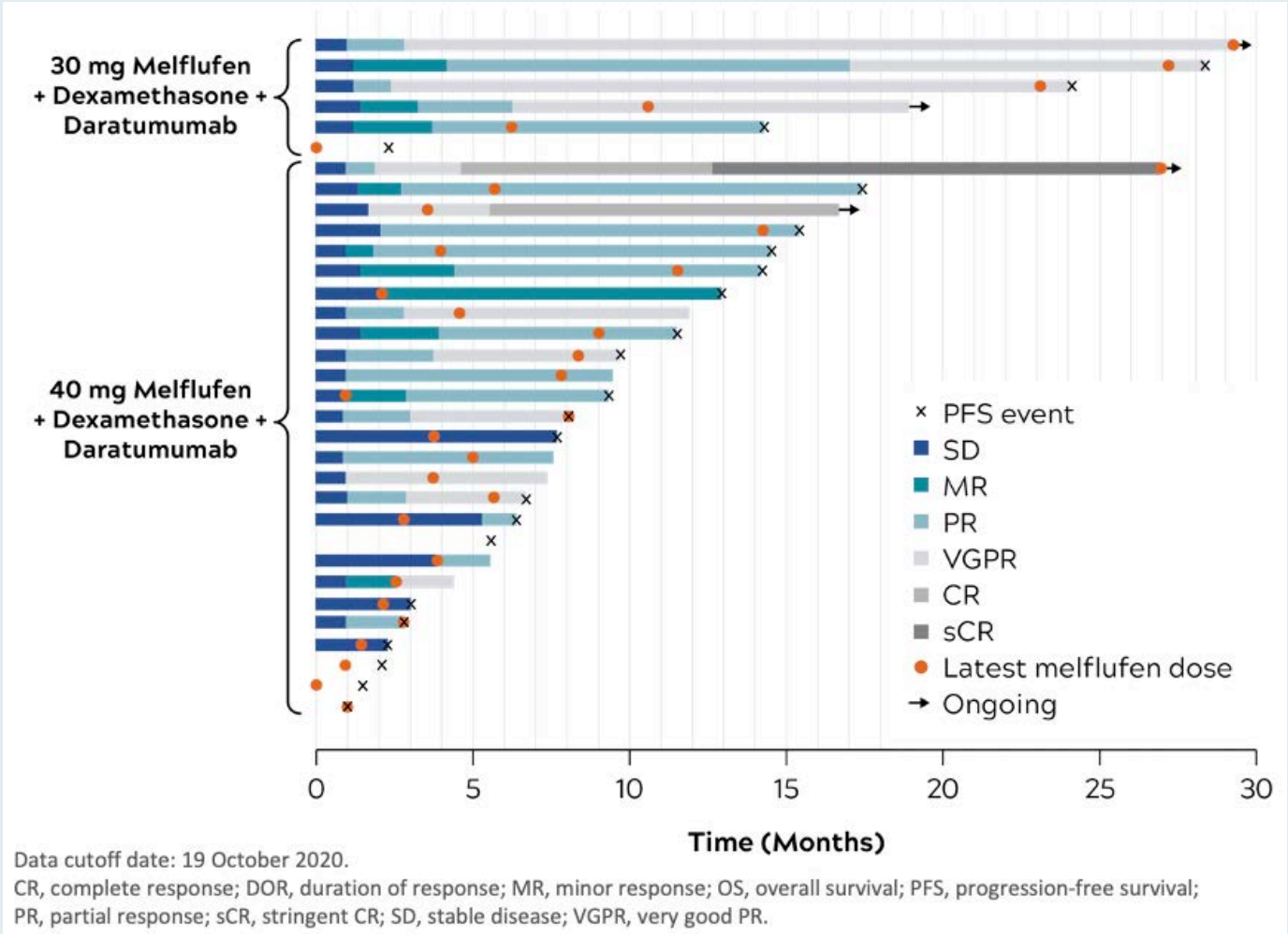


- In the pivotal phase 2 HORIZON study (OP-106), the activity of melflufen plus dexamethasone was further shown in heavily pretreated RRMM patients refractory to pomalidomide and/or anti-CD38 mAb therapy, with acceptable safety[6]
  - ORR was 29%; median PFS was 4.2 months, and median OS was 11.6 months
  - Grade 3/4 hematologic AEs were common (mainly neutropenia [79%], thrombocytopenia [76%], and anemia [71%]) but clinically manageable; nonhematologic AEs were infrequent

AE, adverse event; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-rate survival; RRMM, relapsed/refractory multiple myeloma.

Ocio E et al. ASH 2020;Abstract 417.

ANCHOR: Melflufen with Dexamethasone and Daratumumab



Data cutoff date: 19 October 2020.
CR, complete response; DOR, duration of response; MR, minor response; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.

- No DLTs were observed at any dose
- 15 patients (45%) experienced SAEs, most commonly pneumonia (12%); influenza (9%); and parainfluenza virus infection, sepsis, urinary tract infection, and febrile neutropenia (6% each)[a]
  - 30 mg: 4 patients (67%)
  - 40 mg: 11 patients (41%)
- Four AEs with fatal outcomes
  - 30 mg: sepsis (unrelated to study treatment)
  - 40 mg: sepsis (possibly related to melflufen), and cardiac failure chronic and and general physical health deterioration (unrelated to study treatment)[b]

Ocio E et al. ASH 2020;Abstract 417.

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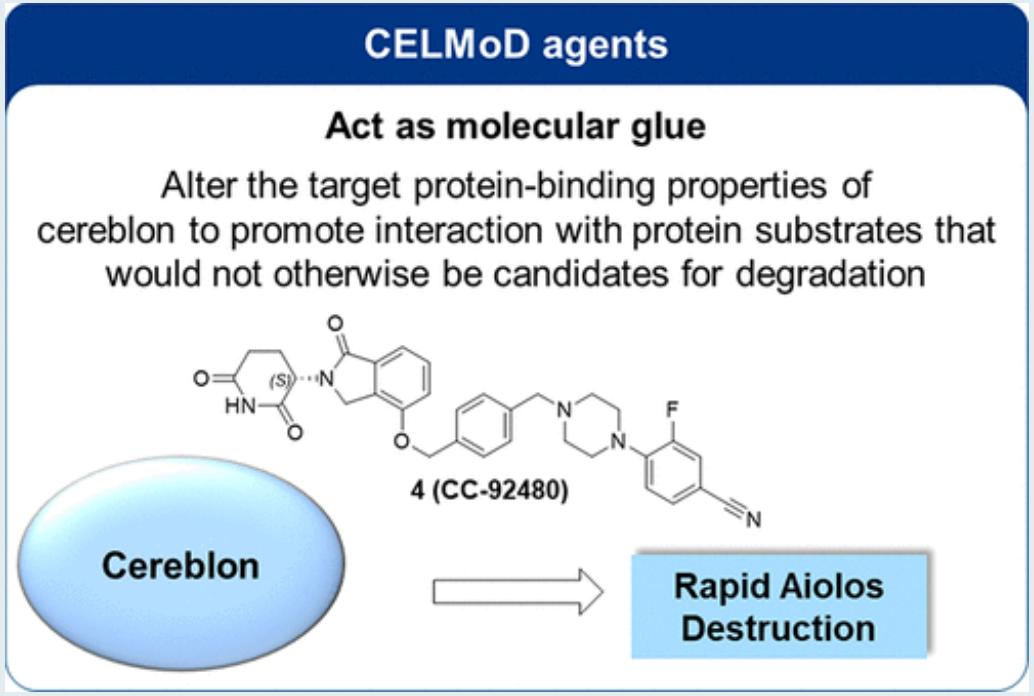
- **Key Relevant Data Set**
  - Novel CELMoD agent CC-92480 + dexamethasone for patients with R/R MM

Cereblon E3 Ligase Modulators (CELMoDs): Mechanism of Action

- CC-92480 binds to cereblon, thereby affecting the ubiquitin E3 ligase activity, and targeting certain substrate proteins for ubiquitination…
- … this induces proteasome-mediated degradation of certain transcription factors, some of which are transcriptional repressors in T cells…
- … this leads to modulation of the immune system, including activation of T lymphocytes; and antiproliferative effects and induction of apoptosis in myeloma cells



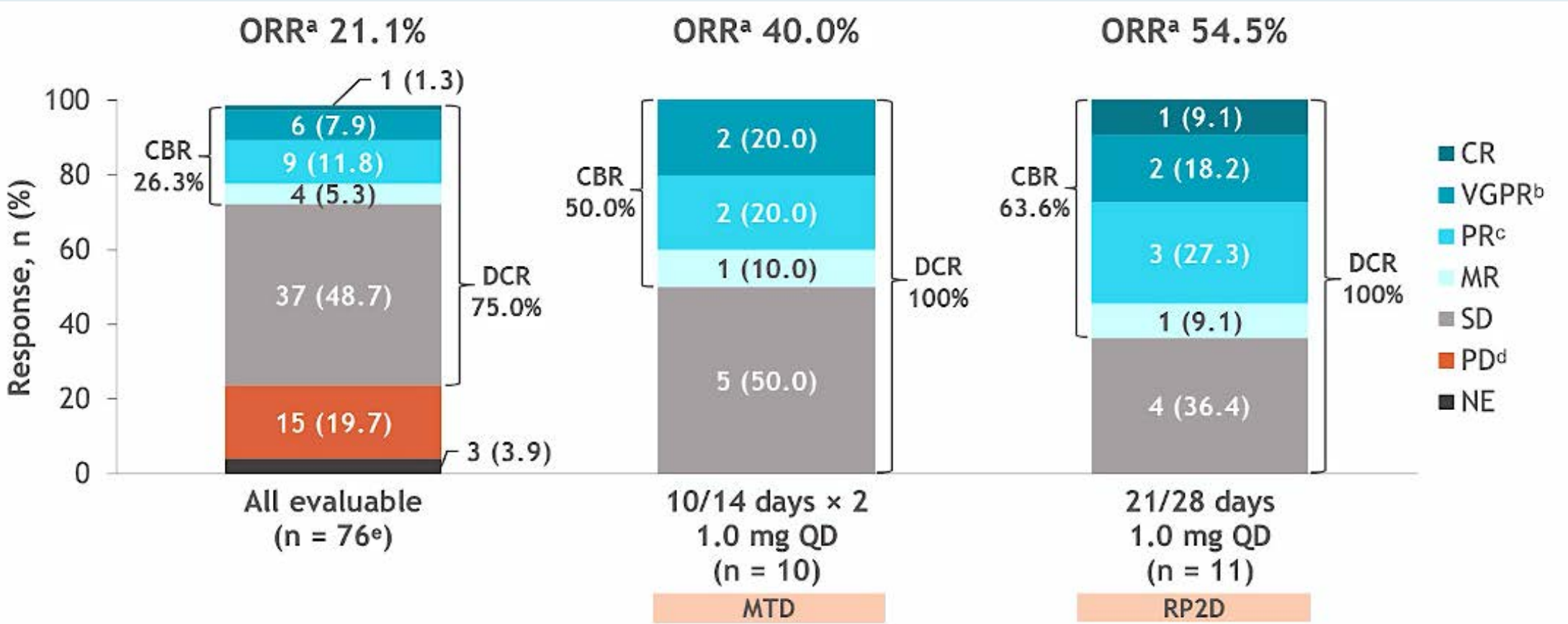
Hansen JD, et al. *J Med Chem* 2020;63(13):6648-76.

First-in-Human Phase I Study of the Novel CELMoD Agent CC-92480 Combined with Dexamethasone (DEX) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

Richardson PG et al.

ASCO 2020;Abstract 8500.

CC-92480 with Dexamethasone: Response



- At the RP2D 1.0 mg QD 21/28 days, 7 out of 11 patients were triple-class-refractory[f]
  - 1 patient had CR, 1 VGPR, 2 PR, and 1 MR

Richardson PG et al. ASCO 2020;Abstract 8500.

CC-92480 with Dexamethasone: Adverse Events

Common (> 20 % all grade) TEAEs and events of interest, n (%)	All doses (N = 76)		
	All grade	Grade 3	Grade 4
Neutropenia	56 (73.7)	23 (30.3)	26 (34.2)
Febrile neutropenia	6 (7.9)	4 (5.3)	1 (1.3)
Anemia	42 (55.3)	24 (31.6)	-
Thrombocytopenia	33 (43.4)	5 (6.6)	7 (9.2)
Infections	54 (71.1)	25 (32.9)	2 (2.6)
Pneumonia[a]	13 (17.1)	11 (14.5)	-
Fatigue	29 (38.2)	7 (9.2)	-
Pyrexia	17 (22.4)	3 (3.9)	-
Peripheral sensory neuropathy	4 (5.3)	-	-
Diarrhea	18 (23.7)	1 (1.3)	-
Nausea	17 (22.4)	1 (1.3)	-
Deep vein thrombosis	1 (1.3)	-	-

- Prophylactic G-CSF was not permitted during Cycle 1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reductions of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

Richardson PG et al. ASCO 2020;Abstract 8500.

Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Bladder Cancer and Renal Cell Carcinoma

Tuesday, February 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Sumanta K Pal, MD
David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

RTP Year in Review 2020

Thank you for joining us!

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

RTP Year in Review 2020