Meet The Professor

Optimizing the Management of Multiple Myeloma

Thursday, December 15, 2022
5:00 PM – 6:00 PM ET

Faculty

Shaji K Kumar, MD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, GlaxoSmithKline, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, and Karyopharm Therapeutics.

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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 Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, 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, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, 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, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics 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, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, 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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Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Dr Kumar — Disclosures

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Consulting Agreements (No Personal Payments)	AbbVie Inc, Amgen Inc, Arcellx, AstraZeneca Pharmaceuticals LP, bluebird bio, Bristol-Myers Squibb Company, Epizyme Inc, Genentech, a member of the Roche Group, Janssen Biotech Inc, K36 Therapeutics, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Monte Rosa Therapeutics, Sanofi, Secura Bio, Takeda Pharmaceuticals USA Inc, Trillium Therapeutics Inc
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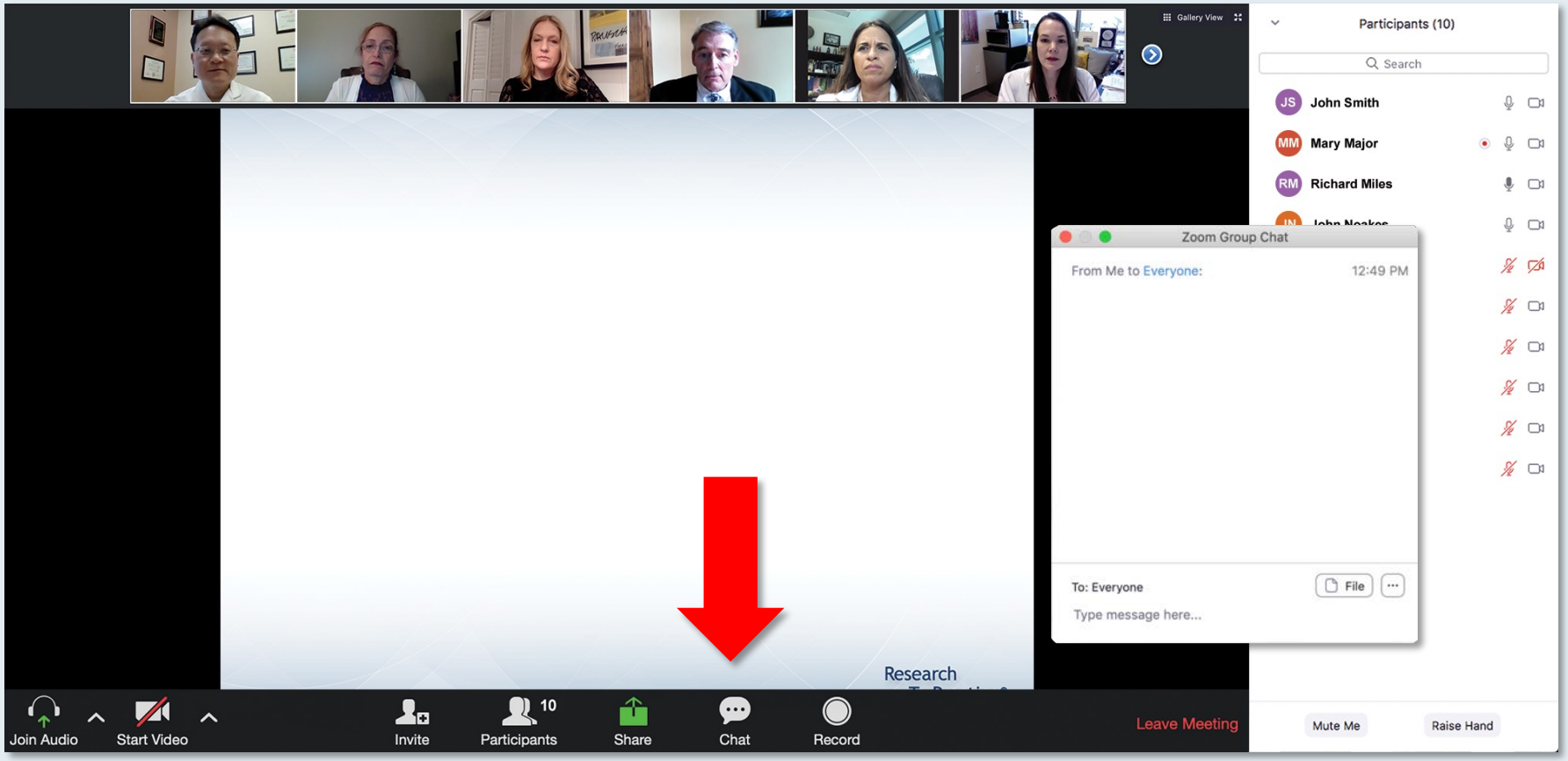
We Encourage Clinicians in Practice to Submit Questions



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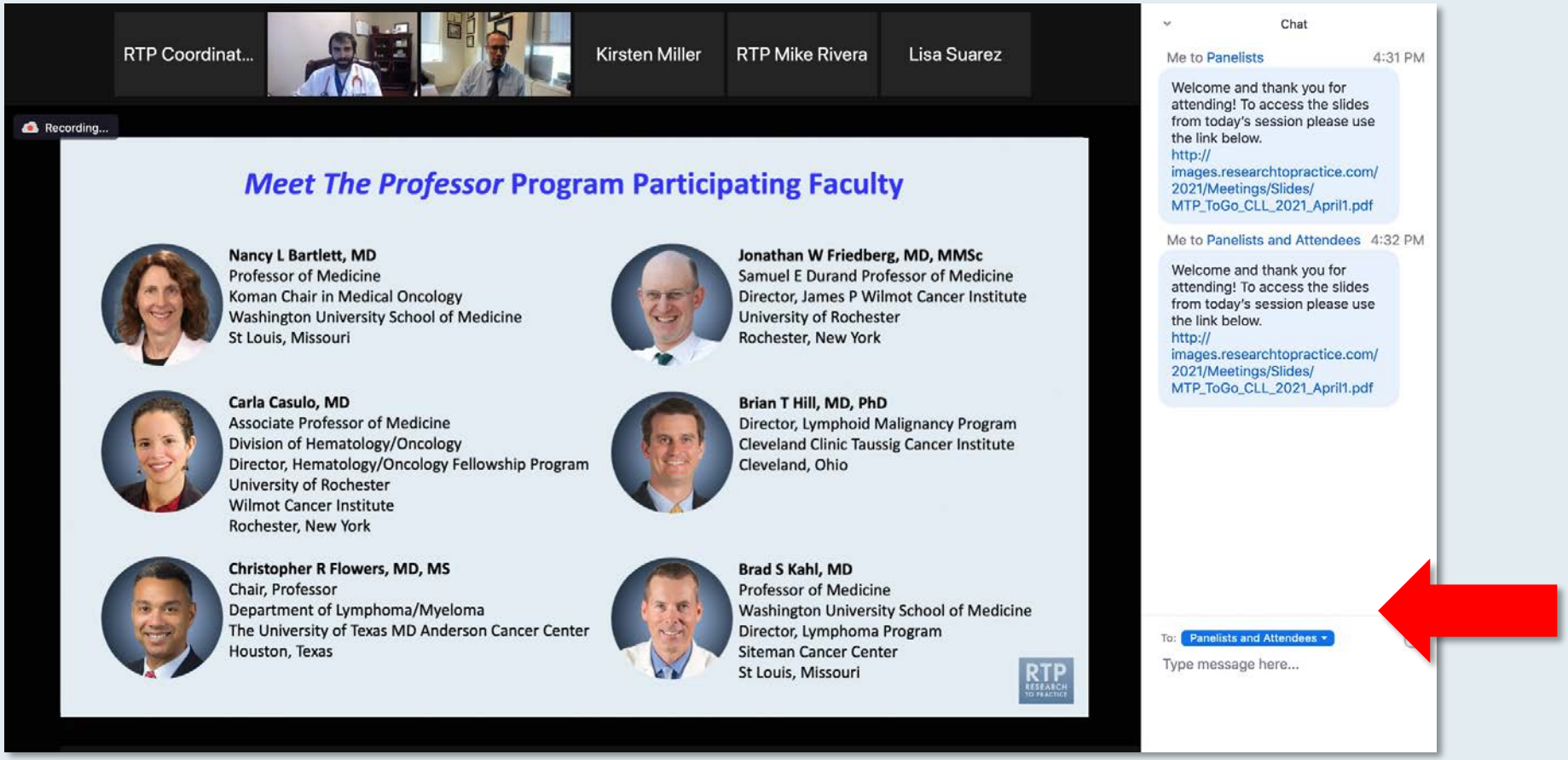

Drag the white line above the submission box up to create more space for your message.

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Familiarizing Yourself with the Zoom Interface

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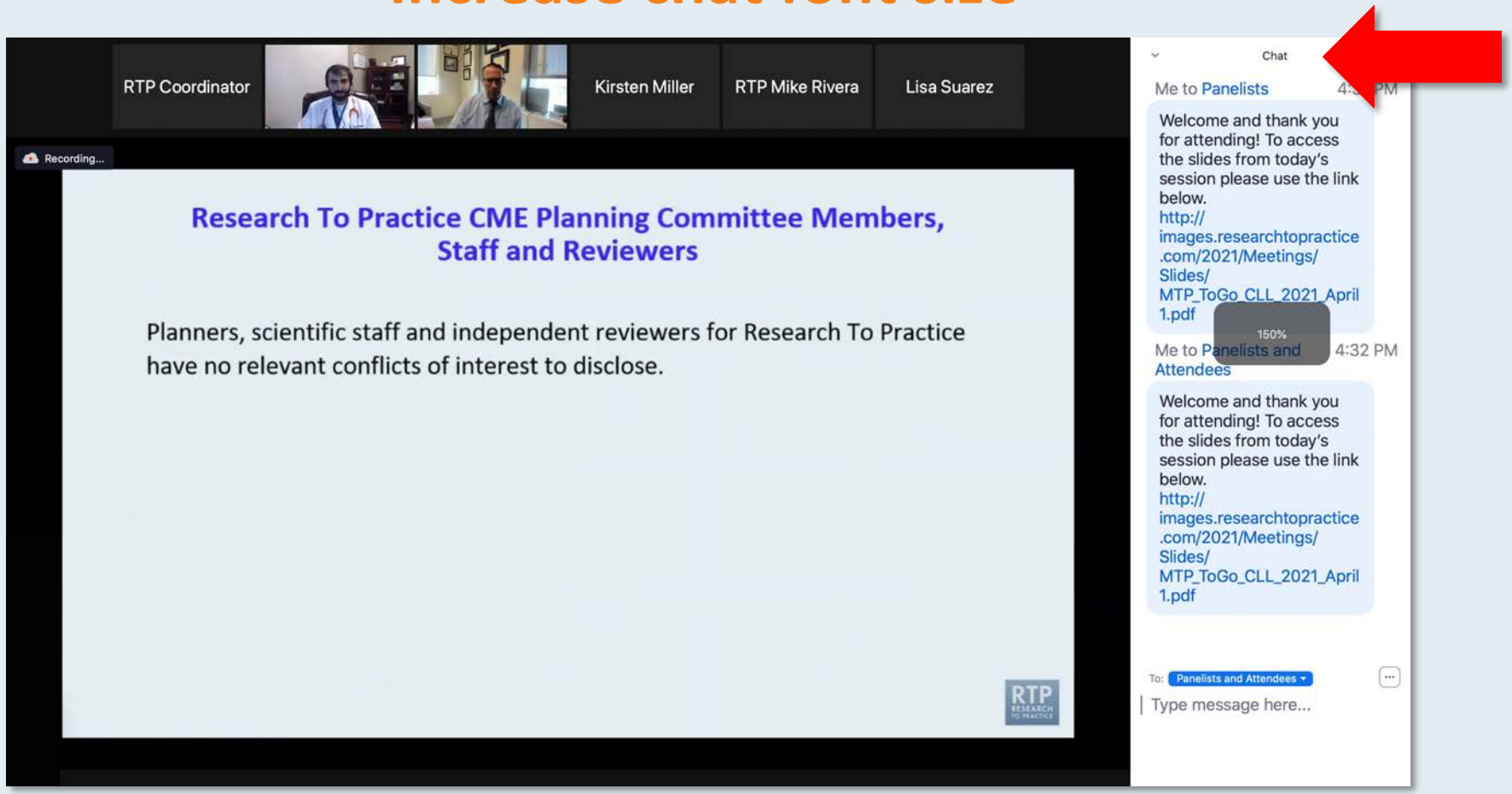

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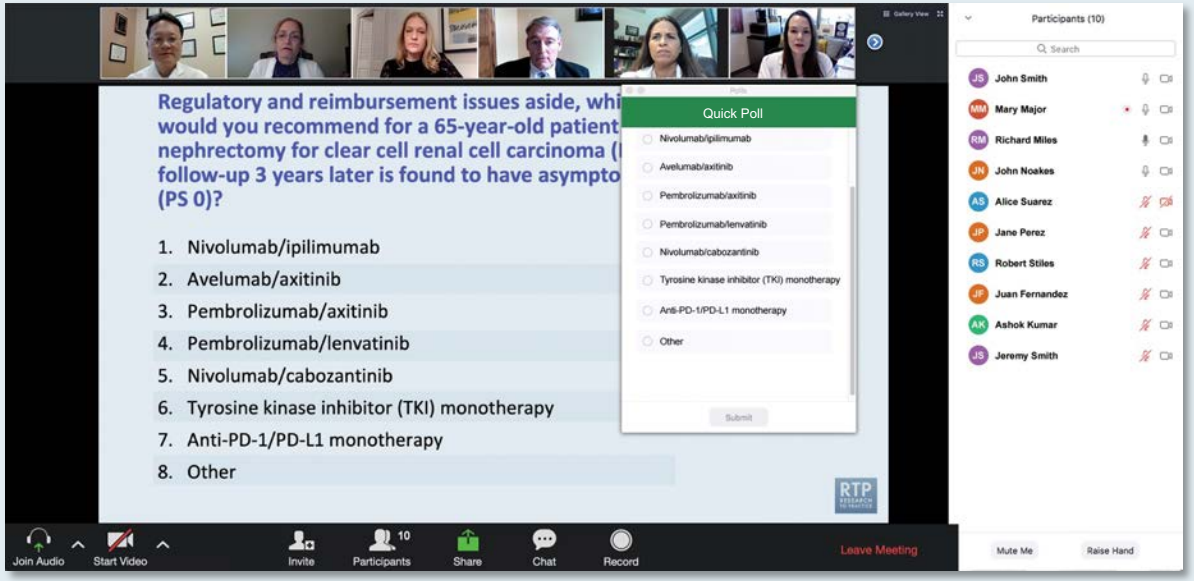
You may do this as many times as you need for readability.

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



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WITH DR NEIL LOVE

BCMA-Directed Therapies for Multiple Myeloma

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CITY OF HOPE CANCER CENTER

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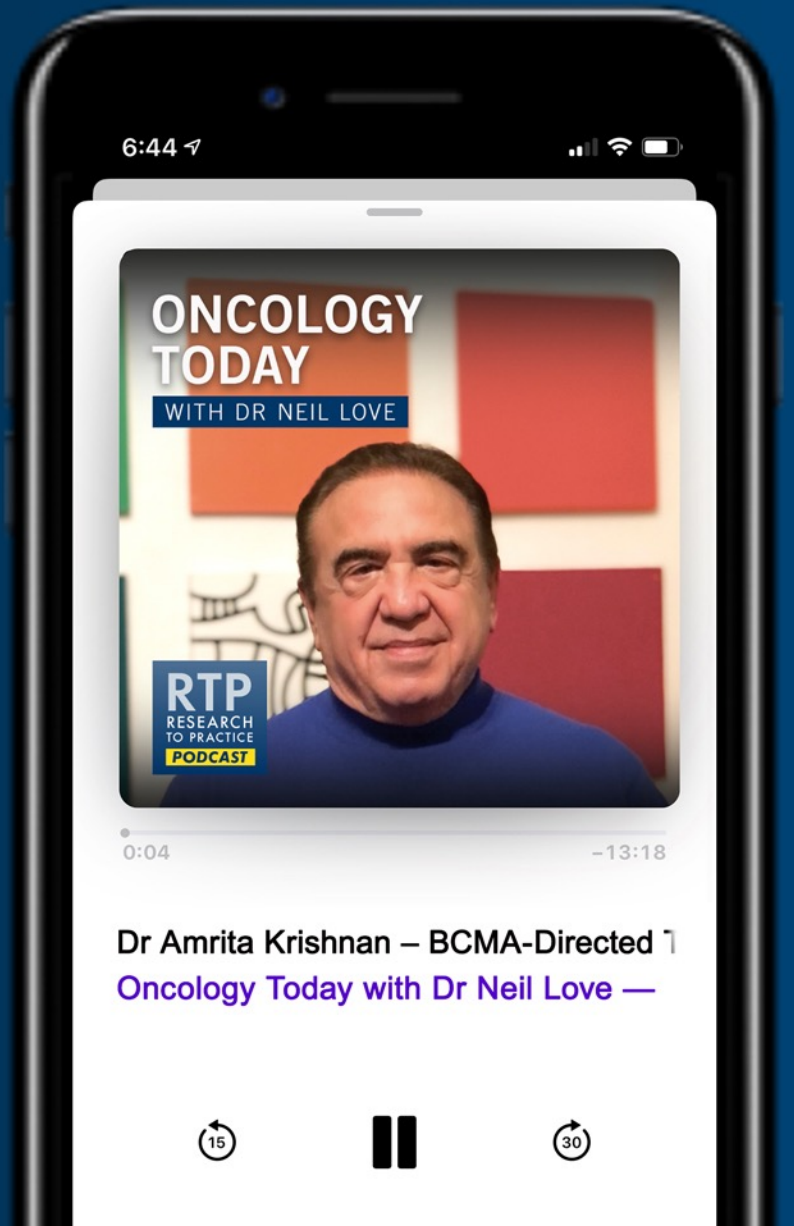

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Breast Cancer

A Multitumor CME/MOC-Accredited Live Webinar Series

Wednesday, January 4, 2023
5:00 PM – 6:00 PM ET

Faculty

Joyce O'Shaughnessy, MD
Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2023

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Chronic Lymphocytic Leukemia

A Multitumor CME/MOC-Accredited Live Webinar Series

Thursday, January 5, 2023
5:00 PM – 6:00 PM ET

Faculty

Jennifer R Brown, MD, PhD
Deborah Stephens, DO

Moderator

Neil Love, MD

RTP Year in Review 2023

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Multiple Myeloma

A Multitumor CME/MOC-Accredited Live Webinar Series

Tuesday, January 10, 2023
5:00 PM – 6:00 PM ET

Faculty

Joseph Mikhael, MD, MEd
Ajay K Nooka, MD, MPH

Moderator

Neil Love, MD

RTP Year in Review 2023

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Targeted Therapy for Non-Small Cell Lung Cancer

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastrointestinal Cancers

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Gynecologic Oncology

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Tuesday, January 24, 2023
5:00 PM – 6:00 PM ET

Faculty

Kathleen N Moore, MD, MS

Additional faculty to be announced

Moderator

Neil Love, MD

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Thank you for joining us!

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

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Shaji K Kumar, MD
Mark and Judy Mullins Professor of Hematological Malignancies
Consultant, Division of Hematology
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

Meet The Professor Program Participating Faculty

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

Shaji K Kumar, MD
Mark and Judy Mullins Professor
of Hematological Malignancies
Consultant, Division of Hematology
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

Ola Landgren, MD, PhD
Professor of Medicine
Leader, Experimental Therapeutics Program
Leader, Myeloma Division
Co-Leader of Tumor Biology Program
Sylvester Comprehensive Cancer Center
University of Miami
Miami, Florida

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Anne and Bernard Gray Family Chair in Cancer
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Joseph Mikhael, MD, MEd
Professor, Applied Cancer Research and Drug Discovery
Translational Genomics Research Institute (TGen)
City of Hope Cancer Center
Chief Medical Officer
International Myeloma Foundation
Consultant Hematologist and Director, Myeloma
Research, Phase 1 Program
HonorHealth Research Institute
Adjunct Professor, College of Health Solutions
Arizona State University
Phoenix, Arizona

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Meet The Professor Program Participating Faculty

Noopur Raje, MD
Director, Center for Multiple Myeloma
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Paul G Richardson, MD
Clinical Program Leader and Director of Clinical Research
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
RJ Corman Professor of Medicine
Harvard Medical School
Boston, Massachusetts

MODERATOR
Neil Love, MD
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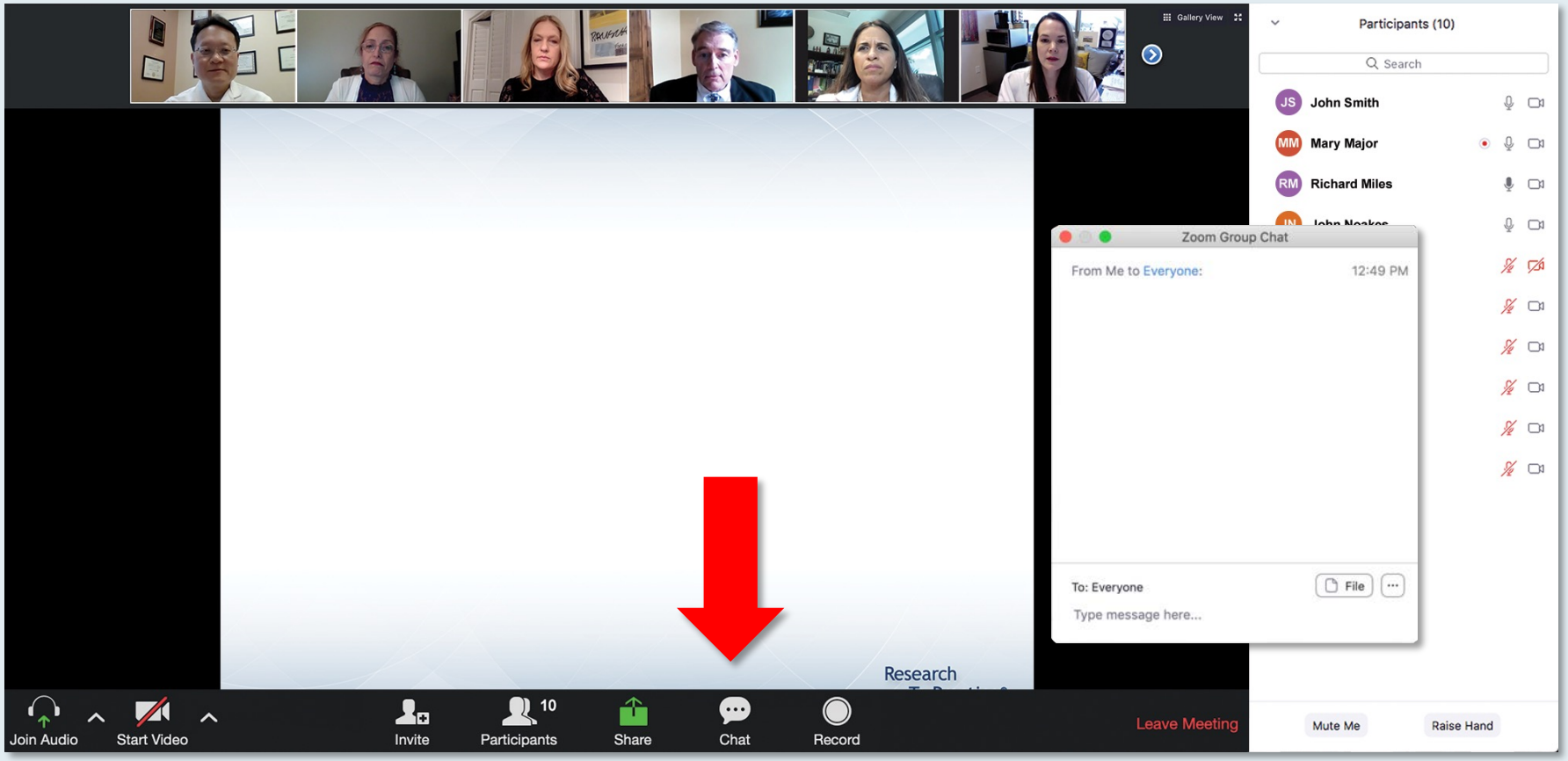

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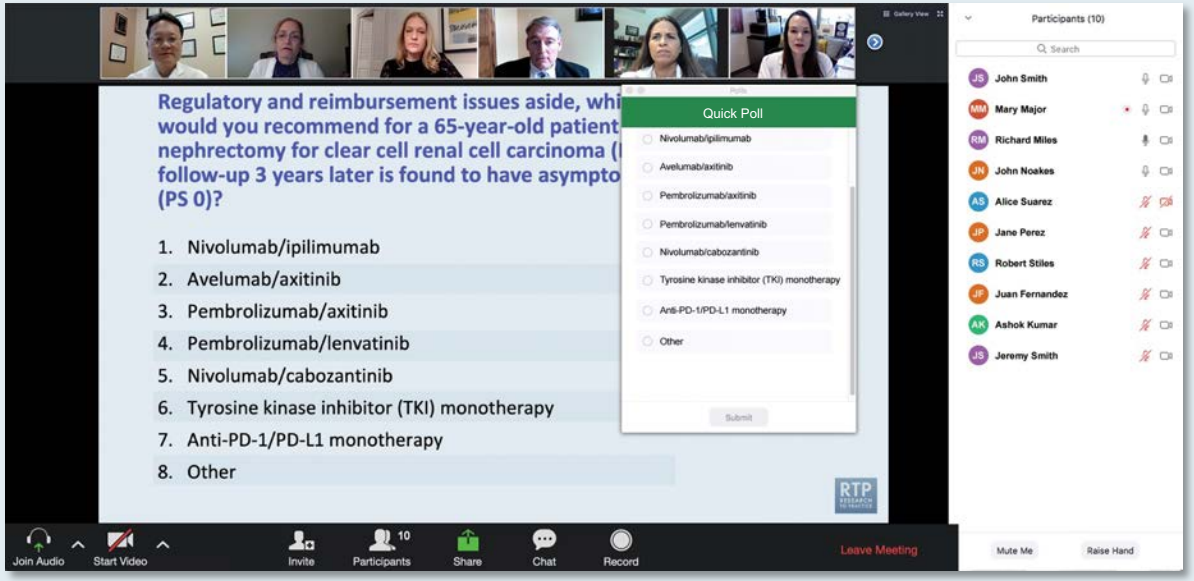

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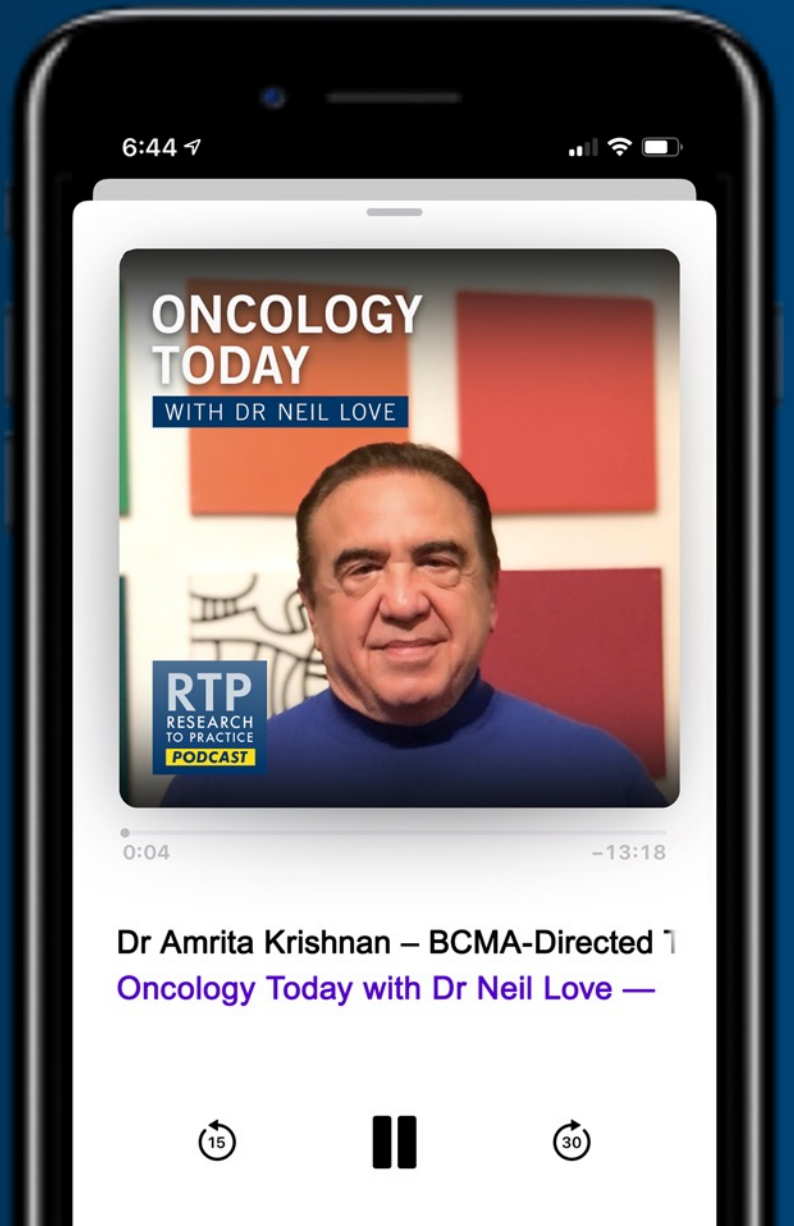

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Spencer Henick Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Yanjun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee

Jennifer L Dallas, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Amany R Keruakous, MD, MS
Georgia Cancer Center
Augusta University
Augusta, Georgia

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

Hans Lee, MD
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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Meet The Professor with Dr Kumar

INTRODUCTION

MODULE 1: Case Presentations

MODULE 2: Journal Club with Dr Kumar

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Clin Cancer Res 2022 January 1;28(1):23-6.

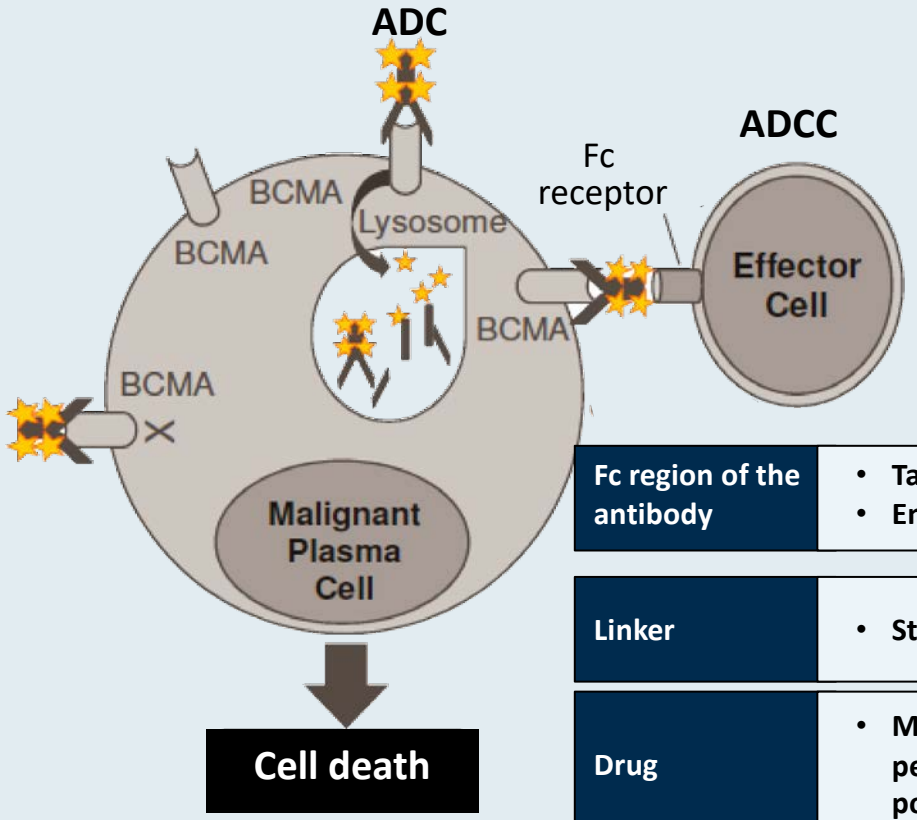
CLINICAL CANCER RESEARCH | CCR PERSPECTIVES IN REGULATORY SCIENCE AND POLICY

Perspectives on Drug Development in Multiple Myeloma—Looking Forward to 2025

Peter M. Voorhees[1], Andrzej J. Jakubowiak[2], Shaji K. Kumar[3], Bindu Kanapuru[4], Andrea C. Baines[4], Vishal Bhatnagar[5], Rachel Ershler[4], Marc R. Theoret[5], Nicole J. Gormley[4], and Richard Pazdur[5]

Belantamab Mafodotin: 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

ADC = antibody-drug conjugate; ADCC = antibody-dependent cell-mediated cytotoxicity

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

Phase III DREAMM-3 Trial of Belantamab Mafodotin Monotherapy versus Pomalidomide in Combination with Low-Dose Dexamethasone Does Not Meet Its Primary Endpoint

Press Release: November 7, 2022

The DREAMM-3 Phase III open-label, randomized, head-to-head superiority trial of belantamab mafodotin monotherapy versus pomalidomide in combination with low dose dexamethasone (PomDex) for patients with relapsed or refractory multiple myeloma did not meet its primary endpoint of progression-free survival (PFS).

“In the DREAMM-3 trial, the primary endpoint of PFS demonstrated a hazard ratio of 1.03 (95% CI: 0.72, 1.47). The observed median progression-free survival was longer for belantamab mafodotin vs PomDex (11.2 months vs 7 months).”

“Data from DREAMM-3 is in the process of being shared with health authorities. Discussions with health authorities are currently ongoing. Additional trials within the DREAMM (DRiving Excellence in Approaches to Multiple Myeloma) clinical trial programme will continue.”

“Data from the DREAMM-7 and DREAMM-8 phase III trials are anticipated in the first half of 2023.”

https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-dreamm-3-phase-iii-trial-for-blenrep/

US Marketing Authorization to Be Withdrawn for Belantamab Mafodotin for Multiple Myeloma

Press Release: November 22, 2022

Following a request from the FDA, the process for withdrawal of the US marketing authorization for belantamab mafodotin-blmf has begun. This move comes shortly after it was disclosed that the antibody-drug conjugate failed to show superiority over the combination of pomalidomide and low-dose dexamethasone in the confirmatory Phase III DREAMM-3 trial for patients with relapsed or refractory multiple myeloma (RRMM).

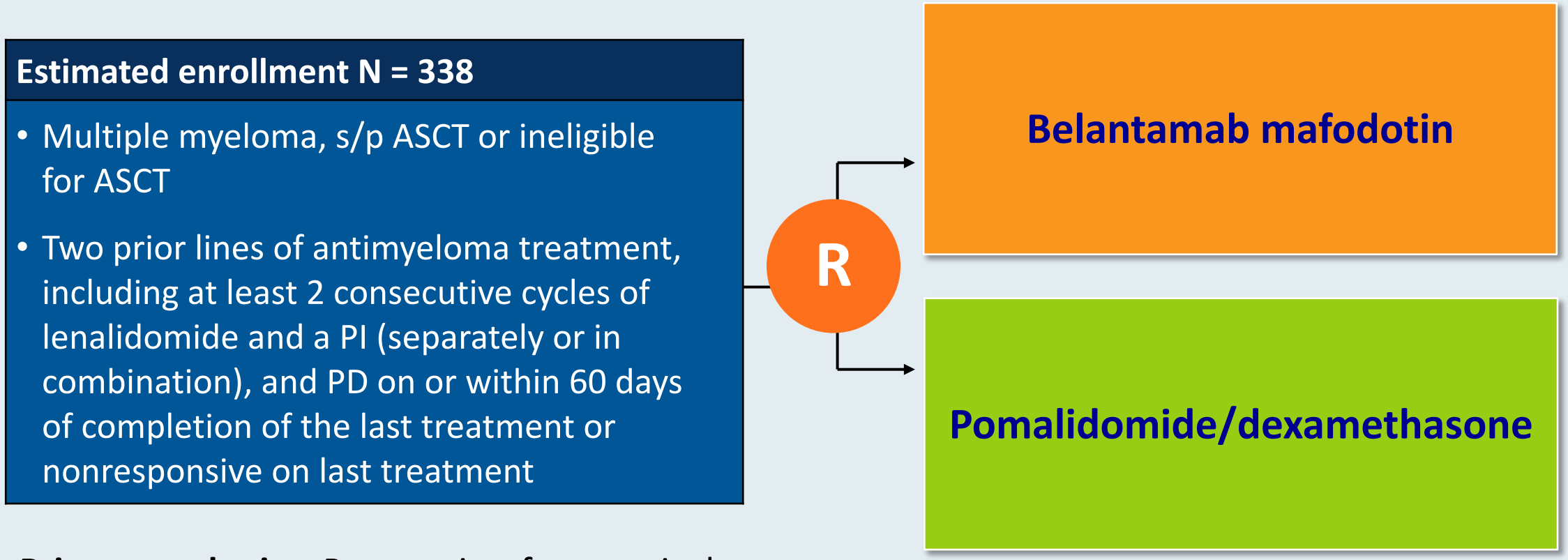
Earlier this month it was reported that in the DREAMM-3 study median progression-free survival was 11.2 months with belantamab mafodotin and 7 months with pomalidomide and dexamethasone, with a hazard ratio (HR) of 1.03 for the primary endpoint. Meanwhile, median overall survival was 21.2 months with belantamab mafodotin and 21.1 months with pomalidomide and dexamethasone, with a HR of 1.14.

Belantamab mafodotin is also being evaluated in the late-stage DREAMM-7 and DREAMM-8 trials investigating earlier use of the drug in combination with novel therapies and standard treatments.

Belantamab mafodotin remains available in other countries.

https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-blenrep-us-marketing-authorisation/

DREAMM-3 Phase III Trial Design



Primary endpoint: Progression-free survival

Secondary endpoints: Overall survival, overall response rate, clinical benefit rate, duration of response, time to response, time to disease progression, others

PI = proteasome inhibitor; PD = disease progression

https://clinicaltrials.gov/ct2/show/NCT04162210. Accessed November 2022.

Ongoing Phase III Trials of Belantamab Mafodotin

Study	N	Setting	Treatment arms	Estimated primary completion
DREAMM-8 (NCT04484623)	450	• RRMM • ≥1 prior line of treatment, including a lenalidomide-containing regimen	• Belantamab mafodotin + pomalidomide/dexamethasone • Bortezomib + pomalidomide/dexamethasone	March 2023
DREAMM-7 (NCT04246047)	575	• RRMM • ≥1 prior line of treatment	• Belantamab mafodotin + bortezomib/dexamethasone • Daratumumab + bortezomib/dexamethasone	April 2023

www.clinicaltrials.gov. Accessed August 2022.

Meet The Professor with Dr Kumar

MODULE 1: Case Presentations

- Dr Morganstein: 71-year-old woman with standard-risk NDMM, “borderline transplant eligible,” receiving daratumumab-RVd; with transportation limitations and missed treatments
- Dr Narayanan: 53-year-old woman with Stage III, high-risk NDMM (1q21+), multiple bone lesions and acute renal impairment; s/p RVd, transplant, now on DRAMMATIC trial
- Dr Keruakous: 60-year-old man with relapsed t(11;14) multiple myeloma and renal failure s/p RVd and ASCT, now on venetoclax/bortezomib/dex
- Dr Lee: 56-year-old woman with high-risk t(11;14) smoldering multiple myeloma
- Dr Ma: 77-year-old man with NDMM, transplant-ineligible, who received daratumumab-Rd but discontinued daratumumab due to a severe rash
- Dr Bachow: 84-year-old man with a prior history of NMIBC, now with multiregimen-refractory multiple myeloma and biochemical disease progression
- Dr Dallas: 57-year-old man with multiple comorbidities diagnosed with standard-risk multiple myeloma who receives induction RVd → maintenance bortezomib and develops chalazion ocular toxicity

RTP RESEARCH TO PRACTICE

Case Presentation: 71-year-old woman with standard-risk NDMM, “borderline transplant eligible,” receiving daratumumab-RVd; with transportation limitations and missed treatments

Dr Neil Morganstein (Summit, New Jersey)

Received: 7 February 2022 | Revised: 24 February 2022 | Accepted: 25 February 2022

DOI: 10.1002/ajh.26512

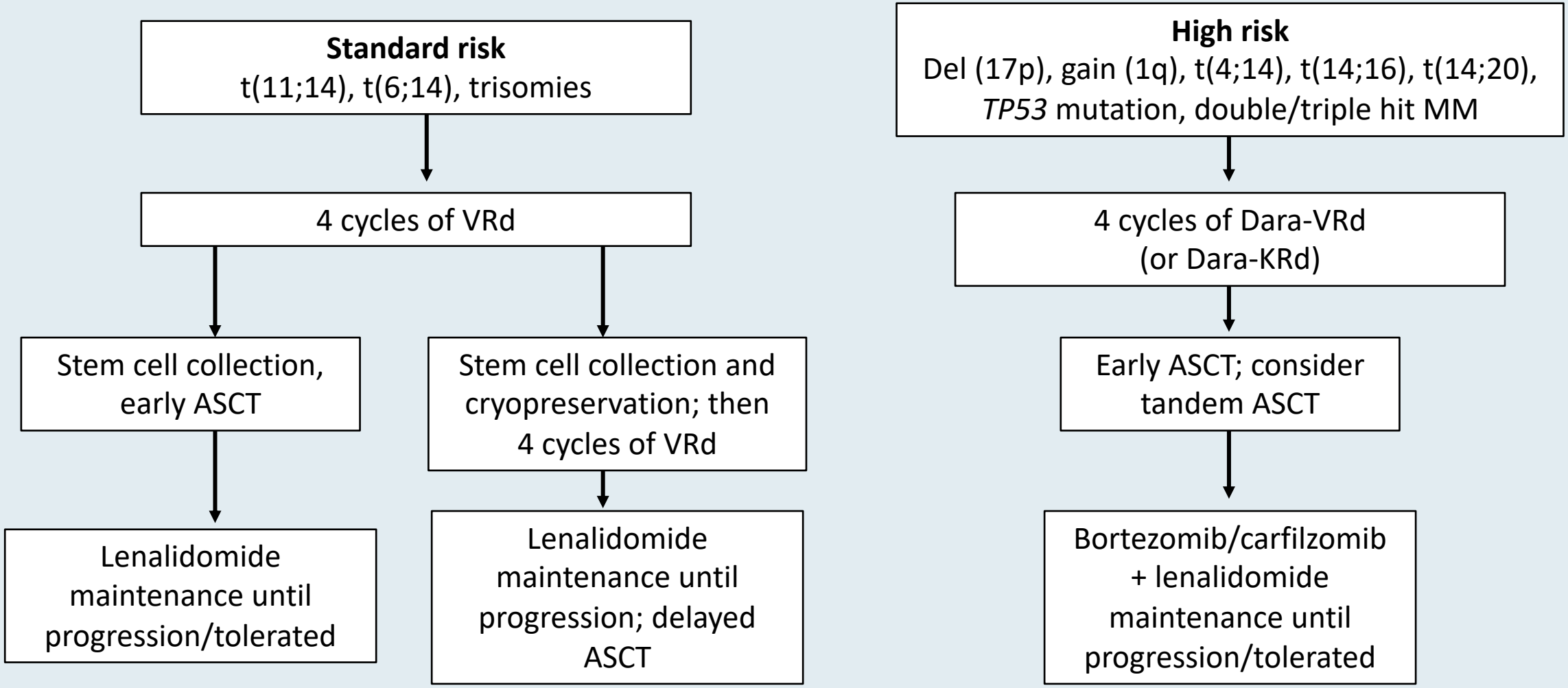
CRITICAL REVIEW

Current approaches to management of newly diagnosed multiple myeloma

Utkarsh Goel[1] | Saad Usmani[2] | Shaji Kumar[1]

Am J Hematol 2022 May;97(Suppl 1):3-25.

Treatment Approach for Transplant-Eligible Patients



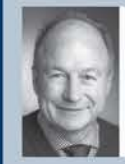
Goel U et al. *Am J Hematol* 2022 May;97(Suppl 1):3-25.

Fixed Duration Daratumumab, Ixazomib, Lenalidomide, and Dexamethasone Quadruplet for Newly Diagnosed Multiple Myeloma – MRD Negativity and Survival Outcomes

Kumar SK et al.

ASH 2022;Abstract 4556.

Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger patient with MM and no high-risk features?

 Dr Fonseca	Daratumumab/KRd	 Dr Lonial	Daratumumab/RVd
 Dr Kumar	RVd	 Dr Mikhael	Daratumumab/RVd
 Dr Landgren	Daratumumab/KRd	 Dr Richardson	Daratumumab/RVd

KRd = carfilzomib/lenalidomide/dexamethasone; RVd = lenalidomide/bortezomib/dexamethasone

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2022 ASCO ANNUAL MEETING

Abstract LBA4

RVd ± ASCT and Lenalidomide Maintenance to Progression for NDMM

The Phase 3 DETERMINATION Trial

Paul G. Richardson, MD, 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, MA

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2022 July 14;387(2):132-47.

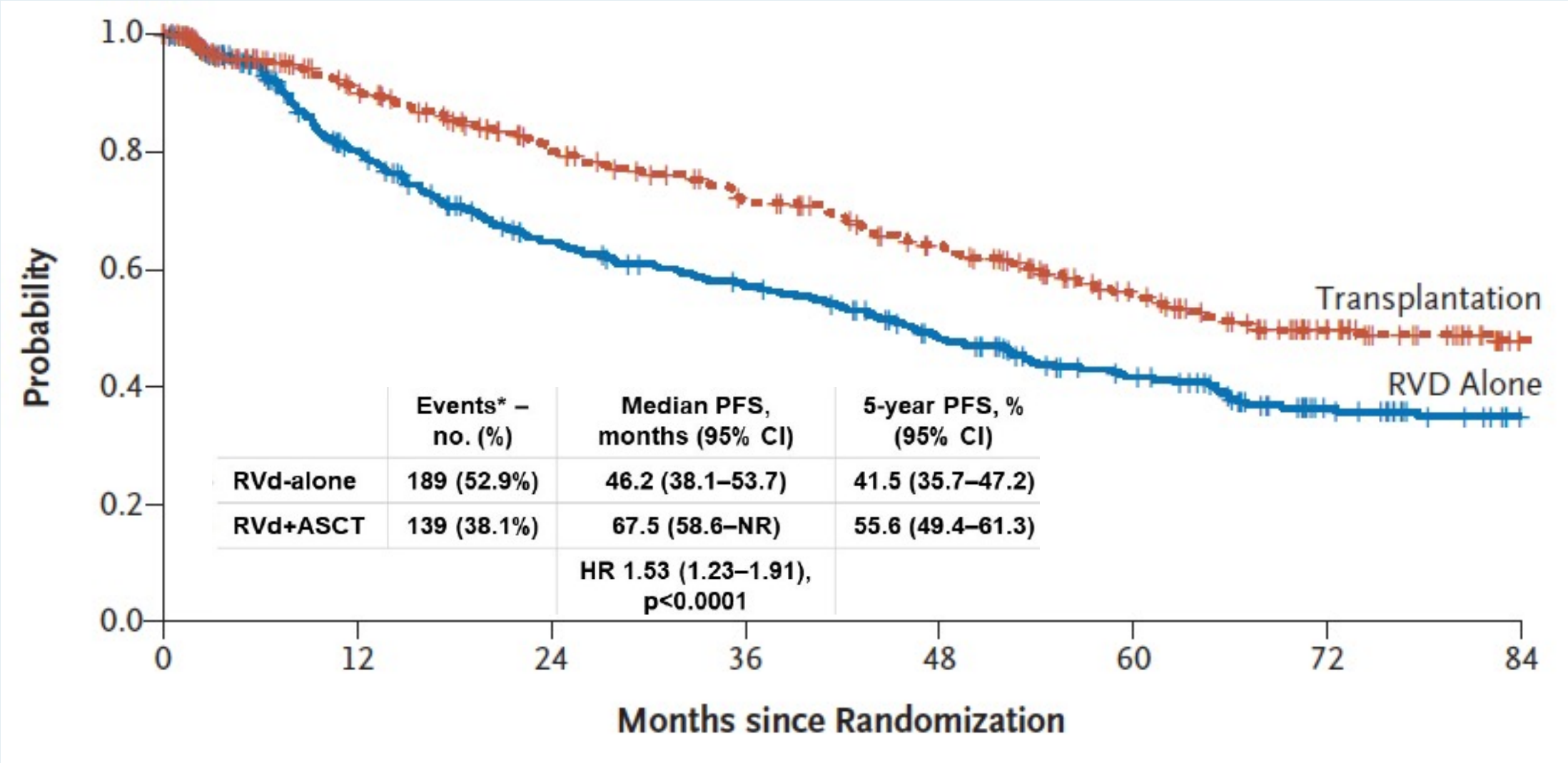
ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

P.G. Richardson, S.J. Jacobus, E.A. Weller, H. Hassoun, S. Lonial, N.S. Raje, E. Medvedova, P.L. McCarthy, E.N. Libby, P.M. Voorhees, R.Z. Orlowski, L.D. Anderson, Jr., J.A. Zonder, C.P. Milner, C. Gasparetto, M.E. Agha, A.M. Khan, D.D. Hurd, K. Gowin, R.T. Kamble, S. Jagannath, N. Nathwani, M. Alsina, R.F. Cornell, H. Hashmi, E.L. Campagnaro, A.C. Andreescu, T. Gentile, M. Liedtke, K.N. Godby, A.D. Cohen, T.H. Openshaw, M.C. Pasquini, S.A. Giralt, J.L. Kaufman, A.J. Yee, E. Scott, P. Torka, A. Foley, M. Fulciniti, K. Hebert, M.K. Samur, K. Masone, M.E. Maglio, A.A. Zeytoonjian, O. Nadeem, R.L. Schlossman, J.P. Laubach, C. Paba-Prada, I.M. Ghobrial, A. Perrot, P. Moreau, H. Avet-Loiseau, M. Attal, K.C. Anderson, and N.C. Munshi, for the DETERMINATION Investigators*

RTP RESEARCH TO PRACTICE

DETERMINATION: Progression-Free Survival (Primary Endpoint)

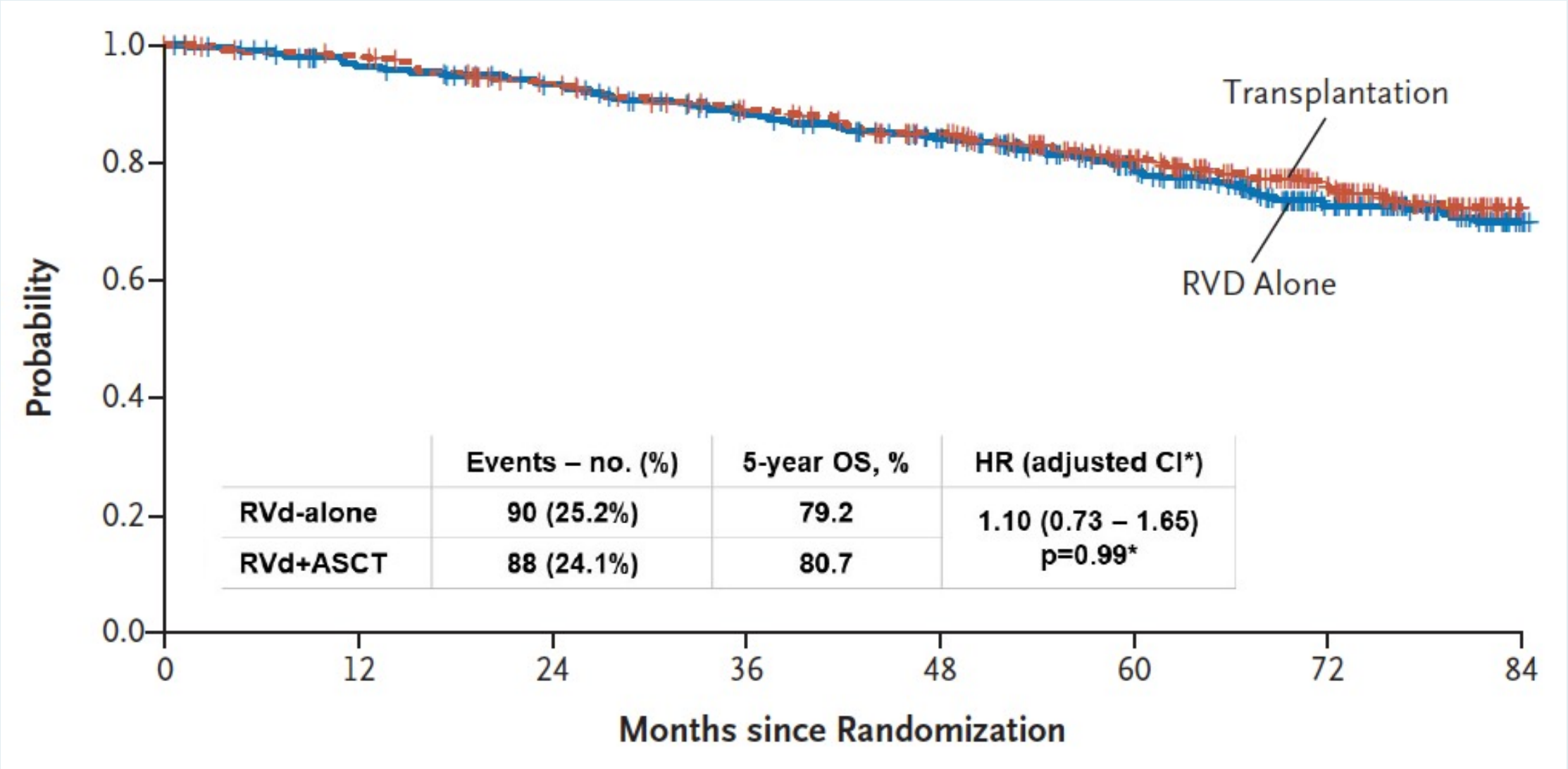


	Events* – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

Richardson PG et al. *N Engl J Med* 2022 July 14;387(2):132-47; ASCO 2022;Abstract LBA4.

RTP RESEARCH TO PRACTICE

DETERMINATION: Overall Survival (Key Secondary Endpoint)



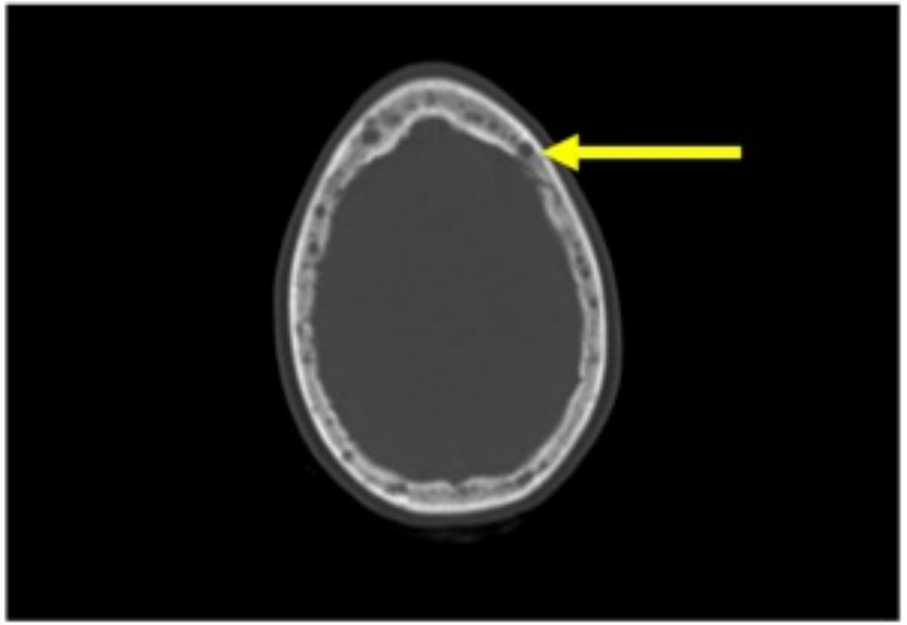
	Events – no. (%)	5-year OS, %	HR (adjusted CI*)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

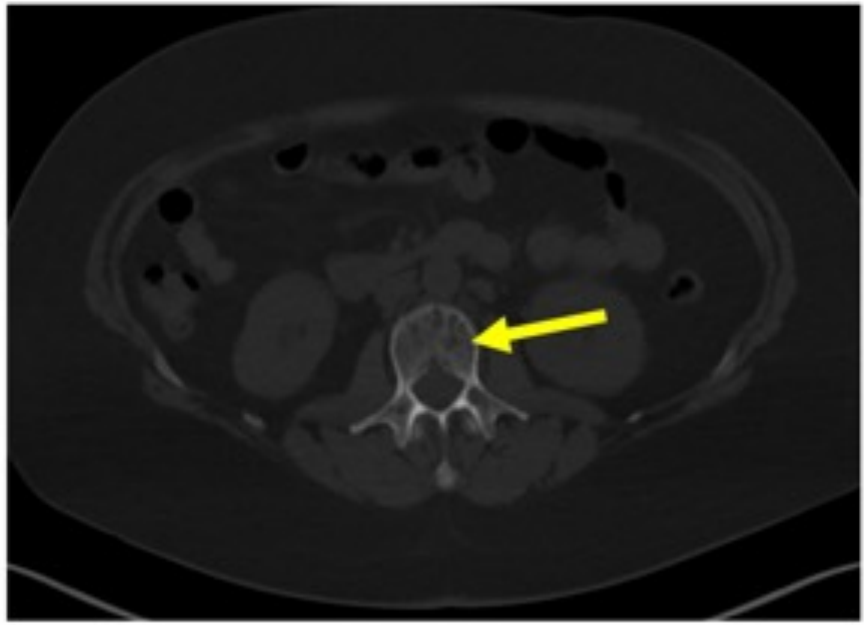
Richardson PG et al. *N Engl J Med* 2022 July 14;387(2):132-47; ASCO 2022;Abstract LBA4.

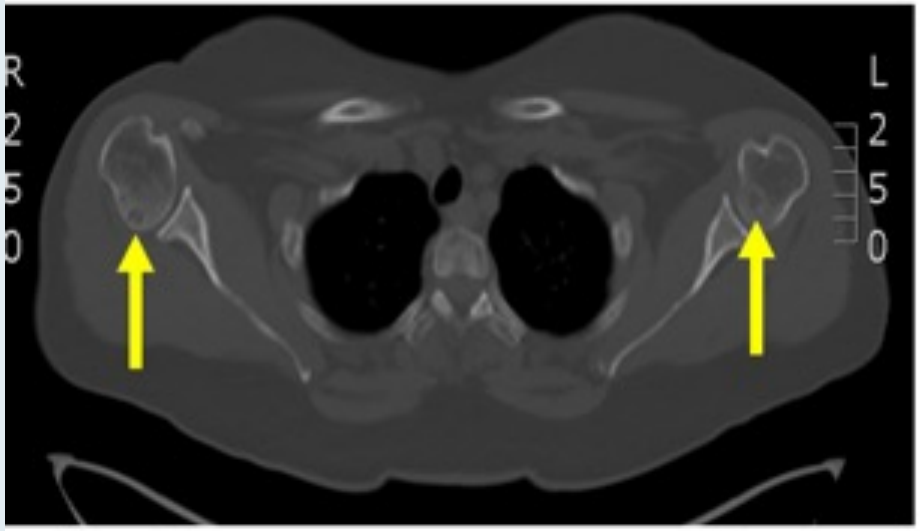
Case Presentation: 53-year-old woman with Stage III, high-risk NDMM (1q21+), multiple bone lesions and acute renal impairment; s/p RVd, transplant, now on DRAMMATIC trial

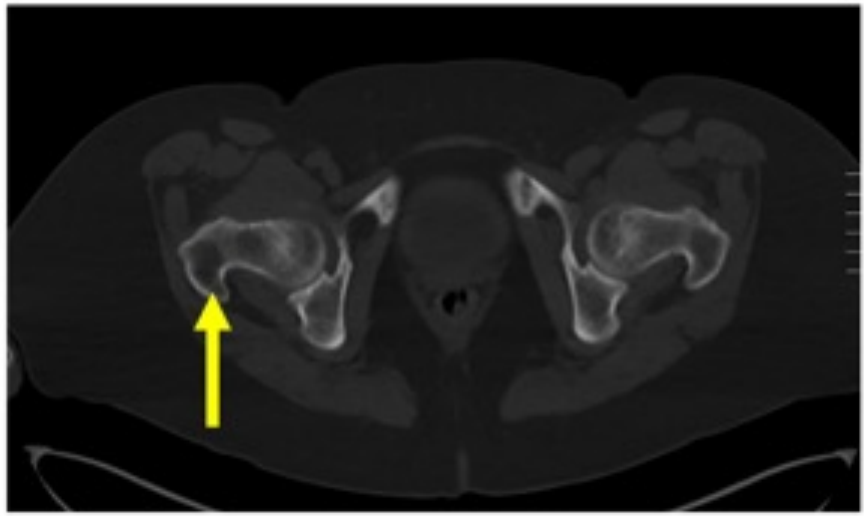
Dr Vignesh Narayanan (Lone Tree, Colorado)

RTP
RESEARCH
TO PRACTICE









Assessment of Clinical Use Parameters Associated with a Switch from Intravenous to Subcutaneous Daratumumab Administration in Patients with Multiple Myeloma at Mayo Clinic

Soefje S et al.

EHA 2021;Abstract EP1051.

Clinical Administration Characteristics of Subcutaneous and Intravenous Administration of Daratumumab in Multiple Myeloma Patients at Mayo Clinic

Soefje S et al.

ASH 2021;Abstract 2717.

When you administer daratumumab to patients with MM, do you generally use the subcutaneous formulation?

 Dr Fonseca	Yes	 Dr Lonial	Yes
 Dr Kumar	Yes	 Dr Mikhael	Yes
 Dr Landgren	Yes	 Dr Richardson	Yes

RTP RESEARCH TO PRACTICE

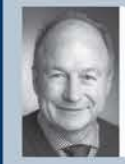
Oncol Ther (2021) 9:69–88
https://doi.org/10.1007/s40487-021-00143-7

REVIEW

Post-Transplant Maintenance Treatment Options in Multiple Myeloma

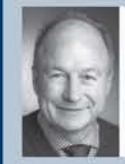
Dhauna Karam · Shaji Kumar

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

 Dr Fonseca	Daratumumab/KRd	 Dr Lonial	KRd
 Dr Kumar	Daratumumab/RVd	 Dr Mikhael	Daratumumab/KRd
 Dr Landgren	Daratumumab/KRd	 Dr Richardson	Daratumumab/KRd

RTP RESEARCH TO PRACTICE

In general, for a patient with standard-risk MM who is receiving maintenance therapy with lenalidomide after autologous stem cell transplant (ASCT), would you offer to discontinue the lenalidomide if a minimal residual disease (MRD) assessment were negative?

 Dr Fonseca	Yes, for select patients	 Dr Lonial	No
 Dr Kumar	Yes, for select patients	 Dr Mikhael	No
 Dr Landgren	No	 Dr Richardson	No

RTP RESEARCH TO PRACTICE

Dr Amany Keruakous
(Augusta, Georgia)

Case Presentation: 60-year-old man with relapsed t(11;14) multiple myeloma and renal failure s/p RVd and ASCT, now on venetoclax/bortezomib/dex

Dr Hans Lee
(Houston, Texas)

Case Presentation: 56-year-old woman with high-risk t(11;14) smoldering multiple myeloma

RTP
RESEARCH
TO PRACTICE

Am J Cancer Res 2022;12(7):2950-2965

Review Article

Multiple myeloma with t(11;14): unique biology and evolving landscape

Susan Bal[1], Shaji K Kumar[2], Rafael Fonseca[3], Francesca Gay[4], Vania TM Hungria[5], Ahmet Dogan[6], Luciano J Costa[1]

Real-World Effectiveness of Bortezomib plus Dexamethasone in Patients with t(11;14) Positive Multiple Myeloma

Emechebe N et al.

ASH 2021;Abstract 4725.

Current Testing Practices for t(11;14) Rearrangements in Patients with Newly Diagnosed Multiple Myeloma in the United States

Baughn LB et al.

ASH 2022;Abstract 4544.

Clinical Genomic Analyses Demonstrate t(11;14) Multiple Myeloma Retains B-Cell Biology and Distinct Mitochondrial Metabolism That Convey Increased Sensitivity to BCL-2 Inhibition by Venetoclax

Sharon D et al.

ASH 2022;Abstract 1847.

REGULAR ARTICLE

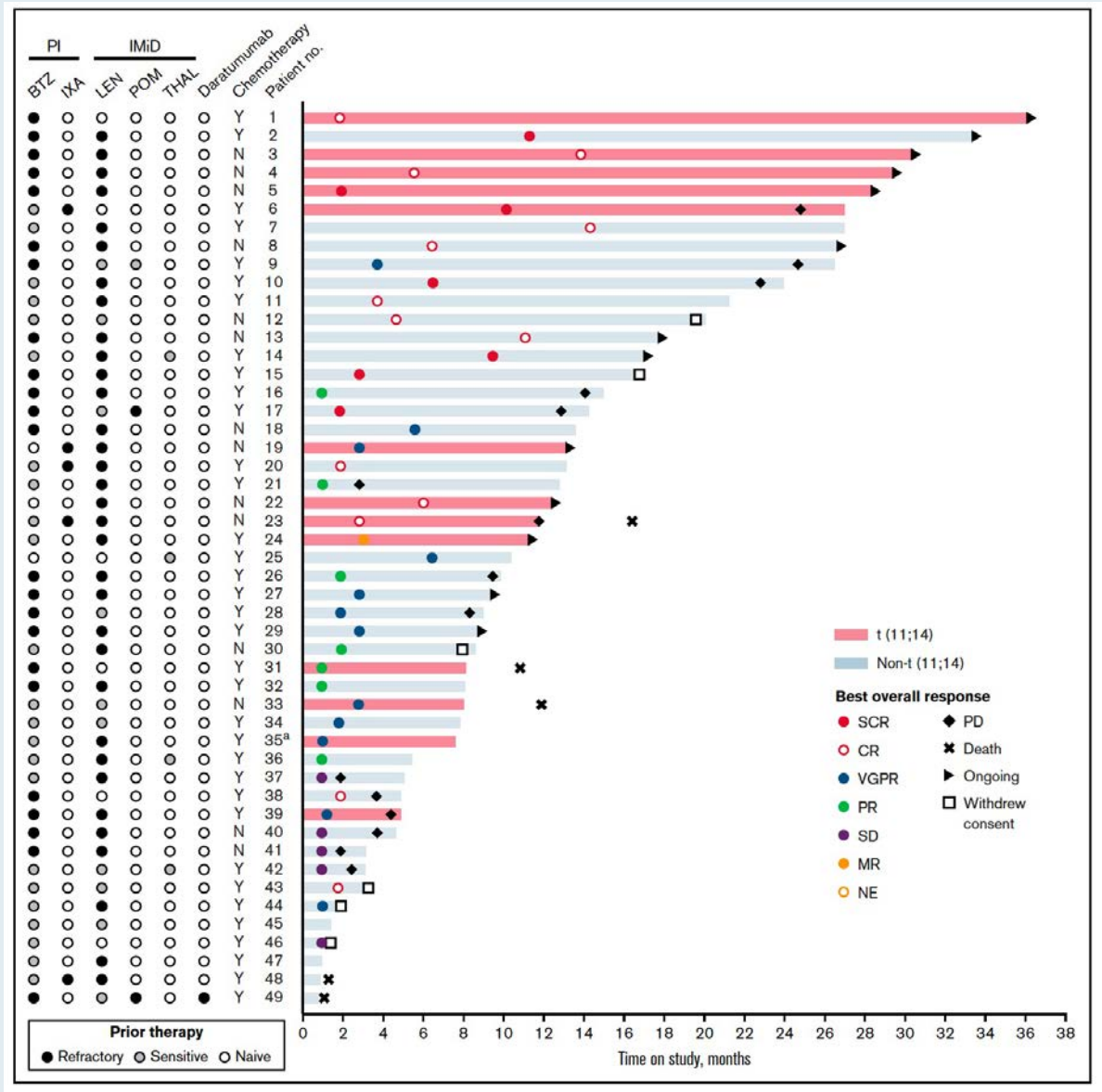
blood advances

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] and Edward A. Stadtmauer[12]

Blood Adv 2021 October 12;5(19):3748-59.

Prior Therapy Status, Best Response and Time in the Study for All Patients



Costa LJ et al. *Blood Adv* 2021 October 12;5(19):3748-59.

Received: 24 January 2021 | Revised: 31 May 2021 | Accepted: 1 June 2021

Am J Hematol 2021 September 1;96(9):1131-6.

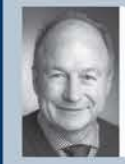
DOI: 10.1002/ajh.26269

RESEARCH ARTICLE

Venetoclax for the treatment of multiple myeloma: Outcomes outside of clinical trials

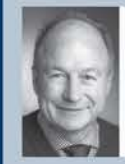
M. Hasib Sidiqi[1] | Abdullah S. Al Saleh[2,3,4] | Shaji K. Kumar[5] | Nelson Leung[5,6] | Dragan Jevremovic[7] | Eli Muchtar[5] | Wilson I. Gonsalves[5] | Taxiarchis V. Kourelis[5] | Rahma Warsame[5] | Francis K. Buadi[5] | Martha Q. Lacy[5] | Robert A. Kyle[5] | Ronald Go[5] | Miriam Hobbs[5] | Angela Dispenzieri[5] | David Dingli[5] | Suzanne R. Hayman[5] | Morie A. Gertz[5] | S. Vincent Rajkumar[5] | Prashant Kapoor[5]

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

 Dr Fonseca	Up front	 Dr Lonial	Second line
 Dr Kumar	Second line	 Dr Mikhael	Third line
 Dr Landgren	Second line	 Dr Richardson	Second line

RTP RESEARCH TO PRACTICE

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

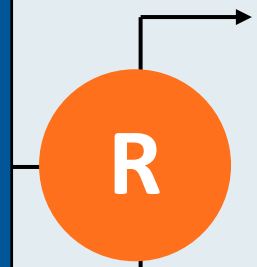
 Dr Fonseca	In combination	 Dr Lonial	In combination, 400 mg
 Dr Kumar	In combination, 200 mg - 400 mg	 Dr Mikhael	In combination
 Dr Landgren	In combination, escalating dose (200 mg → 800 mg)	 Dr Richardson	In combination, 200 mg - 800 mg

RTP RESEARCH TO PRACTICE

Ongoing Phase III M13-494 Study Design

Estimated enrollment (N = 254)

- Relapsed/refractory multiple myeloma
- Translocation 11;14
- At least 2 prior lines of antimyeloma therapy, including anti-CD38 mAb alone or in combination
- At least 2 prior consecutive cycles of lenalidomide
- At least 2 prior consecutive cycles of a proteasome inhibitor



Venetoclax + dexamethasone

Pomalidomide + dexamethasone

Primary endpoint: Progression-free survival

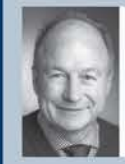
www.clinicaltrials.gov. NCT03539744. Accessed August 2022.

Case Presentation: 77-year-old man with NDMM, transplant-ineligible, who received daratumumab-Rd but discontinued daratumumab due to a severe rash

Dr Yanjun Ma (Murfreesboro, Tennessee)

RTP
RESEARCH
TO PRACTICE

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

 Dr Fonseca	Daratumumab/Rd	 Dr Lonial	Daratumumab/Rd
 Dr Kumar	Daratumumab/Vd	 Dr Mikhael	Daratumumab/Rd
 Dr Landgren	Daratumumab/Rd	 Dr Richardson	Daratumumab/RVd or Daratumumab/RVd lite

Rd = lenalidomide/dexamethasone; Vd = bortezomib/dexamethasone

Case Presentation: 84-year-old man with a prior history of NMIBC, now with multiregimen-refractory multiple myeloma and biochemical disease progression

Dr Spencer Bachow (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

Leukemia 2022 March;36(3):877-80. www.nature.com/leu

LETTER

MULTIPLE MYELOMA, GAMMOPATHIES

Treatment outcomes of triple class refractory multiple myeloma: a benchmark for new therapies

Susan Bal[1]✉, Ehsan Malek[2], Ankit Kansagra[3], Saad Z. Usmani[4], Ravi Vij[5], Kelly N. Godby[1], Robert F. Cornell[6], Yubin Kang[7], Elvira Umyarova[8], Smith Giri[1], Saurabh Chhabra[9], Michaela Liedtke[10], Natalie S. Callander[11], Parameswaran Hari[9], Shaji Kumar[12] and Luciano J. Costa[1]

clinical reviews

Immunotherapy in Multiple Myeloma—Time for a Second Major Paradigm Shift

Meera Mohan, MD, MS[1]; Parameswaran Hari, MD, MS[1]; and Binod Dhakal, MD, MS[1]

JCO Oncol Pract 2021;17(7):405-13.

commentaries

Multiple Myeloma: From Baby Steps to Giant Strides

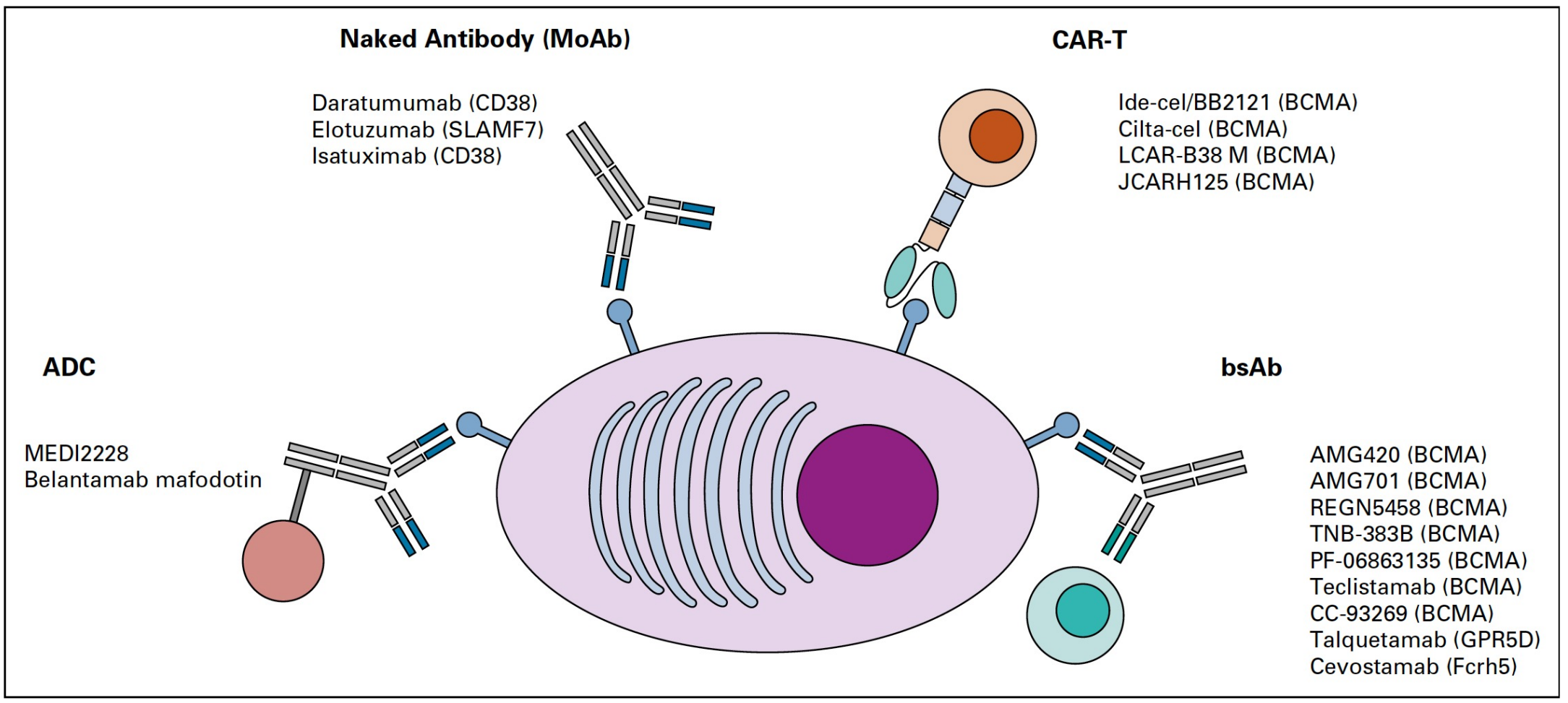
Shaji Kumar, MD[1]

JCO Oncol Pract 2021 July;17(7):419-20.

JC JOURNAL CLUB

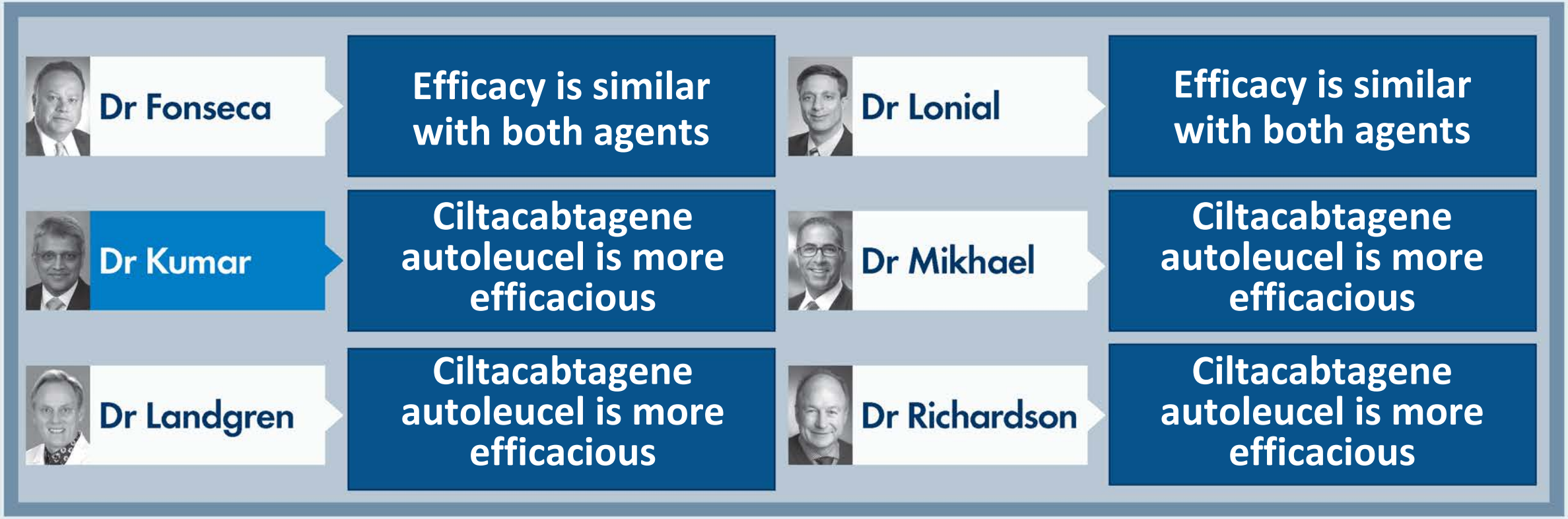
RTP RESEARCH TO PRACTICE

Recent Immunotherapeutic Approaches to Treating Multiple Myeloma

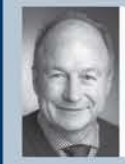


Mohan M et al. *JCO Oncol Pract* 2021;17(7):405-13.

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

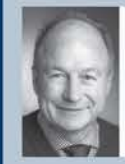


Based on your personal clinical experience and knowledge of available data, how would you compare the tolerability of ciltacabtagene autoleucel to that of idecabtagene vicleucel for patients with R/R MM?

 Dr Fonseca	Tolerability is similar with both agents	 Dr Lonial	Tolerability is similar with both agents
 Dr Kumar	Idecabtagene vicleucel is more tolerable	 Dr Mikhael	Tolerability is similar with both agents
 Dr Landgren	Tolerability is similar with both agents	 Dr Richardson	Idecabtagene vicleucel is more tolerable

RTP RESEARCH TO PRACTICE

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

 Dr Fonseca	At first relapse	 Dr Lonial	At second relapse
 Dr Kumar	At first relapse	 Dr Mikhael	At first relapse
 Dr Landgren	At first relapse	 Dr Richardson	After second relapse and beyond

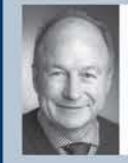
RTP RESEARCH TO PRACTICE

Currently, how available is CAR T-cell therapy commercially for the treatment of R/R MM?

 Dr Fonseca	Very poorly	 Dr Lonial	Manufacturing remains a major roadblock
 Dr Kumar	Limited	 Dr Mikhael	Very limited; not an option for most patients
 Dr Landgren	Way too limited	 Dr Richardson	Waiting list up to 6 months

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside and assuming you had access to CAR T-cell therapies and bispecific antibodies, how would you generally sequence these 2 treatments for a patient with multiregimen-relapsed MM who is eligible to receive CAR T-cell therapy?

 Dr Fonseca	Bispecific antibody → CAR T-cell therapy	 Dr Lonial	CAR T-cell therapy → bispecific antibody
 Dr Kumar	CAR T-cell therapy → bispecific antibody	 Dr Mikhael	CAR T-cell therapy → bispecific antibody
 Dr Landgren	CAR T-cell therapy → bispecific antibody	 Dr Richardson	Bispecific antibody → CAR T-cell therapy

Key Select Ongoing Studies of BCMA-Directed CAR T-Cell Therapy with Idecabtagene Vicleucel (Ide-cel) and Ciltacabtagene Autoleucel (Cilta-cel)

Study	Phase	N	Setting	Treatments
CARTITUDE-4	III	419	Relapsed and lenalidomide-refractory	• Pomalidomide/bortezomib/dexamethasone or daralutamide/pomalidomide/dexamethasone • Cilta-cel
CARTITUDE-5	III	650	NDMM, with no ASCT planned	• VRd → cilta-cel • VRd → lenalidomide/dexamethasone
CARTITUDE-6	III	750	NDMM, ASCT eligible	• DVRd → cilta-cel • DVRd →k ASCT
KarMMa-4	I	13	NDMM, high risk	• Ide-cel → lenalidomide maintenance
KarMMa-2	II	235	RRMM, high risk NDMM	• Ide-cel • Ide-cel + lenalidomide

NDMM = newly diagnosed multiple myeloma; ASCT = autologous stem cell transplant; VRd = bortezomib/lenalidomide/dexamethasone; RRMM = relapsed/refractory multiple myeloma; PI = proteasome inhibitor; IMiD = immunomodulatory drug

www.clinicaltrials.gov. Accessed August 2022.

Topline Results from the KarMMa-3 Trial: Ide-cel Significantly Improves Progression-Free Survival versus Standard Regimens for Relapsed and Refractory Multiple Myeloma

Press Release: August 10, 2022

Positive topline results were announced from KarMMa-3, a Phase III, global, randomized, multicenter, open-label study evaluating idecabtagene vicleucel compared to standard combination regimens for adults with multiple myeloma that is relapsed and refractory after 2 to 4 prior lines of therapy and refractory to the last regimen.

"KarMMa-3 is the first randomized clinical trial to evaluate a CAR T cell therapy in multiple myeloma. Results of a pre-specified interim analysis conducted through an independent review committee showed that KarMMa-3 met its primary endpoint of demonstrating a statistically significant improvement in progression-free survival. Treatment with idecabtagene vicleucel also showed an improvement in the key secondary endpoint of overall response rate compared to standard regimens. Follow-up for overall survival, a key secondary endpoint, remains ongoing.

Safety results in the trial were consistent with the well-established and predictable safety profile of idecabtagene vicleucel previously demonstrated in the pivotal KarMMa trial. No new safety signals were reported in this study."

https://news.bms.com/news/corporate-financial/2022/Bristol-Myers-Squibb-and-2seventy-bio-Announce-Topline-Results-from-KarMMa-3-Trial-Showing-Abecma-idecabtagene-vicleucel-Significantly-Improves-Progression-Free-Survival-Versus-Standard-Regimens-in-Relapsed-and-Refractory-Multiple-Myeloma/default.aspx

RTP RESEARCH TO PRACTICE

BCMA x CD3 Bispecific Antibodies: Summary

Therapy	Characteristics	N	Population	Safety	Response
Teclistamab[1]	▪ Bispecific ▪ IV/SC (RP2D: 1500 µg/kg SC) ▪ Weekly and every other week in f/u	157	▪ At SC cohorts: ▪ Median of 5PL ▪ 79% triple refractory ▪ 38% penta refractory	▪ At RP2D: ▪ CRS 70% G1-2 ▪ Neurotox 1% (G1) ▪ Infections 50%	At RP2D, ORR: 65% with 40% sCR/CR
AMG 701[2]	▪ BiTE modified ▪ IV ▪ Weekly	82	▪ Median of 6PL ▪ 62% triple refractory	▪ CRS 55%, G3-4: 9% ▪ No ICANS ▪ 20% cytopenias	83% ORR at the top dose level and 50% VGPR
REGN5458[3]	▪ Bispecific ▪ IV ▪ Weekly and every other week C4→	49	▪ Median of 5PL ▪ 100% triple refractory ▪ 57% penta refractory	▪ CRS 39%, no G3-4 ▪ ICANS 12% ▪ Cytopenias 47% and infections 18%	62.5% at 96 mg and 95% of responders were VGPR. Some CR in lower dose levels
TNB-383B[4]	▪ Triple chain anti-BCMA bispecific ▪ IV fixed doses ▪ Every 3 weeks	58	▪ Median of 6PL ▪ 64% triple refractory ▪ 34% penta refractory	▪ CRS 45% and no G3-4 ▪ No ICANS ▪ Cytopenias 21% and infections 14%	80% (13% CR) at the dose levels 40-60 mg
Elranatamab (PF-3135[5])	▪ Bispecific ▪ SC and weekly ▪ RP2D: 1000 µg/kg	30	▪ Median of 8PL ▪ 87% triple refractory ▪ 23% prior BCMA-based therapy	▪ CRS 73% and no G3-4 ▪ ICANS 20% ▪ ISR 50%	83% ORR at RP2D

1. Usmani SZ et al. *Lancet* 2021. 2. Harrison SJ et al. ASH 2020;Abstract 181. 3. Madduri D et al. ASH 2020;Abstract 291.
4. Rodriguez C et al. ASH 2020;Abstract 293.5. Bahlis NJ et al. ASCO 2021;Abstract 8006.

Content courtesy of Noopur Raje, MD

ASCO 2022;Abstract 8007.

Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Results From MajesTEC-1

Ajay K Nooka (anooka@emory.edu)[1], Philippe Moreau[2], Saad Z Usmani[3], Alfred L Garfall[4], Niels WCJ van de Donk[5], Jesús San-Miguel[6], Albert Oriol[7], Ajai Chari[8], Lionel Karlin[9], Maria-Victoria Mateos[10], Rakesh Popat[11], Joaquín Martínez-López[12], Surbhi Sidana[13], Danielle Trancucci[14], Raluca Verona[15], Suzette Girgis[15], Clarissa Uhlar[15], Tara Stephenson[15], Arnob Banerjee[15], Amrita Krishnan[16]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]University Hospital Hôtel-Dieu, Nantes, France; [3]Memorial Sloan Kettering Cancer Cent NY, USA; [4]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Amsterdam University Medical Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [6]University of Navarra, Pamplona, Spain; [7]Hospital Germans Trias I Pu Spain; [8]Mount Sinai School of Medicine, New York, NY, USA; [9]Centre Hospitalier Lyon Sud, France; [10]University Hospital of Salamanca/IBSAL/CIC, Salar [11]University College London Hospitals, NHS Foundation Trust, London, UK; [12]Hematología Hospital 12 de Octubre, Madrid, Spain; [13]Stanford Universit Medicine, Stanford, CA, USA; [14]Janssen Research & Development, Raritan, NJ, USA; [15]Janssen Research & Development, Spring House, PA, USA; [16]City Comprehensive Cancer Center, Duarte, CA, USA

Presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL

N Engl J Med 2022 June 5;[Online ahead of print].

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

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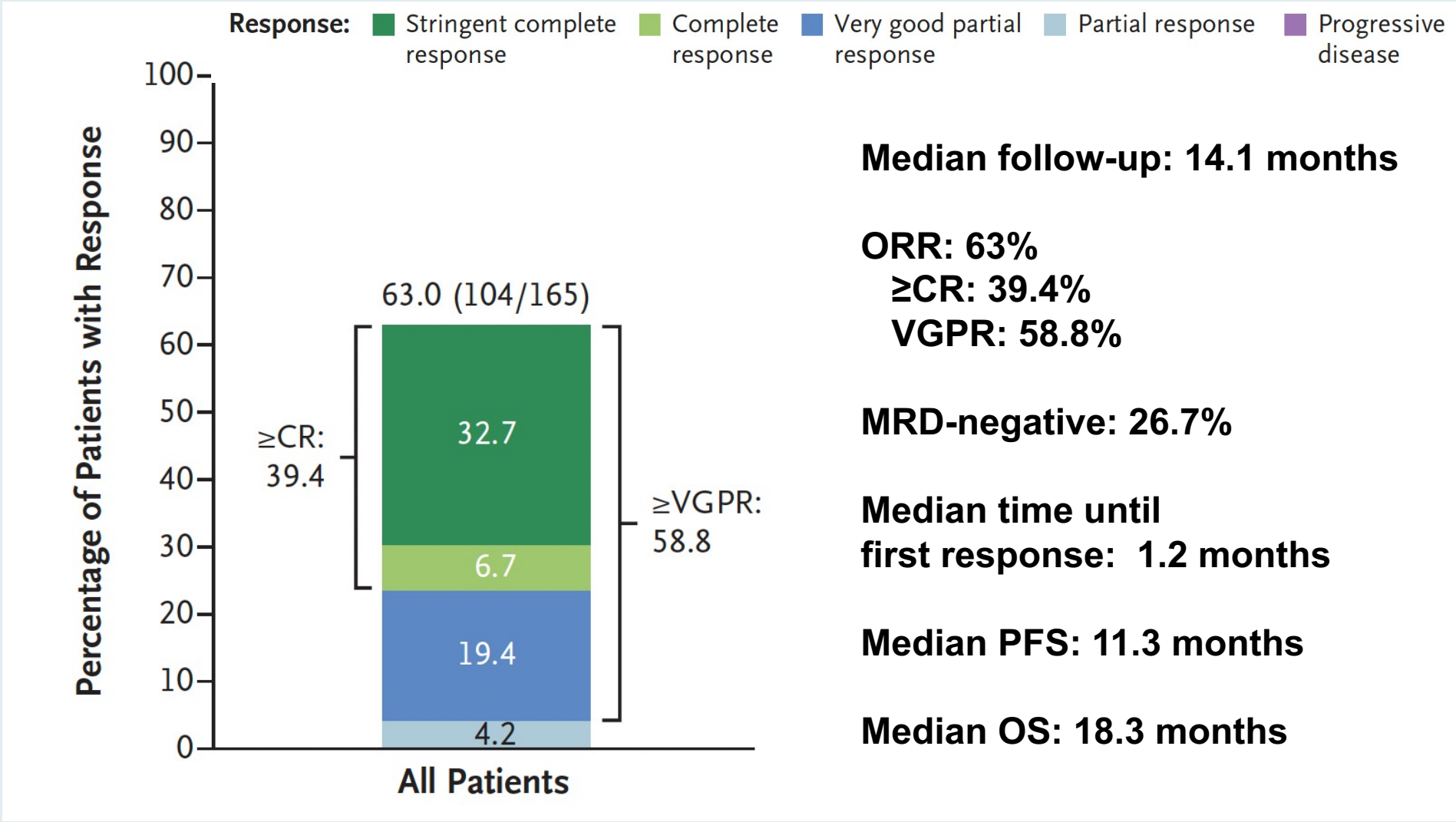
MajesTEC-1: Response and Survival



Median follow-up: 14.1 months

ORR: 63%
≥CR: 39.4%
VGPR: 58.8%

MRD-negative: 26.7%

Median time until first response: 1.2 months

Median PFS: 11.3 months

Median OS: 18.3 months

Moreau P et al. *N Engl J Med* 2022 June 5;[Online ahead of print].

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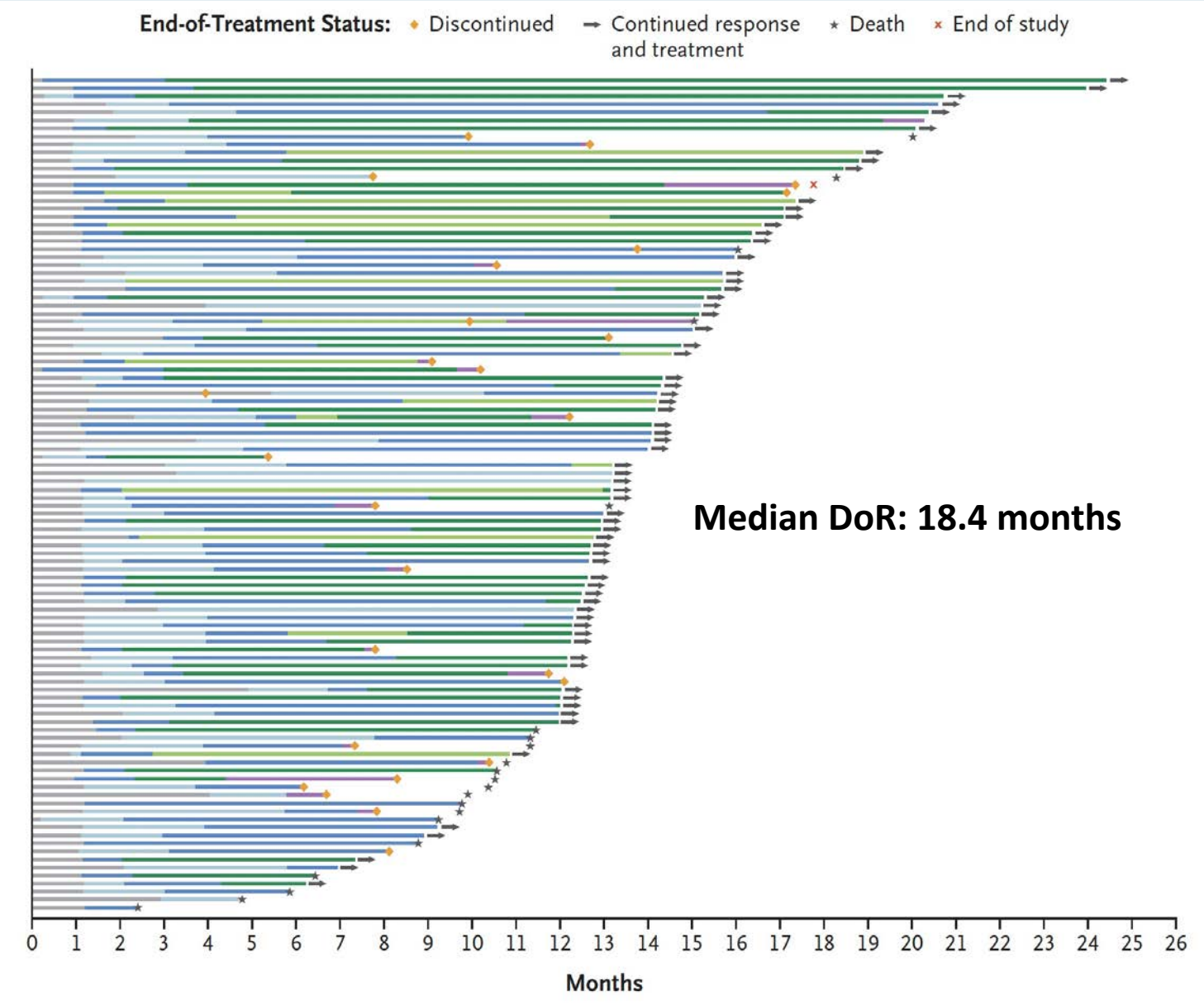
MajesTEC-1: Duration of Response (DoR)



Moreau P et al. *N Engl J Med* 2022 June 5;[Online ahead of print].

MajesTEC-1: Adverse Events

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Nonhematologic		
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

Moreau P et al. *N Engl J Med* 2022 June 5;[Online ahead of print].

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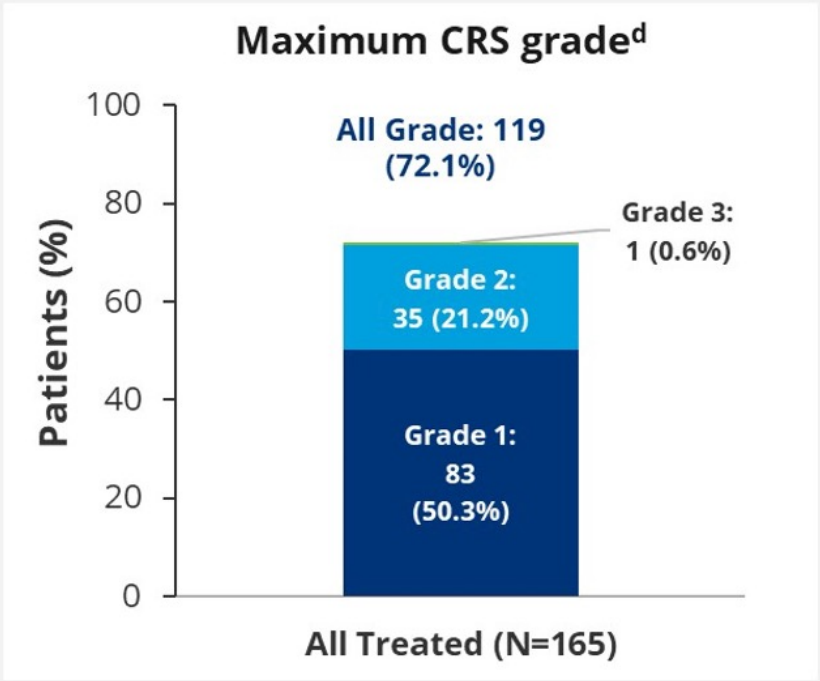
MajesTEC-1: Cytokine Release Syndrome

Parameter	N=165
Patients with CRS, n (%)	119 (72.1)
Patients with ≥2 CRS events	55 (33.3)
Time to onset[a] (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Received supportive measures[a] for CRS, n (%)	110 (66.7)
Tocilizumab[b]	60 (36.4)
Low-flow oxygen by nasal cannula[c]	21 (12.7)
Corticosteroids	14 (8.5)
Single vasopressor	1 (0.6)



- Most CRS events were confined to step-up and first full treatment doses
- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that occurred in the context of concurrent pneumonia (resolved in 2 days)
- All CRS events fully resolved without treatment discontinuation or dose reduction

Nooka AK et al. ASCO 2022;Abstract 8007.

MajesTEC-1: Neurotoxic Events

Parameter	N=165
Neurotoxic event[a], n (%)	**24 (14.5)**
Headache	**14 (8.5)**
ICANS[b]	**5 (3.0)**
Dysgeusia	**2 (1.2)**
Lethargy	**2 (1.2)**
Tremor	**2 (1.2)**
Grade ≥3 events, n (%)	**1 (0.6)**
Time to onset, median (range) days	**3.0 (1–13)**
Duration, median (range) days	**7.0 (1–291)**
Received supportive measures for neurotoxic events[c], n (%)	**14 (8.5)**
Tocilizumab	**3 (1.8)**
Dexamethasone	**3 (1.8)**
Levetiracetam	**2 (1.2)**
Gabapentin	**1 (0.6)**

- The overall incidence of neurotoxic events was low
- All neurotoxic events were grade 1/2, except for 1 grade 4 seizure (in the context of bacterial meningitis during cycle 7)
- 5 patients (3.0%) had a total of 9 ICANS events
  - 7 events were concurrent with CRS
  - All ICANS events were grade 1/2 and fully resolved
- There were no treatment discontinuations or dose reductions due to neurotoxic events, including ICANS

Nooka AK et al. ASCO 2022;Abstract 8007.

Teclistamab in Combination With Subcutaneous Daratumumab and Lenalidomide in Patients With Multiple Myeloma: Results From One Cohort of MajesTEC-2, a Phase 1b, Multicohort Study

Emma Searle[1], Hang Quach[2], Sandy W Wong[3], Luciano J Costa[4], Cyrille Hulin[5], Wojciech Janowski[6], Jesus Berdeja[7], Sébastien Anguille[8], Jeffrey V Matous[7,9], Cyrille Touzeau[10], Anne-Sophie Michallet[11], Marla Husnik[12], Deeksha Vishwamitra[13], Zhuolu Niu[14], Julie Larsen[15], Lingling Chen[13], Jenna D Goldberg[16], Rakesh Popat[17], Andrew Spencer[18]

[1]The University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; [2]University of Melbourne, St. Vincent's Hospital, Melbourne, VIC, Australia; [3]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]University of Alabama at Birmingham, Birmingham, AL, USA; [5]Hôpital Haut Leveque, University Hospital, Pessac, France; [6]Calvary Mater Newcastle, Waratah, New South Wales, Australia; [7]Sarah Cannon Research Institute, Nashville, TN, USA; [8]Vaccine and Infectious Disease Institute, University of Antwerp, Edegem, Belgium, Center for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, Edegem, Belgium; [9]Colorado Blood Cancer Institute, Denver, CO, USA; [10]Centre Hospitalier Universitaire de Nantes, Nantes, France; [11]Centre Hospitalier Lyon Sud, Hospices Civils, Pierre Bénite, France; [12]Janssen Research & Development, San Diego, CA, USA; [13]Janssen Research & Development, Spring House, PA, USA; [14]Janssen Research & Development, Shanghai, China; [15]Janssen Research & Development, Los Angeles, CA, USA; [16]Janssen Research & Development, Raritan, NJ, USA; [17]University College London Hospitals, NHS Foundation Trust, London, UK; [18]Monash University, Melbourne, VIC, Australia

ASH 2022;Abstract 160.

Presented at the 64th American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA, USA.

MajesTEC-2 Phase Ib Multicohort Study

Key eligibility criteria
- Measurable MM
- 1–3 prior lines of therapy, including an IMiD and a PI

Primary endpoints
- Safety[a]
- Dose-limiting toxicities

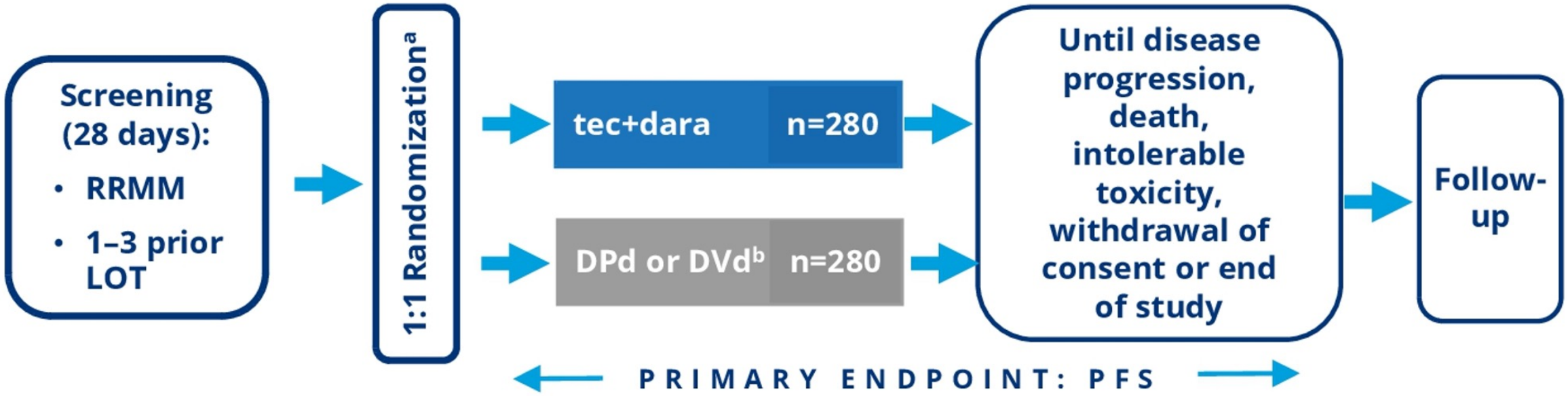
Key secondary endpoints
- ORR[b]
- Rate of ≥VGPR and ≥CR[b]
- Duration of response
- Time to response

Tec-Dara-Len Dosing Schedule:

Tec	Dara	Len
Following step-up dosing 0.72 mg/kg or 1.5 mg/kg SC QW, with transition to 3 mg/kg SC Q2W starting at cycle 3	1800 mg SC (per approved schedule) Cycles 1–2: QW Cycles 3–6: Q2W Cycles 7+: Q4W	25 mg PO daily for 21 days of a 28-day cycle, starting at cycle 2 Cycles 2–4: dexamethasone 40 mg PO given QW

Searle E et al. ASH 2022;Abstract 160.

MajesTEC-3 Ongoing Phase III Study Design



Key Eligibility Criteria:

- Received 1-3 prior lines of therapy, including PI and lenalidomide
  - Patients with only 1 prior line of therpay must be lenalidomide-refractory
- No prior BCMA-directed therapy and/or not refractory to anti-CD38 mAb

Mateos MV et al. ASCO 2022;Abstract TPS8072.

Novel Non-BCMA Bispecific Antibodies: Summary

Therapy	Characteristics	N	Population	Safety	Response
Talquetamab[1]	▪ G protein-coupled receptor family C group 5 member D (GPRC5D) x CD3 bispecific antibody ▪ IV or SC admin	184, 30 at RP2D (405 µg/kg)	▪ Median of 6PL (6PL at RP2D) ▪ 76% triple refractory ▪ 28% penta refractory	▪ Infections in 37% of SC and RP2D patients; G3-4 3% at RP2D ▪ Neurotoxicity in 4 SC patients; 2 (7%) at RP2D ▪ CRS 73%, G3-4 2% at RP2D	At RP2D: 70% ORR with ≥ VGPR 60%
Cevostamab (BFCR4350A)[2]	▪ FcRH5/CD3 bispecific T-cell engager ▪ Q3W IV infusions	53	▪ Median of 6PL ▪ 72% triple refractory ▪ 45% penta refractory	▪ Thrombocytopenia 32%, G3-4 25% ▪ CRS 76%, G3-4 2% ▪ Neurotoxicity 28%, no G3-4	ORR in ≥3.6/20-mg cohorts: 53% (18/34) in all pts 63% (5/8) in pts with prior anti-BCMA

1. Berdeja JG et al. ASCO 2021;Abstract 8008. 2. Cohen A et al. ASH 2020;Abstract 292.

Content courtesy of Noopur Raje, MD

FDA Grants Breakthrough Therapy Designation to Talquetamab for Relapsed/Refractory Multiple Myeloma

Press Release: June 29, 2022

"Talquetamab was granted breakthrough therapy designation by the FDA for the treatment of patients with relapsed/refractory multiple myeloma who were treated with a minimum of 4 previous lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody.

The designation is supported by findings from the phase 1/2 MonumenTAL-1 trial (NCT03399799; NCT04634552), which assessed the agent in patients with relapsed/refractory disease. Data from the study, which were presented at the 2022 American Society of Clinical Oncology Annual Meeting, indicated that patients who were treated with 405 µg/kg of talquetamab (n = 30) experienced an overall response rate (ORR) of 70.0%, including a very good partial response (VGPR) rate or better of 56.7%. Additionally, the ORR among patients treated at the 800 µg/kg dose was 63.6%, including a VGPR or better of 56.8%. Moreover, the stringent complete response (CR) rates were 23.3% and 9.1%, CR rates were 6.7% and 11.4%, the VGPR rates were 26.7% and 36.4%, and PR rates were 13.3% and 6.8% in each respective arm.

Talquetamab is an off-the-shelf T-cell–redirecting bispecific antibody that targets GPRC5D on myeloma cells and CD3 on T cells."

https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-to-talquentamab-for-relapsed-refractory-multiple-myeloma

RTP RESEARCH TO PRACTICE

ASH 2022;Abstract 157.

Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Phase 1/2 Results From MonumenTAL-1

Ajai Chari[1], Cyrille Touzeau[2], Carolina Schinke[3], Monique C Minnema[4], Jesus G Berdeja[5], Albert Oriol[6], Niels WCJ van de Donk[7], Paula Rodriguez-Otero[8], Elham Askari[9], María-Victoria Mateos[10], Luciano J Costa[11], Jo Caers[12], Leo Rasche[13], Amrita Krishnan[14], Deeksha Vishwamitra[15], Xuewen Ma[15], Xiang Qin[15], Katharine S Gries[16], Michela Campagna[17], Tara Masterson[15], Brandi Hilder[15], Jaszianne Tolbert[15], Thomas Renaud[18], Jenna D Goldberg[18], Christoph Heuck[15], Jesús San-Miguel[8], Philippe Moreau[19]

[1]Mount Sinai School of Medicine, New York, NY, USA; [2]Centre Hospitalier Universitaire de Nantes, Nantes, France; [3]Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [4]University Medical Center Utrecht, Utrecht, Netherlands; [5]Sarah Cannon Research Institute, Nashville, TN, USA; [6]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias I Pujol, Badalona, Barcelona, Spain; [7]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [8]University of Navarra, Pamplona, Spain; [9]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [10]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [11]University of Alabama at Birmingham, Birmingham, AL, USA; [12]University of Liège, Liège, Belgium; [13]University Hospital of Würzburg, Würzburg, Germany; [14]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [15]Janssen Research & Development, Spring House, PA, USA; [16]Janssen Global Services, Raritan, NJ, USA; [17]Janssen-Cilag, Madrid, Spain; [18]Janssen Research & Development, Raritan, NJ, USA; [19]University Hospital Hotel-Dieu, Nantes, France

Presented at the 64th American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA, USA.

https://www.congresshub.com/Oncology/ASH2022/Talquetamab/Chari

MonumenTAL-1 Phase I/II Study Design

Key objectives

- Describe the efficacy and safety at the RP2Ds

Key eligibility criteria

- Adults with measurable MM
- Phase 1: Progression on or intolerance to all established therapies, ECOG PS 0–1
- Phase 2: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody, ECOG PS 0–2

RP2D 0.4 mg/kg QW SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=21] + Phase 2 [n=122]: N=143)

RP2D 0.8 mg/kg Q2W SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

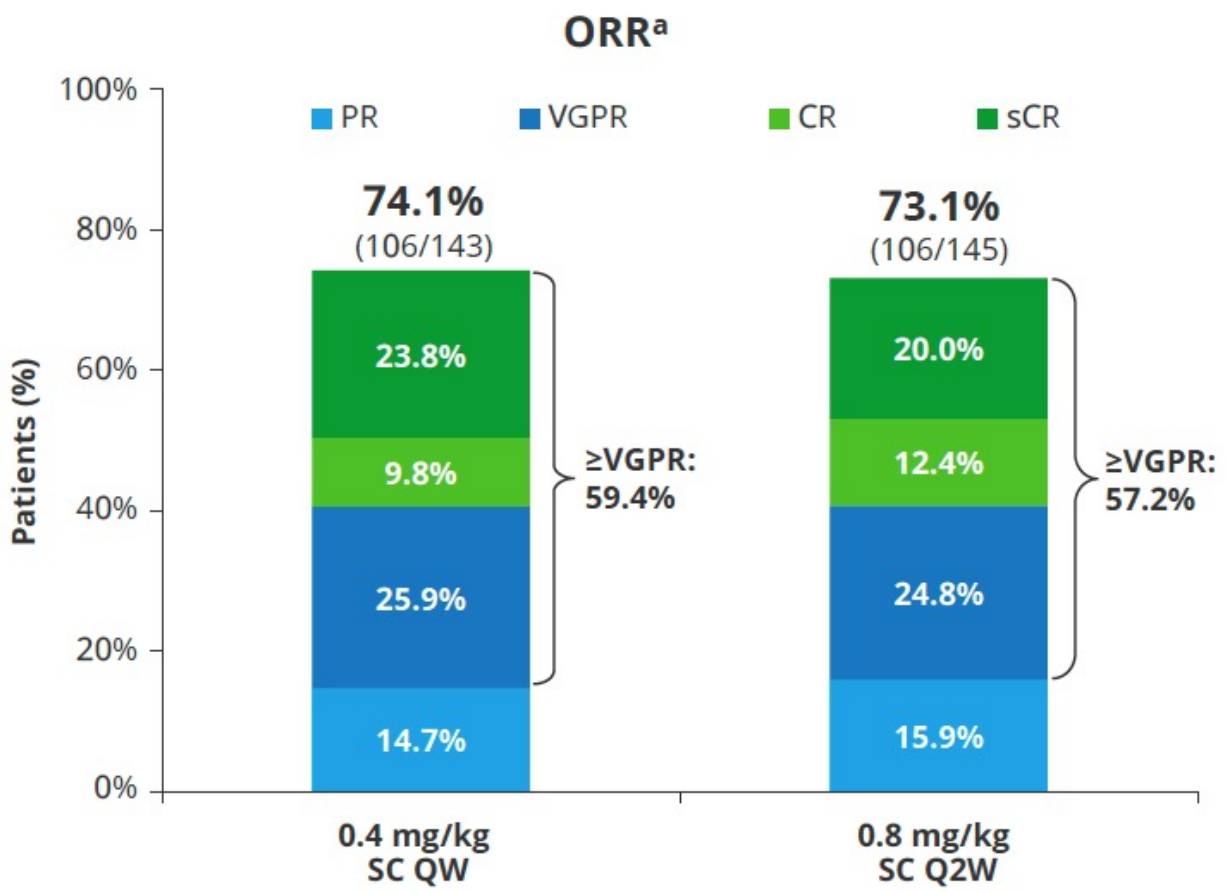
(Phase 1 [n=36] + Phase 2 [n=109]: N=145)

Prior T-cell redirection (QW and Q2W)
Previously exposed to T-cell redirection therapies
Dosed with either 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC

(Phase 1 [n=17] + Phase 2 [n=34]: N=51)

Chari A et al. ASH 2022;Abstract 157.

MonumenTAL-1: Overall Response Rate with Talquetamab



- ORR was similar for QW and Q2W schedules
  - **Triple-class refractory: 72.6%** (95% CI, 63.1–80.9) and **71.0%** (95% CI, 61.1–79.6)
  - **Penta-drug refractory: 71.4%** (95% CI, 55.4–84.3) and **70.6%** (95% CI, 52.5–84.9)
  - ORR was consistent across subgroups including baseline ISS stage III disease, baseline cytogenetic risk, number of prior therapies, refractoriness to prior therapy, and belantamab exposure, except among patients with baseline plasmacytomas

Timing, months	0.4 mg/kg SC QW n=143	0.8 mg/kg SC Q2W n=145
Median (range) follow-up, efficacy	14.9 (0.5[b]–29.0)	8.6 (0.2[b]–22.5)
Median (range) time to first response[c]	1.2 (0.2–10.9)	1.3 (0.2–9.2)
Median (range) time to best response[c]	2.2 (0.8–12.7)	2.7 (0.3–12.5)

Chari A et al. ASH 2022;Abstract 157.

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MonumenTAL-1: Nonhematologic Adverse Events (AEs) with Talquetamab

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
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)

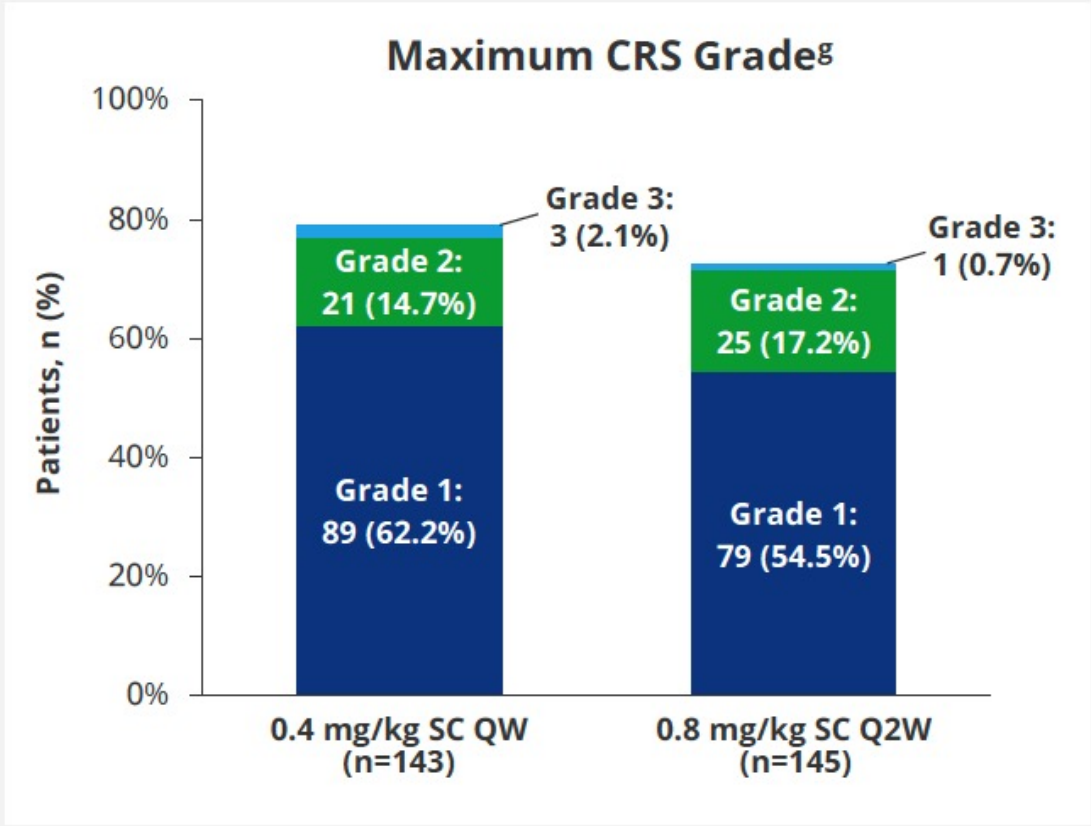
- **Low rates of grade 3/4 nonhematologic AEs** were observed
- **Low rates of discontinuation due to AEs** were observed with QW (4.9%) and Q2W (6.2%) schedules
- **Most common AEs were CRS, skin-related events, nail-related events, and dysgeusia**
  - Rates of high-grade skin, nail, and rash-related events were low
  - Dysgeusia was managed with supportive care, and at times with dose reduction
- At 0.4 mg/kg QW and at 0.8 mg/kg Q2W,
  - 8.4% and 13.8% had dose delays due to AEs
  - 14.7% and 6.2% had dose reductions due to AEs
- At time of data cut-off, no patients in these cohorts died due to drug-related AEs

Chari A et al. ASH 2022;Abstract 157.

RTP RESEARCH TO PRACTICE

MonumenTAL-1: Cytokine Release Syndrome (CRS) with Talquetamab

Parameter	0.4 mg/kg SC QW[a] (n=143)	0.8 mg/kg SC Q2W[a] (n=145)
Patients with CRS, n (%)	113 (79.0)	105 (72.4)
Time to onset (days),[b] median (range)	2.0 (1–8)	2.0 (1–8)
Duration (days), median (range)	2 (1–13)	2 (1–29)
Patients with CRS up to 1st full dose, n (%)		
1st step-up dose	48 (34)	38 (26)
2nd step-up dose	70 (49)	58 (40)[c]
1st full dose	38 (27)	19 (13)
Patients with CRS after 1st full dose,[d] n (%)	19 (13.3)	13 (9.0)
Patients who received supportive measures,[e] n (%)	106 (74.1)	100 (69.0)
Tocilizumab[f]	50 (35.0)	53 (36.6)
Steroids	5 (3.5)	4 (2.8)
Oxygen	8 (5.6)	10 (6.9)
Vasopressor	2 (1.4)	1 (0.7)
Patients with >1 CRS event, n (%)	46 (32.2)	46 (31.7)



- Most CRS events were grade 1/2 and largely confined to the step-up doses and first full dose

Chari A et al. ASH 2022;Abstract 157.

Dr Vignesh Narayanan
(Lone Tree, Colorado)

Questions and Comments: Use of selinexor in relapsed disease

Dr Joseph Mikhael
(Phoenix, Arizona)

Questions and Comments: Choice of agent(s) to combine with selinexor

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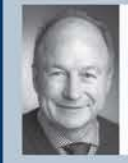
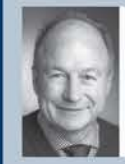
RESEARCH
TO PRACTICE

For a patient with R/R MM who is ineligible for CAR T-cell therapy because of age or performance status and whose disease is refractory to anti-CD38 antibodies, proteasome inhibitors and immunomodulatory drugs (IMiDs), how do you generally sequence belantamab mafodotin and selinexor?

 Dr Fonseca	Selinexor → belantamab mafodotin	 Dr Lonial	Belantamab mafodotin → selinexor
 Dr Kumar	Belantamab mafodotin → selinexor	 Dr Mikhael	Selinexor → belantamab mafodotin
 Dr Landgren	Selinexor → belantamab mafodotin	 Dr Richardson	Selinexor → belantamab mafodotin

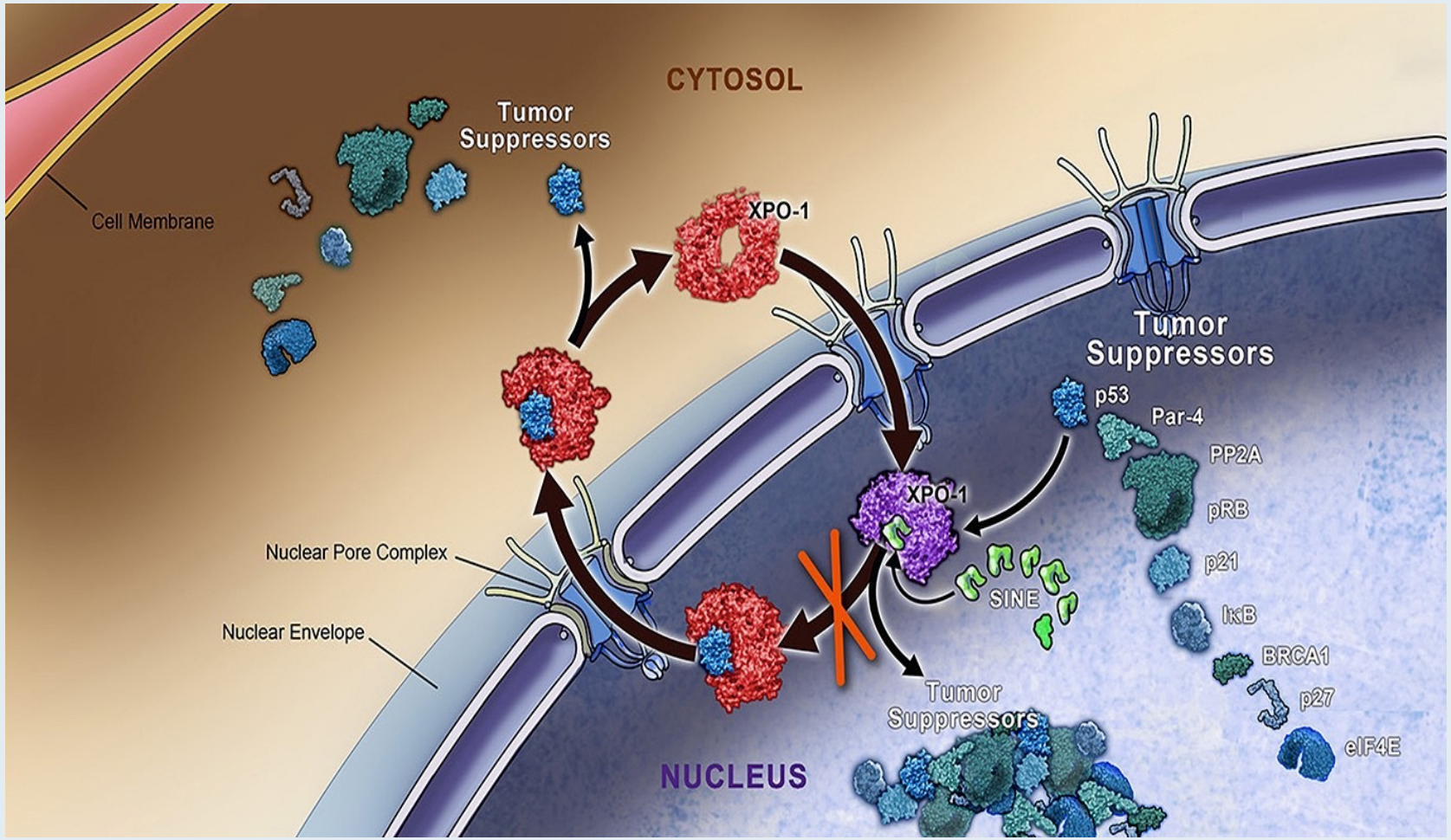
RTP RESEARCH TO PRACTICE

In general, how would you prefer to administer selinexor in the treatment of R/R MM?

 Dr Fonseca	Once a week, usually with carfilzomib	 Dr Lonial	Once a week with bort/dex
 Dr Kumar	Once a week with bort/dex	 Dr Mikhael	Once weekly with carfilzomib/dex
 Dr Landgren	Once a week with bort/dex	 Dr Richardson	Once a week with bort/dex or carfilzomib/dex

Bort/dex = bortezomib/dexamethasone

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, Bcl-2, 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.

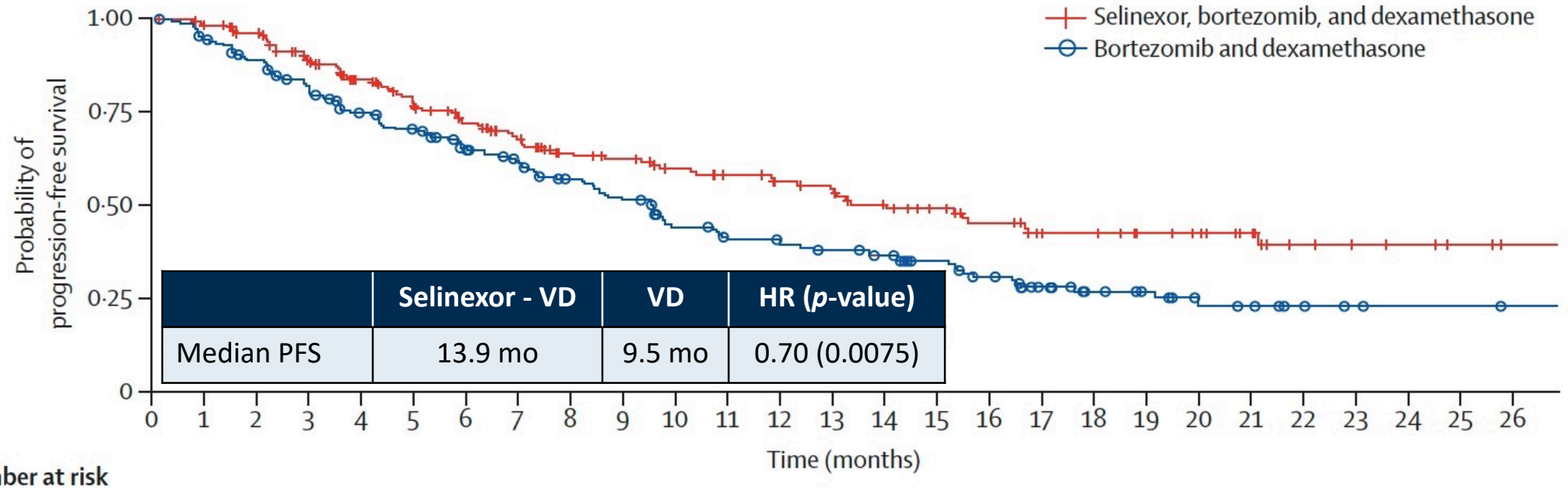
RTP RESEARCH TO PRACTICE

Lancet 2020;396(10262):1563-73.

Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial

Sebastian Grosicki, Maryana Simonova, Ivan Spicka, Ludek Pour, Iryrna Kriachok, Maria Gavriatopoulou, Halyna Pylypenko, Holger W Auner, Xavier Leleu, Vadim Doronin, Ganna Usenko, Nizar J Bahlis, Roman Hajek, Reuben Benjamin, Tuphan K Dolai, Dinesh K Sinha, Christopher P Venner, Mamta Garg, Mercedes Gironella, Artur Jurczyszyn, Pawel Robak, Monica Galli, Craig Wallington-Beddoe, Atanas Radinoff, Galina Salogub, Don A Stevens, Supratik Basu, Anna M Liberati, Hang Quach, Vesselina S Goranova-Marinova, Jelena Bila, Eirini Katodritou, Hanna Oliynyk, Sybiryna Korenkova, Jeevan Kumar, Sundar Jagannath, Phillipe Moreau, Moshe Levy, Darrell White, Moshe E Gatt, Thierry Facon, Maria V Mateos, Michele Cavo, Donna Reece, Larry D Anderson Jr, Jean-Richard Saint-Martin, Jacqueline Jeha, Anita A Joshi, Yi Chai, Lingling Li, Vishnuvardhan Peddagali, Melina Arazy, Jatin Shah, Sharon Shacham, Michael G Kauffman, Meletios A Dimopoulos, Paul G Richardson, Sosana Delimpasi**

BOSTON: Progression-Free Survival (ITT)



	Selinexor - VD	VD	HR (*p*-value)
Median PFS	13.9 mo	9.5 mo	0.70 (0.0075)

Number at risk (number censored)

Selinexor, bortezomib, and dexamethasone	195 (0)	187 (5)	175 (12)	152 (21)	135 (31)	117 (37)	106 (42)	89 (50)	79 (57)	76 (59)	69 (63)	64 (66)	57 (71)	51 (73)	45 (76)	41 (80)	35 (83)	27 (89)	26 (90)	22 (94)	19 (97)	14 (102)	9 (106)	7 (108)	6 (109)	4 (111)	2 (113)
Bortezomib and dexamethasone	207 (0)	187 (8)	175 (10)	152 (15)	138 (20)	127 (22)	111 (29)	100 (32)	90 (37)	81 (37)	66 (41)	59 (43)	56 (44)	53 (45)	49 (47)	42 (52)	35 (55)	26 (60)	20 (65)	16 (69)	10 (73)	8 (75)	5 (78)	4 (79)	3 (80)	3 (80)	2 (81)

VD = bortezomib and low-dose dexamethasone

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

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BOSTON: Response

Response	Selinexor + VD (n = 195)	VD (n = 207)
Overall response rate	76.4%	62.3%
Best overall response		
Stringent complete response	10%	6%
Complete response	7%	4%
Very good partial response	28%	22%
Partial response	32%	30%
Minimal response	8%	10%
Stable disease	13%	19%
Progressive disease	1%	5%
Nonevaluable	2%	4%
Minimal residual disease-negative	5%	4%

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

BOSTON: Select Adverse Events

Adverse event	Selinexor + bort/dex (n = 195)		Bort/dex (n = 204)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	60%	39%	27%	17%
Fatigue	42%	13%	18%	1%
Anemia	36%	16%	23%	10%
Peripheral neuropathy	32%	5%	47%	9%
Neutropenia	15%	9%	6%	3%
Treatment discontinuation due to TEAEs	21%		16%	

TEAEs = treatment emergent adverse events

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

Case Presentation: 57-year-old man with multiple comorbidities diagnosed with standard-risk multiple myeloma who receives induction RVd → maintenance bortezomib and develops chalazion ocular toxicity

Dr Jennifer Dallas (Charlotte, North Carolina)

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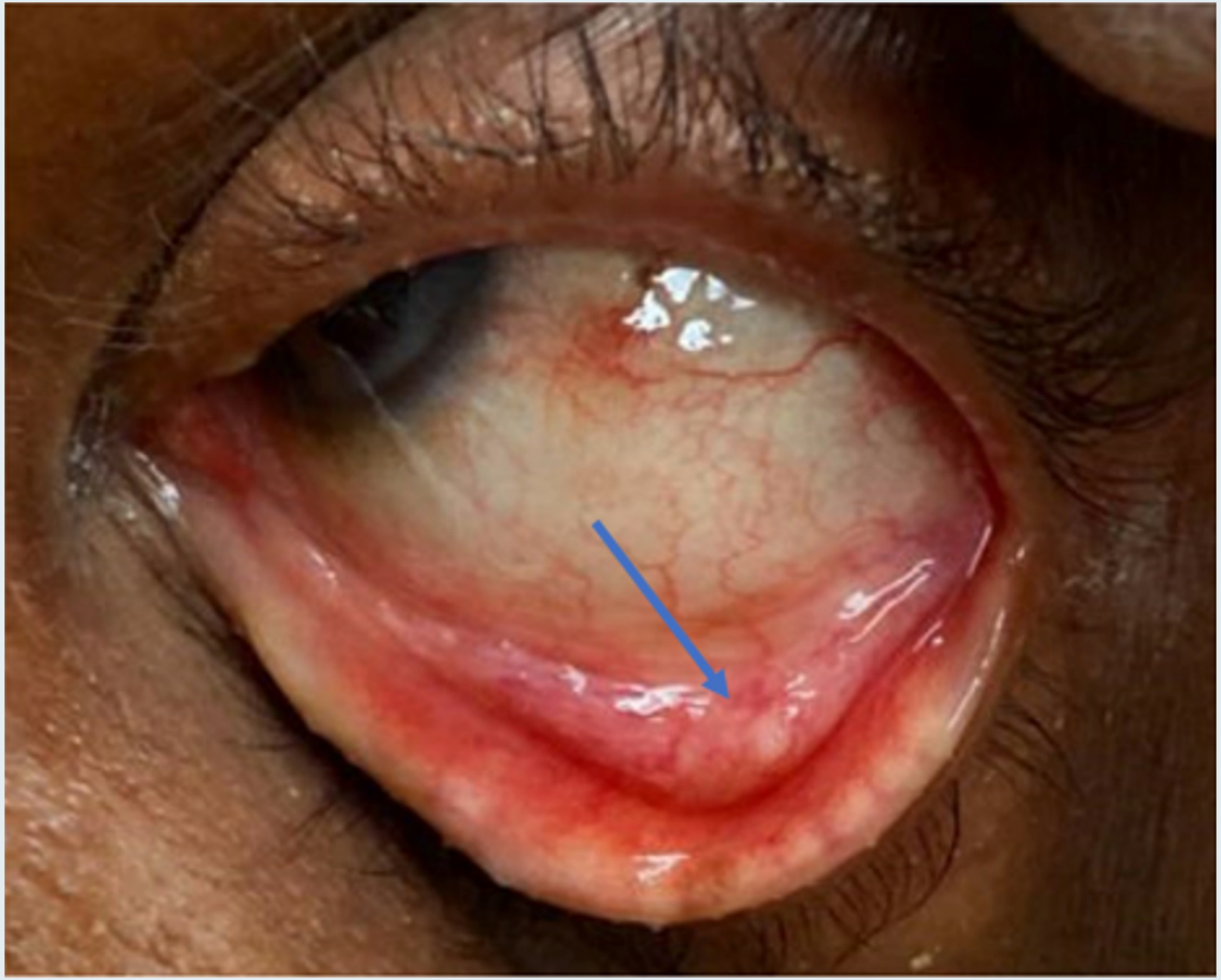

Meet The Professor with Dr Kumar

INTRODUCTION

MODULE 1: Case Presentations

MODULE 2: Journal Club with Dr Kumar

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2021 September 29;11(9):161.

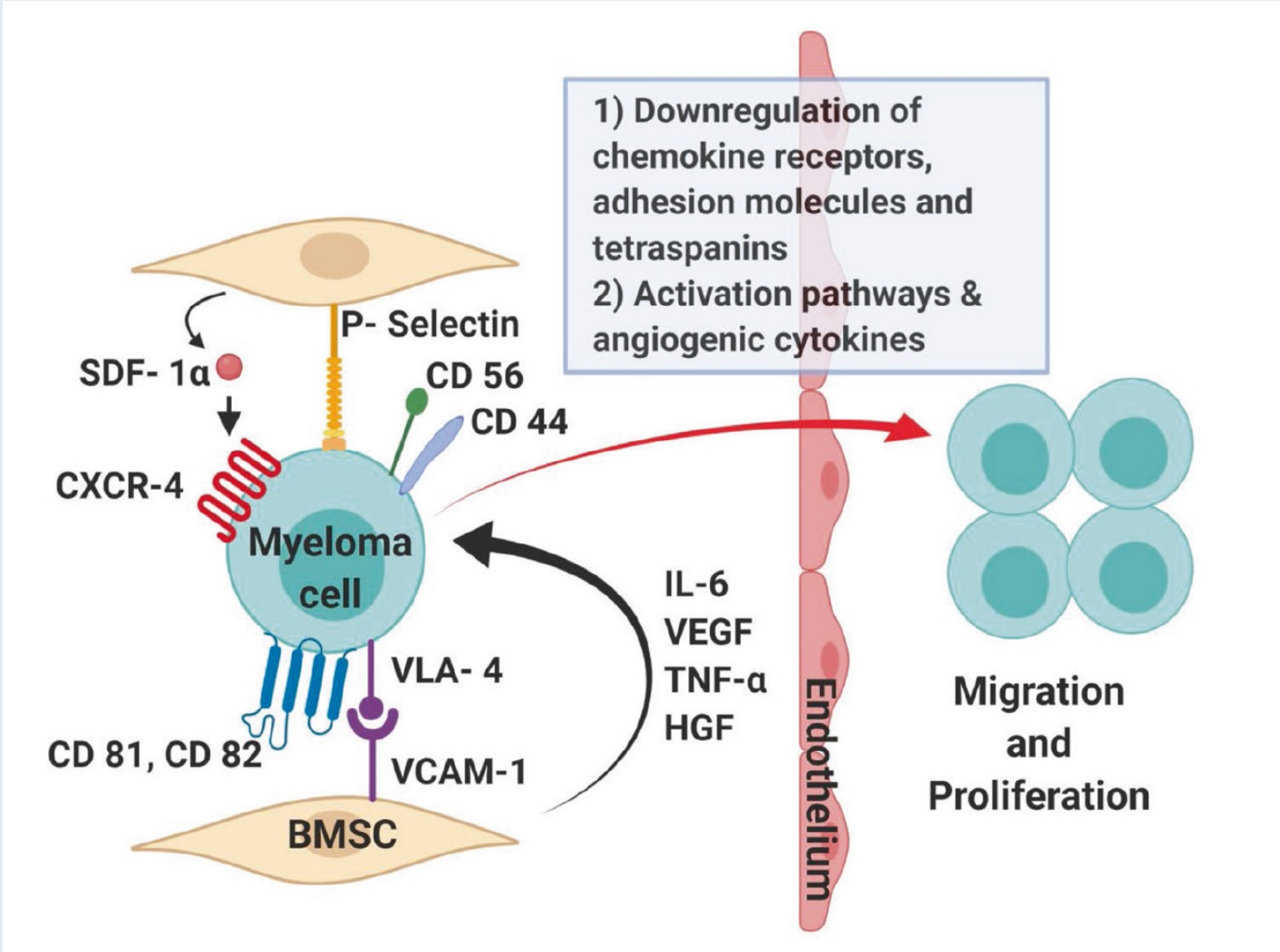
Blood Cancer Journal

REVIEW ARTICLE OPEN

Extramedullary disease in multiple myeloma

Radhika Bansal[1], Sagar Rakshit[1] and Shaji Kumar[1]✉

Pathogenesis of Extramedullary Spread in Multiple Myeloma



Bansal R et al. *Blood Cancer J* 2021 September 29;11(9):161.

Blood Cancer Journal 2022 Sep 5;12(9):129. www.nature.com/bcj

CURRENT TREATMENT ALGORITHM OPEN

Smoldering multiple myeloma current treatment algorithms

S. Vincent Rajkumar[1]✉, Shaji Kumar[1], Sagar Lonial[2] and Maria Victoria Mateos[3]

Fixed Duration Therapy with Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone for High Risk Smoldering Multiple Myeloma — Results of the Ascent Trial

Kumar S et al.

ASH 2022;Abstract 757.

PERSPECTIVE

Perspectives on the Risk-Stratified Treatment of Multiple Myeloma

Faith E. Davies[1], Charlotte Pawlyn[2,3], Saad Z. Usmani[4], Jesus F. San-Miguel[5], Hermann Einsele[6], Eileen M. Boyle[1], Jill Corre[7,8], Daniel Auclair[9], Hearn Jay Cho[9,10], Sagar Lonial[11], Pieter Sonneveld[12], A. Keith Stewart[13], P. Leif Bergsagel[14], Martin F. Kaiser[3,15], Katja Weisel[16], Jonathan J. Keats[17], Joseph R. Mikhael[18], Kathryn E. Morgan[19], Irene M. Ghobrial[20], Robert Z. Orlowski[21], C. Ola Landgren[22], Francesca Gay[23], Joseph Caers[24], Wee Joo Chng[25,26,27], Ajai Chari[10], Brian A. Walker[28], Shaji K. Kumar[29], Luciano J. Costa[30], Kenneth C. Anderson[20], and Gareth J. Morgan[1]

Blood Cancer Discov 2022 July 6;3(4):273-84.

BOX 1: THE HIGH-RISK MULTIPLE MYELOMA DISEASE SEGMENT

The challenges of HR disease

- HR disease is seen in up to 30% of NDMM.
- The proportion of patients with HR disease increases with each successive relapse.
- HR disease is a significant cause of mortality in multiple myeloma.
- Current therapy has not significantly improved the outcome of HR.

The biology of HR disease

- HRMM is an acquired biological trait that is characterized by a phenotype of:
  - increased proliferation rate
  - resistance to apoptosis
  - focal growth
  - bone marrow–independent growth
  - more than one type of biology
  - intraclonal heterogeneity
- HR subclones may be selected for by treatment.
- Treatment needs to address intraclonal heterogeneity.

Features of HR disease

- Clinical features
  - extra-medullary disease
  - large focal lesions
  - plasma cell leukemia
  - primary refractoriness to treatment
- Laboratory and genetic features
  - R-ISS
  - cytogenetic features
    - t(4;14)
    - t(14;16)
    - t(14;20)
    - gain(1q)
    - deletion and mutation of TP53
  - HR gene expression profiles
- Functional features
  - Initial response to therapy with relapse within 12–18 months.
- Novel features
  - Microenvironment features identified by single-cell analysis and advanced imaging.

Davies FE et al. *Blood Cancer Discov* 2022 July 6;3(4):273-84.

BOX 2: RECOMMENDATIONS FOR IMPROVING OUTCOMES FOR HIGH-RISK DISEASE

- Health care systems should:
  - recognize the importance of HRMM.
  - approve reimbursement of novel diagnostic tests.
  - provide appropriate reimbursement policies to enable personalized therapy.
- Clinical and molecular stratification should be performed on all NDMM.
  - Testing should be performed on purified bone marrow plasma cells.
  - Panels should include identification of:
    - adverse translocations
      - t(4;14), t(14;16)
    - other translocations
      - t(11;14)
    - copy number abnormalities
      - the odd number chromosomes to identify hyperdiploidy
      - gain and amplification of 1q
      - deletion of 1p
      - deletion of 17p
      - the number of clonal cells carrying these markers
    - mutational analysis
      - of *TP53*
      - cancer clonal fraction with the abnormality
- Moving forward, we should move from iFISH to NGS-based diagnostic panels that:
  - detect all clinically relevant prognostic variables in a single rapid turn-around test.
  - targetable lesions such as RAS and BRAF should be included in the panel design.
- Clinical care should be optimized based on risk status.
  - Appropriate treatments should be chosen from the current therapeutic armamentarium.
  - The achievement of MRD negativity should be an early treatment goal.
  - Whenever possible, patients should enter a clinical trial.

Davies FE et al. *Blood Cancer Discov* 2022 July 6;3(4):273-84.

BOX 3: RECOMMENDATIONS FOR THE DESIGN OF HRMM HIGH-RISK MULTIPLE MYELOMA CLINICAL TRIALS

- Appropriate clinical trial designs include:
  - risk-stratified treatment studies
    - using standard inclusion criteria.
    - with phase II studies that explore highly active regimens.
  - all-comer trials
    - where randomization is stratified based on risk to avoid arm imbalance.
    - with a planned analysis of HR patients included in the statistical analysis plan.
- The methodology used to define risk should be reported including:
  - cytogenetics, iFISH, GEP, DNA panels.
  - the percentage of cells positive or the cancer clonal fraction for specific abnormalities.
- Reporting of trials should be standardized and include:
  - depth of response with
    - PR, VGPR, and CR.
    - MRD negativity.
    - PFS and OS at set time points.
  - proportion of patients reaching predetermined protocol time points.
  - safety data.
- Biological samples
  - should be collected in all studies.
  - aim to further understand the biology of HR.
  - should refine:
    - current risk markers.
    - novel risk makers.
    - novel targets for therapy.
  - Data should be shared with the community.

Davies FE et al. *Blood Cancer Discov* 2022 July 6;3(4):273-84.

Oncol Ther (2022) 10:105–122
https://doi.org/10.1007/s40487-022-00195-3

REVIEW

Current Role of Allogeneic Stem Cell Transplantation in Multiple Myeloma

Jean-Sébastien Claveau · Francis K. Buadi · Shaji Kumar

2022 December 6;12(12):164.

Blood Cancer Journal

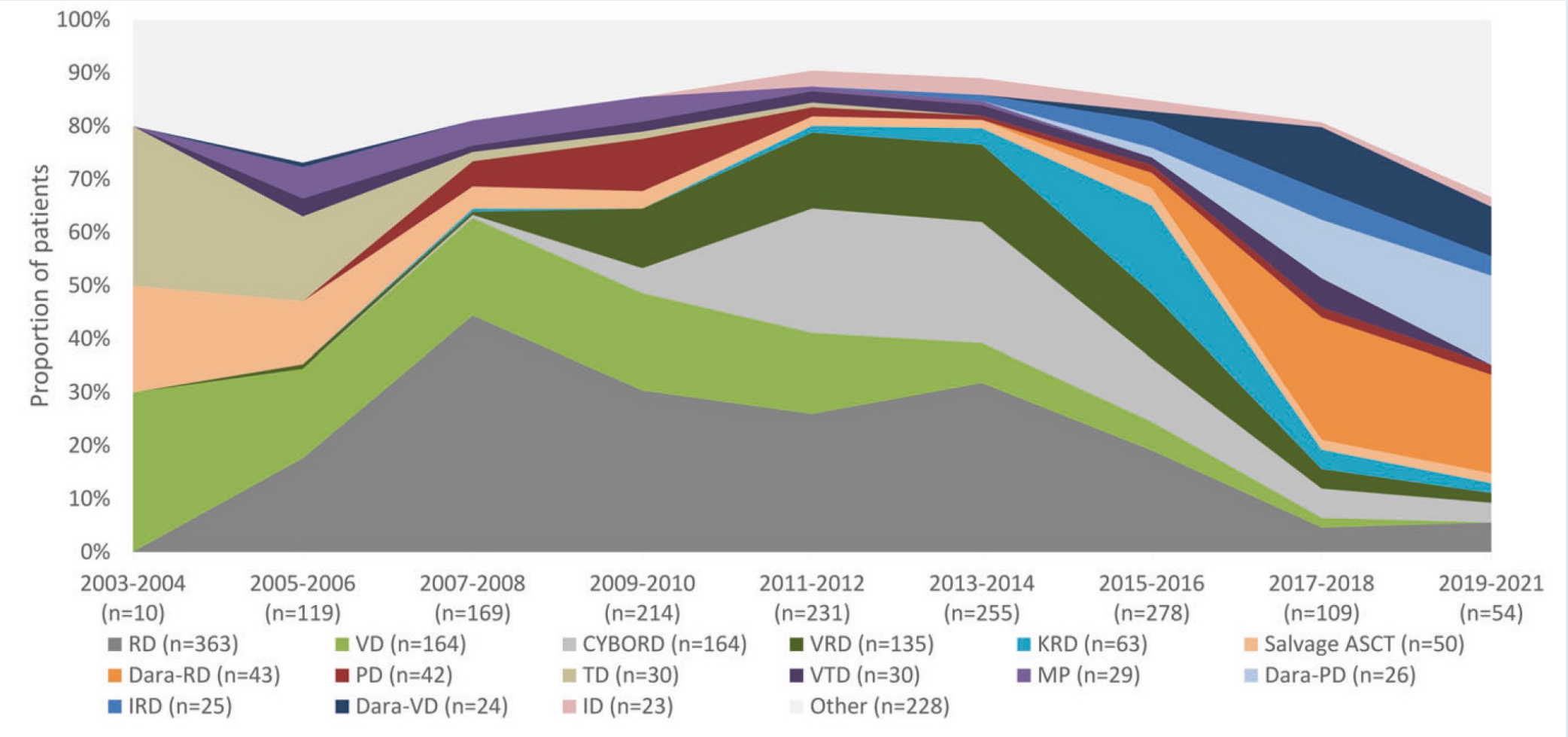
www.nature.com/bcj

ARTICLE OPEN

Second- and third-line treatment strategies in multiple myeloma: a referral-center experience

Sarah Goldman-Mazur[1], Alissa Visram[1,2], S. Vincent Rajkumar[1], Prashant Kapoor[1], Angela Dispenzieri[1], Martha Q. Lacy[1], Morie A. Gertz[1], Francis K. Buadi[1], Suzanne R. Hayman[1], David Dingli[1], Taxiarchis Kourelis[1], Wilson Gonsalves[1], Rahma Warsame[1], Eli Muchtar[1], Nelson Leung[3], Robert A. Kyle[1] and Shaji K. Kumar[1] ✉

Most Frequently Applied Second-Line Treatment Regimens for Multiple Myeloma and Initiation of Second-Line Treatment 2003-2021



Goldman-Mazur S et al. *Blood Cancer J* 2022 Dec 6;12(12):164.

MonumenTAL-5: A Phase 3 Study of Talquetamab versus Belantamab Mafodotin in Patients with Relapsed/Refractory Multiple Myeloma Who Received ≥4 Prior Lines of Therapy, Including a Proteasome Inhibitor, an Immunomodulatory Drug, and an Anti-CD38 Monoclonal Antibody

Kumar SK et al.

ASH 2022;Abstract 3243.

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Breast Cancer

A Multitumor CME/MOC-Accredited Live Webinar Series

Wednesday, January 4, 2023
5:00 PM – 6:00 PM ET

Faculty

Joyce O'Shaughnessy, MD
Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2023

Thank you for joining us!

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

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