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

Part 3 — Multiple Myeloma

Wednesday, February 10, 2021
5:00 PM – 6:00 PM ET

Faculty

Robert Z Orlowski, MD, PhD
S Vincent Rajkumar, MD
Edward A Stadtmauer, MD

Moderator

Neil Love, MD

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Faculty

Robert Z Orlowski, MD, PhD
Florence Maude Thomas Cancer Research Professor
Department of Lymphoma and Myeloma
Professor, Department of Experimental Therapeutics
Director, Myeloma Section
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Edward A Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow and Shaffer Families President's Distinguished Professor
University of Pennsylvania
Abramson Cancer Center of the University of Pennsylvania
Philadelphia, Pennsylvania

S Vincent Rajkumar, MD
Edward W and Betty Knight Scripps Professor of Medicine
Mayo Clinic
Rochester, Minnesota

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Bristol-Myers Squibb Company, GlaxoSmithKline, Karyopharm Therapeutics, Oncopeptides, Sanofi Genzyme and Takeda Oncology.

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Dr Love — Disclosures

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Ownership Interest	Asylia Therapeutics Inc (founder, patents, equity)

Dr Rajkumar — Disclosures

No financial interests or affiliations to disclose.

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Dr Stadtmauer — Disclosures

Consulting Agreements	Amgen Inc, Celgene Corporation, Genentech, a member of the Roche Group, Janssen Biotech Inc, Sanofi Genzyme, Takeda Oncology

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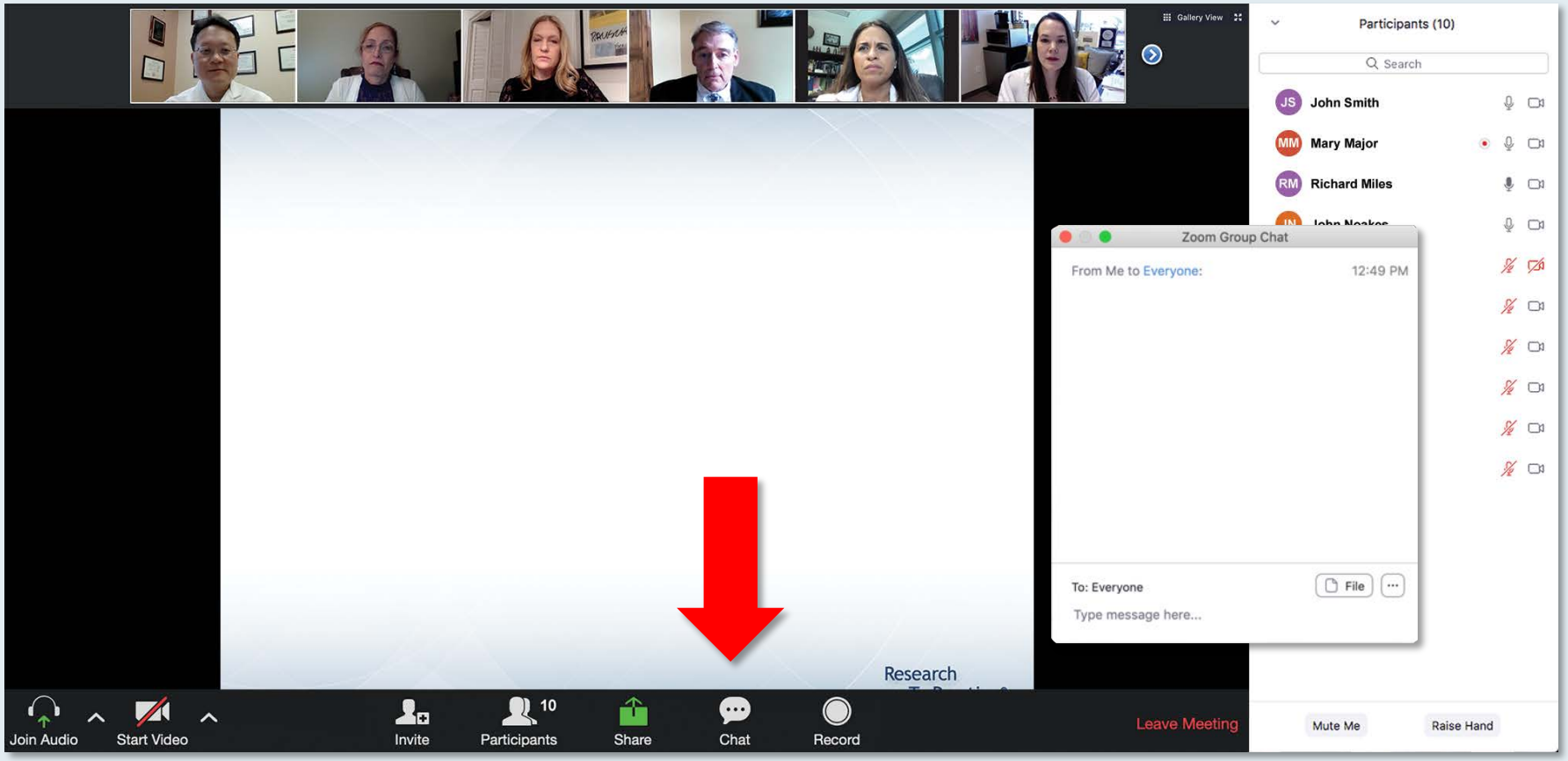
We Encourage Clinicians in Practice to Submit Questions



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Familiarizing Yourself with the Zoom Interface

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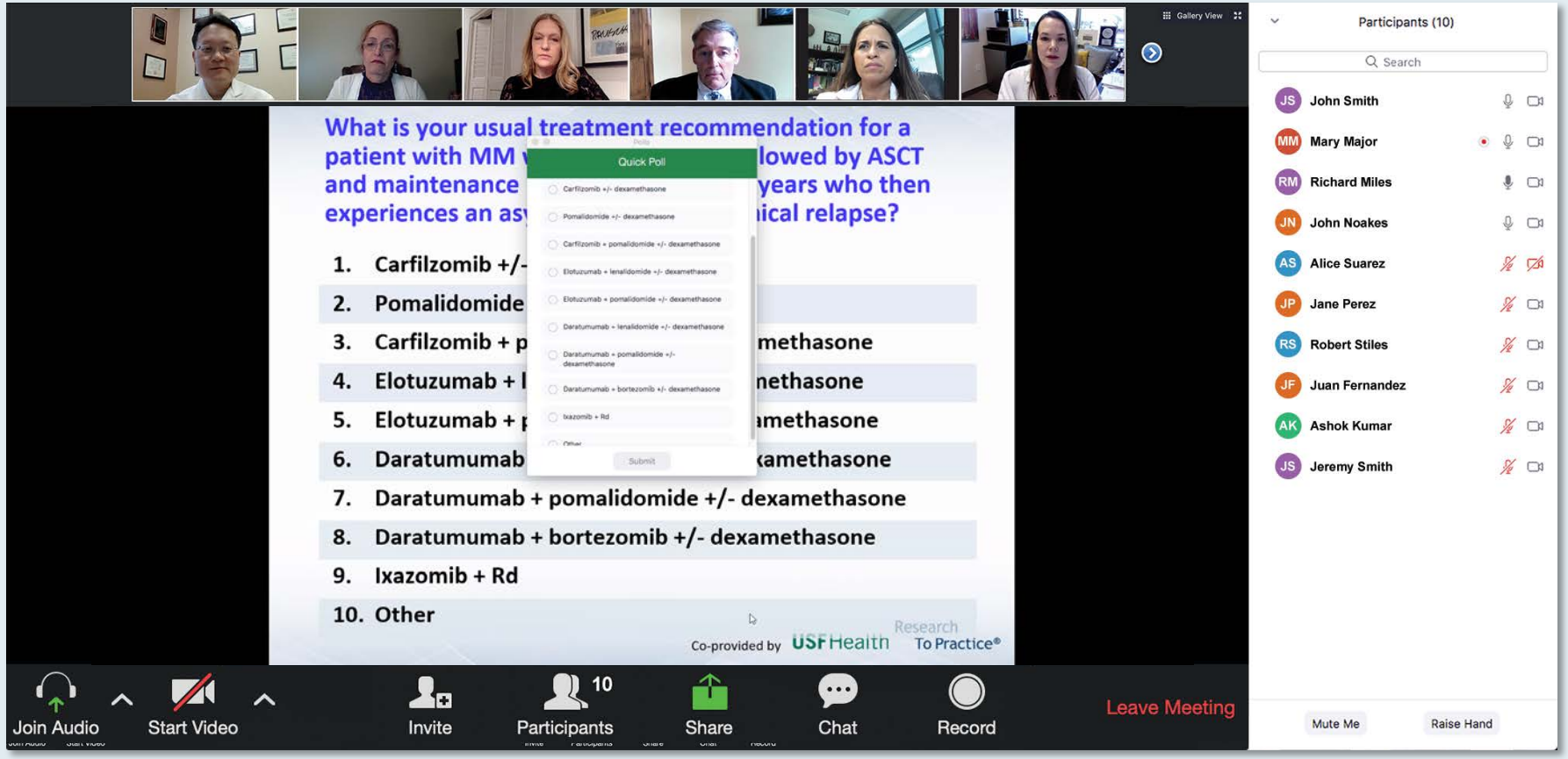

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Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Colorectal Cancer (Part 3 of a 3-Part Series)

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Eric Van Cutsem, MD, PhD

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John M Pagel, MD, PhD
Alexander Perl, MD
Daniel P Petrylak, MD
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Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

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What Clinicians Want to Know: Understanding the Factors Affecting the Optimal Diagnosis and Management of Ovarian Cancer

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Kathleen Moore, MD
David M O'Malley, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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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?
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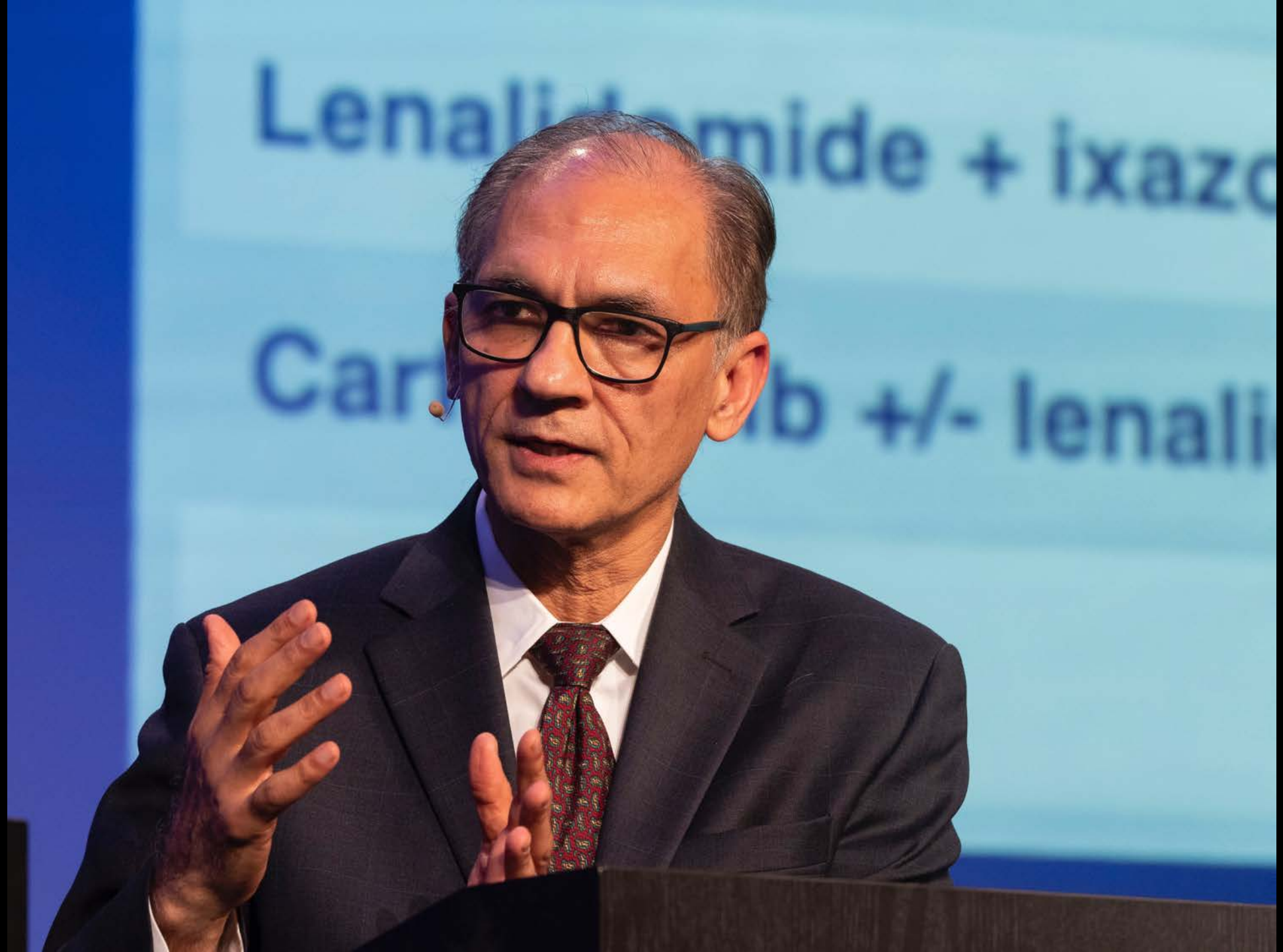
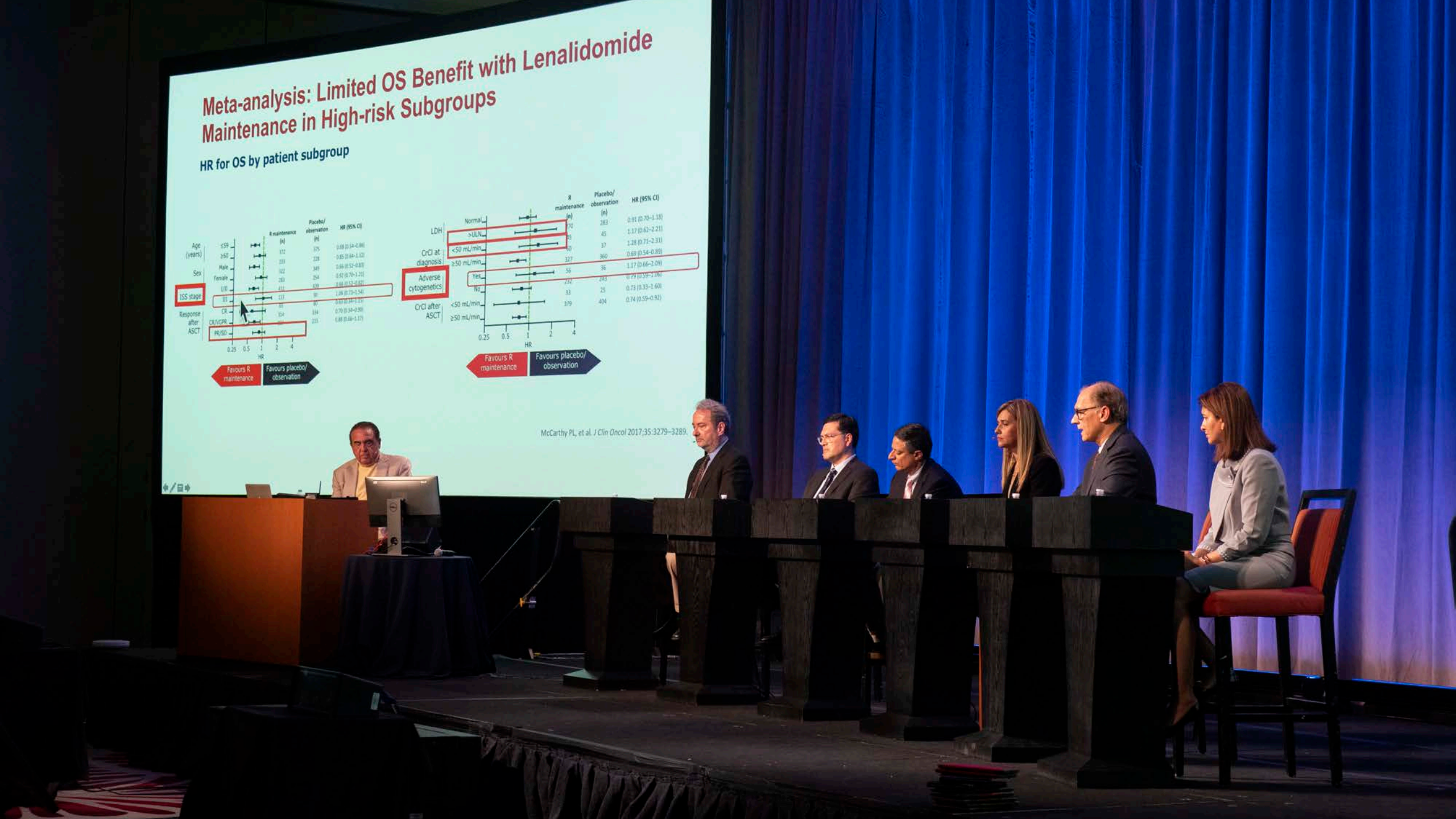

Lenalidomide + ixazo
Carfilzomib +/- lenali


Meta-analysis: Limited OS Benefit with Lenalidomide Maintenance in High-risk Subgroups
HR for OS by patient subgroup
Age (years)
Sex
ISS stage
Response after ASCT
R maintenance (n)
Placebo/ observation (n)
HR (95% CI)
HR
Favours R maintenance
Favours placebo/ observation
LDH
CrCl at diagnosis
Adverse cytogenetics
CrCl after ASCT
McCarthy PL, et al. J Clin Oncol 2017;35:3279–3289.


What is your usual induction regimen for a 77-year-old patient with ISS Stage II MM who is transplant ineligible, has a creatinine level of 5 mg/dL and no high-risk features?
Lenalidomide
Rd
Bortezomib
RVd or RVd lite
KRd
CyBorD
MPV/daratumumab
Rd/daratumumab
VTd/daratumumab
3%
4%
16%
13%
1%
48%
4%
3%
4%
5%


Ixazomib Maintenance Associated with Low Toxicity
Common AEs of any cause
Hematologic
Nonhematologic
•No difference in the rate of new primary malignancy (3% versus 3%)
•AEs leading to study treatment discontinuation occurred in 7% (ixazomib) and 5% (placebo) of patients
Dimopoulos MA et al. Lancet 2019;393(10168):253-64.
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Thomas Itel, MD


• 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
Months from Randomization
Ixazomib
Placebo
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

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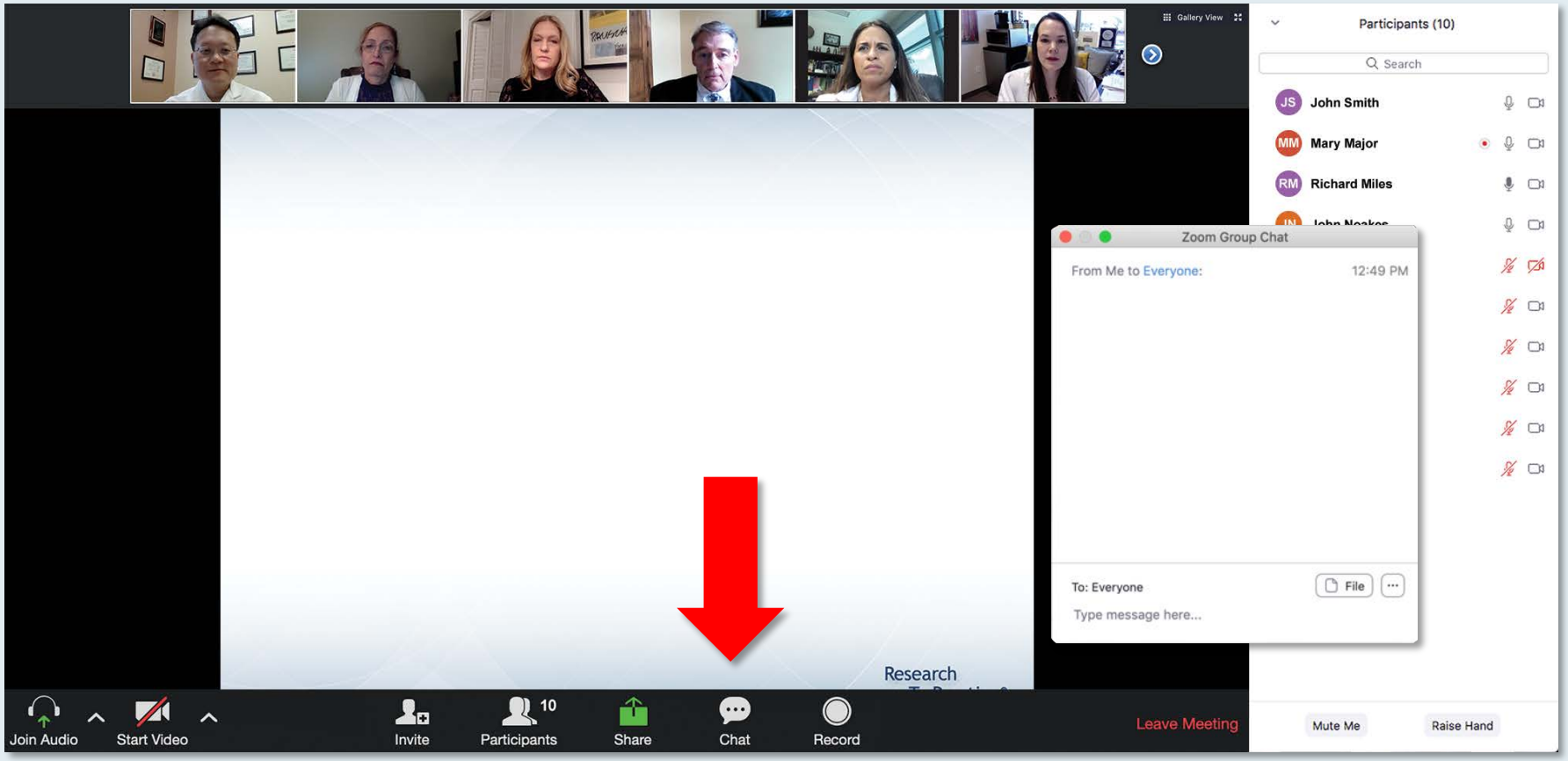

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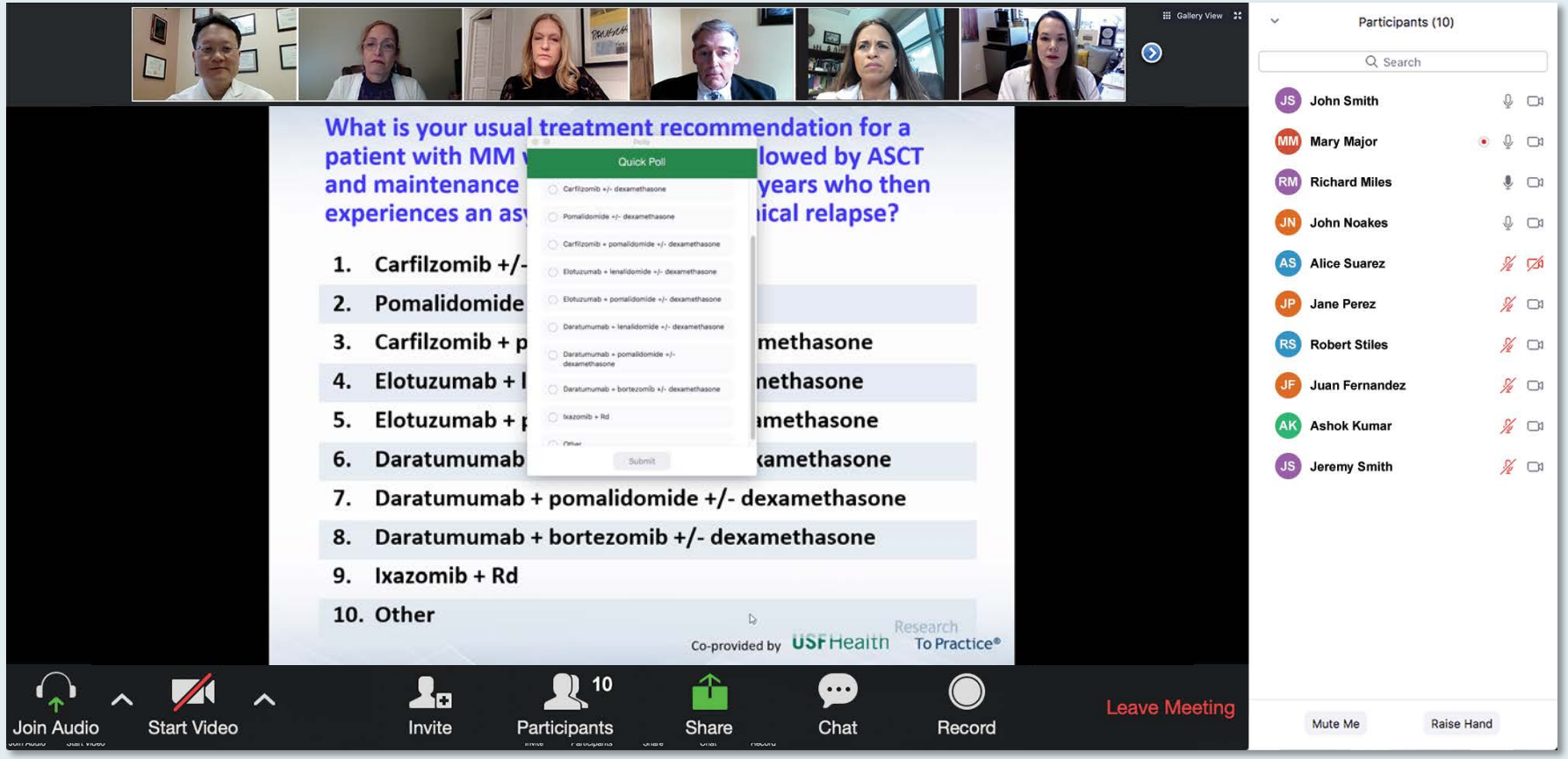

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A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer has developed multiple minimally symptomatic bone metastases 3 years after starting adjuvant anastrozole. Which endocrine-based treatment would you most likely recommend?
Fulvestrant
Tamoxifen
Other aromatase inhibitor
Palbociclib + fulvestrant
Palbociclib + letrozole
Ribociclib + fulvestrant
Ribociclib + letrozole
Abemaciclib + fulvestrant
Abemaciclib + letrozole
Other

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Agenda

Module 1: Up-front management

- **GRIFFIN, APOLLO, IMF 2009, TOURMALINE-MM2**

Module 2: Relapsed/refractory disease

- **Isatuximab, belantamab mafadotin, selinexor**

Module 3: Chimeric antigen receptor T-cell therapy; bispecific antibodies

Module 4: Other novel strategies

- **Venetoclax, melflufen, iberdomide, BRAF inhibitors**

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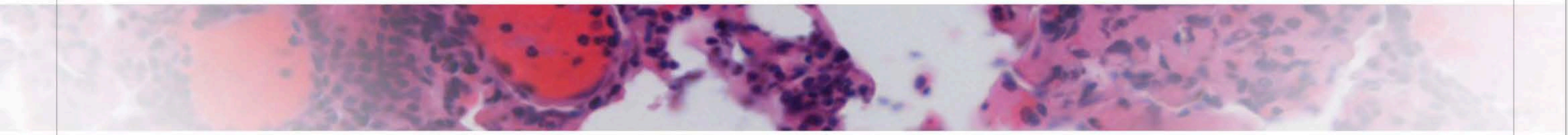


Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of GRIFFIN after 12 Months of Maintenance Therapy*

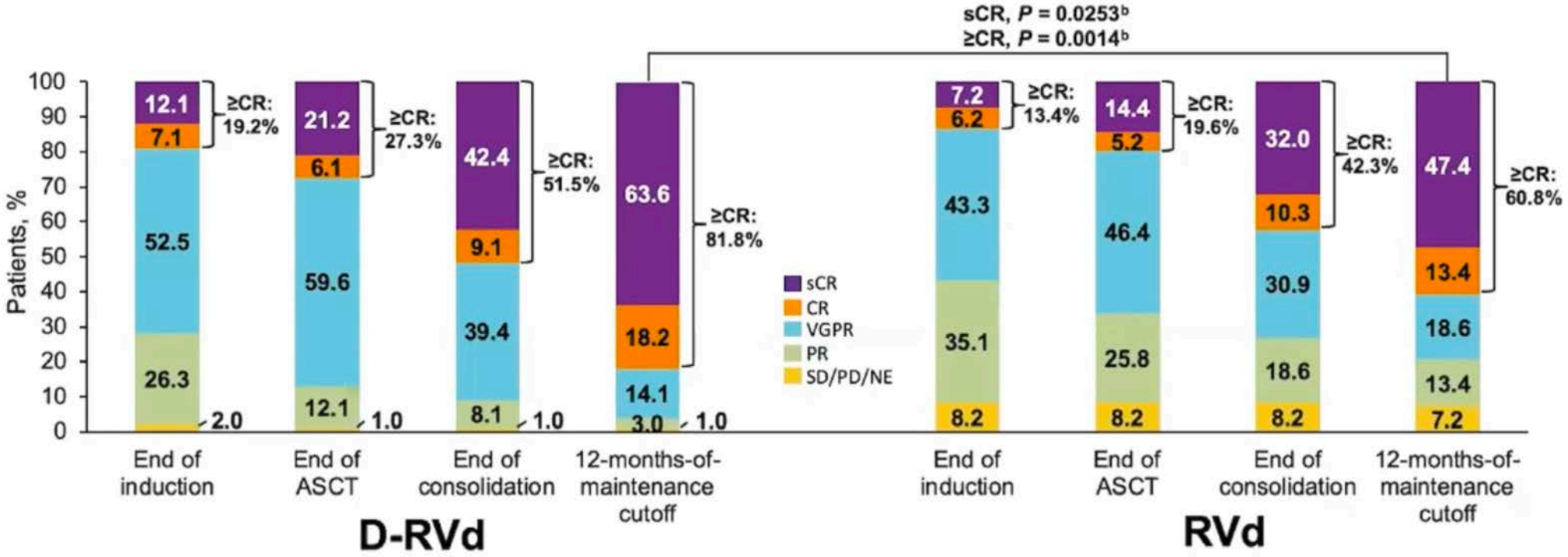
Jonathan L. Kaufman,[1] Jacob Laubach,[2] Douglas W. Sborov,[3] Brandi Reeves,[4] Cesar Rodriguez,[5] Ajai Chari,[6] Rebecca Silbermann,[7] Luciano J. Costa,[8] Larry D. Anderson Jr,[9] Nitya Nathwani,[10] Nina Shah,[11] Yvonne A. Efebera,[12] Sarah A. Holstein,[13] Caitlin Costello,[14] Andrzej Jakubowiak,[15] Tanya M. Wildes,[16] Robert Z. Orlowski,[17] Kenneth H. Shain,[18] Andrew J. Cowan,[19] Yana Lutska,[20] Padma Bobba,[20] Huiling Pei,[21] Jon Ukropec,[22,†] Jessica Vermeulen,[23] Thomas S. Lin,[20] Paul G. Richardson,[2] Peter M. Voorhees[24]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; [4]University of North Carolina – Chapel Hill, Chapel Hill, NC, USA; [5]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [6]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [7]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [8]University of Alabama at Birmingham, Birmingham, AL, USA; [9]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [10]Judy and Bernard Briskin Center for Multiple Myeloma Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [11]Department of Medicine, University of California San Francisco, San Francisco, CA, USA; [12]The Ohio State University Comprehensive Cancer Center; Columbus OH, USA; [13]Division of Oncology & Hematology, University of Nebraska Medical Center, Omaha, NE, USA; [14]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [15]University of Chicago Medical Center, Chicago, IL, USA; [16]Division of Oncology, Section Medical Oncology, Washington University School of Medicine, St. Louis, MO, USA; [17]Department of Lymphoma–Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [18]Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL, USA; [19]Division of Medical Oncology, University of Washington, Seattle, WA, USA; [20]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [21]Janssen Research & Development, LLC, Titusville, NJ, USA; [22]Janssen Global Medical Affairs, Horsham, PA, USA; [23]Janssen Research & Development, LLC, Leiden, The Netherlands; [24]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA. ([†] At the time of study)

*ClinicalTrials.gov Identifier: NCT02874742.

Additional information can be viewed by scanning the QR code or accessing this link: https://epg-digital.com/u/ASH2020-Kaufman. The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Responses Deepened over Time[a]



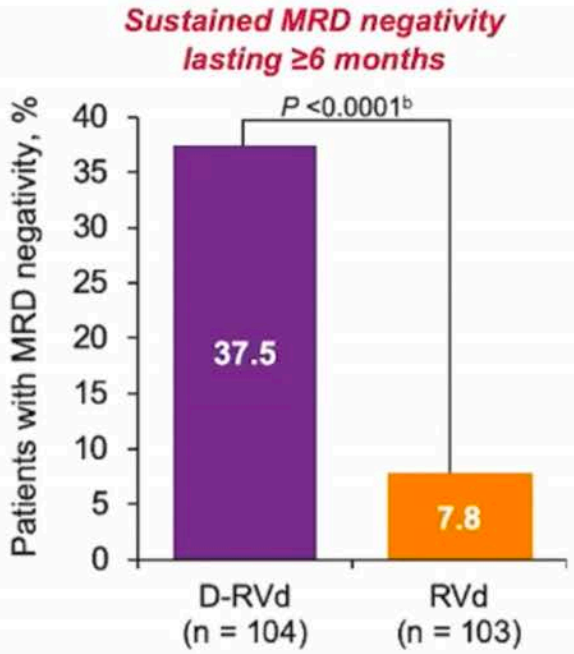
- *Results for end of induction, ASCT, and consolidation are based on a median follow up of 13.5 months at the primary analysis*
- *Median follow up at 12-months-of-maintenance therapy cutoff was 27.4 months*

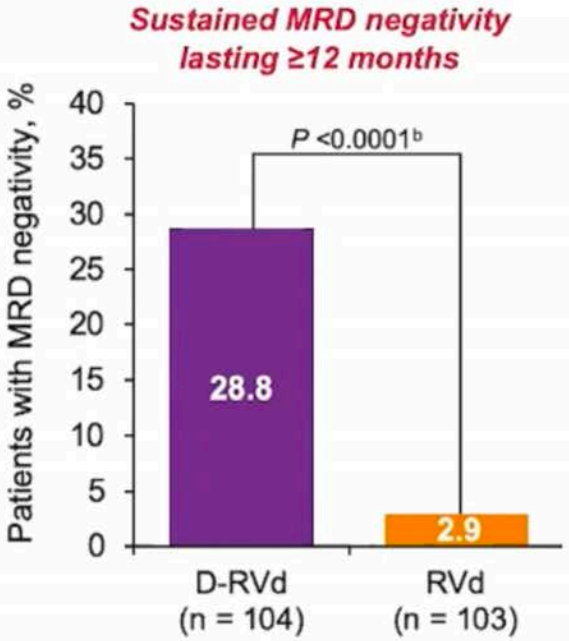
Response rates and depths were greater for D-RVd at all time points

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





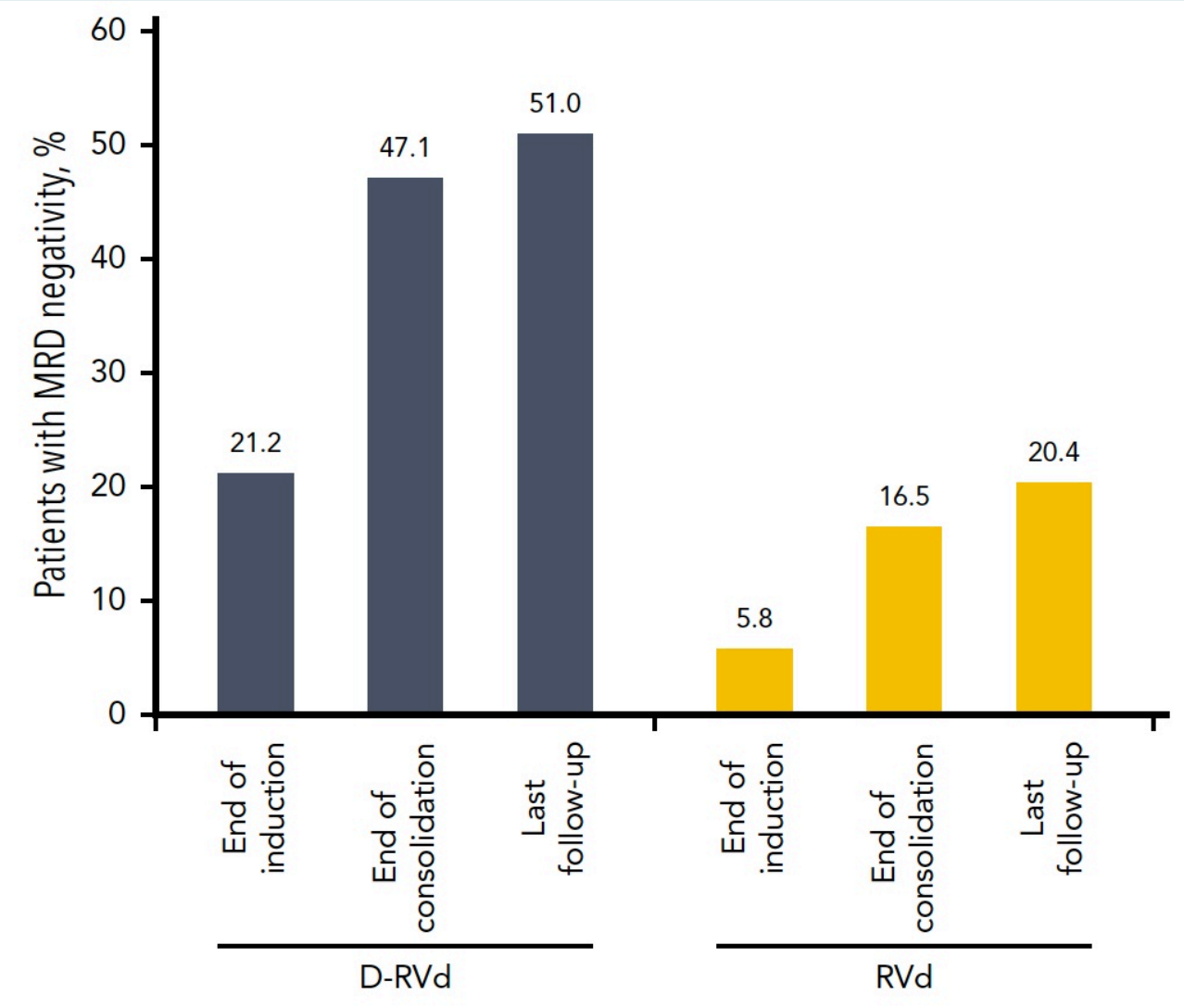
- *Among patients who achieved MRD negative (10^{-5}) status, sustained MRD negativity lasting ≥12 months was noted in 30/65 (46.2%) and 3/28 (10.7%) patients*

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.

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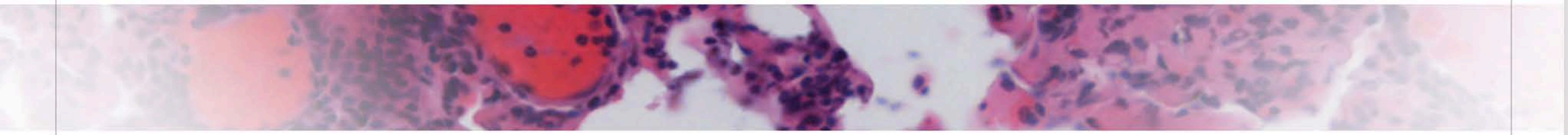


APOLLO: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM)*

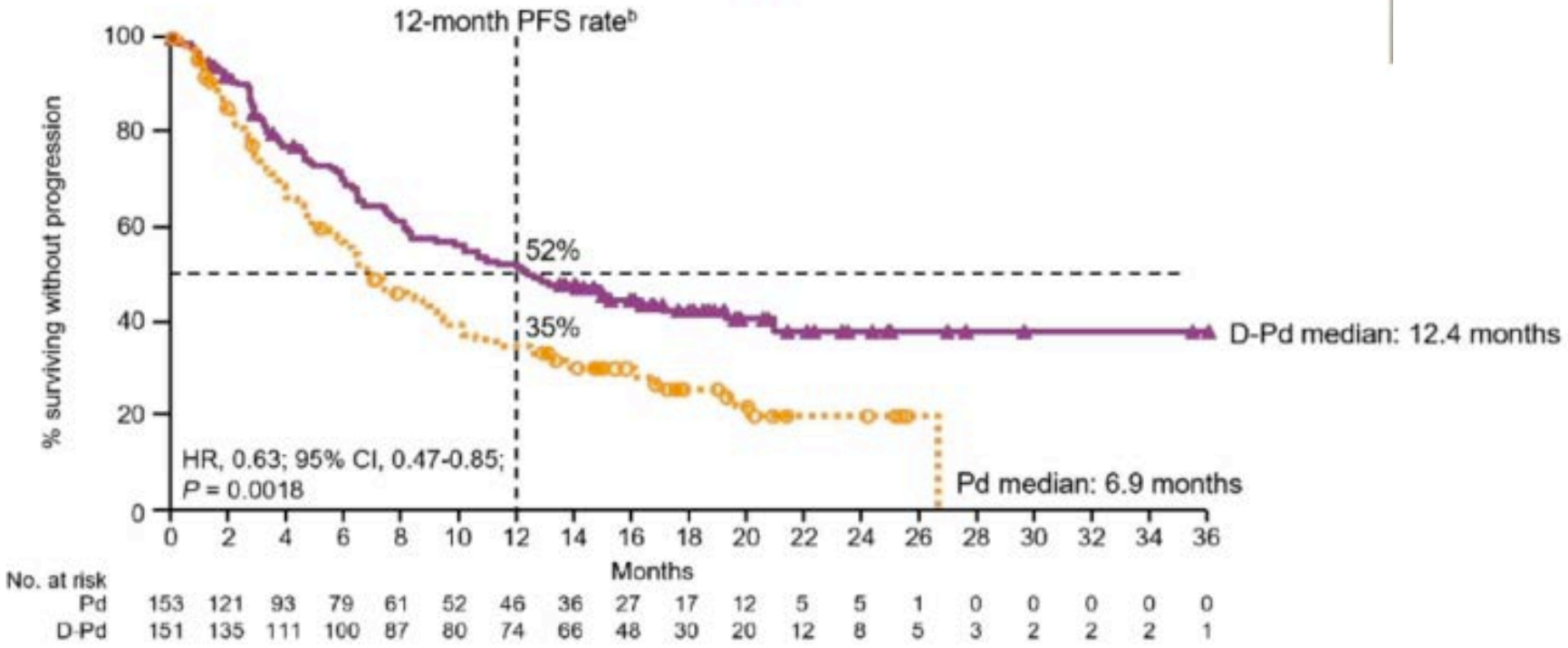
Meletios A. Dimopoulos,[1] Evangelos Terpos,[1] Mario Boccadoro,[2] Sosana Delimpasi,[3] Meral Beksac,[4] Eirini Katodritou,[5] Philippe Moreau,[6] Luca Baldini,[7] Argiris Symeonidis,[8] Jelena Bila,[9] Albert Oriol,[10] Maria-Victoria Mateos,[11] Hermann Einsele,[12] Ioannis Orfanidis,[13] Tahamtan Ahmadi,[14] Jon Ukropec,[15,†] Tobias Kampfenkel,[16] Jordan M. Schecter,[17] Yanping Qiu,[18] Himal Amin,[17] Jessica Vermeulen,[16] Robin Carson,[19] Pieter Sonneveld[20]

[1]National and Kapodistrian University of Athens, Athens, Greece; [2]University of Torino, Turin, Italy; [3]Evangelismos Hospital, Athens, Greece; [4]Ankara University, Ankara, Turkey; [5]Theagenio Cancer Hospital, Thessaloniki, Greece; [6]Hematology, University Hospital Hôtel-Dieu, Nantes, France; [7]UO Ematologia, Fondazione IRCCS Cà Granda, OM Policlinico, Università degli Studi, Milan, Italy; [8]University of Patras, Patras, Greece; [9]University of Belgrade, Belgrade, Serbia; [10]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias I Pujol, Barcelona, Spain; [11]University Hospital of Salamanca/IBSAL/Cancer Research Center-IBMCC (USAL-CSIC), Salamanca, Spain; [12]Würzburg University Medical Centre, Würzburg, Germany; [13]Health Data Specialists S.A., Dublin, Ireland; [14]Genmab US, Inc., Princeton, NJ, USA; [15]Janssen Global Medical Affairs, Horsham, PA, USA; [16]Janssen Research & Development, LLC, Leiden, The Netherlands; [17]Janssen Research & Development, LLC, Raritan, NJ, USA; [18]Janssen Research & Development, Beijing, China; [19]Janssen Research & Development, LLC, Spring House, PA, USA; [20]Erasmus University Medical Center Cancer Institute, Rotterdam, The Netherlands. ([†]At the time of study)

*ClinicalTrials.gov Identifier: NCT03180736.

Additional information can be viewed by scanning the QR code or accessing this link: https://epg-digital.com/u/ASH2020-Dimopoulos. The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

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. [a]Intent-to-treat population. [b]Kaplan–Meier estimate.

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Dimopoulos MA et al. ASH 2020;Abstract 412.

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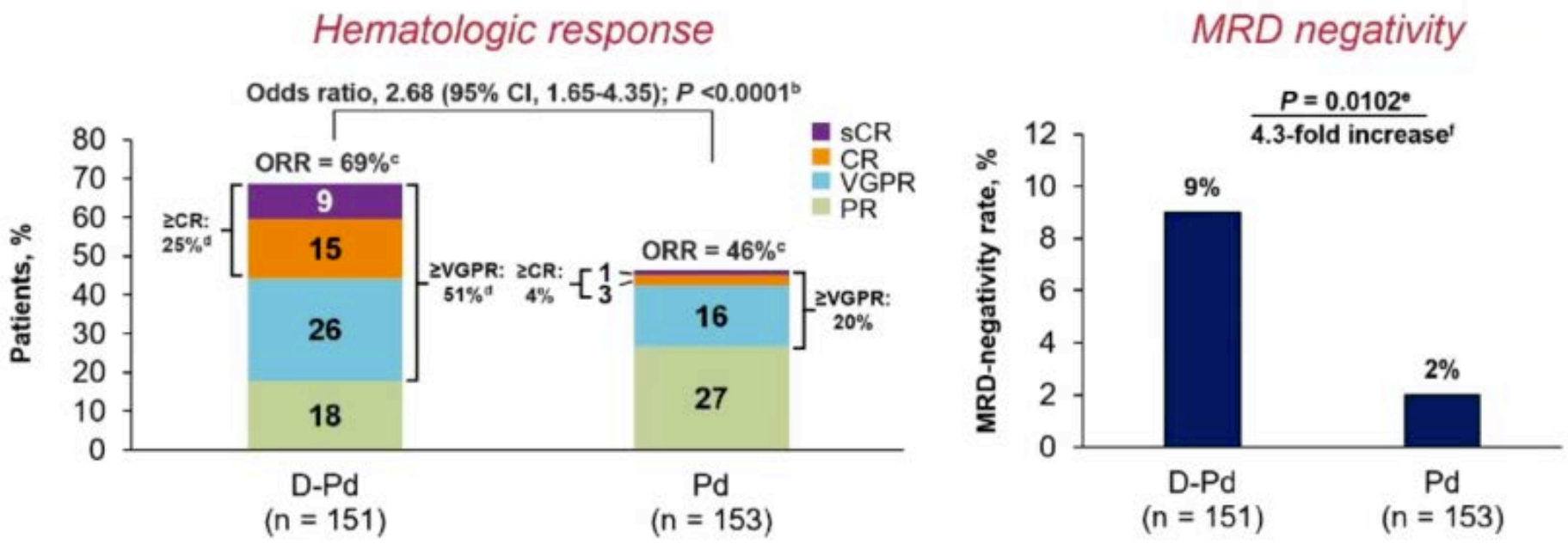
Depth of Response[a]



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.

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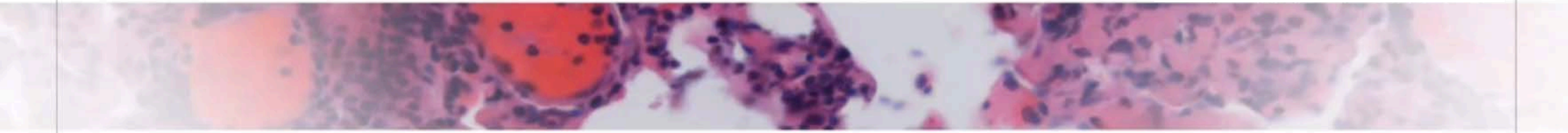


Autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial

Aurore Perrot[1], Valérie Lauwers-Cances[2], Titouan Cazaubiel[3], Thierry Facon[4], Denis Caillot[5], Lauriane Clément-Filliatre[6], Margaret Macro[7], Olivier Decaux[8], Karim Belhadj[9], Mohamad Mohty[10], Lionel Karlin[11], Jean Claude Eisenmann[12], Mourad Tiab[13], Frédérique Orsini[14], Cyrille Touzeau[15], Xavier Leleu[16], Hervé Avet-Loiseau[17], Nikhil C. Munshi[18], Kenneth Anderson[19], Paul G. Richardson[20], Philippe Moreau[21], Michel Attal[22].

[1]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [2]USMR, service d'Epidémiologie, CHU Toulouse, Toulouse, France; [3]CHU de Bordeaux, Service d'Hématologie et de Thérapie Cellulaire, Bordeaux, France; [4]Centre Hospitalier Universitaire (CHU) Lille, Service des Maladies du Sang, University of Lille, Lille, France; [5]CHU de Dijon, Service d'Hématologie, Dijon, France; [6]CHU de Nancy, Service d'Hématologie, Nancy, France; [7]Service d'Hématologie, CHU de Caen, Caen, France; [8]Service d'Hématologie, CHU de Rennes, Rennes, France; [9]Lymphoid Malignancies, Centre Hospitalier Universitaire Henri Mondor, Créteil, France; [10]Hôpital Saint Antoine, Service d'Hématologie et Thérapie Cellulaire, Paris, Paris, France; [11]Hématologie, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France; [12]Centre Hospitalier de Mulhouse, MULHOUSE, FRA; [13]CH la Roche Sur Yon, La Roche Sur Yon Cedex 9, France; [14]Service Hématologie, CH Annecy, ANNECY, France; [15]Hématologie, CHU de Nantes, Nantes, France; [16]CHU de Poitiers - Hôpital La Milétrie, Service d'Hématologie et Thérapie Cellulaire, Pôle Régional de Cancérologie, POITIERS, France; [17]Unite de Génomique du Myélome, IUC-T Oncopole, Toulouse, France; [18]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [19]Jerome Lipper Multiple Myeloma Center, LeBow Institute for Myeloma Therapeutics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [20]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [21]Department of Hematology, University Hospital of Nantes, Nantes, France; [22]Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

IFM 2009 Study design

700 patients randomized stratified on ISS and FISH

Arm A – RVD alone	Arm B - Transplantation
3 RVD	3 RVD

PBSC collection (cyclophosphamide 3g/m^2 and GCSF 10 µg/kg/d)

5 RVD	HD Melphalan 200 mg/m^2 + ASCT
	2 RVD

Lenalidomide maintenance 13 cycles (10-15 mg/d)

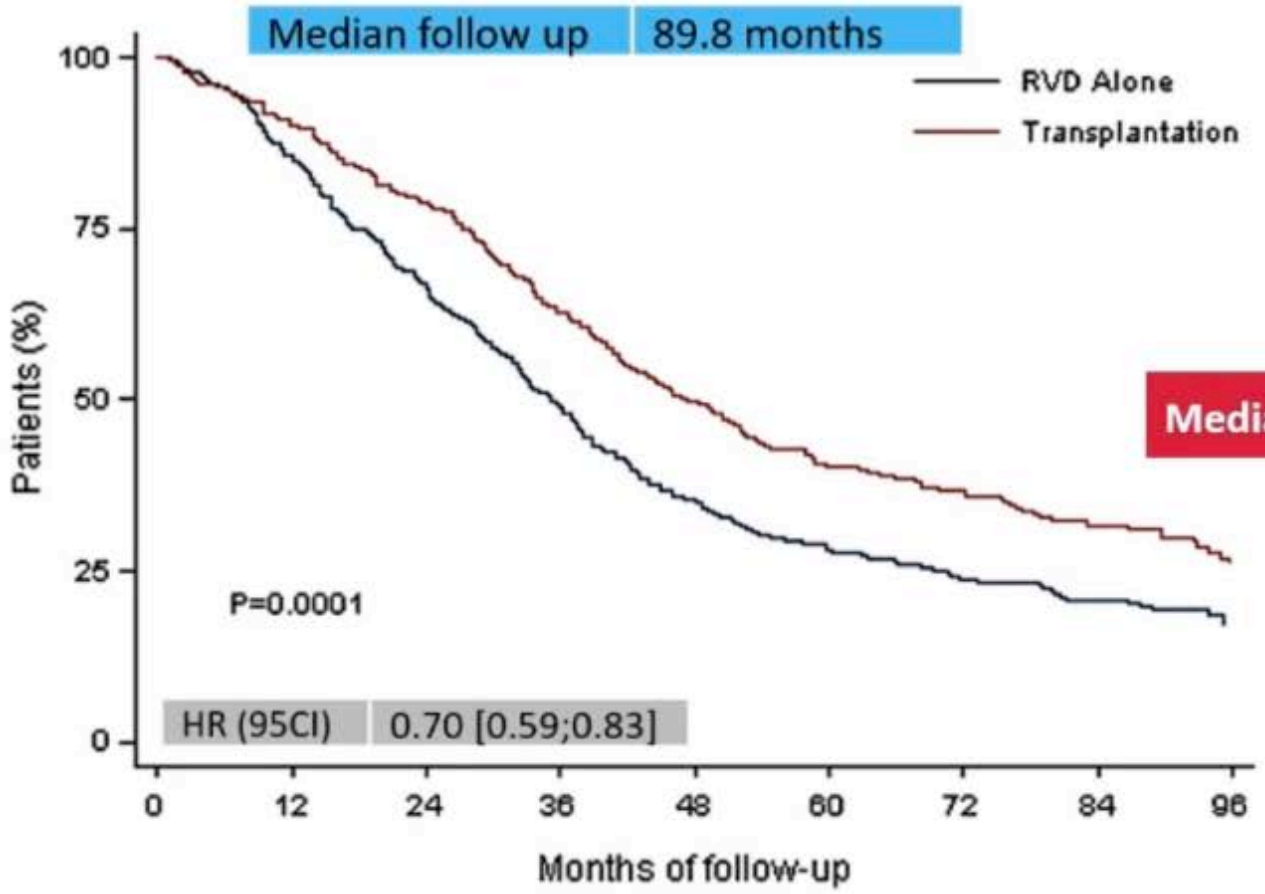
RVd 21d cycles
. Lenalidomide 25 mg/d: D1-D14
. Bortezomib 1.3 mg/m^2 D1, D4, D8, D11
. Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS

Secondary endpoints
. ORR, MRD
. TTP
. OS
. Toxicity

Perrot A et al. ASH 2020;Abstract 143.

Updated PFS (primary endpoint)



Median PFS 47.3 months (Transplantation, arm B)

Median PFS 35 months (RVD alone, arm A)

Perrot A et al. ASH 2020;Abstract 143.

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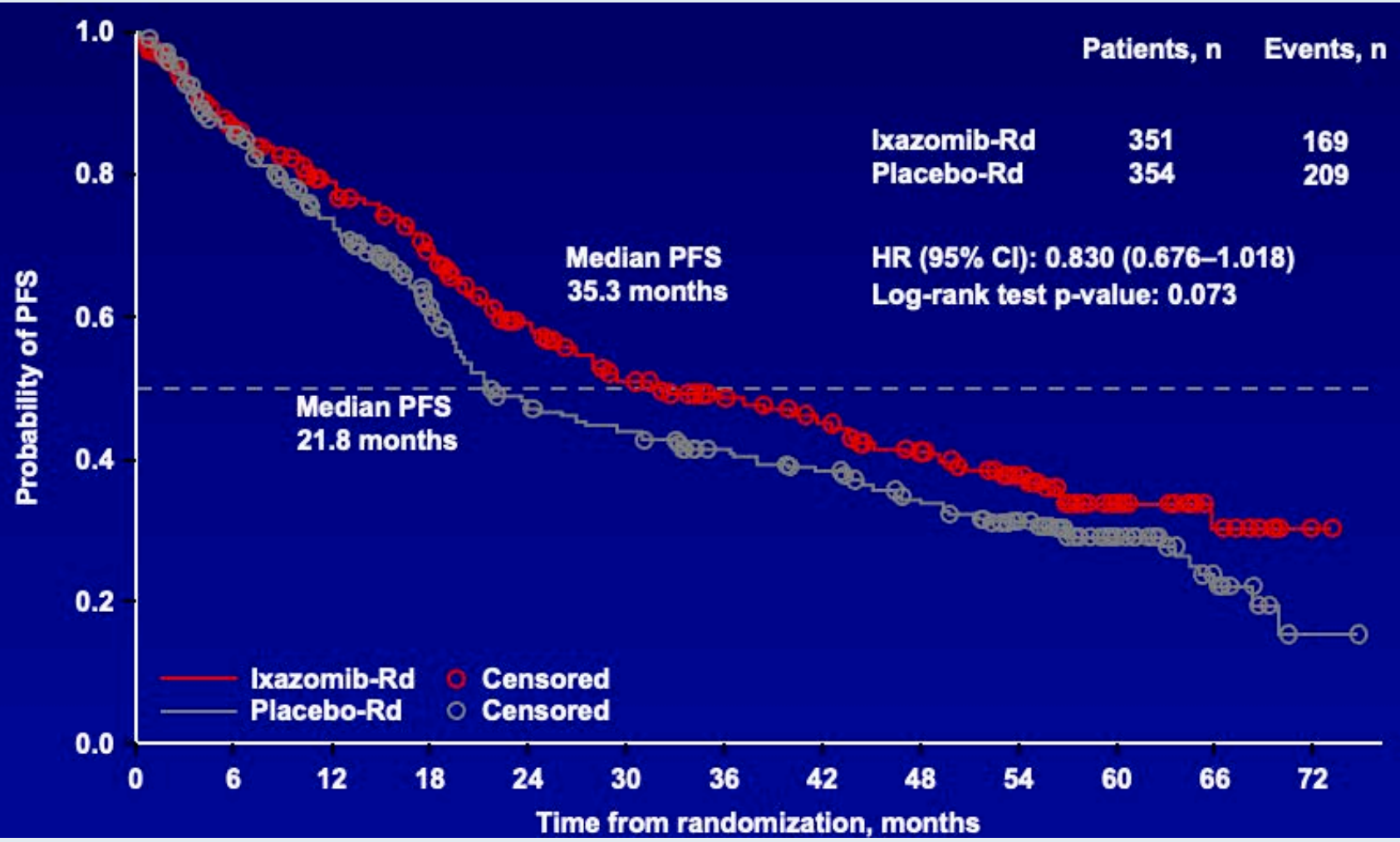
The Phase 3 TOURMALINE-MM2 Trial: Oral Ixazomib, Lenalidomide, and Dexamethasone Vs Placebo-Rd for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

Thierry Facon,[1] Christopher P. Venner,[2] Nizar J. Bahlis,[3] Fritz Offner,[4] Darrell J. White,[5] Lotfi Benboubker,[6] Sophie Rigaudeau,[7] Philippe Rodon,[8] Sung-Soo Yoon,[9] Kenshi Suzuki,[10] Hirohiko Shibayama,[11] Xiaoquan Zhang,[12] Godwin Yung,[12] Robert M. Rifkin,[13] Philippe Moreau,[14] Sagar Lonial,[15] Shaji K. Kumar,[16] Paul G. Richardson,[17] and S. Vincent Rajkumar[16] on behalf of the TOURMALINE-MM2 study group

[1]Centre Hospitalier Universitaire (CHU) Lille, Service des Maladies du Sang, University of Lille, Lille, France; [2]Division of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [3]Division of Hematology and Oncology, Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada; [4]Hematology, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium; [5]QEII Health Sciences Center and Dalhousie University, Halifax, NS, Canada; [6]Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; [7]Department of Clinical Hematology, Centre Hospitalier Versailles, Le Chesnay, France; [8]Unité d'Hématologie et d'Oncologie, Centre Hospitalier Périgueux, Périgueux, France; [9]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [10]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [11]Department of Hematology and Oncology, Osaka University Graduate School of Medicine, Suita, Japan; [12]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [13]Rocky Mountain Cancer Centers/US Oncology Research, Denver, CO, USA; [14]Department of Hematology, University Hospital Hôtel Dieu, University of Nantes, Nantes, France; [15]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [16]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [17]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

TOURMALINE-MM2: Progression-Free Survival

- Median follow-up for PFS: 53.3 vs 55.8 months in ixazomib-Rd and placebo-Rd arms, respectively.
- Median DOT: 20 cycles in each arm.
  - 54% of patients in the ixazomib-Rd arm and 54% in the placebo-Rd arm entered cycle 19.
  - Mean relative dose intensity for all agents was similar between arms.



Facon T et al. ASH 2020;Abstract 551.

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Treatment of High Risk Smoldering Myeloma with Carfilzomib, Lenalidomide, and Dexamethasone followed by Lenalidomide Maintenance: A Phase 2 Clinical and Correlative Study

Dickran Kazandjian[1], Elizabeth Hill[1], Candis Morrison[1], Alexander Dew[7], Neha Korde[8], Sham Mailankody[8], Elisabet Manasanch[9], Mary Kwok[7], Manisha Bhutani[10], Nishant Tageja[11], Yong Zhang[1], Ashley Carpenter[1], Monica Epstein[1], Michael Emanuel[1], Crystal Lu[5], Raul Braylan[6], Katherine Calvo[6], Peter Choyke[6], Alina Dulau-Florea[6], Esther Mena[2], Liza Lindenberg[2], Irina Maric[6], Nisha Patel[6], Maryalice Stetler-Stevenson[3], Hao-Wei Wang[3], Constance Yuan[3], Jane Trepel[4], Seth Steinberg[4], William Figg[4], Mark Roschewski[1], and Ola Landgren[8]

[1]Multiple Myeloma Program, Lymphoid Malignancies Branch, [2]Molecular Imaging Program, and [3]Laboratory of Pathology at [4]Center for Cancer Research, National Cancer Institute and Clinical Center [5]Pharmacy and [6]Hematopathology Section, National Institutes of Health; [7]Walter Reed Medical Center; [8]Myeloma Service, Memorial Sloan Kettering Cancer Center; [9]Department of Lymphoma and Myeloma, MD Anderson Cancer Center; [10]Levine Cancer Institute; [11]Wheeling Hospital

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Conclusions

- Treatment of HR-SMM with KRd-R to prevent symptomatic multiple myeloma resulted in an MRD negative CR rate of 70.2% with a median duration of 5.5 years
- At the 8-year landmark, less than 10% of patients developed symptomatic MM which is favorable compared to historical rates of >75% with no treatment
- The use of KRd-R triplet therapy appeared to be more tolerable (less treatment discontinuation) and significantly more efficacious than alternative approaches using lenalidomide +/- dexamethasone
- Efficacy of KRd-R appeared similar to more aggressive approaches incorporating HDM-ASCT with KRd-R
- Overall, the benefit compared to risk with KRd in SMM is very favorable however, future randomized trials will be needed to confirm and lock down this conclusion

Kazandjian D et al. ASH 2020;Abstract 548.

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

RAFAEL FONSECA, MD	KRd
OLA LANDGREN, MD, PHD	KRd/daratumumab
NIKHIL C MUNSHI, MD	RVd
ROBERT Z ORLOWSKI, MD, PHD	RVd
EDWARD A STADTMAUER, MD	RVd
SAGAR LONIAL, MD	RVd/daratumumab
S VINCENT RAJKUMAR, MD	RVd
PAUL G RICHARDSON, MD	RVd
GENERAL MEDICAL ONCOLOGISTS (N = 75)	RVd, RVd/daratumumab

K = carfilzomib; R = lenalidomide; d = dexamethasone; V = bortezomib

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
2. KRd
3. CyBorD
4. Rd/daratumumab
5. RVd/daratumumab
6. KRd/daratumumab
7. MPV (melphalan/prednisone/bortezomib)/daratumumab
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)?

RAFAEL FONSECA, MD	KRd	EDWARD A STADTMAUER, MD	RVd/daratumumab
OLA LANDGREN, MD, PHD	KRd/daratumumab	SAGAR LONIAL, MD	KRd
NIKHIL C MUNSHI, MD	RVd/daratumumab	S VINCENT RAJKUMAR, MD	RVd/daratumumab
ROBERT Z ORLOWSKI, MD, PHD	RVd/daratumumab	PAUL G RICHARDSON, MD	RVd/daratumumab

GENERAL MEDICAL ONCOLOGISTS (N = 75)	RVd, KRd

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 del(17p)?

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

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 del(17p)?

RAFAEL FONSECA, MD	RVd/daratumumab	EDWARD A STADTMAUER, MD	Rd/daratumumab
OLA LANDGREN, MD, PHD	RVd/daratumumab	SAGAR LONIAL, MD	RVd or RVd lite
NIKHIL C MUNSHI, MD	Rd/daratumumab	S VINCENT RAJKUMAR, MD	RVd or RVd lite
ROBERT Z ORLOWSKI, MD, PHD	RVd or RVd lite	PAUL G RICHARDSON, MD	RVd or RVd lite

GENERAL MEDICAL ONCOLOGISTS (N = 75)	RVd or RVd lite, Rd/daratumumab

Outside of a clinical trial setting, have you ordered or would you order a minimal residual disease (MRD) assay to inform the decision regarding autotransplant after induction treatment?

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

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Outside of a clinical trial setting, have you ordered or would you order an MRD assay to inform the decision regarding treatment in the postinduction autotransplant setting?

RAFAEL FONSECA, MD	I haven't but would for the right pt
OLA LANDGREN, MD, PHD	I have
NIKHIL C MUNSHI, MD	I have
ROBERT Z ORLOWSKI, MD, PHD	I have
EDWARD A STADTMAUER, MD	I haven't and would not
SAGAR LONIAL, MD	I haven't and would not
S VINCENT RAJKUMAR, MD	I haven't and would not
PAUL G RICHARDSON, MD	I have
GENERAL MEDICAL ONCOLOGISTS (N = 75)	I haven't and would not

Agenda

Module 1: Up-front management

- **GRIFFIN, APOLLO, IMF 2009, TOURMALINE-MM2**

Module 2: Relapsed/refractory disease

- **Isatuximab, belantamab mafadotin, selinexor**

Module 3: Chimeric antigen receptor T-cell therapy; bispecific antibodies

Module 4: Other novel strategies

- **Venetoclax, melflufen, iberdomide, BRAF inhibitors**

Therapeutic Advances in Multiple Myeloma

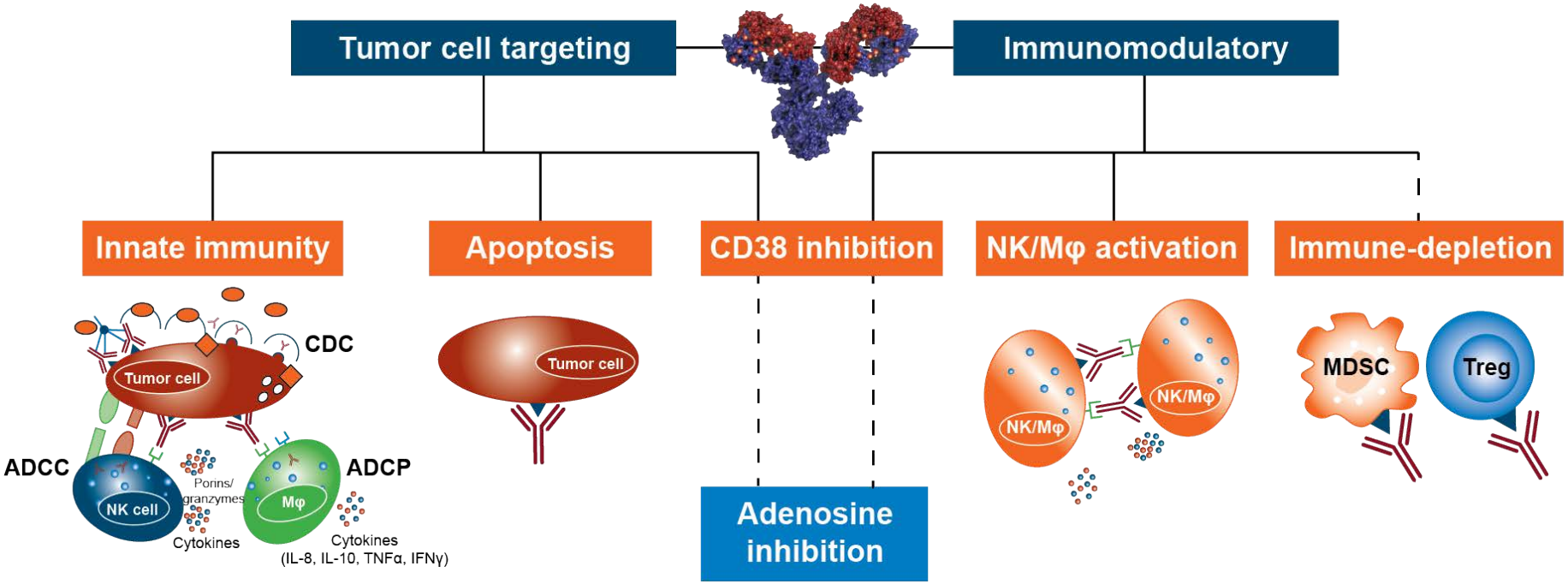
- ~~11~~ 12 new Agents in last 15 years:
- Proteasome inhibitors: bortezomib, Carfilzomib, Ixazomib
- Immunomodulator: thalidomide, lenalidomide, pomalidomide
- HDAC inhibitor: Panobinostat
- Monoclonal antibodies: elotuzumab, daratumumab Isatuximab, Belantamab mafodotin
- Exportin inhibitor: Selinexor
- Alkylating Agent: bendamustine
- Existing older agents: melphalan, dexamethasone. cyclophosphamide, anthracycline, etoposide
- Near approval: Ide-cel, Cilta-cel, melflufen, venetoclax, BCMA-bispecifics

- 2-, 3-, 4-drug combinations - effective in relapsed/refractory myeloma

Courtesy of Nikhil C Munshi, MD

Isatuximab: Mechanism of Action

- Active in combination studies in R/R MM



- **Effective combinations**
  - **ICARIA-MM – Isa Pd**
  - **IKEMA – Isa Kd**

Courtesy of Nikhil C Munshi, MD

IKEMA Depth of Response and Response Kinetics of Isatuximab plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: IKEMA Interim Analysis

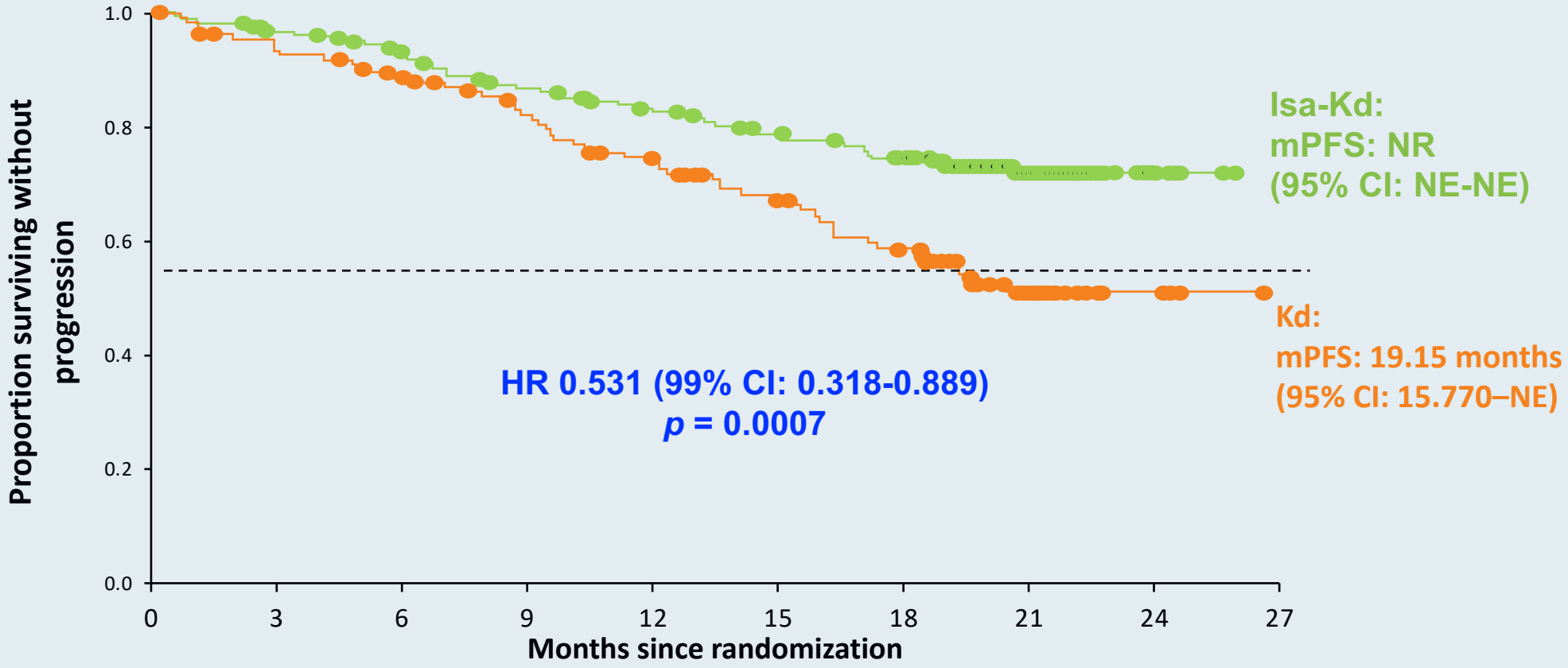
Thomas Martin,[1] Joseph Mikhael,[2] Roman Hajek,[3] Kihyun Kim,[4] Kenshi Suzuki,[5] Cyrille Hulin,[6] Mamta Garg,[7] Hang Quach,[8] Hanlon Sia,[9] Anup George,[10] Tatiana Konstantinova,[11] Marie-Laure Risse,[12] Gaelle Asset,[13] Sandrine Macé,[12] Helgi van de Velde,[14] Philippe Moreau[15]

[1]Department of Medicine, University of California, San Francisco, CA, USA; [2]Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, AZ, USA; [3]Faculty of Medicine, University Hospital Ostrava, Ostrava, Czech Republic; [4]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [5]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [6]Department of Hematology, University Hospital Bordeaux, Bordeaux, France; [7]Department of Haematology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [8]Faculty of Medicine, University of Melbourne and St Vincent's Hospital, Victoria, Australia; [9]Cancer Care & Haematology Unit, The Tweed Hospital, Tweed Heads, NSW, Australia; [10]Wellington Blood and Cancer Center, Wellington, New Zealand; [11]Hematology Department, Regional Hospital #1, Ekaterinburg, Russia; [12]Sanofi Research and Development, Vitry-Sur-Seine, France; [13]Sanofi Research and Development, Chilly-Mazarin, France; [14]Sanofi, Cambridge, MA; [15]Department of Hematology, University Hospital of Nantes, Nantes, France

Presentation at the 62nd American Society of Hematology (ASH) Virtual Scientific Meeting, December 5–8, 2020

Presentation Code: 414

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.

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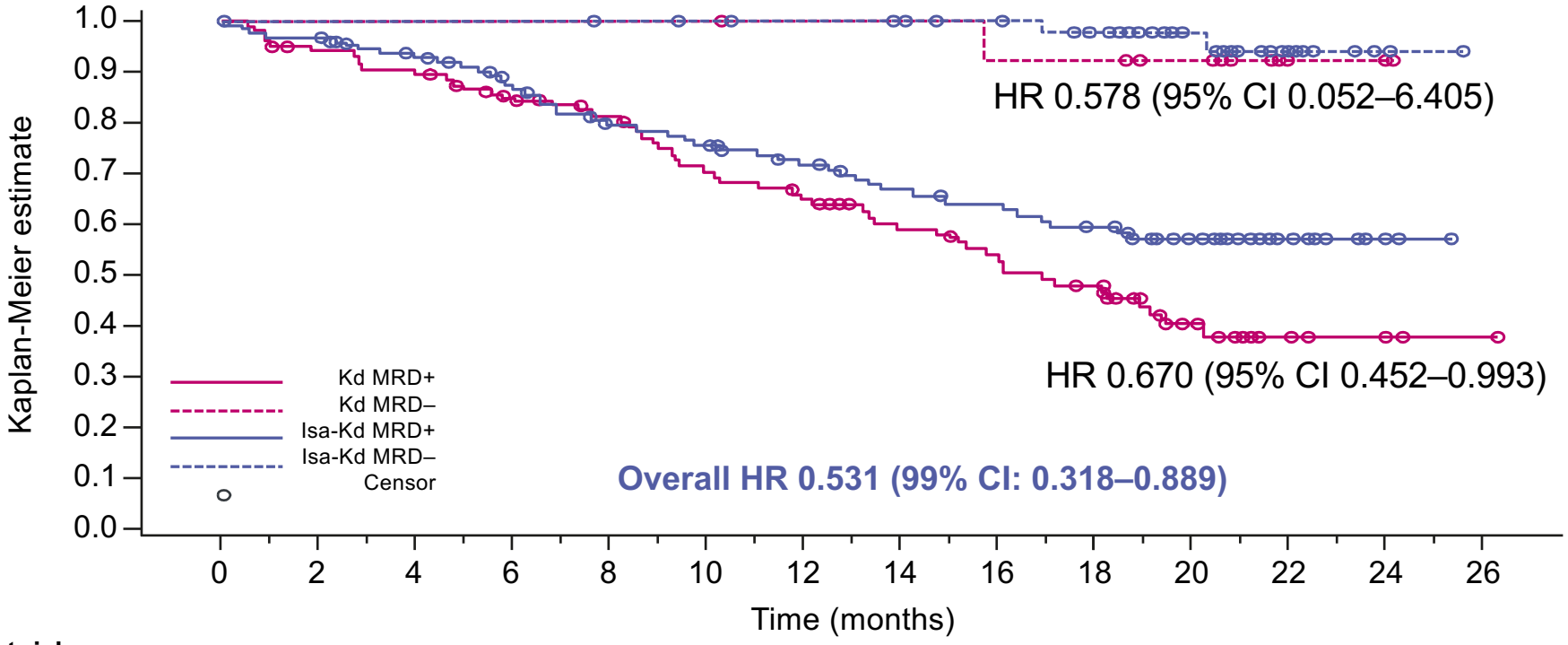
IKEMA: PFS According to MRD Status



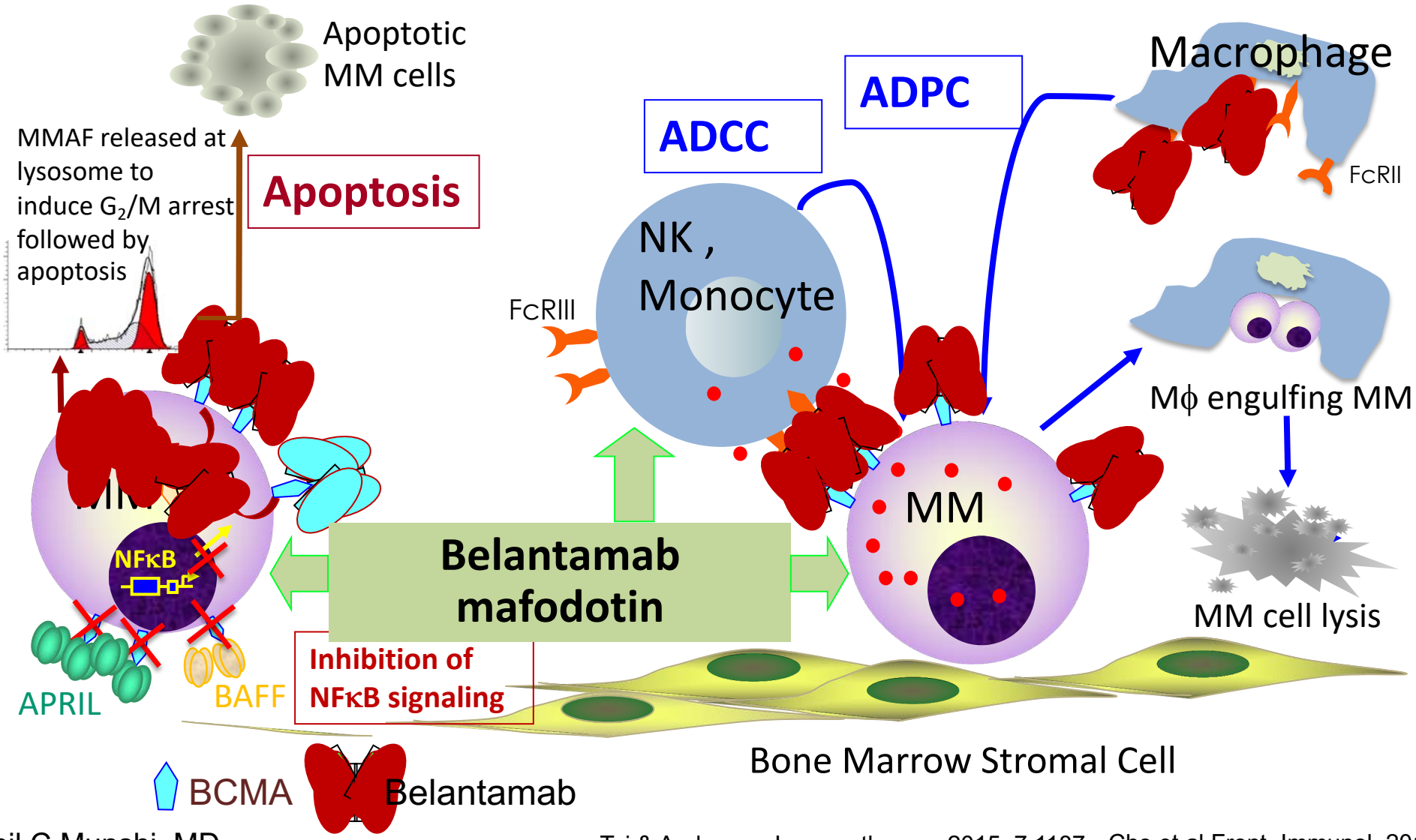
Number at risk					
Kd - MRD+	107	83	58	38	4
Kd - MRD−	16	16	14	12	2
Isa-Kd - MRD+	126	98	73	57	3
Isa-Kd - MRD−	53	53	51	43	2

A more pronounced PFS benefit was seen in MRD– patients
PFS HR in favor of Isa-Kd for both MRD– and MRD+ patients and consistent with the primary PFS HR

d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; PFS, progression-free survival.

Martin T et al. ASH 2020:Abstract 414

Belantamab Mafodotin - a BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects via Multiple MOAs



Courtesy of Nikhil C Munshi, MD Tai et al Blood 2014 123:3128 Tai & Anderson Immunotherapy 2015 ;7:1187 Cho et al Front. Immunol. 2018. 01821

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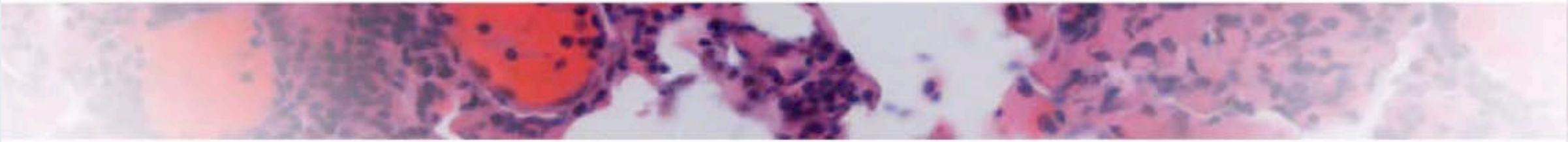

DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) – 1-Year Outcomes by Prior Therapies

Sagar Lonial[1], Hans C. Lee[2], Ashraf Badros[3], Suzanne Trudel[4], Ajay K. Nooka[1], Ajai Chari[5], Al-Ola Abdallah[6], Natalie Callander[7], Douglas Sborov[8], Attaya Suvannasankha[9], Katja Weisel[10], Peter M. Voorhees[11], Joanna Opalinska[12], Eric Zhi[12], January Baron[12], Trisha Piontek[12], Ira Gupta[12], Adam D. Cohen[13]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of Maryland at Baltimore, Baltimore, MD, USA; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]University of Kansas Cancer Center, Fairway, KS, USA; [7]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [8]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [9]Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN, USA; [10]University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; [11]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [12]GlaxoSmithKline, Philadelphia, PA, USA; [13]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

Poster No. 1417 | Presented at the 62nd American Society of Hematology Annual Meeting and Exposition | December 5–8, 2020

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DREAMM-2: Single-Agent Belantamab Mafodotin 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)

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

Lonial S et al. ASH 2020;Abstract 1417.

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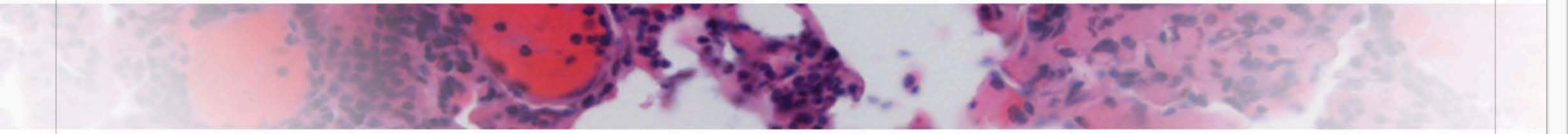

Recovery of Ocular Events with Longer-term Follow-up in the DREAMM-2 Study of Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

Sagar Lonial,[1] Ajay K. Nooka,[1] Praneetha Thulasi,[2] Ashraf Z. Badros,[3] Bennie H. Jeng,[4] Natalie S. Callander,[5] Douglas Sborov,[6] Brian E. Zaugg,[7] Rakesh Popat,[8] Simona Degli Esposti,[9] Julie Byrne,[10] Joanna Opalinska,[10] January Baron,[10] Trisha Piontek,[10] Ira Gupta,[10] Reza Dana,[11] Asim V. Farooq,[12] Andrzej Jakubowiak[12]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Emory Eye Center, Emory University, Atlanta, GA, USA; [3]University of Maryland School of Medicine, Baltimore, MD, USA; [4]Department of Ophthalmology and Visual Sciences, University of Maryland School of Medicine, Baltimore, MD, USA; [5]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [6]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [7]Moran Eye Center, University of Utah, Salt Lake City, UT, USA; [8]University College London Hospitals, NHS Foundation Trust, London, UK; [9]NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK; [10]GlaxoSmithKline, Upper Providence, PA, USA; [11]Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA; [12]University of Chicago Medical Center, Chicago, IL, USA

Poster No. 3224 | Presented at the 62nd American Society of Hematology Annual Meeting and Exposition | December 5–8, 2020

Conclusions

Long-term follow-up in this DREAMM-2 post-hoc analysis demonstrated that although ocular events were common, the majority of patients recovered while remaining on treatment. No new ocular safety signals were observed at 13-month follow-up

Though keratopathy (MECs) were frequently observed on eye exam (72% of patients), 44% of patients did not experience symptoms such as a clinically meaningful BCVA decline, and treatment discontinuation was rare

Most patients recovered from the first keratopathy (MECs) event (77%) or from clinically meaningful BCVA decline (82%)

With some patients lost to follow-up, it is not possible to obtain full recovery data for all events

Implications for managing belamaf-treated patients

The recovery of most ocular events is consistent with the established safety profile of belamaf[1]

Events can be asymptomatic so close monitoring by an eye care professional is important

Ocular events can be managed by dose modifications, without impacting efficacy[2-4]

Lonial S et al. ASH 2020;Abstract 3224.

RTP RESEARCH TO PRACTICE

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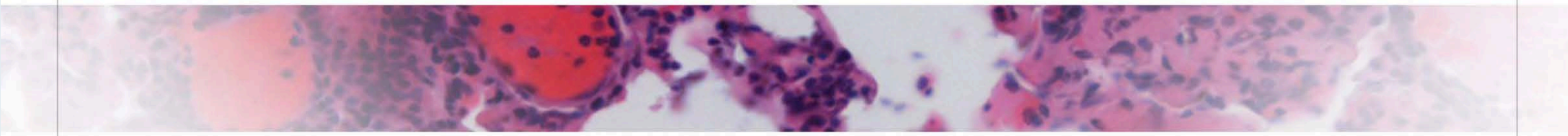


DREAMM-6: Safety, Tolerability, and Clinical Activity of Belantamab Mafodotin (Belamaf) in Combination with Bortezomib/Dexamethasone (Vd) in Relapsed/Refractory Multiple Myeloma (RRMM)

Rakesh Popat,[1] Ajay Nooka,[2] Keith Stockerl-Goldstein,[3] Rafat Abonour,[4] Ryan Ramaekers,[5] Amit Khot,[6] Adam Forbes,[7] Cindy Lee,[8] Bradley Augustson,[9] Andrew Spencer,[10] Maria Victoria Mateos,[11] Bikramjit Chopra,[12] Rachel Rogers,[13] Deborah A. Smith,[14] Jacqueline Davidge,[12] Rocio Montes de Oca,[13] Geraldine Ferron-Brady,[13] Anne Yeakey,[13] Mala Talekar,[13] Brandon E. Kremer,[13] Ira Gupta,[13] Hang Quach,[15]

[1]University College London Hospitals, NHS Foundation Trust, London, UK; [2]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [3]Washington University Medical School, St. Louis, MO, USA; [4]Queen Elizabeth Hospital, Adelaide, SA, Australia; [5]CHI Health St Francis Cancer Treatment Center, Grand Island, NE, USA; [6]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia; [7]Royal Cornwall Hospital, Truro, Cornwall, UK; [8]Department of Haematology, Queen Elizabeth Hospital, Adelaide, SA, Australia; [9]Department of Haematology, Sir Charles Gairdner Hospital, Perth, WA, Australia; [10]Department of Haematology, The Alfred Hospital, Melbourne, VIC, Australia; [11]University Hospital of Salamanca-Instituto de Investigación Biomédica de Salamanca, Cancer Research Center-IBMCC (USAL-CSIC), Salamanca, Spain; [12]GlaxoSmithKline (GSK), Uxbridge, Middlesex, UK; [13]GSK, Upper Providence, PA, USA; [14]GSK, Waltham, MA, USA; [15]University of Melbourne, St. Vincent's Hospital Melbourne, VIC, Australia.

Poster No. 1419| Presented at the 62nd American Society of Hematology Annual Meeting and Exposition (Virtual Format) | December 5–8, 2020

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

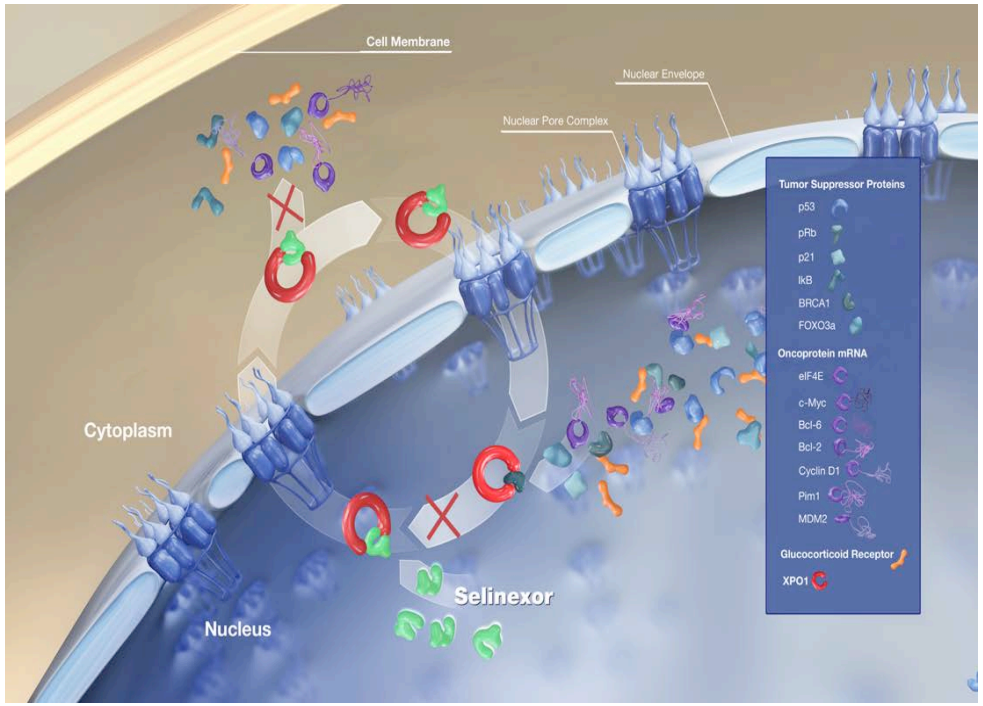
Patients with AE, n (%)	Belamaf 2.5 mg/kg SINGLE + BorDex (N = 18) [Parts 1 and 2]
AEs related to study treatment	18 (100)
Grade 3/4 AE	16 (89)
AEs leading to permanent discontinuation of a study treatment	5 (28)
AEs leading to permanent discontinuation of belamaf	0
AEs leading to dose reductions	13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

Popat R et al. ASH 2020;Abstract 1419.

Targeting XPO-1

Selinexor approved for use in pts with RRMM who have received four prior therapies (including pts refractory to two proteasome inhibitors or IMiDs and an anti-CD38 antibody)

Selinexor is an oral XPO-1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids, and suppresses oncoprotein expression[1]

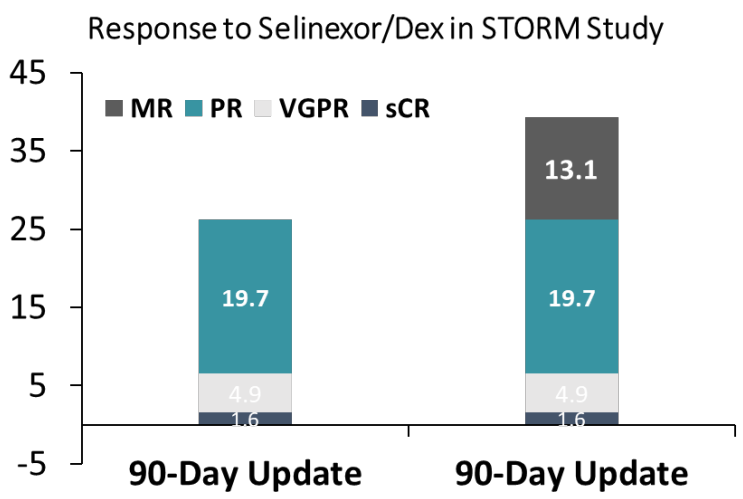


Courtesy of Nikhil C Munshi, MD

[1]Schmidt et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018 [4]Turner et al, 2017 unpublished

Targeting Nuclear Transport
Selinexor

- Inhibits XPO1
  - XPO1 is the major nuclear export protein
  - XPO1 is overexpressed in MM
- Results of STORM Study
  - N = 122; median 7 prior treatments
  - 86% refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
  - mDOR = 4.4 months
  - Associated with hematologic and GI toxicity
    - Aggressive supportive care needed



FDA-Approved July 2019
In combination with Dex in adults with RRMM after ≥ 4 prior therapies (≥ 2 PIs, ≥ 2 immunomodulatory drugs, and an anti-CD38 antibody)

- Chari A, et al. *N Engl J Med.* 2019;381:727-738.

Courtesy of Nikhil C Munshi, MD

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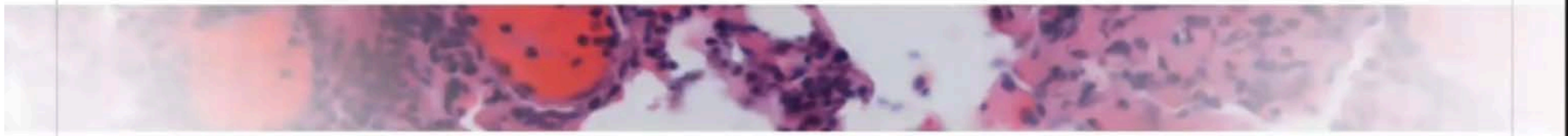


Selinexor in Combination with Pomalidomide and Dexamethasone (SPd) for Treatment of Patients with Relapsed Refractory Multiple Myeloma (RRMM)

Christine I Chen MD[1], Nizar Bahlis MD[2], Cristina Gasparetto MD[3], Sascha A Tuchman MD[4], Brea C Lipe MD[5], Muhamed Baljevic MD[6], Rami Kotb MD[7], Heather J Sutherland MD PhD[8], William I. Bensinger MD[9], Michael Sebag MD PhD[10], Richard LeBlanc MD FRCPC[11], Christopher P Venner MD[12], Gary J Schiller MD[13], Suzanne Lentzsch MD PhD[14], Natalie Scott Callander MD[15], Adriana C Rossi MD[16], Noa Biran[17], Heidi Sheehan[18], Dane Van Domelen[18], Kazuharu Kai MD PhD[18], Hongwei Wang MD[18], Jatin Shah MD[18], Sharon Shacham PhD MBA[18], Michael G Kauffman MD PhD[18] and **Darrell J White MD**[19]

[1]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [2]Charbonneau Cancer Research Institute, Calgary, AB, Canada; [3]Duke Univ. Medical Center, Durham, NC; [4]University of North Carolina, Chapel Hill, NC; [5]University of Rochester Medical College, Rochester, NY; [6]University of Nebraska Medical Center, Omaha, NE; [7]Cancer Care Manitoba, Winnipeg, MB, Canada; [8]Vancouver General Hospital, Vancouver, BC, Canada; [9]Myeloma and Transplant Program, Swedish Cancer Institute, Seattle, WA; [10]Royal Victoria Hospital, Montreal, QC, Canada; [11] Maisonneuve-Rosemont Hospital, University of Montreal, QC, Canada; [12]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [13]David Geffen School of Medicine at UCLA, Los Angeles, CA; [14]Colombia University, New York; [15]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI; [16]NYPH Weill Cornell, New York, NY; [17] Hackensack Meridian Health, Hackensack University Medical Center; [18]Karyopharm Therapeutics, Newton, MA; [19]Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada

Summary and Conclusions

Selinexor, once-weekly, can be safely combined with pomalidomide and low-dose dexamethasone (SPd) in patients with heavily pretreated MM

- **RP2D is selinexor 60 mg QW (pomalidomide 4 mg QD + dexamethasone 40 mg QW)**
- The most common TRAEs were: nausea, neutropenia, anemia, thrombocytopenia, fatigue
  - Expected and can be managed with appropriate supportive care and/or dose modifications

The all oral SPd combination is very active and responses are durable

- **ORR 60%** (≥ VGPR 30%) at the RP2D (compared to expected ORR ≤30% for pomalidomide + dex)[1]
- **CBR was 70% across all patient at RP2D**
- **PFS was 12.2 months for all patients and not reached for RP2D**

Data support planned phase 3 study of all oral combination of SPd vs Pd in patients with a prior PI, Imid and CD-38 mAb (XPORT-MM-031)

Chen CI et al. ASH 2020;Abstract 726.

RTP RESEARCH TO PRACTICE

What is your usual treatment recommendation for a 65-year-old patient with MM treated with RVd → ASCT and maintenance lenalidomide for 1.5 years who then experiences asymptomatic biochemical relapse?

1. Carfilzomib + dexamethasone (dex)
2. Pomalidomide + dex
3. Carfilzomib + pomalidomide + dex
4. Elotuzumab + lenalidomide + dex
5. Elotuzumab + pomalidomide + dex
6. Daratumumab + lenalidomide + dex
7. Daratumumab + pomalidomide + dex
8. Other

What is your usual treatment recommendation for a 65-year-old patient with MM treated with RVd → ASCT and maintenance lenalidomide for 1.5 years who then experiences asymptomatic biochemical relapse?

RAFAEL FONSECA, MD	Observation	EDWARD A STADTMAUER, MD	Daratumumab/ lenalidomide/dex
OLA LANDGREN, MD, PHD	Daratumumab/ pomalidomide/dex	SAGAR LONIAL, MD	Observation
NIKHIL C MUNSHI, MD	Elotuzumab/ lenalidomide/dex	S VINCENT RAJKUMAR, MD	Daratumumab/ pomalidomide/dex
ROBERT Z ORLOWSKI, MD, PHD	Daratumumab/ pomalidomide/dex	PAUL G RICHARDSON, MD	Elotuzumab/ lenalidomide/dex

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Dara/len/dex, Elo/len/dex

Which of the following agents would you generally use first for a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?

1. Isatuximab
2. Selinexor
3. Belantamab mafodotin
4. BCMA-directed CAR T-cell therapy
5. I would not recommend any of these

Which of the following agents would you generally use first for a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?

RAFAEL FONSECA, MD	BCMA-directed CAR T-cell therapy
OLA LANDGREN, MD, PHD	BCMA-directed CAR T-cell therapy
NIKHIL C MUNSHI, MD	BCMA-directed CAR T-cell therapy
ROBERT Z ORLOWSKI, MD, PHD	BCMA-directed CAR T-cell therapy
EDWARD A STADTMAUER, MD	Belantamab mafodotin
SAGAR LONIAL, MD	Belantamab mafodotin
S VINCENT RAJKUMAR, MD	Belantamab mafodotin
PAUL G RICHARDSON, MD	Selinexor
GENERAL MEDICAL ONCOLOGISTS (N = 75)	BCMA-directed CAR T-cell therapy, Belantamab mafodotin

Who performs eye examinations for your patients with MM receiving belantamab mafodotin?

1. Optometrist
2. Ophthalmologist
3. I do not recommend regular eye examinations for my patients receiving belantamab mafodotin
4. I have not administered belantamab mafodotin to a patient with MM
5. Other

Who performs eye examinations for your patients with MM receiving belantamab mafodotin?

RAFAEL FONSECA, MD	Ophthalmologist
OLA LANDGREN, MD, PHD	Ophthalmologist
NIKHIL C MUNSHI, MD	Ophthalmologist
ROBERT Z ORLOWSKI, MD, PHD	Ophthalmologist
EDWARD A STADTMAUER, MD	Ophthalmologist
SAGAR LONIAL, MD	Ophthalmologist
S VINCENT RAJKUMAR, MD	Optometrist
PAUL G RICHARDSON, MD	Ophthalmologist

Agenda

Module 1: Up-front management

- **GRIFFIN, APOLLO, IMF 2009, TOURMALINE-MM2**

Module 2: Relapsed/refractory disease

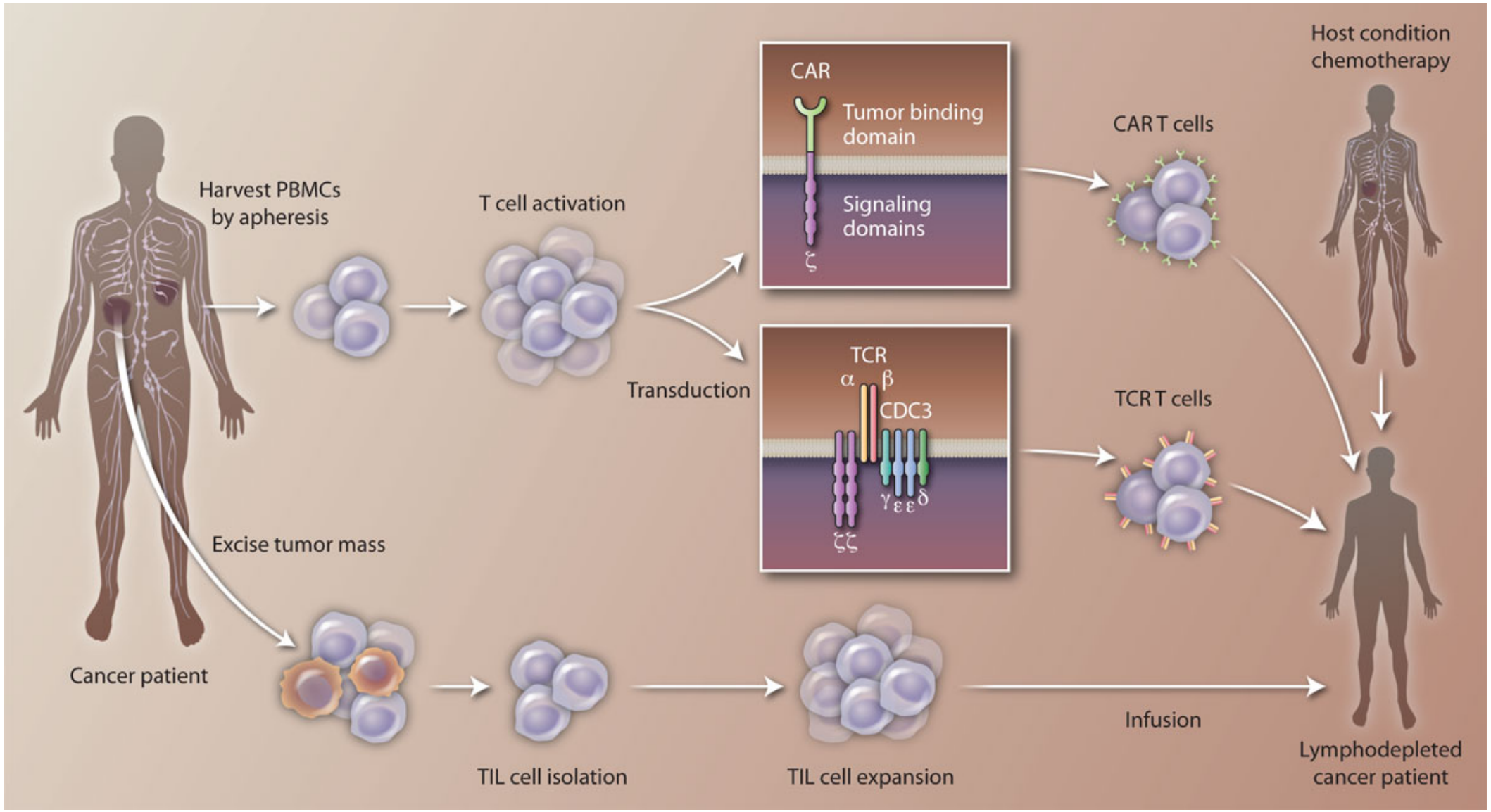
- **Isatuximab, belantamab mafadotin, selinexor**

Module 3: Chimeric antigen receptor T-cell therapy; bispecific antibodies

Module 4: Other novel strategies

- **Venetoclax, melflufen, iberdomide, BRAF inhibitors**

Adoptive T-cell therapy (three major approaches)

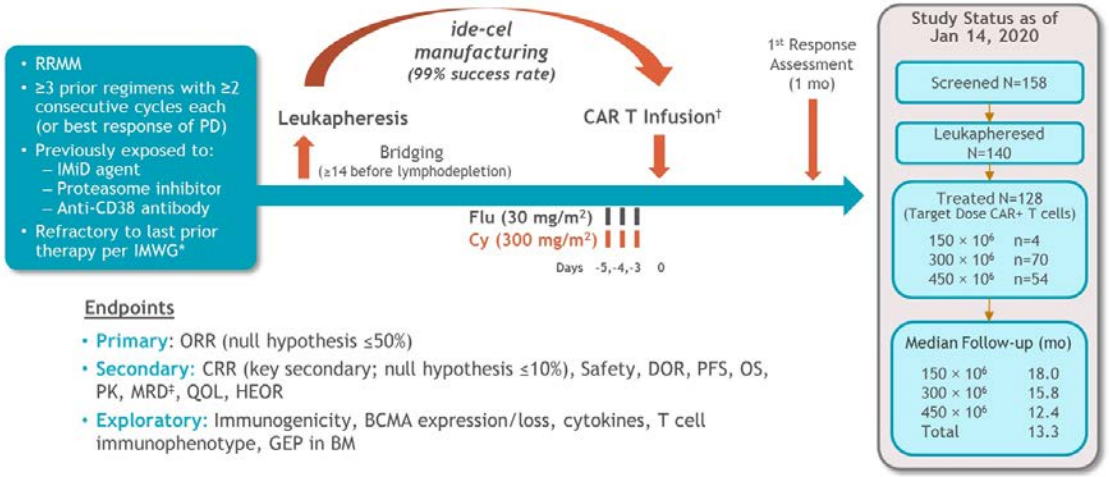


June et al *Sci Trans Med 2015*

Courtesy of Edward A Stadtmauer, MD

BCMA Directed CAR T Studies: ASH 2019, ASCO 2020

Phase II Pivotal KarMMa Study



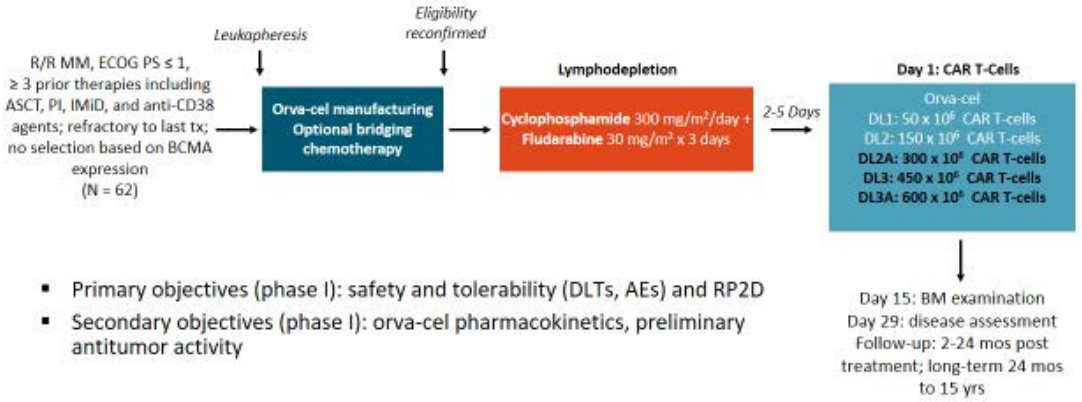
Endpoints

- **Primary:** ORR (null hypothesis ≤50%)
- **Secondary:** CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory:** Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.
*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. †Patients were required to be hospitalized for 14 d post infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.

EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

EVOLVE: Study Design



- Primary objectives (phase I): safety and tolerability (DLTs, AEs) and RP2D
- Secondary objectives (phase I): orva-cel pharmacokinetics, preliminary antitumor activity

Mailankody. ASCO 2020. Abstr 8504.

CARTITUDE-1: Phase 1b/2 Study Design

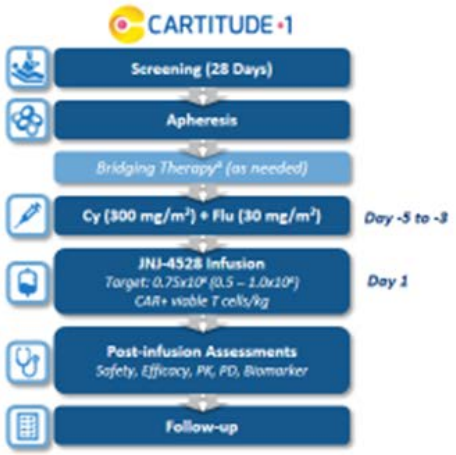
Primary Objectives

- **Phase 1b:** Characterize safety and confirm phase 2 dose as informed by the LEGEND-2 study
- **Phase 2:** Evaluate efficacy of JNJ-4528

Key Eligibility Criteria

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

- Median administered dose = 0.73x10⁶ (0.52 – 0.89x10⁶) CAR+ viable T cells/kg
- Median follow-up at data cut-off = 6 mo (3 – 14)



Similar approach in 3 studies:

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

BCMA Directed CAR T Studies: ASH 2019, ASCO 2020

Response Rates

	KarMMa	EVOLVE	CARTITUDE-1
↓ANC ≥G3, %	89	90	100
↓plts ≥G3, %	52	47	69
CRS: all, ≥G3,%	84, 6	89, 3	93, 7
Med. time to CRS, duration, days	1 (1-12) 5 (1-63)	2 (1-4) 4 (1-10)	7 (2-12) 4 (2-64)
ICANS: all, ≥G3,%	17, 3	13, 3	10, 3
HLH/MAS, %	--	5	? 7 (lfts)
Infections: all, ≥G3 %	69, --	40, 13	--, 19
Toci/steroid/ anakinra use, %	52/15/0	76/52/23	79/21/21

	KarMMa (n = 128)	EVOLVE (n = 62)	CARTITUDE-1 (n = 29)
ORR, %	73 (66-81)	92	100
sCR/CR, %	33	36	86
MRD neg ≥10^{-5}, % (of evaluable)	94	84	81
PFS/DoR, months	8.8/10.7	NR*	NR**
Screened Apheresed Treated	150 140 128	--	35 35 29

Presented By Krina Patel at ASCO 2020

Courtesy of Edward A Stadtmauer, MD

Efficacy and safety of idecabtagene vicleucel (ide-cel, bb2121) in elderly patients with relapsed and refractory multiple myeloma: KarMMa subgroup analysis

Jesús Berdeja,[1] Noopur S. Raje,[2] David S. Siegel,[3] Yi Lin,[4] Larry D. Anderson, Jr,[5] Paula Rodriguez-Otero,[6] Salomon Manier,[7] Hermann Einsele,[8] Michele Cavo,[9] Anna Truppel-Hartmann,[10] Everton Rowe,[11] Jill Sanford,[11] Julie Wang,[11] Timothy B. Campbell,[11] and Sundar Jagannath[12]

[1]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [2]Massachusetts General Hospital, Boston, MA, USA; [3]Hackensack University Medical Center, Hackensack, NJ, USA; [4]Mayo Clinic, Rochester, MN, USA; [5]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [6]Clinical Universidad de Navarra, Navarra, Spain; [7]Service des Maladies du Sang, CHU Lille, Lille, France; [8]University Hospital of Würzburg, Würzburg, Germany; [9]"Seràgnoli" Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [10]bluebird bio, Cambridge, MA, USA; [11]Bristol Myers Squibb, Princeton, NJ, USA; and [12]Mount Sinai Medical Center, New York, NY, USA

ASH 2020, Presentation 1367

KarMMa: Ide-Cel for Elderly Patients with R/R MM Subgroup Analysis by Age

		Age ≥65 Years (n=45)	Age ≥70 Years (n=20)	All ide-cel Treated (N=128)
Efficacy Outcomes				
ORR, n (%) [95% CI]		38 (84) [70.5–93.5]	18 (90) [76.9–100]	94 (73) [65.8–81.1]
CR rate, n (%) [95% CI]		14 (31) [18.2–46.6]	7 (35) [14.1–55.9]	42 (33) [24.7–40.9]
PFS, median (95% CI), mo		8.6 (4.9–12.2)	10.2 (3.1–12.3)	8.8 (5.6–11.6)
DOR,[a] median (95% CI), mo		10.9 (4.5–11.4)	11.0 (3.9–11.4)	10.7 (9.0–11.3)
Adverse Events of Interest[b]				
CRS, n (%)	Overall	40 (89)	20 (100)	107 (84)
	Grade ≥3	2 (4)	2 (10)	7 (5)
NT, n (%)	Overall	11 (24)	6 (30)	23 (18)
	Grade ≥3	4 (9)	1 (5)	4 (3)

CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NT, investigator-identified neurotoxicity; ORR, overall response rate; PFS, progression-free survival.
[a]Duration of response among responders.
[b]NT was graded according to NCI CTCAE v4.03. CRS was graded according to Lee et al. criteria (*Blood* 2014; 124:188-95).

Berdeja J et al. ASH 2020;Abstract 1367.

RTP RESEARCH TO PRACTICE

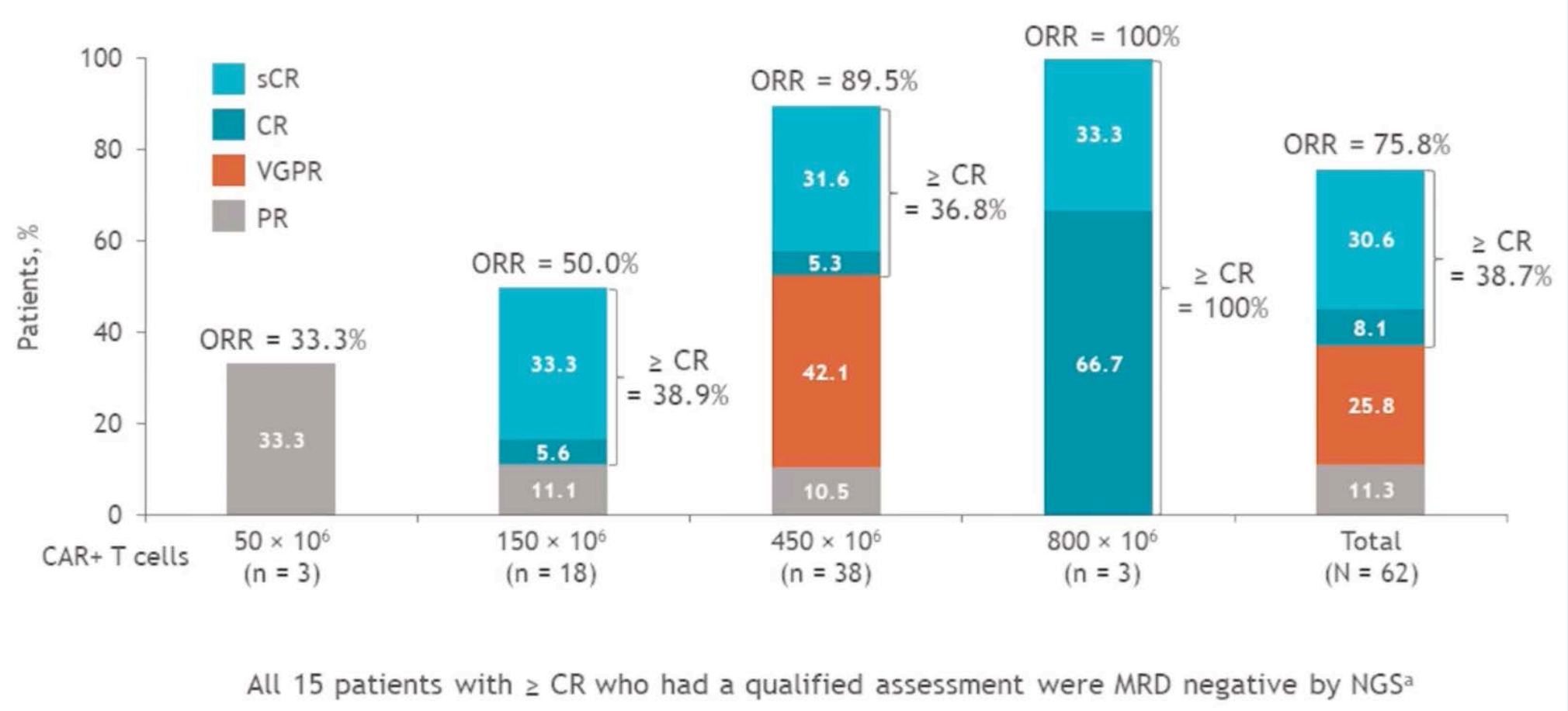
Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in patients with relapsed and refractory multiple myeloma: updated results from phase 1 CRB-401 study

Yi Lin,[1] Noopur S. Raje,[2] Jesús G. Berdeja,[3] David S. Siegel,[4] Sundar Jagannath,[5] Deepu Madduri,[5] Michaela Liedtke,[6] Jacalyn Rosenblatt,[7] Marcela V. Maus,[2] Monica Massaro,[8] Fabio Petrocca,[8] Andrea Caia,[9] Zhihong Yang,[9] Timothy B. Campbell,[9] Kristen Hege,[9] Nikhil C. Munshi,[10] and James N. Kochenderfer[11]

[1]Mayo Clinic, Rochester, MN; [2]Massachusetts General Hospital Cancer Center, Boston, MA; [3]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; [4]Hackensack University Medical Center, Hackensack, NJ; [5]Mount Sinai Medical Center, New York, NY; [6]Stanford University Medical Center, Palo Alto, CA; [7]Beth Israel Deaconess Medical Center, Boston, MA; [8]bluebird bio, Inc, Cambridge, MA; [9]Bristol Myers Squibb, Princeton, NJ; [10]Dana-Farber Cancer Institute, Boston, MA; [11]Surgery Branch, National Cancer Institute/National Institutes of Health, Bethesda, MD

ASH 2020, Presentation 131

CRB-401: Response, Survival, Duration of Response, Rates of CRS and Neurotoxicity



- PFS = 8.8 months
- OS = 19.4 months
- DoR = 10.7 months

- CRS: common but typically not severe
- Neurologic toxicity: uncommon and rarely severe

Lin Y et al. ASH 2020;Abstract 131.

RTP RESEARCH TO PRACTICE

CRB-401: Safety and Tolerability

AEs of special interest, n (%)	Any grade N = 62	Grade 3/4 N = 62
Any AE	62 (100)	61 (98.4)
Neutropenia	57 (91.9)	55 (88.7)
Febrile neutropenia	10 (16.1)	8 (12.9)
Anemia	47 (75.8)	35 (56.5)
Infection[a]	47 (75.8)	14 (22.6)
CRS[b]	47 (75.8)	4 (6.5)
Thrombocytopenia	46 (74.2)	35 (56.5)
Leukopenia	40 (64.5)	38 (61.3)
Lymphopenia	23 (37.1)	22 (35.5)
Neurologic toxicity[c]	22 (35.5)	1 (1.6)

- Median time to recovery of grade 3/4 neutropenia and thrombocytopenia (in patients without recovery by month 1) was 1.9 and 2.2 months, respectively[d]
- 1 (1.6%) death within 8 weeks of infusion
  - Grade 2 CRS events on days 1 and 8 resolved on days 4 and 12, respectively
  - MR on day 31; persistent cytopenias requiring transfusions
  - Withdrew from care and died in hospice of unknown cause 51 days after infusion
- 7 (11.3%) additional deaths within 6 months
  - 1 (1.6%) due to AE (cardiopulmonary arrest not attributable to ide-cel)
  - 6 (9.7%) due to myeloma

Lin Y et al. ASH 2020;Abstract 131.

ASH 2020

Updated Results from the Phase 1 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

Melissa Alsina, MD[1], Nina Shah, MD[2], Noopur S. Raje, MD[3], Sundar Jagannath, MD[4], Deepu Madduri, MD[5], Jonathan L. Kaufman, MD[6], David S. Siegel, MD, PhD[7], Nikhil C. Munshi, MD[8], Jacalyn Rosenblatt, MD[9], Yi Lin, MD, PhD[10], Andrzej Jakubowiak, MD, PhD[11], Jagoda Jasielec, MD[11], Alison Timm, MS[12], Ashley Turka[12], Pingping Mao, PhD[12], Nathan Martin, PhD[13], Timothy B. Campbell, MD, PhD[13], Kristen Hege, MD[13], Hans Bitter, PhD[12], Fabio Petrocca, MD[12] and Jesus G. Berdeja, MD[14]

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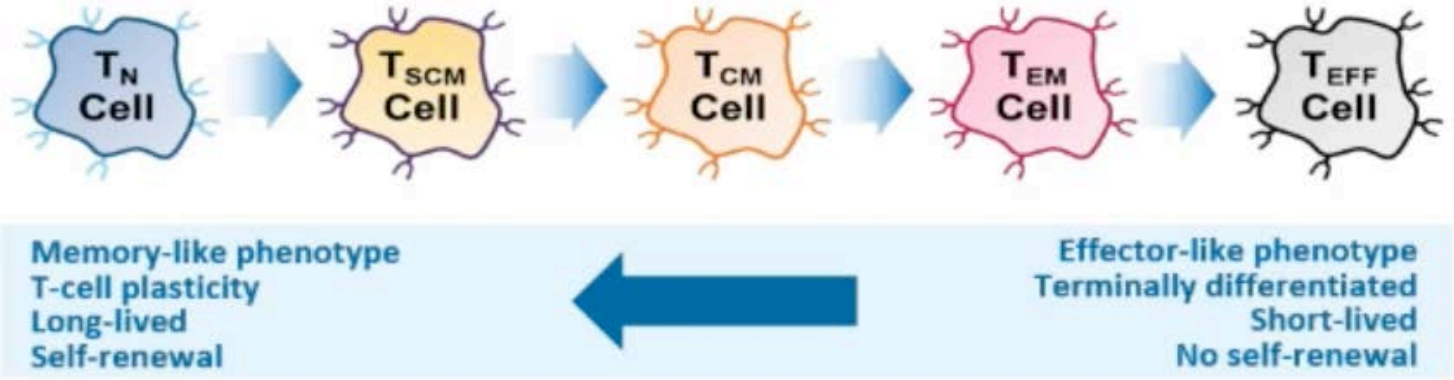
bb21217: Mechanism of Action

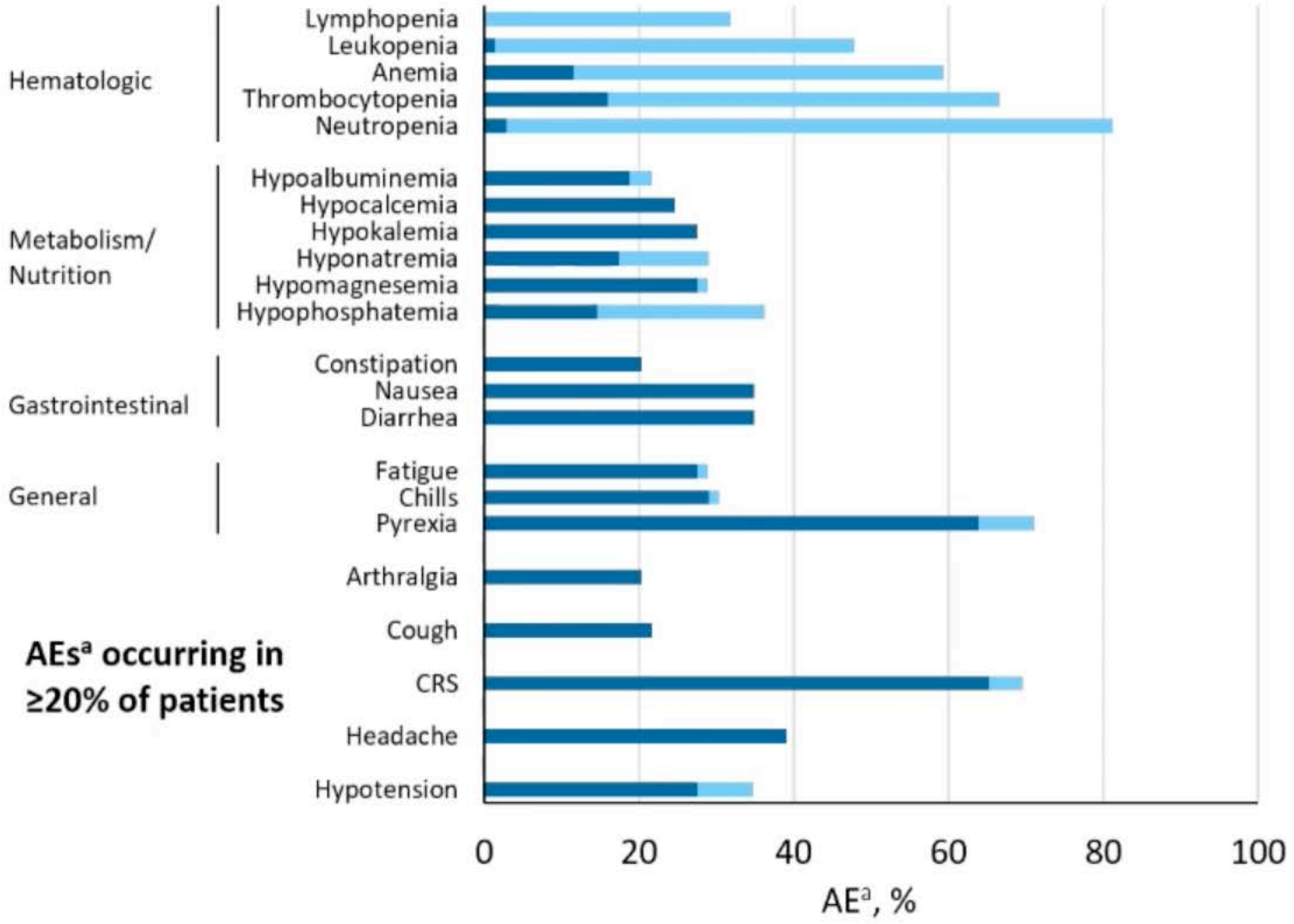
- bb21217 uses the same CAR molecule as bb2121,[1] but is cultured with the PI3K inhibitor, bb007, to enrich for T cells displaying a memory-like phenotype
- CAR T cells enriched for this phenotype may persist and function for longer than non-enriched CAR T cells[2]
- Persistence of functional CAR T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

CRB-402: Safety and Tolerability (Primary Endpoint)



Grade 1/2

Grade 3/4

- Cytopenias were common and not dose related
  - Median time to recovery of Gr 3/4 neutropenia and Gr 3/4 thrombocytopenia was 2.0 mos and 2.2 mos
- Grade 3/4 infections were reported in 18 patients (26%)[b]
  - One death from infection within 6 months, in the absence of MM progression
- Two deaths within 8 weeks of bb21217 infusion, both due to CRS

Alsina M et al. ASH 2020;Abstract 130.

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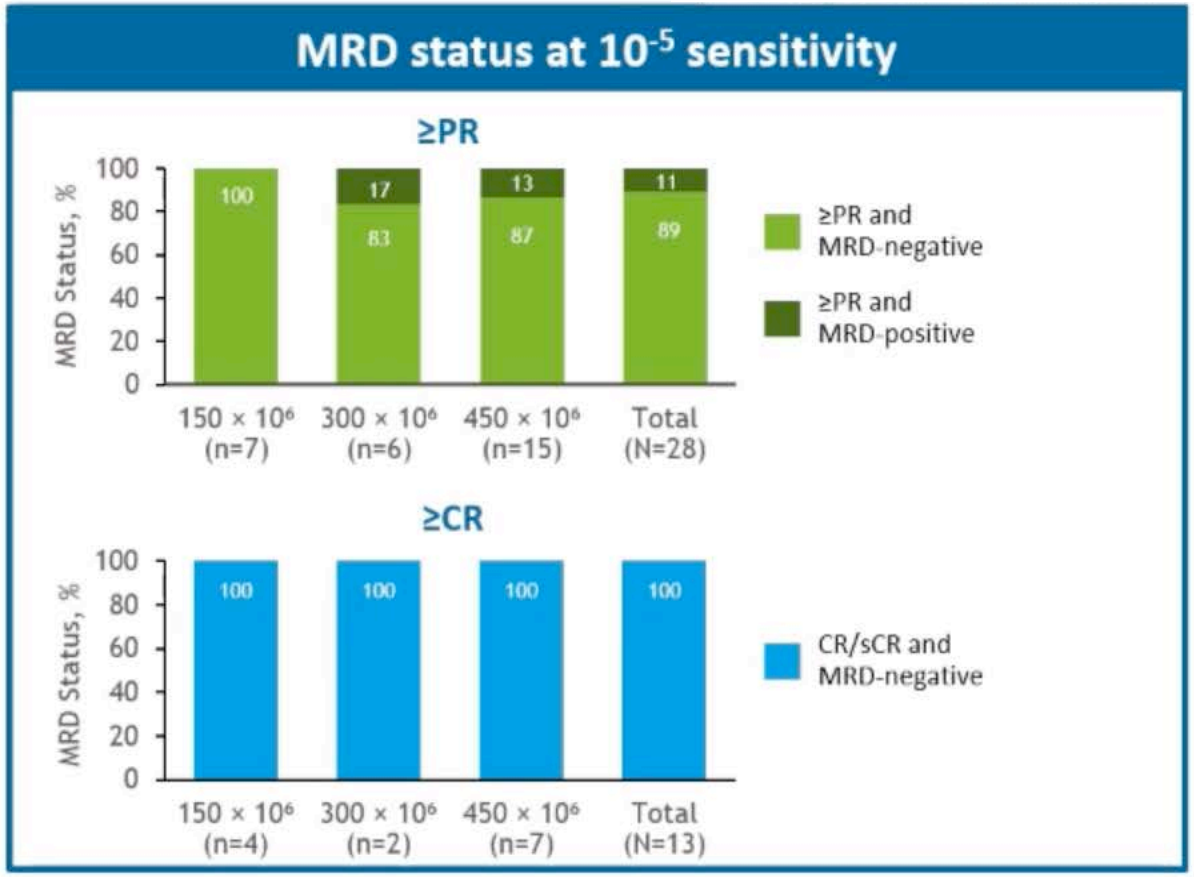
CRB-402: Response, MRD Status, Duration of Response, Rates of CRS and Neurotoxicity

	CAR+ T-Cell Dose			Overall (N=69)
	150×10^6 (n=12)	300×10^6 (n=14)	450×10^6 (n=43)	
Median follow-up (min, max), mo	20 (4, 35)	11 (3, 21)	4 (<1, 17)	6 (<1, 35)
Tumor response,[a] n/N (%)				
ORR	10/12 (**83**)	6/14 (**43**)	24/33 (**73**)	40/59 (**68**)
sCR/CR	5 (42)	2 (14)	10 (30)	17 (29)
VGPR	5 (42)	3 (21)	7 (21)	15 (25)
PR	0	1 (7)	7 (21)	8 (14)
Median time to first response (min, max), mo				
≥PR	1 (1, 2)	1 (1, 1)	1 (1, 2)	1 (1, 2)
≥CR	6 (1, 24)	12 (6, 18)	1 (1, 13)	2 (1, 24)



- Median duration of response across all doses = 17 months
- Low rates of Grade 3 or higher CRS (4%) and neurotoxicity (4%)

Alsina M et al. ASH 2020;Abstract 130.

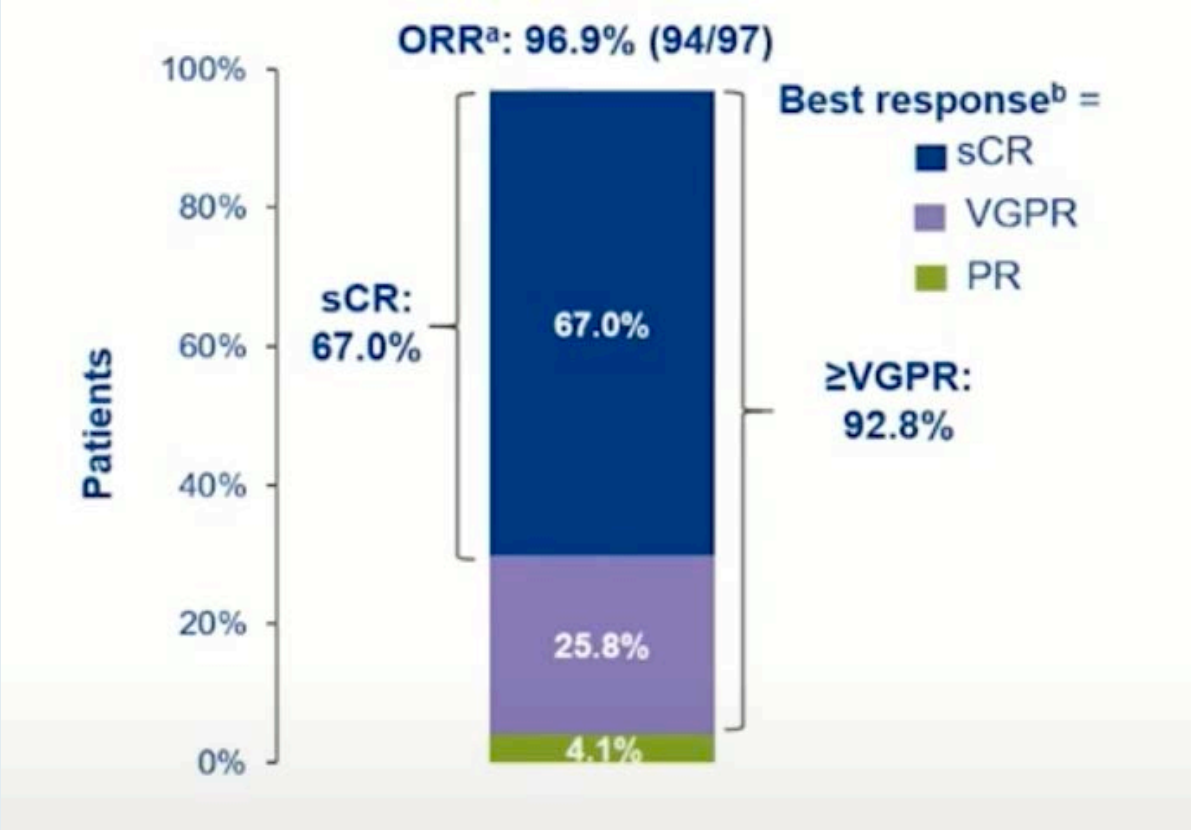
CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T-Cell Therapy, in Relapsed/Refractory Multiple Myeloma

Deepu Madduri[1], Jesus G Berdeja[2], Saad Z Usmani[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], A Keith Stewart[7], Parameswaran Hari[8], Myo Htut[9], Elizabeth O'Donnell[10], Nikhil C Munshi[11], David Avigan[12], Abhinav Deol[13], Alexander Lesokhin[14], Indrajeet Singh[15], Enrique Zudaire[15], Tzu-Min Yeh[16], Alicia J Allred[15], Yunsi Olyslager[17], Arnob Banerjee[15], Jenna D Goldberg[16], Jordan M Schecter[16], Carolyn C Jackson[16], William Deraedt[17], Sen Hong Zhuang[16], Jeffrey Infante[16], Dong Geng[18], Xiaoling Wu[18], Marlene J Carrasco-Alfonso[18], Muhammad Akram[18], Farah Hossain[18], Syed Rizvi[18], Frank Fan[19], Sundar Jagannath[1], Yi Lin[20], Thomas Martin[21]

[1]Mount Sinai Medical Center, New York, NY, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [4]University of Chicago, Chicago, IL, USA; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [7]UHN and the Princess Margaret Cancer Centre, Toronto, ON, Canada; [8]Medical College of Wisconsin, Milwaukee, WI, USA; [9]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [10]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [11]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [12]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA; [13]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [14]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [15]Janssen R&D, Spring House, PA, USA; [16]Janssen R&D, Raritan, NJ, USA; [17]Janssen R&D, Beerse, Belgium; [18]Legend Biotech USA, Inc, Piscataway, NJ, USA; [19]Nanjing Legend Biotechnology Co, Ltd, Nanjing, China; [20]Mayo Clinic, Rochester, MN, USA; [21]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

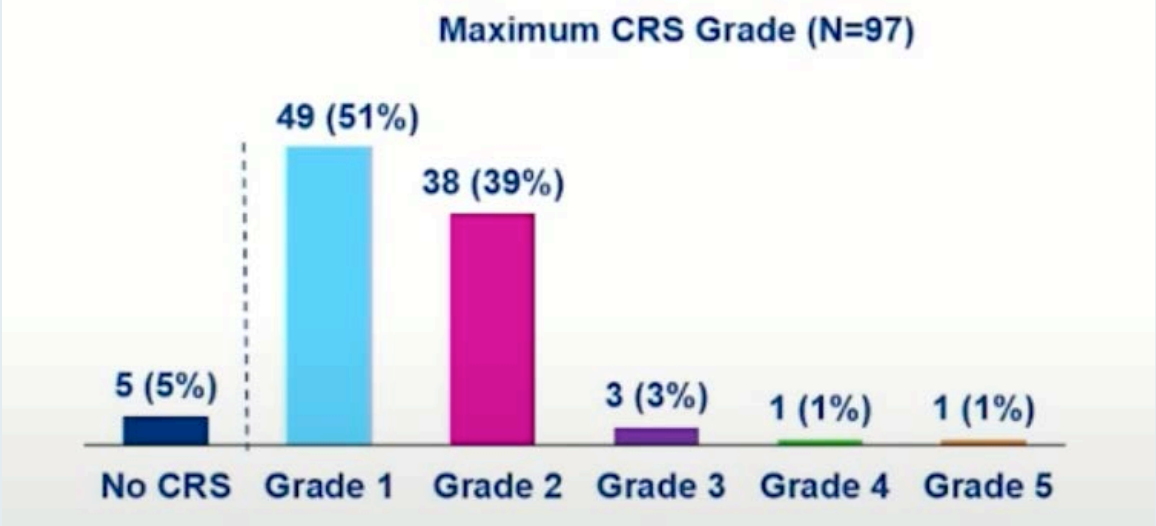
PRESENTED AT THE 62ND AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING & EXPOSITION; DECEMBER 5–8, 2020 PRESENTATION #177

CARTITUDE-1 – Ciltacabtagene Autoleucel (JNJ-4528) for R/R MM: Response and Rates of CRS



- Median time to first response: 1 month (0.9–8.5)
- Responses ongoing in 70 (72.2%) patients
- 93.0% (evaluable patients) achieved MRD 10^{-5} negativity in median 1 month[c]
- In patients with 6 months follow-up, most had cilta-cel CAR+ T cells below the level of quantification in peripheral blood

	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]



- CRS onset
  - Day 4 or later: 89.1% (n=82)
  - Day 6 or later: 73.9% (n=68)
- CRS resolved in 91 (98.9%) patients within 14 days of onset

Madduri D et al. ASH 2020;Abstract 177.

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

Alfred L. Garfall[1], Saad Z. Usmani[2], María-Victoria Mateos[3], Hareth Nahi[4], Niels W.C.J. van de Donk[5], Jesus F. San-Miguel[6], Albert Oriol[7], Laura Rosinol[8], Ajai Chari[9], Manisha Bhutani[2], Lixia Pei[10], Raluca Verona[10], Suzette Girgis[10], Tara Stephenson[10], Jenna D. Goldberg[10], Arnob Banerjee[10], Amrita Krishnan[11]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [2]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [3]Hospital Clinico Universitario de Salamanca, Salamanca, Spain; [4]Karolinska University Hospital at Huddinge, Stockholm, Sweden; [5]Amsterdam University Medical Center, Location VU University Medical Center, Amsterdam, The Netherlands; [6]Clínica Universidad de Navarra, Navarra, Spain; [7]Institut Català d'Oncologia and Institut Josep Carreras. Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [8]Hospital Clínic, Barcelona, Spain; [9]Mt. Sinai School of Medicine, New York, NY, USA; [10]Janssen R&D, Spring House, PA, USA; [11]City of Hope, Duarte, CA, USA

Additional information can be viewed by scanning the QR code or accessing this link: https://oncologysciencehub.com/ASH2020/bispecifics/Garfall.
The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way

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)

Ajai Chari[1], Jesus G. Berdeja[2], Albert Oriol[3], Niels W.C.J. van de Donk[4], Paula Rodriguez-Otero[5], Elham Askari[6], Maria-Victoria Mateos[7], Monique C. Minnema[8], Raluca Verona[9], Suzette Girgis[9], Thomas Prior[9], Brandi W. Hilder[9], Jeffery Russell[9], Jenna D. Goldberg[9], Amrita Krishnan[10]

[1]Mount Sinai Medical Center, New York, NY, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Institut Català d'Oncologia and Institut Josep Carreras. Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [4]Amsterdam University Medical Center, Location VU University Medical Center, Amsterdam, The Netherlands; [5]Clínica Universidad de Navarra, Navarra, Spain; [6]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [7]Hospital Clínico Universitario de Salamanca, Salamanca, Spain; [8]University Medical Center Utrecht, Utrecht, The Netherlands; [9]Janssen R&D, Spring House, PA, USA; [10]City of Hope, Duarte, CA, USA

Additional information can be viewed by scanning the QR code or accessing this link: https://oncologysciencehub.com/ASH2020/bispecifics/Chari.
The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Initial Clinical Activity and Safety of Cevostamab (BFCR4350A), a FcRH5xCD3 T-Cell-Engaging Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma

Adam D Cohen[1], Simon Harrison[2], Amrita Krishnan[3], Rafael Fonseca[4], Peter A Forsberg[5], Andrew Spencer[6], Jesus G Berdeja[7], Jacob P Laubach[8], Mengsong Li[9], Voleak Choeurng[9], Anjali Vaze[9], Divya Samineni[9], Teiko Sumiyoshi[9], James Cooper[9], Bernard M Fine[9], Suzanne Trudel[10]

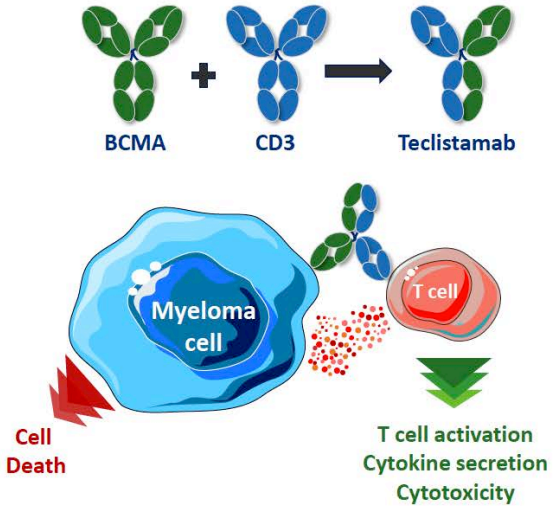
[1]Abramson Cancer Center and University of Pennsylvania, Philadelphia, PA, USA; [2]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia; [3]City of Hope, Duarte, CA, USA; [4]Mayo Clinic in Arizona, Phoenix, AZ, USA; [5]University of Colorado School of Medicine, Aurora, CO, USA; [6]Alfred Health-Monash University, Melbourne, VIC, Australia; [7]Sarah Cannon Research Institute, Nashville, TN, USA; [8]Dana-Farber Cancer Institute, Boston, MA, USA; [9]Genentech, Inc., South San Francisco, CA, USA; [10]Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada

Accepted as an Oral Presentation at the 62nd ASH Annual Meeting and Exposition

Bispecific Antibodies for R/R MM

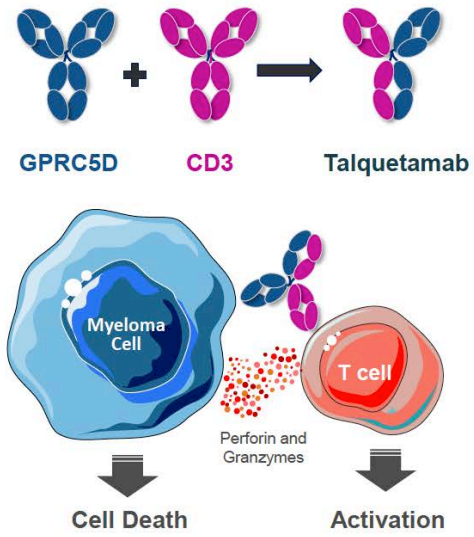
Teclistamab: BCMA × CD3 DuoBody® Antibody

- Prognosis is poor for patients who progress on available classes of therapies, with ORR ~30%, mPFS of ~3 months, and mOS between 6–11 months[1]
- Teclistamab (JNJ-64007957)[a] is a humanized BCMA × CD3 bispecific IgG-4 antibody that redirects CD3+ T cells to BCMA-expressing myeloma cells
- Teclistamab induces T cell-mediated killing of myeloma cells from heavily-treated patients and in xenograft models[2-4]
- Updated results from an ongoing phase 1 study of teclistamab administered IV or SC in patients with RRMM (NCT03145181) are presented here[5]



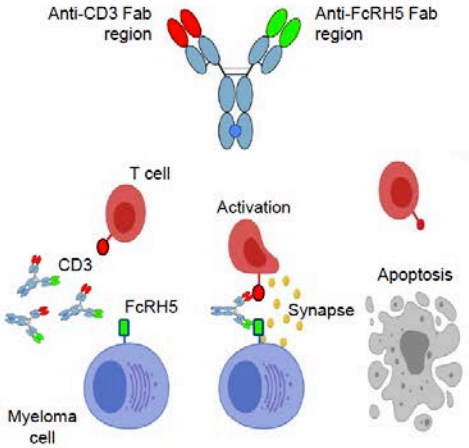
Talquetamab: GPRC5D x CD3 Bispecific Antibody

- Talquetamab is a first-in-class DuoBody® IgG4 PAA antibody that binds to both GPRC5D and CD3
- Talquetamab redirects T cells to GPRC5D-expressing myeloma cells to mediate cell killing
- Antitumor activity was demonstrated in primary myeloma cells and xenograft models of MM[1-3]
- Talquetamab's pharmacokinetic profile presents an opportunity for less frequent SC dosing
- First-in-human phase 1 study is ongoing to evaluate talquetamab in patients with RRMM (NCT03399799)



Cevostamab: FcRH5xCD3 bispecific antibody

- Fc receptor-homolog 5 (FcRH5)
  - Expressed on myeloma cells with near 100% prevalence[1]
  - Expression on myeloma and plasma cells > normal B cells[1]
- Cevostamab
  - Humanized IgG-based T-cell-engaging bispecific antibody[1]
  - Targets FcRH5 on myeloma cells and CD3 on T cells[1]
- Ongoing Phase I dose-escalation and expansion trial (NCT03275103) is evaluating the safety and activity of cevostamab monotherapy in patients with RRMM[2]



Garfall AL et al. ASH 2020;Abstract 180;
Chari A et al. ASH 2020;Abstract 290;
Cohen AD et al. ASH 2020;Abstract 292.

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Teclistamab: Conclusions

- **Teclistamab was well-tolerated at the RP2D of 1500 µg/kg SC**
  - Maximum tolerated dose has not been identified
  - All CRS events were grade 1–2 and generally confined to step-up and first full doses
  - One grade 1 reversible neurotoxicity at RP2D
  - No new safety signals were identified
- **High response rate observed at the RP2D**
  - ORR at the RP2D (1500 µg/kg SC) was 73%; ≥VGPR was 55% and ≥CR was 23%
    - 14/20 (70%) triple-class refractory patients responded; 6/8 (75%) penta-drug refractory patients responded
  - Responses appeared durable and deepened over time
  - At median 3.9-month follow-up, 15/16 (94%) responders are alive and progression-free
- **Selection of the 1500 µg/kg SC RP2D was supported by promising safety, efficacy, PK, and pharmacodynamics**
- **Teclistamab, an off-the-shelf therapy targeting BCMA, showed promising efficacy in heavily-pretreated patients with RRMM**
  - Phase 1 of the study is ongoing, and phase 2 expansion study has started

Garfall AL et al. ASH 2020;Abstract 180.

Talquetamab: Conclusions

- **Talquetamab has a tolerable safety profile at the RP2D of 405 µg/kg SC**
  - Safety profile at the RP2D was generally consistent with safety at lower doses, with low incidence of infections
  - Early DLT of Gr 3 maculopapular rash and dose reductions due to certain toxicities (skin rash, oral toxicity, back pain) were observed in 4/11 patients (36%) at 800 µg/kg SC weekly
  - CRS was generally low grade with no grade ≥3 CRS with SC dosing
  - Low incidence of neurotoxicity with no grade ≥3 events with SC dosing
- **High response rate observed at the RP2D**
  - ORR was 69% (9/13) at the RP2D of 405 µg/kg SC; 39% ≥VGPR
    - Median time to first confirmed response was 1 month
    - 6/9 triple-class refractory patients responded; 2/2 penta-drug refractory patients responded
  - Responses were durable and continued to deepen over time
- **PK results indicate target exposure levels at the RP2D, and pharmacodynamic data demonstrate consistent T cell activation, cytokine production, and redistribution at the RP2D**
- **SC dosing is more convenient and may offer an opportunity for less frequent dosing**
- **Talquetamab, a first-in-class, off-the-shelf therapy targeting GPRC5D, showed encouraging efficacy in heavily-pretreated patients with RRMM**
  - Dose expansion is ongoing and phase 2 is planned

Chari A et al. ASH 2020;Abstract 290.

Cevostamab Conclusions

- Cevostamab safety profile is manageable, with C1 single step-up dosing effectively mitigating the risk for severe CRS
  - CRS in 76% (40/53 pts); Gr 3 in 2% (1 pt)
- Cevostamab is highly active in heavily pre-treated RRMM patients
  - 53% ORR in patients receiving active doses
  - Responses in penta-drug refractory patients and in patients with prior anti-BCMA therapy
  - MRD negative responses in patients with ≥VGPR
  - Response irrespective of target expression level in patients assessed to date (Nakamura et al. ASH 2020; poster presentation 3213, Monday, December 7, 2020)
- These data establish FcRH5 as a novel target in multiple myeloma and demonstrate the activity of cevostamab monotherapy in late-line RRMM; dose-escalation and dose-expansion are ongoing

Cohen AD et al. ASH 2020;Abstract 292.

What do you currently believe is the optimal point at which chimeric antigen receptor (CAR) T-cell therapy should be administered in MM?

RAFAEL FONSECA, MD	At first relapse
OLA LANDGREN, MD, PHD	At first relapse
NIKHIL C MUNSHI, MD	At third relapse
ROBERT Z ORLOWSKI, MD, PHD	At second relapse
EDWARD A STADTMAUER, MD	After third relapse
SAGAR LONIAL, MD	At third relapse
S VINCENT RAJKUMAR, MD	After third relapse
PAUL G RICHARDSON, MD	At third relapse
GENERAL MEDICAL ONCOLOGISTS (N = 75)	At third relapse, At second relapse

A patient with MM should be in adequate physical condition to undergo ASCT in order to be a suitable candidate for BCMA-targeted CAR T-cell therapy.

1. Agree
2. Disagree
3. I don’t know

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A patient with MM should be in adequate physical condition to undergo ASCT in order to be a suitable candidate for BCMA-targeted CAR T-cell therapy.

RAFAEL FONSECA, MD	Disagree	EDWARD A STADTMAUER, MD	Agree
OLA LANDGREN, MD, PHD	Disagree	SAGAR LONIAL, MD	Agree
NIKHIL C MUNSHI, MD	Disagree	S VINCENT RAJKUMAR, MD	Disagree
ROBERT Z ORLOWSKI, MD, PHD	Agree	PAUL G RICHARDSON, MD	Agree

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Agree

How would you compare the risk of cytokine release syndrome and CNS toxicity with BCMA-targeted CAR T-cell therapy to that with the CD19-targeted CAR T-cell therapy that is approved in lymphoma and acute lymphocytic leukemia?

RAFAEL FONSECA, MD	The risk is greater with CD19 CAR T
OLA LANDGREN, MD, PHD	The risk is greater with CD19 CAR T
NIKHIL C MUNSHI, MD	The risk is greater with CD19 CAR T
ROBERT Z ORLOWSKI, MD, PHD	The risk is greater with CD19 CAR T
EDWARD A STADTMAUER, MD	The risk is about the same
SAGAR LONIAL, MD	The risk is greater with CD19 CAR T
S VINCENT RAJKUMAR, MD	The risk is greater with CD19 CAR T
PAUL G RICHARDSON, MD	The risk is greater with CD19 CAR T

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Risk is about the same, Greater with BCMA-targeted CAR T

Agenda

Module 1: Up-front management

- **GRIFFIN, APOLLO, IMF 2009, TOURMALINE-MM2**

Module 2: Relapsed/refractory disease

- **Isatuximab, belantamab mafadotin, selinexor**

Module 3: Chimeric antigen receptor T-cell therapy; bispecific antibodies

Module 4: Other novel strategies

- **Venetoclax, melflufen, iberdomide, BRAF inhibitors**

Targeting Bcl-2 for the treatment of multiple myeloma

- Overexpression of anti-apoptotic proteins are hallmarks of cancer
- Tumor cell proliferation is regulated through interactions between anti-apoptotic (Mcl-1, Bcl-2 and Bcl-xL) and pro-apoptotic (Bax and Bak) members
- Subset of myeloma cells with high Bcl-2 expression and low Mcl-1 expression commonly found in CCND1 subset, characterized by the presence of the translocation (11;14)
- Venetoclax binds to Bcl-2 and Bcl-x_L but not to Mcl-1. It induces apoptosis by displacing proapoptotic BH3-only proteins (Bim and Puma) from Bcl-2, leading to caspase-dependent cell death

Bodet L, et al. *Blood*. 2011 Oct 6;118(14):3901-3910

Courtesy of Ola Landgren, MD, PhD

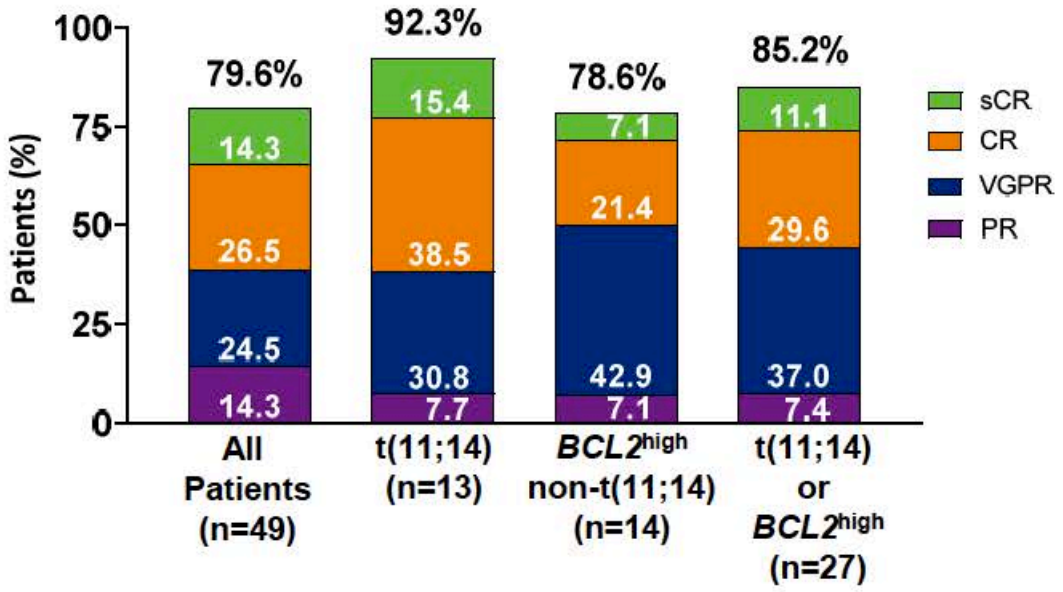
Assessment of Minimal Residual Disease by Next-generation Sequencing and Fluorodeoxyglucose-positron Emission Tomography in Relapsed/Refractory Multiple Myeloma Patients Treated with Venetoclax in Combination with Carfilzomib and Dexamethasone

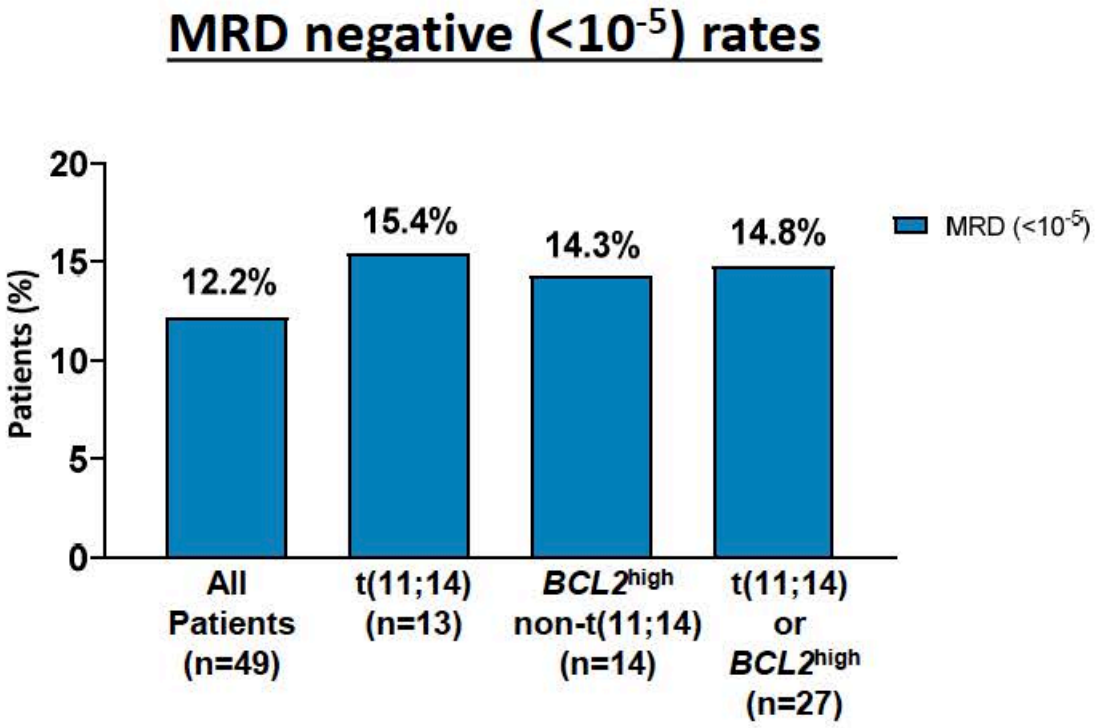
Luciano J. Costa[1], Tibor Kovacsovics[2], Nicholas Burwick[3], Andrzej Jakubowiak[4], Jonathan L. Kaufman[5], Fernando Cabanillas[6], Monique Dail[7], Abdullah Masud[8], Xiaoqing Yang[8], Orlando F. Bueno[8], Sarah R. Mudd[8], Jeremy A. Ross[8], Faith Davies[9]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [3]VA Puget Sound Health Care System, University of Washington, Seattle, WA; [4]The University of Chicago Medicine, Chicago, IL; [5]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [6]Auxilio Mutuo Cancer Center, San Juan, PR; [7]Genentech Inc., South San Francisco, CA; [8]AbbVie Inc., North Chicago, IL; [9] Perlmutter Cancer Center, New York University Grossman School of Medicine, New York City, NY

American Society of Hematology (ASH) – 62th Annual Meeting
San Diego, CA, USA ● December 06, 2020

Response Rates in Overall Population and Biomarker Sub-groups





Costa LJ et al. ASH 2020;Abstract 2251.

ANCHOR (OP-104): Melflufen Plus Dexamethasone and Daratumumab or Bortezomib in Relapsed/Refractory Multiple Myeloma Refractory to an IMiD and/or a Proteasome Inhibitor — Updated Efficacy and Safety

Enrique M. Ocio, MD, PhD[1]; Yvonne A. Efebera, MD[2]; Roman Hájek, MD, PhD[3]; Miquel Granell, MD[4]; Vladimir Maisnar, MD[5]; Jan Straub, MD[6]; Jean-Richard Eveillard, MD[7]; Lionel Karlin, MD[8]; Vincent Ribrag, MD[9]; María-Victoria Mateos, MD, PhD[10]; Albert Oriol, MD[11]; Malin Sydvander, MSc[12]; Stefan Norin, MD[12]; Sofia Mannikko, MSc[12]; and Luděk Pour, MD[13]

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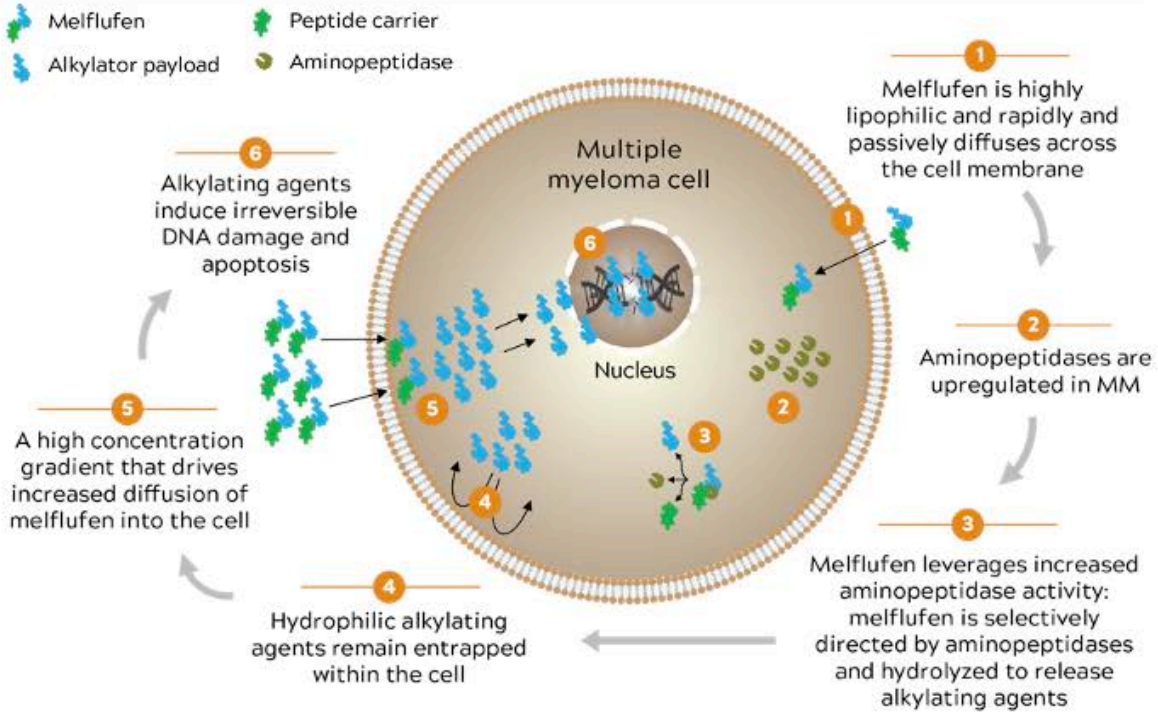
Melphalan Flufenamide (Melflufen): Mechanism of Action

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



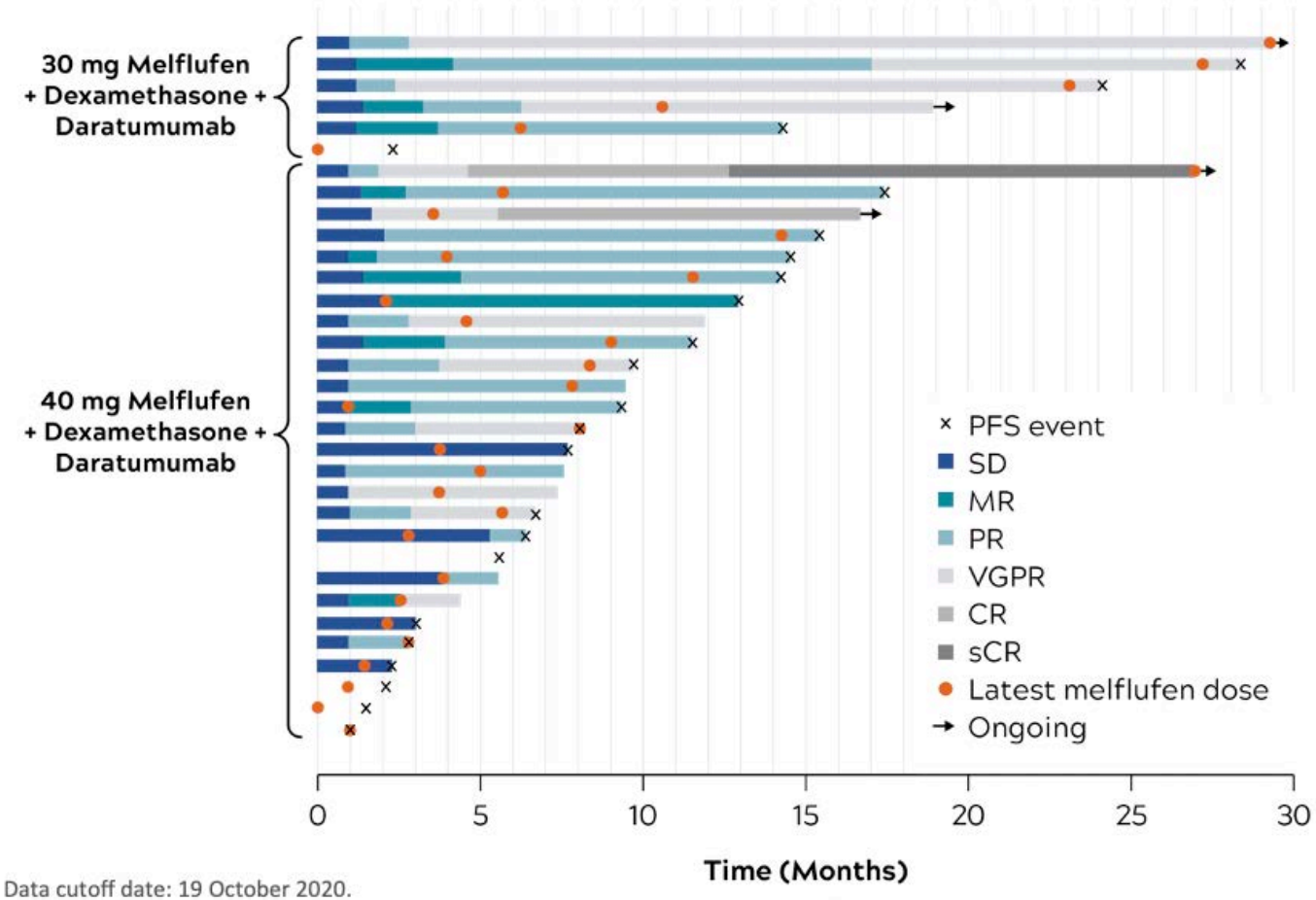
- In the pivotal phase 2 HORIZON study (OP-106), the activity of melflufen plus dexamethasone was further shown in heavily pretreated RRMM patients refractory to pomalidomide and/or anti-CD38 mAb therapy, with acceptable safety[6]
  - ORR was 29%; median PFS was 4.2 months, and median OS was 11.6 months
  - 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 EM et al. ASH 2020;Abstract 417.

RTP RESEARCH TO PRACTICE

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 EM et al. ASH 2020;Abstract 417.

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First Results of Iberdomide (IBER; CC-220) in Combination with Dexamethasone (DEX) and Daratumumab (DARA) or Bortezomib (BORT) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Niels W.C.J. van de Donk[1], Rakesh Popat[2], Jeremy Larsen[3], Monique C. Minnema[4], Sundar Jagannath[5], Albert Oriol[6], Jeffrey A. Zonder[7], Paul G. Richardson[8], Paula Rodríguez Otero[9], Ashraf Z. Badros[10], Edward Stadtmauer[11], Sara Bringhen[12], Erica Campagnaro[13], David S. Siegel[14], Barbara Gamberi[15], Mercedes Gironella Mesa[16], Pieter Sonneveld[17], Tuong Vi Nguyen[18], Antonia Di Micco[19], April Sorrell[18], Min Chen[18], Michael Amatangelo[18], Elisabeth Kueenburg[19], Sagar Lonial[20]

[1]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Department of Hematology, Cancer Center Amsterdam, Amsterdam, Netherlands; [2]NIHR UCLH Clinical Research Facility, University College London Hospitals NHS Foundation Trust, London, UK; [3]Mayo Clinic, Scottsdale, AZ; [4]Department of Hematology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; [5]The Mount Sinai Hospital, New York, NY; [6]Institut de Recerca contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [7]Karmanos Cancer Institute, Detroit, MI; [8]Dana-Farber Cancer Institute, Boston, MA; [9]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [10]The University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland Medical Center, Baltimore, MD; [11]University of Pennsylvania, Philadelphia, PA; [12]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; [13]Michigan Medicine Hematology Clinic, University of Michigan Rogel Cancer Center, Ann Arbor, MI; [14]Division of Multiple Myeloma, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [15]Hematology Unit, AUSL-IRCSS, Reggio Emilia, Italy; [16]Hospital Vall d'Hebron, Barcelona, Spain; [17]Erasmus Medical Center, Rotterdam, Netherlands; [18]Bristol Myers Squibb, Princeton, NJ; [19]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [20]Winship Cancer Institute, Emory University, Atlanta, GA

CC-220-MM-001: Study Design and Objectives

Key eligibility criteria (Cohorts E and F)

- RRMM
- ≥2 prior regimens (≥1 in Cohort F) including LEN/POM and PI
- Disease progression on or within 60 days of last antimyeloma therapy

Study endpoints

- Primary: determine MTD/RP2D and efficacy
- Secondary: assess safety

Phase 1: dose escalation	Phase 2: dose expansion[a]
Cohort A IBER	Cohort D IBER (RP2D)[b] + DEX
Cohort B IBER + DEX	Cohort I (post-BCMA) IBER (RP2D)[b] + DEX
Cohort E IBER + DARA + DEX	Cohort J1 (NDMM TNE) IBER + BORT + DEX
Cohort F IBER + BORT + DEX	Cohort J2 (NDMM TE) IBER + BORT + DEX
Cohort G IBER + CFZ + DEX	

Objective: To present safety and efficacy of IBER + DARA + DEX (Cohort E) and IBER + BORT + DEX (Cohort F)

- [a]Cohort C (IBER monotherapy expansion) was planned, but not opened. [b]1.6 mg qd.
- BCMA, B-cell maturation antigen; CFZ, carfilzomib; MTD, maximum tolerated dose; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; qd, once daily; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

Van De Donk NWCJ et al. ASH 2020;Abstract 724.

Safety and Preliminary Efficacy Results from a Phase II Study Evaluating Combined BRAF and MEK Inhibition in Relapsed/Refractory Multiple Myeloma (RRMM) Patients with Activating BRAF V600E Mutations: the GMMG-BIRMA Trial

Marc S. Raab, Nicola Giesen, Christof Scheid, Britta Besemer, Kaya Miah, Axel Benner, Ivana v. Metzler, Cyrus Khandanpour, Andrea Seidel-Glaetzer, Karolin Trautmann-Grill, Gunhild Mechtersheimer, Benjamin Goeppert, Albrecht Stenzinger, Hartmut Goldschmidt, Katja Weisel and Manik Chatterjee

HEIDELBERG UNIVERSITY HOSPITAL

GMMG

UK HD

GMMG-BIRMA: Summary

- Combined BRAF/MEK inhibition by encorafenib and binimetinib induces rapid and deep responses in BRAF V600E-mutant relapsed/refractory MM
- Overall Response Rate of >80% in heavily pre-treated MM patients
- Managable safety profile, in line with melanoma experience
- Survival data not mature, but durable responses exceeding 1 year observed
- Emerging RAS mutations and structural variants involving BRAF drive relapse under BRAF/MEK inhibition
- Pre-existing RAS mutations may predict poor response

Raab MS et al. ASH 2020;Abstract 294.

Are there situations in which you would attempt to use venetoclax outside a trial setting for relapsed/refractory MM?

1. Yes
2. Yes, but only for patients with t(11;14) or high Bcl-2 expression
3. No

Are there situations in which you would attempt to use venetoclax outside a trial setting for relapsed/refractory MM?

RAFAEL FONSECA, MD	Yes, only in t(11;14) or high Bcl-2
OLA LANDGREN, MD, PHD	Yes, only in t(11;14) or high Bcl-2
NIKHIL C MUNSHI, MD	Yes, only in t(11;14) or high Bcl-2
ROBERT Z ORLOWSKI, MD, PHD	Yes, only in t(11;14) or high Bcl-2
EDWARD A STADTMAUER, MD	Yes, only in t(11;14) or high Bcl-2
SAGAR LONIAL, MD	Yes, only in t(11;14)
S VINCENT RAJKUMAR, MD	Yes, only in t(11;14)
PAUL G RICHARDSON, MD	Yes, only in t(11;14) or high Bcl-2
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Yes, only in t(11;14) or high Bcl-2

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

RAFAEL FONSECA, MD	First line
OLA LANDGREN, MD, PHD	Beyond third line
NIKHIL C MUNSHI, MD	Third line
ROBERT Z ORLOWSKI, MD, PHD	Second line
EDWARD A STADTMAUER, MD	Second line or third line
SAGAR LONIAL, MD	Second line
S VINCENT RAJKUMAR, MD	Beyond third line
PAUL G RICHARDSON, MD	Second line
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Beyond third line, Second line

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

Thursday, February 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Kristen K Ciombor, MD, MSCI
Eric Van Cutsem, MD, PhD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with North Carolina Oncology Association (NCOA) and South Carolina Oncology Society (SCOS)

Saturday, February 13, 2021
8:30 AM – 4:30 PM ET

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FACULTY

Courtney D DiNardo, MD, MSCE
Robert Dreicer, MD, MS
Justin F Gainor, MD
Sara Hurvitz, MD
Ian E Krop, MD, PhD
John M Pagel, MD, PhD
Alexander Perl, MD
Daniel P Petrylak, MD
Philip A Philip, MD, PhD, FRCP
Paul G Richardson, MD
Mitchell R Smith, MD, PhD
Eric Van Cutsem, MD, PhD
Peter Voorhees, MD
Heather Wakelee, MD

MODERATOR

Neil Love, MD

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Saturday, February 13, 2021

8:30 AM — Chronic Lymphocytic Leukemia and Lymphomas

John Pagel, Mitchell Smith

9:30 AM — Multiple Myeloma

Paul Richardson, Peter Voorhees

10:45 AM — Genitourinary Cancers

Robert Dreicer, Daniel Petrylak

11:45 AM — Lung Cancer

Justin Gainor, Heather Wakelee

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Saturday, February 13, 2021

1:15 PM — Gastrointestinal Cancers

Philip Philip, Eric Van Cutsem

2:15 PM — Breast Cancer

Sara Hurvitz, Ian Krop

3:30 PM — Acute Myeloid Leukemia and Myelodysplastic Syndromes

Courtney DiNardo, Alexander Perl

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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