Meet The Professor

Optimizing the Management of Multiple Myeloma

Tuesday, October 11, 2022
5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD

Moderator

Neil Love, MD

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Commercial Support

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Dr Love — Disclosures

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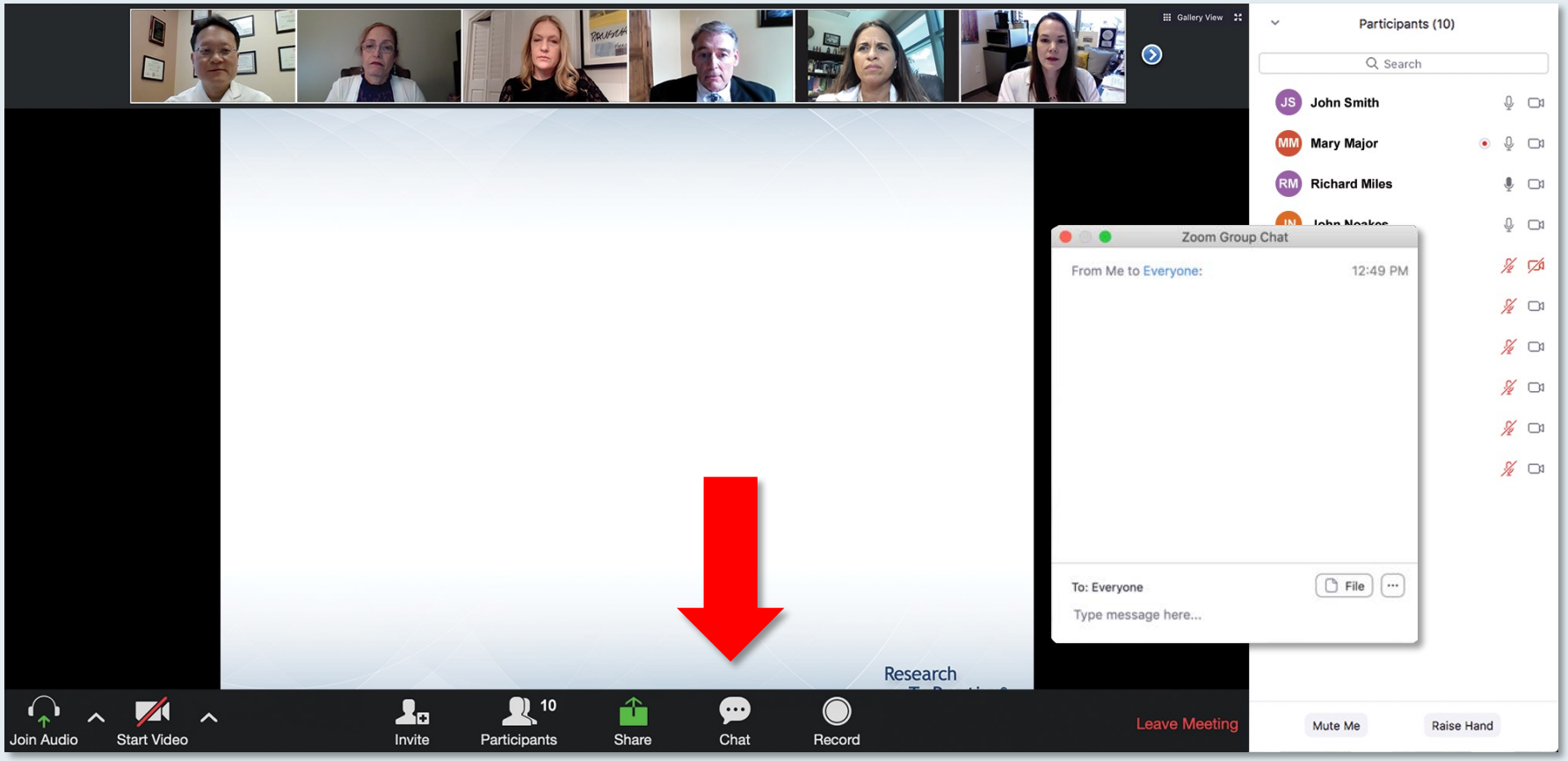
We Encourage Clinicians in Practice to Submit Questions



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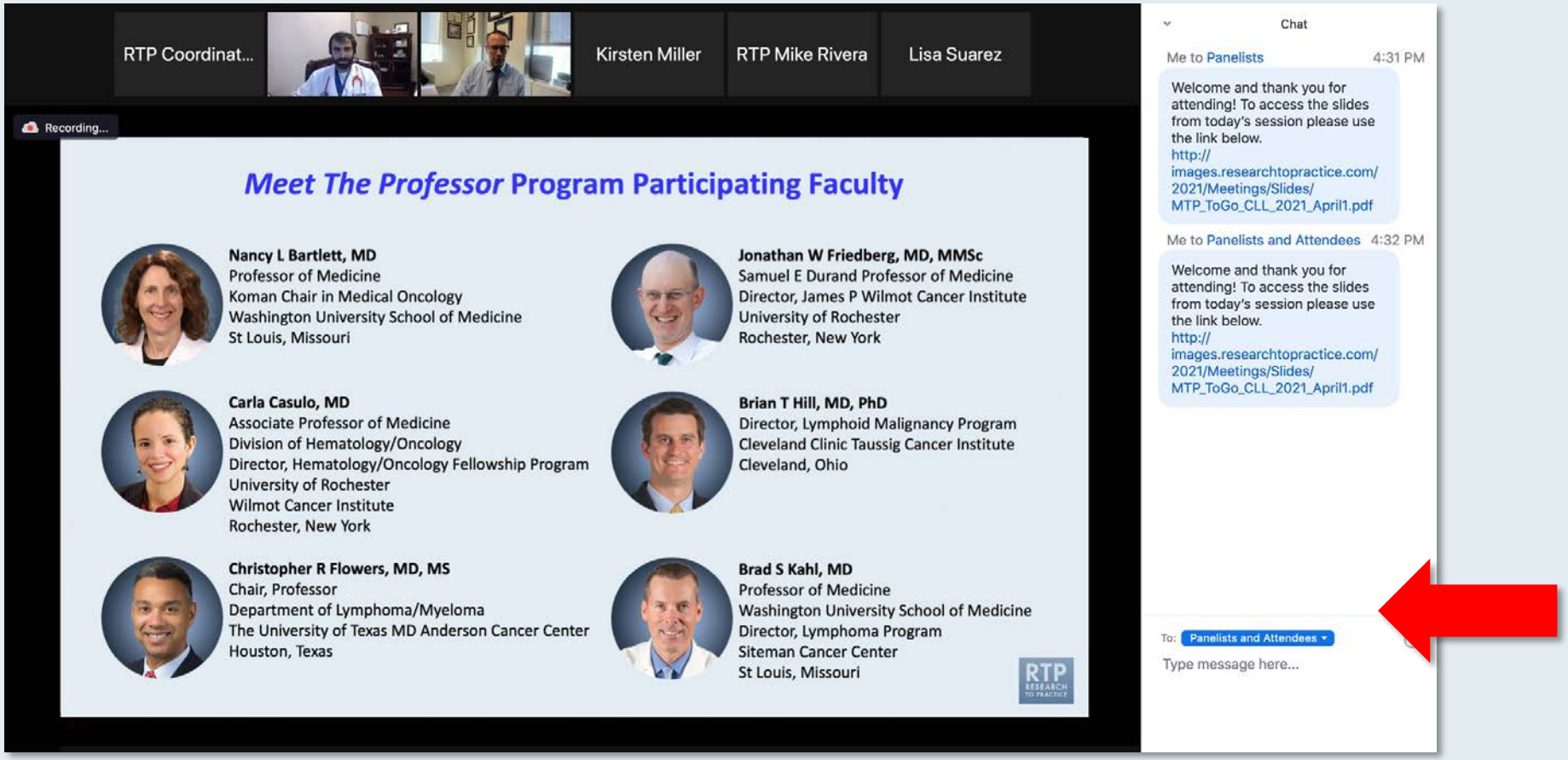

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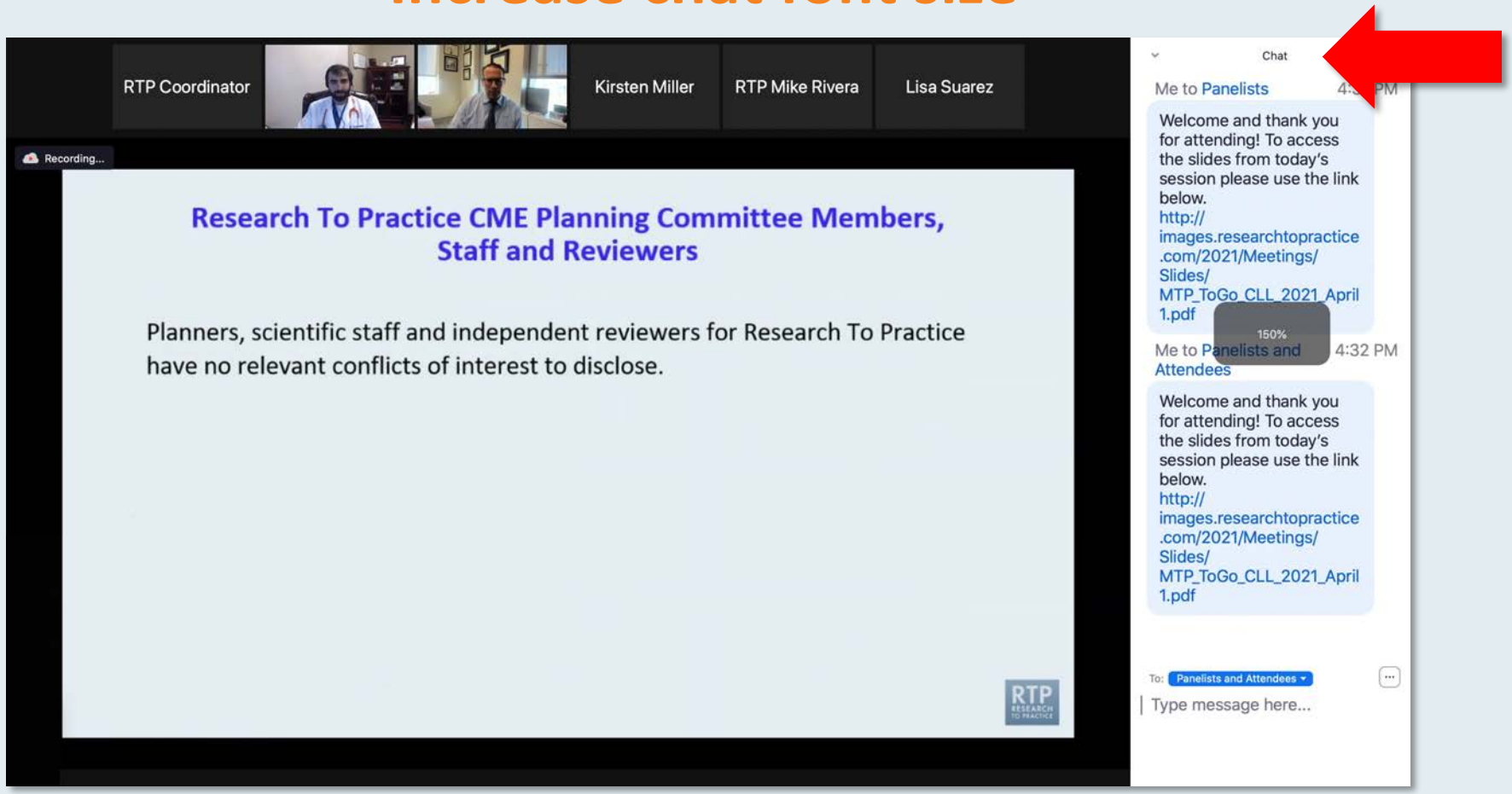

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You may do this as many times as you need for readability.

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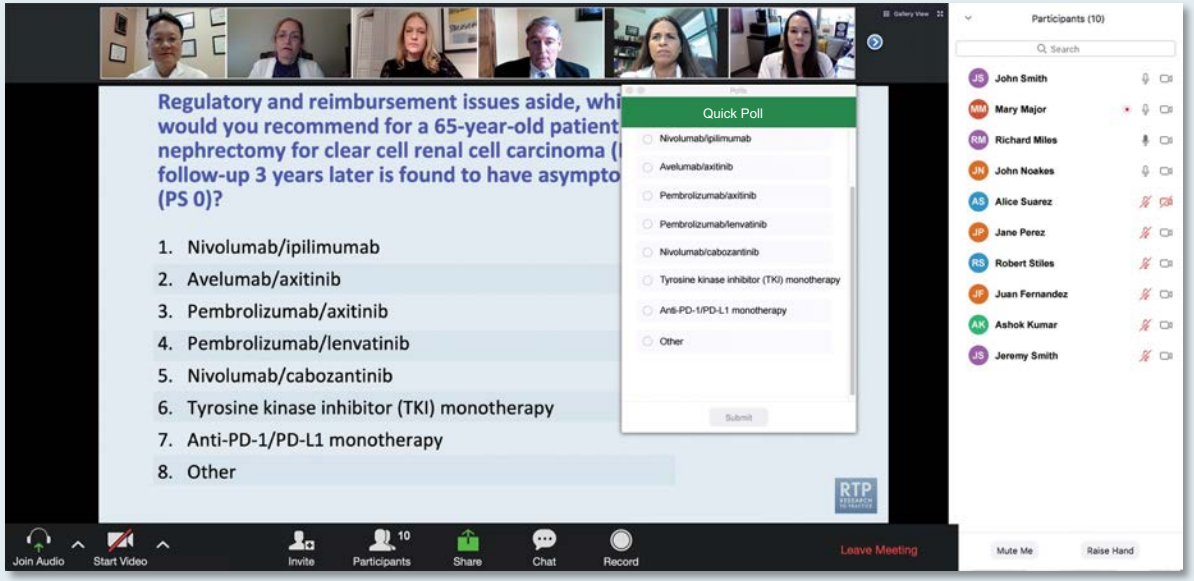

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WITH DR NEIL LOVE

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DR AMRITA KRISHNAN
CITY OF HOPE CANCER CENTER

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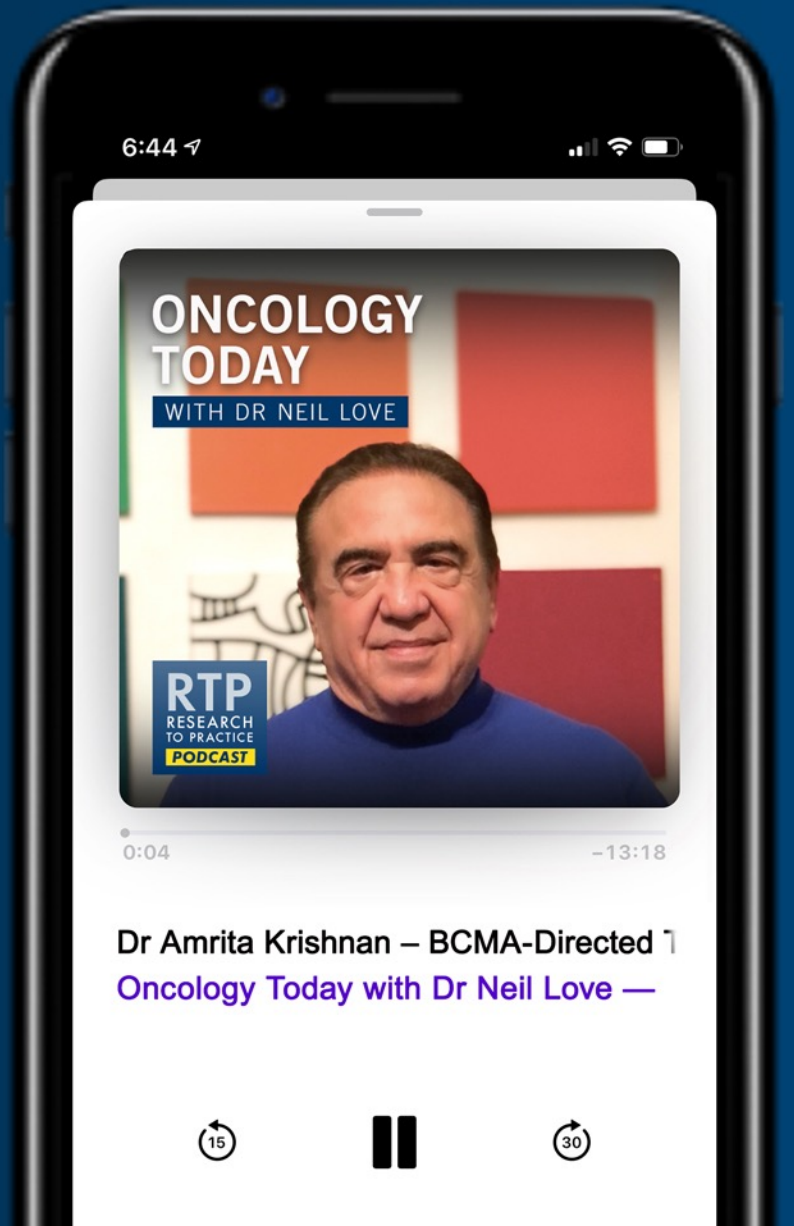

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Anthony R Mato, MD, MSCE
William G Wierda, MD, PhD

Moderator

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RTP RESEARCH TO PRACTICE

The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

Saturday, October 22, 2022

7:30 AM – 5:30 PM ET

JW Marriott Orlando | Orlando, Florida

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Ghassan Abou-Alfa, MD, MBA
Matthew P Goetz, MD
Ian E Krop, MD, PhD
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Prof Georgina Long, AO, BSc, PhD, MBBS
Christine M Lovly, MD, PhD
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Thomas Powles, MBBS, MRCP, MD
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CME and MOC credit information will be emailed to each participant within 5 business days.

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Anne and Bernard Gray Family Chair in Cancer
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Meet The Professor Program Participating Faculty

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

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

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

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

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Meet The Professor Program Participating Faculty

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

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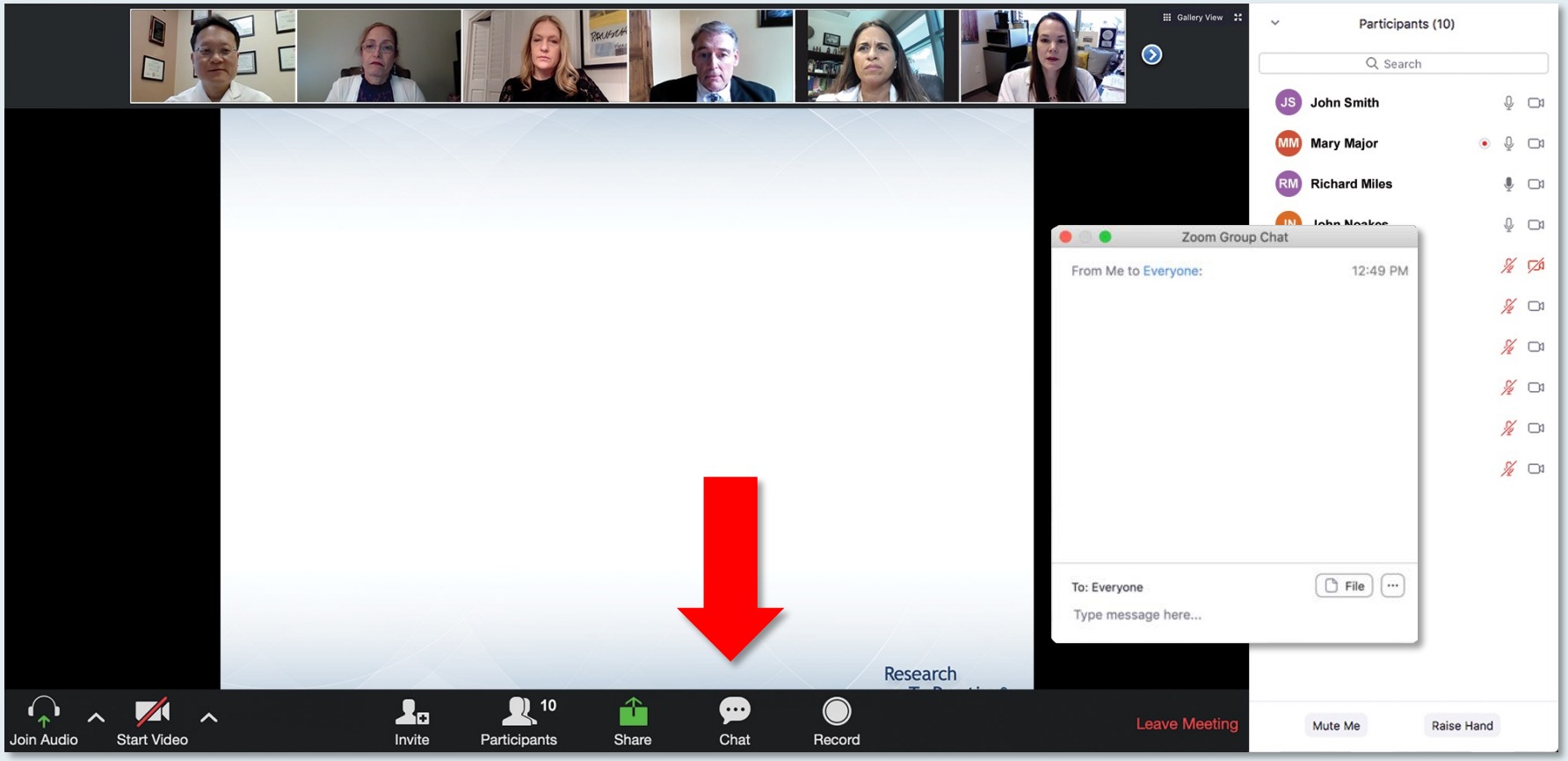

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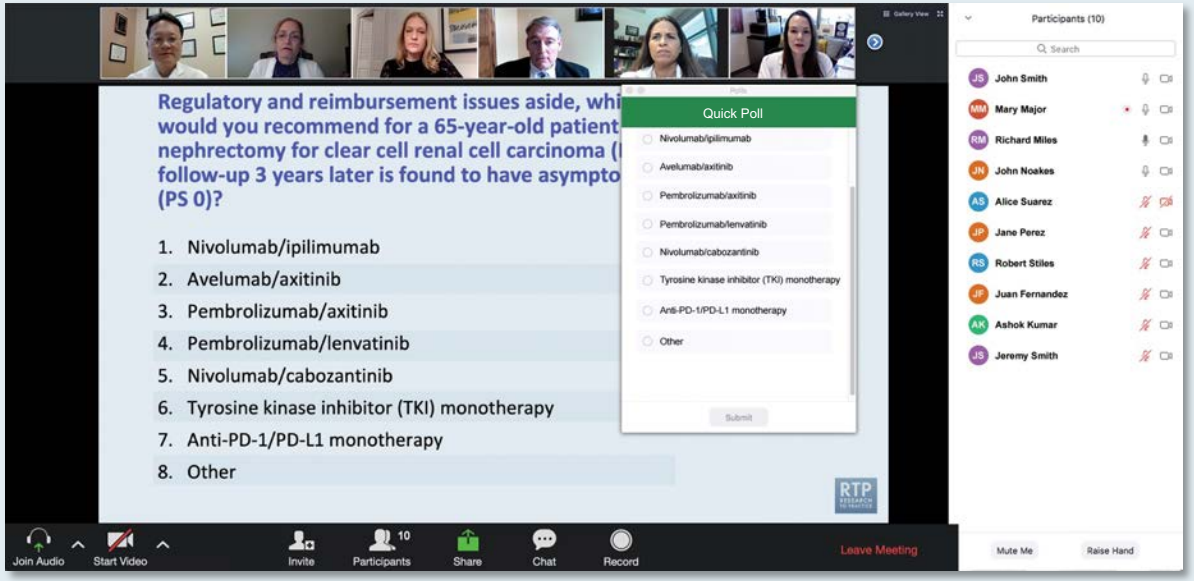

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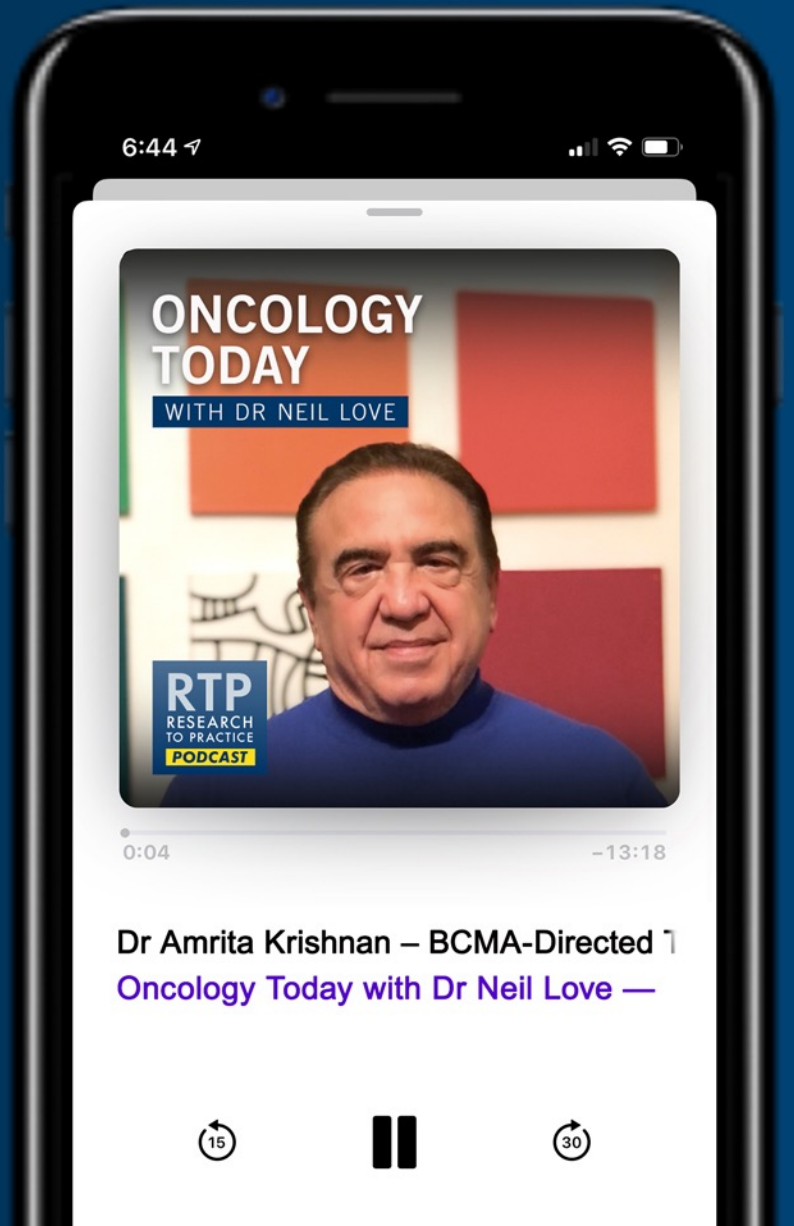

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Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Ranju Gupta, MD
Lehigh Valley Health Network
Bethlehem, Pennsylvania

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

Jeremy Lorber, MD
Cedars-Sinai Medical Center
Beverly Hills, California

Rajalaxmi McKenna, MD
Southwest Medical
Consultants SC
Willowbrook, Illinois

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Erik Rupard, MD
The Reading Hospital
West Reading, Pennsylvania

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Meet The Professor with Dr Lonial

INTRODUCTION: Journal Club with Dr Lonial – Part 1

MODULE 1: Case Presentations – Part 1

MODULE 2: Faculty Survey

MODULE 3: Case Presentations – Part 2

MODULE 4: Journal Club with Dr Lonial – Part 2

MODULE 5: Appendix of Key Publications

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5 MinuteJournalClub

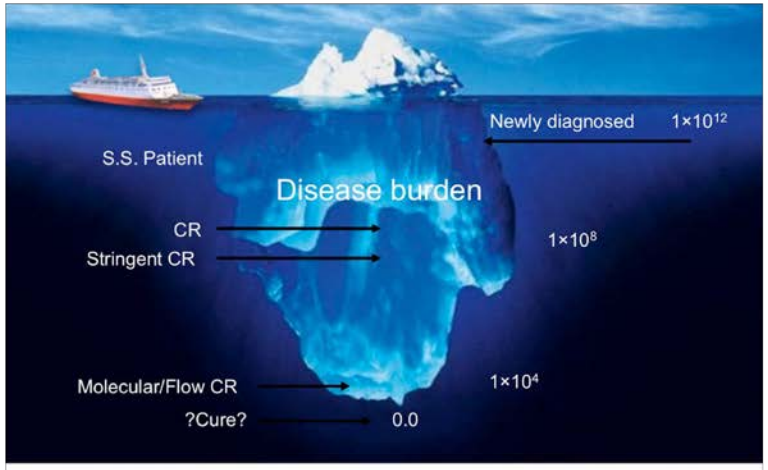
POST-ASH Issue 1, 2014

To go directly to slides and commentary for this issue, click here.

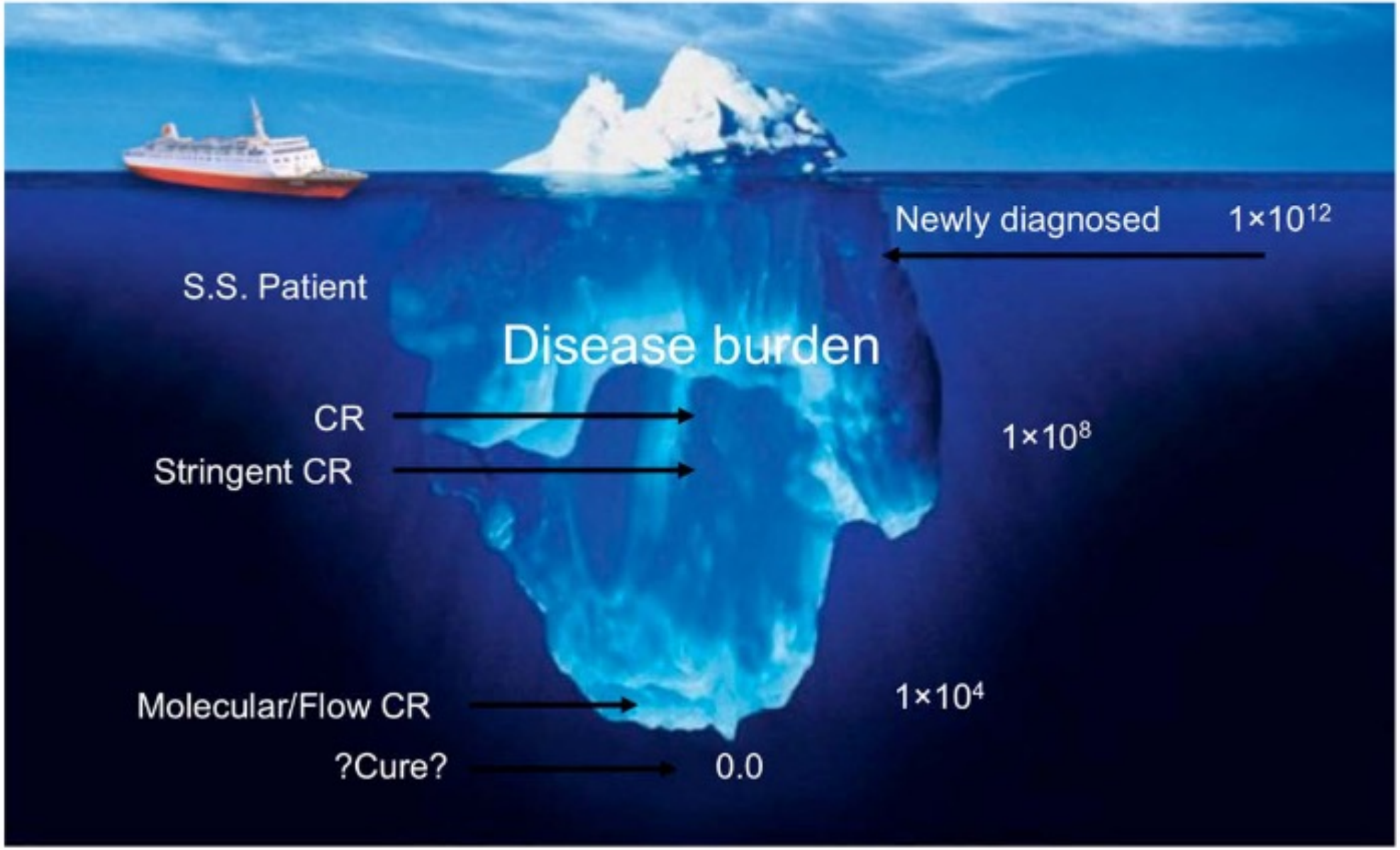
Sagar Lonial, MD

The revolution in myeloma therapy engendered by the development of proteasome inhibitors and immune modulatory drugs has not only changed the natural history of the disease but also has led some investigators to adopt a "more is better" treatment goal whereby efforts are made at diagnosis to maximally drive down the tumor burden and keep it suppressed for as long as possible. Dr Sagar Lonial is among the champions of this concept, and last week I chatted with him to further clarify his vision of this paradigm and better understand how it applies to evolving clinical research, especially new data emerging at ASH.

The fundamental idea behind this strategy is perhaps not that much different than what has been hypothesized for many cancers in the past. As depicted by the innovative "iceberg" graphic (see below) that Sagar has been using in many of his recent presentations, the goal is either a diffuse large B-cell lymphoma-like cure or a much longer duration of freedom from disease progression.



Getting to Minimal Residual Disease (MRD). Lonial, S. Reprinted with permission.



Getting to Minimal Residual Disease (MRD). Lonial, S. Reprinted with permission.

Cancers (Basel) 2021 September 24;13(19):4787.

cancers

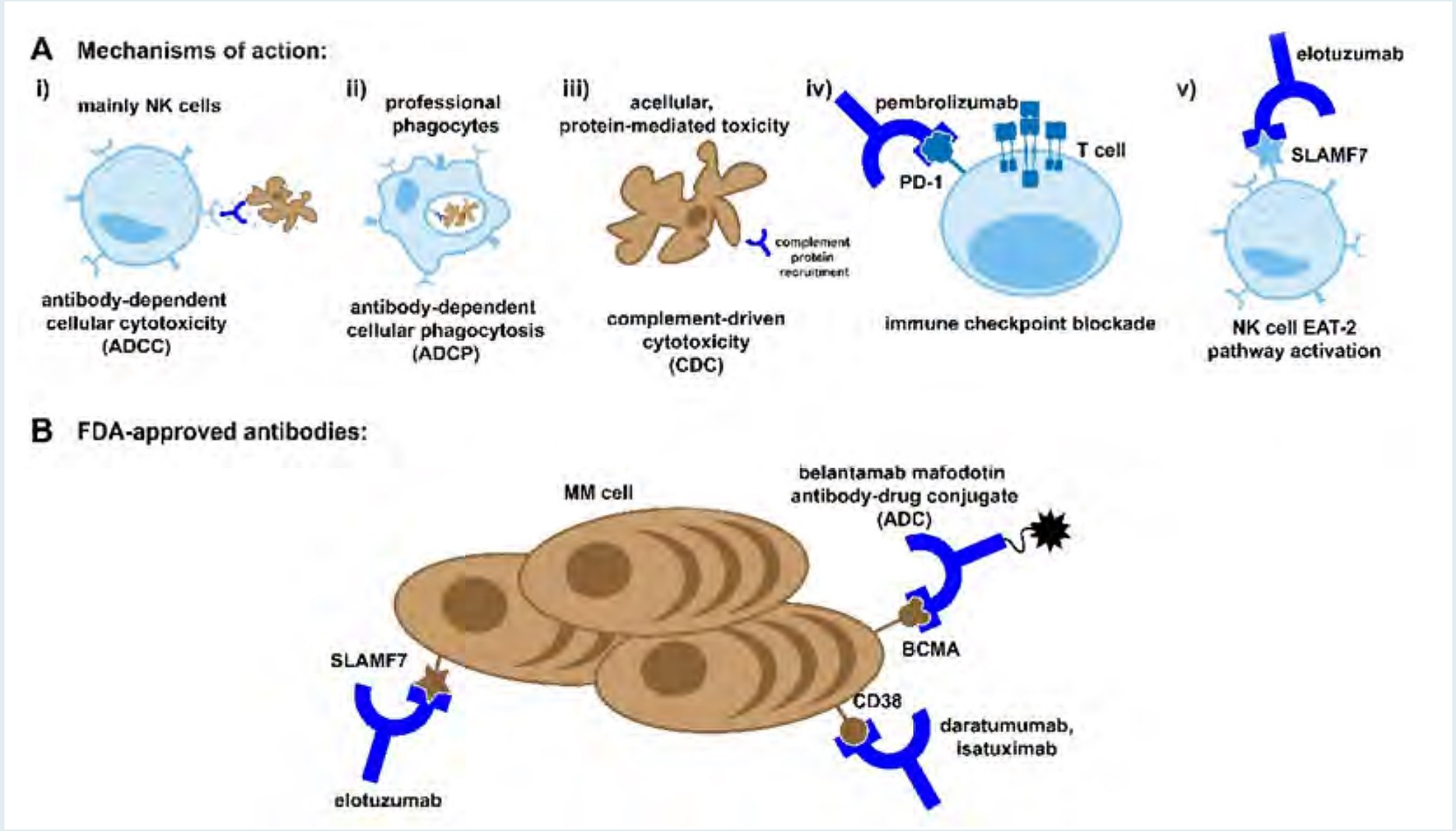
MDPI

Review

Keeping Myeloma in Check: The Past, Present and Future of Immunotherapy in Multiple Myeloma

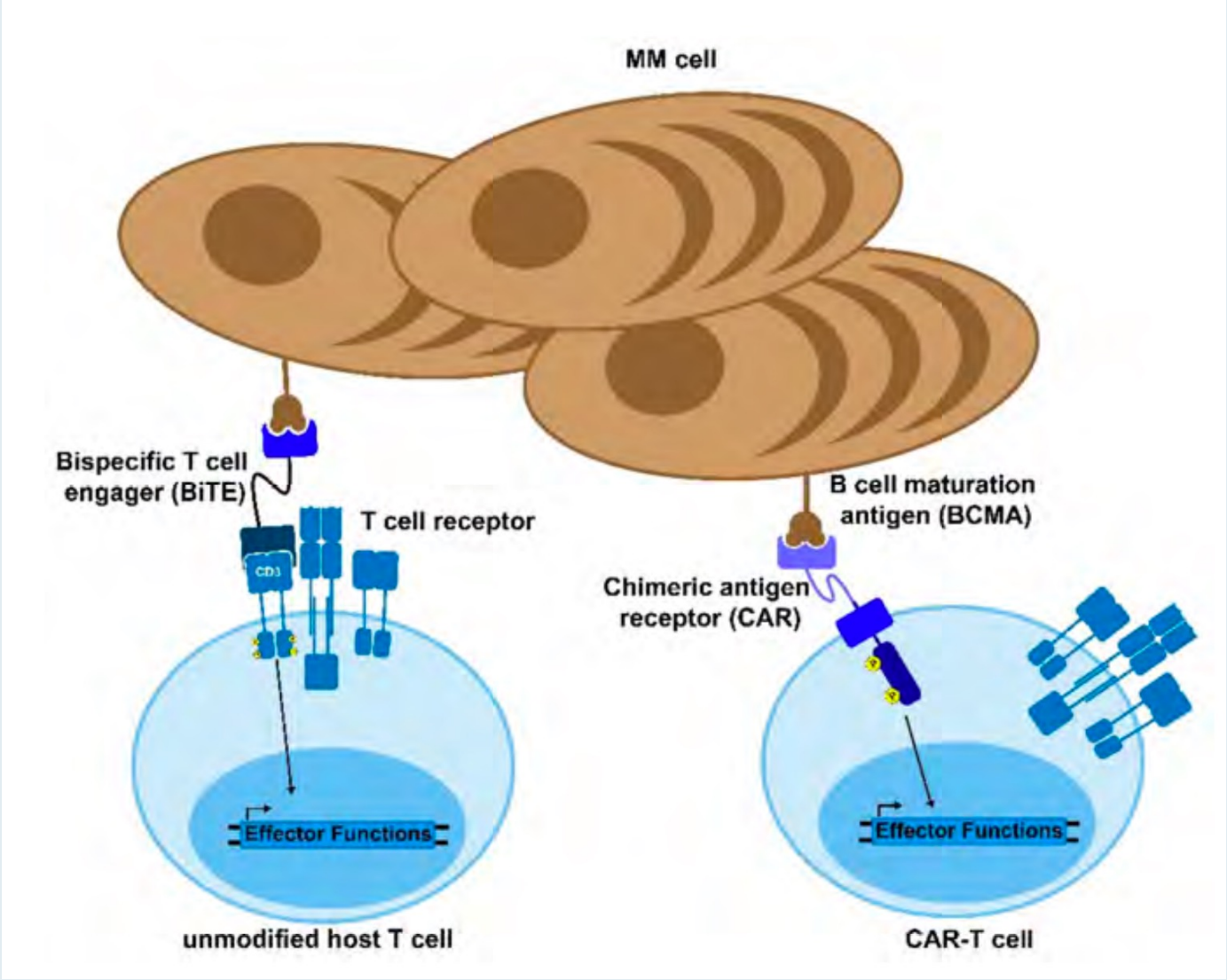
James Ackley [1], Miguel Armenta Ochoa [2,3], Delta Ghoshal [2,3], Krishnendu Roy [2,3,4], Sagar Lonial [1,4] and Lawrence H. Boise [1,4,*]

Antibody-Based Therapies



Ackley J et al. *Cancers (Basel)* 2021 September 24;13(19):4787.

Bispecific Antibodies and CAR T Cells



Ackley J et al. *Cancers (Basel)* 2021 September 24;13(19):4787.

Lancet Haematol 2022;9(6):e403-14.

Articles

Addition of elotuzumab to lenalidomide and dexamethasone for patients with newly diagnosed, transplantation ineligible multiple myeloma (ELOQUENT-1): an open-label, multicentre, randomised, phase 3 trial

Meletios A Dimopoulos, Paul G Richardson, Nizar J Bahlis, Sebastian Grosicki, Michele Cavo, Meral Beksaç, Wojciech Legieć, Anna M Liberati, Hartmut Goldschmidt, Andrew Belch, Hila Magen, Alessandra Larocca, Jacob P Laubach, Maria T Petrucci, Donna Reece, Darrell White, María-Victoria Mateos, Ivan Špička, Mihaela Lazaroiu, Jesús Berdeja, Jonathan L Kaufman, Ying-Ming Jou, Alex Ganetsky, Mihaela Popa McKiver, Sagar Lonial, Katja Weisel, on behalf of the ELOQUENT-1 investigators

Clin Cancer Res 2021 October 1;27(19):5195-212.

CLINICAL CANCER RESEARCH | PERSPECTIVES

Minimal Residual Disease in Myeloma: Application for Clinical Care and New Drug Registration

Kenneth C. Anderson[1], Daniel Auclair[2], Stacey J. Adam[3], Amit Agarwal[4], Melissa Anderson[5], Hervé Avet-Loiseau[6], Mark Bustoros[7], Jessica Chapman[8], Dana E. Connors[3], Ajeeta Dash[5], Alessandra Di Bacco[5], Ling Du[9], Thierry Facon[10], Juan Flores-Montero[11], Francesca Gay[12], Irene M. Ghobrial[13], Nicole J. Gormley[14], Ira Gupta[9], Howard Higley[15], Jens Hillengass[16], Bindu Kanapuru[14], Dickran Kazandjian[17], Gary J. Kelloff[18], Ilan R. Kirsch[19], Brandon Kremer[9], Ola Landgren[17], Elizabeth Lightbody[13], Oliver C. Lomas[13], Sagar Lonial[20], María-Victoria Mateos[21], Rocio Montes de Oca[9], Lata Mukundan[15], Nikhil C. Munshi[22], Elizabeth K. O'Donnell[23], Alberto Orfao[11], Bruno Paiva[24], Reshma Patel[25], Trevor J. Pugh[26], Karthik Ramasamy[27], Jill Ray[28], Mikhail Roshal[8], Jeremy A. Ross[29], Caroline C. Sigman[15], Katie L. Thoren[8], Suzanne Trudel[26], Gary Ulaner[30], Nancy Valente[28], Brendan M. Weiss[25], Elena Zamagni[31], and Shaji K. Kumar[32]

Clinical Case 1 – Use of Minimal Residual Disease (MRD) for a Patient with Smoldering Myeloma

Case 1 - Smoldering Myeloma	
Case Description	A 63-year-old patient was diagnosed three years ago with IgA kappa smoldering myeloma. Bone marrow biopsy and aspirate showed 20% infiltration by monoclonal CD138+ plasma cells. Karyotype and FISH studies revealed hyperdiploid genotype and 1q gain. Laboratory revealed an IgA kappa M protein 1.55 g/dL. Kappa light chains 696 mg/L, and free light chain ratio 81. The patient was otherwise asymptomatic with no myeloma defining events. The patient enrolled in a 2-year clinical trial for treating smoldering myeloma patients, including an induction phase of nine cycles and maintenance phase for 15 cycles. The patient achieved a complete response (CR) by the end of cycle nine, confirmed with bone marrow biopsy, and MRD assessed by next-generation sequencing was negative at 10-6 threshold. The patient completed the clinical trial in February 2019, and remains in CR which persists to July 2020.
What we know with regards to MRD	Two recent trials tested MRD status in response to different regimens in SMM, and reported the results in ASH 2019. In one study, MRD negative state was present in 63% patients who achieved CR (n =51) after induction and consolidation, by next-generation flow cytometry assay. In the other study, MRD negative state was present in 69% patients who achieved CR (n=13) after nine cycles of induction by next-generation sequencing of VDJ rearrangement assay.
Key questions we need to answer	MRD status has been recently tested in the setting of clinical trials in SMM [1,2]. However, these trials are still ongoing, and longer follow up is needed to fully assess the association between MRD negative status and progression-free survival. Data from such studies, once mature, will help in the management of SMM by identifying regimens that lead to better disease control and deeper responses. Moreover, they will help identify the genomic and cytogenetic SMM profiles that would need different treatment strategies, rather than using one approach for all disease subtypes.

Anderson KC et al. *Clin Cancer Res* 2021 October 1;27(19):5195-212.

Clinical Case 2 – Use of MRD for a Transplant-Eligible Patient with Newly Diagnosed Normal-Risk MM

Case 2 - Newly Diagnosed MM Transplant Eligible - Normal Risk	
Case Description	A 64-year-old man presented with back pain and was found to have L3 compression fracture and multiple lytic lesions on whole body CT scan. Laboratory revealed IgG Kappa M spike of 3.2 gram per deciliter, elevated Kappa and Kappa: lambda ratio, serum albumin 3.7 mg/dL and beta two microglobulin of 4.8 mg/L; LDH, serum calcium, and creatinine were normal. Bone marrow biopsy showed 50% plasma cells, with translocation 11;14 on FISH. He was diagnosed with revised ISS stage I MM disease and began lenalidomide bortezomib, and dexamethasone (RVD) therapy. He achieved a complete response after four cycles of RVD therapy, underwent stem cell collection, received 200 mg/m2 melphalan followed by re infusion of his stem cells. At 100 days post-transplant, he was MRD negative by next generation flow cytometry. The patient wanted to know if he would benefit from receiving maintenance therapy, given that he is MRD negative at this time.
What we know with regards to MRD	There is no definitive data from prospective clinical trials to inform whether achievement of MRD negativity prior to transplant can improve long term outcomes of MM patients, including overall survival. And while the role of lenalidomide maintenance therapy has been demonstrated in multiple Phase III trials[1], and in meta-analyses, it remains unclear whether we can decide on the use and type of maintenance based on the MRD status post-transplant. Phase III trials are needed to determine whether MRD negativity can be an indicator to discontine maintenance therapy.
Key questions we need to answer	In patients with standard risk multiple myeloma who have excellent survival with current treatments, the lack of data from prospective clinical trials demonstrating a survival benefit of altering therapy to achieve MRD negativity this approach can potentially expose patients to unnecessary therapy and increase toxicity. At least one European trial has shown benefit for additional consolidation therapy after ASCT prior to initiating maintenance[2], although this has not been consistently demonstrated in all clinical trials. Quadruplet induction regimens have been associated with deeper responses prior to stem cell transplant, but there is limited data on long term outcomes, especially overall survival. It remains unclear if all patients will benefit form use of 4-drug regimens or whether we can develop response adapted strategies where the 4th drug is added for failure to reach a certain depth of response with 3 drugs over a defined period of time.

Anderson KC et al. *Clin Cancer Res* 2021 October 1;27(19):5195-212.

Clinical Case 3 – Use of MRD for a Transplant-Eligible Patient with Newly Diagnosed High-Risk MM

Case 3 - Newly Diagnosed MM Transplant Eligible - High Risk	
Case Description	A 54-year-old man presented with back pain. Laboratory revealed hemoglobin of 10.2 g/dL, normal serum calcium and creatinine, IgG kappa M spike 2.1 gm/L, kappa 36 mg/dL, lambda 0.29 mg/dl, 24-hour urine 240 mg M spike. Skeletal survey revealed numerous lytic lesions. Bone marrow showed 40% PCs, with t(4;14) and chromosome 1q amplification on FISH. He was treated with VRd for 4 cycles, achieved VGPR, and then received 200 mg/m2 melphalan followed by autologous SCT and achieved CR. Marrow evaluation with NGS showed persistent MRD. The role of additional consolidation and or a tandem autologous stem cell transplantation was discussed in detail with the patient.
What we know with regards to MRD	High risk patients do not benefit from current treatment approaches. Given emerging data regarding the improved outcomes in high risk myeloma associated with achieving MRD negativity[1,2], one can make an argument for routine use of MRD testing in these patients, even outside of clinical trials. The observation that the magnitude of benefit associated with MRD negativity appears substantially higher for the high-risk group compared with standard risk myeloma, coupled with the risk of continuing with current treatment approaches, makes this decision easier
Key questions we need to answer	Several important MRD questions need to be answered in carefully designed clinical trials of high risk myeloma. In particular, the importance of reaching MRD negativity, and the need for changing therapy based on not reaching a predefined depth of response by a defined time, are important considerations to improve outcome of high-risk patients. The role of sustained MRD negativity is key for patients with high-risk MM.

Anderson KC et al. *Clin Cancer Res* 2021 October 1;27(19):5195-212.

Clinical Case 4 – Use of MRD for a Transplant-Ineligible Patient with Newly Diagnosed MM

Case 4 - Newly Diagnosed MM Transplant Ineligible	
Case Description	An 84-year-old man with type 2 diabetes well controlled with oral medications and atrial fibrillation was symptomatic and found to have mild anemia (hemoglobin 10.4 g/dL). Evaluation revealed an IgAK spike 3.2 g/dL with low IgM/IgG serum levels, and serum free kappa light chain ratio 100. Whole body low dose CT revealed several lytic lesions, weith 2 dorsal and 3 lumbar vertebral fractures. Bone marrow biopsy showed 50% plasma cells, and FISH revealed del13 and t(11;14). He is a retired engineer who lives alone in a third floor apartment, with no lift available. He began lenalidomide-dexamethasone, but dexamethasone was poorly tolerated and stopped after 8 cycles. Recurrent diarrhea required lenalidomide dose reduction to 10 mg/day from cycle 10. He achieved a VGPR after one year of treatment, and his PS definitely improved.
What we know with regards to MRD	Although mostly studied in transplant-eligible patients, MRD negativity is also achievable in transplant-ineligible patients. A retrospective analysis of concomitant IFE and MRD testing in 289 patients with MM demonstrated 20% 1-year probability of progressive disease if both MRD and IFE negative versus 40% in the MRD negative, IFE positive group[1]. Persistent M-protein despite MRD negativity predicts for a shorter time to progression. Some patients who are IFE positive do ultimately become IFE negative owing to the prolonged M protein half-life and clearance of the M-protein, and there are trends towards improved TTP in those who ultimately become IFE negative. While MRD can be a powerful prognostic tool, other patient characteristics, such as frailty, can predict mortality in the elderly MM population. The Geriatric Assessment can predict both toxicity and mortality. Therapeutic decisions must be based on the collective data available for a patient, weighing the benefits of increased depth of response versus increased treatment-related toxicity.
Key questions we need to answer	We need to incorporate MRD testing into clinical trial design in newly diagnosed transplant-ineligible patients in order to determine the optimal timepoints for MRD evaluation, if MRD evaluation is needed in all patients achieving a specific response, and potential impact of MRD on treatment decisions. These studies will provide an evidence-based foundation for using MRD status to inform decisions regarding treatment duration and discontinuation.

Anderson KC et al. *Clin Cancer Res* 2021 October 1;27(19):5195-212.

Clinical Case 5 – Use of MRD for Treatment-Free Monitoring

Case 5 - Treatment-Free Monitoring	
Case Description	A 59 year old artistic director was diagnosed with ISS stage 1 IgG kappa myeloma. He presented with back pain, and PET CT showed FDG avid fractures of thoracic vertebrae T7 and T8. He had mild anaemia (hemoglobin 10.1 g/dL), with normal calcium and renal function. Bone marrow biopsy showed 35% plasma cells, with FISH testing showing hyperdiploidy. Serum electrophoresis showed an M-protein spike of 3.4 g/dL, serum free kappa/ lambda light chain ratio was 35.2. He was treated with VTD induction, and developed grade 1 peripheral neuropathy and a deep vein thrombosis treated with anticoagulation. He achieved CR with normal FDG PET-CT scan and then received high dose melphalan and ASCT. At 3 months post transplant MRD was negative, assessed by Flow cytometry at a sensitivity of 10-5. Lenalidomide maintenance was started about 4 months post transplant, but was discontinued after 6 months due to gastrointestinal side effects. He is currently on a treatment free monitoring period and has had a bone marrow annually with ongoing MRD negativity, along with 3 monthly blood work which confirms ongoing CR. He has been able to engage with normal day to day activities and work routine.
What we know with regards to MRD	First remission following induction is on average the longest period of remission patients experience[1]. Quality of life has been reported to be better in first remission and large patient survey data have reported this using PROM tools[2]. Myeloma has the potential to relapse during treatment free periods, and patients therefore require monitoring to include blood work, clinical evaluation, MRD assessment, and whole body imaging.
Key questions we need to answer	It is unclear what data is needed to monitor patients who prefer to stop therapy either due to personal preference or due to adverse events. If patients have achieved less than CR, then blood work alone as a standard of care is reasonable. In patients who are in CR, tools to monitor MRD by Flow or NGS and imaging are reasonable to consider. The frequency of application of these tools, and whether both tools should be applied together, requires further evaluation in prospective studies. Currently patients start treatment for MM when IMWG criteria for relapse are met. Future trials will evaluate feasibility and benefit of starting treatment upon change of MRD status.

Anderson KC et al. *Clin Cancer Res* 2021 October 1;27(19):5195-212.

Clinical Case 6 – Use of MRD for a Patient with Relapsed/ Refractory Myeloma

Case 6 - Relapsed Refractory Myeloma	
Case Description	A 63 year old man presented with fatigue and lower back pain. He was found to have Hct 28% Creat 1.8 mg/dL, Calcium 11 mg/dL and diffuse lytic bone disease. Serum IgG kappa was 6 gm/dL, and bone marrow showed 80% plasma cells with t(11:14). He was treated with lenalidomide, bortezomib, and dexamethasone followed by high dose melphalan, ASCT, and lenalidomide maintenance therapy for three years. Increasing back pain, fatigue, and dyspnea on exertion develop on maintenance treatment. Restaging reveals IgG lambda 2.5 g gm/dL, Hct 28%, creat 1.8 mg/dL, and Ca 10.0 mg/dL. BM reveals 40% plasma cells, with t(11;14) and del17p. PET/CT reveals multiple new sites of uptake in thoracic and lumbosacral spine. He is treated with daratumumab, carfilzomib, and dexamethasone and achieves a partial response lasting only 6 months, and then again develops rising IgG lambda protein and new vertebral compression fractures. Due to his t(11:14) translocation, he receives venetoclax and carfilzomib therapy, and achieves a partial response lasting 10 months. Again relapse is noted with rapidly rising IgG lambda and progressive anemia, bone disease, and hypercalcemia. He is treated with anti-BCMA CAR-T cell protocol therapy, and achieves a bone marrow and imaging MRD negative complete response within one month of therapy that lasts for 9 months.
What we know with regards to MRD	Significant responses in patients who literally have exhausted all other treatment options are now being seen in novel immune treatments, including CAR-T cell and bispecific T-cell engager treatments[1-4]. However, to date the duration of response even in those patients who achieve MRD negativity is only 8 to 11 months. Ongoing studies are therefore attempting to prolong these responses by modifying the CAR-T to enhance its activity and survival post infusion, selecting for memory stem T-cells, and treating patients earlier in their disease course
Key questions we need to answer	Ongoing meta-analyses at both a clinical trial and individual patient level are assessing the utility of MRD negativity as a surrogate endpoint predictive of outcome in patients at various stages of disease including RRMM, with distinct genetic subtypes, and receiving various therapies.

Anderson KC et al. *Clin Cancer Res* 2021 October 1;27(19):5195-212.

Meet The Professor with Dr Lonial

MODULE 1: Case Presentations – Part 1

- Dr McKenna: 58-year-old man with relapsed t(11;14) MM 17 years after initial induction treatment and ASCT
- Dr Rupard: 74-year-old man with NDMM receives daratumumab/lenalidomide/dexamethasone in EAA181 clinical trial and develops ileus
- Dr Gupta: 80-year-old man with NDMM, a borderline performance status and multiple medical comorbidities, including DM, CHF and CKD
- Dr Brenner: 67-year-old woman with biochemical progression of del(17p) MM, s/p RVd, ASCT and 1 year of maintenance bortezomib/lenalidomide
- Dr Lorber: Otherwise healthy 75-year-old man with refractory MM, s/p 5 prior lines of therapy

Case Presentation: 58-year-old man with relapsed t(11;14) MM 17 years after initial induction treatment and ASCT

Dr Rajalaxmi McKenna (Willowbrook, Illinois)

RTP
RESEARCH
TO PRACTICE

2022 ASCO ANNUAL MEETING

Abstract LBA4

RVd ± ASCT and Lenalidomide Maintenance to Progression for NDMM

The Phase 3 DETERMINATION Trial

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

The NEW ENGLAND JOURNAL of MEDICINE

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

ORIGINAL ARTICLE

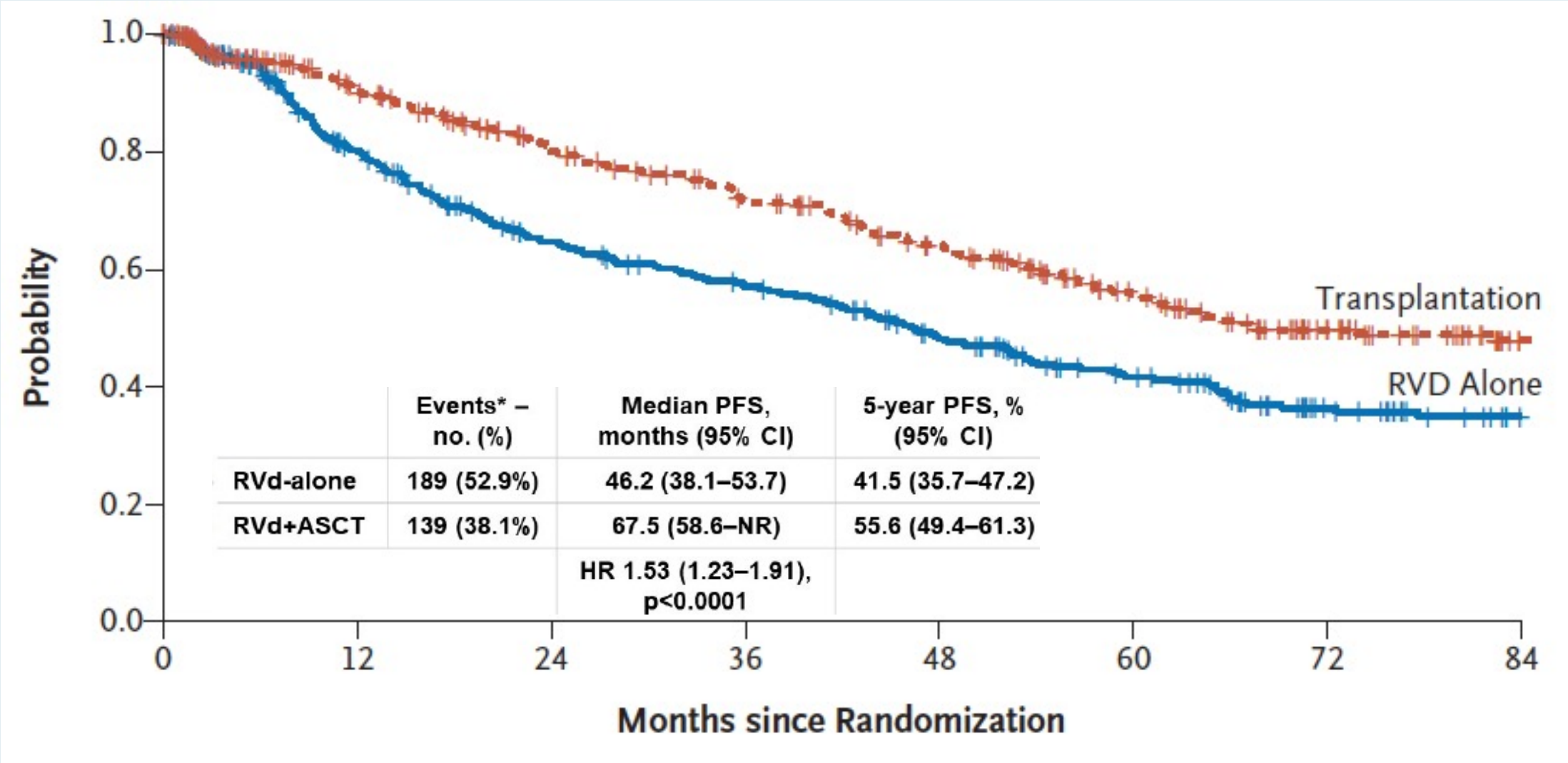
Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

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

JC JOURNAL CLUB

RTP RESEARCH TO PRACTICE

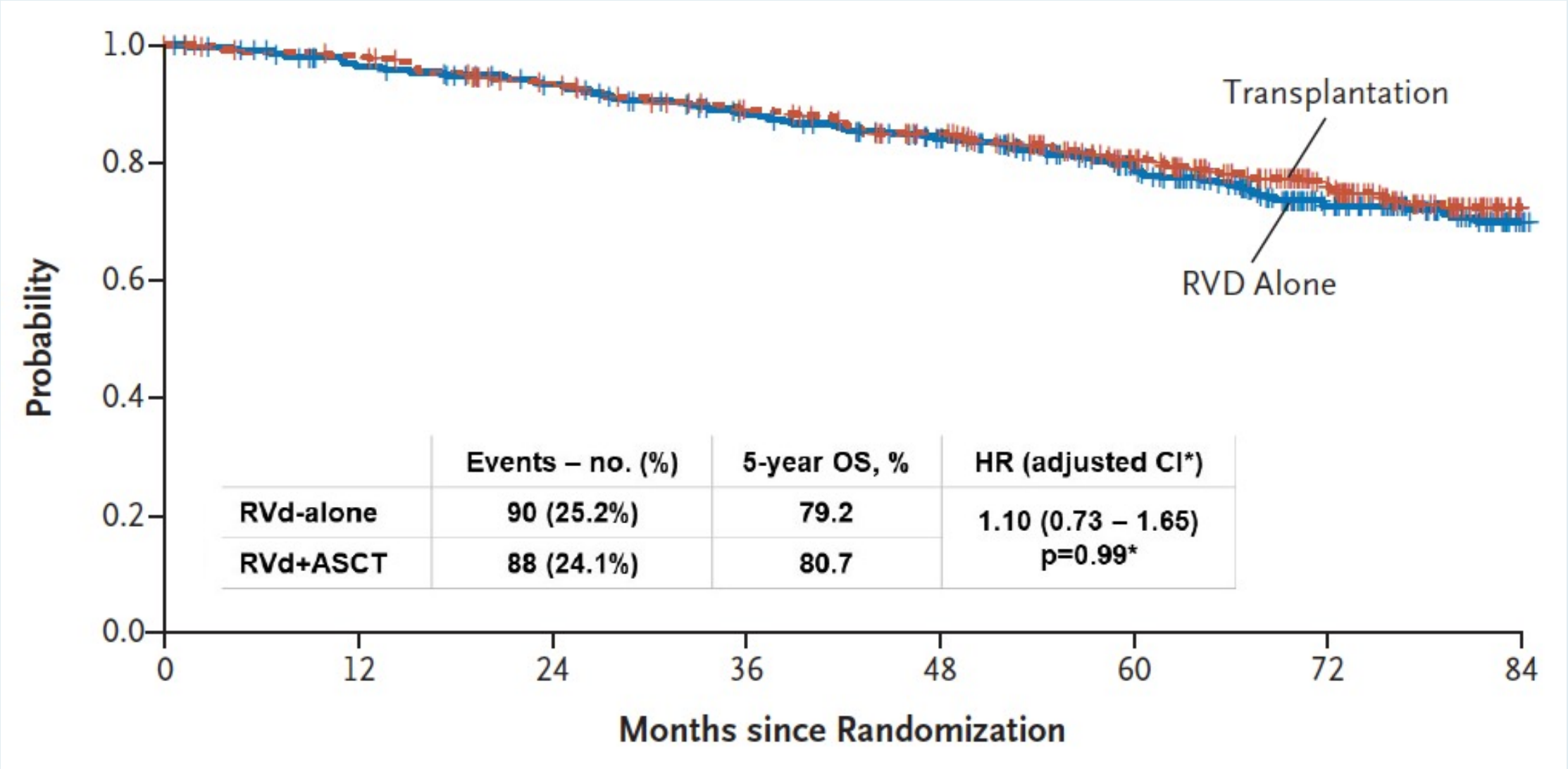
DETERMINATION: Progression-Free Survival (Primary Endpoint)



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

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

DETERMINATION: Overall Survival (Key Secondary Endpoint)



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

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

Transplantation and Cellular Therapy 28 (2022) 284–293

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

Guideline

ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Multiple Myeloma

Binod Dhakal[1], Nina Shah[2], Ankit Kansagra[3], Ambuj Kumar[4], Sagar Lonial[5], Alfred Garfall[6], Andrew Cowan[7], Bishesh Sharma Poudyal[8], Caitlin Costello[9], Francesca Gay[10], Gordon Cook[11], Hang Quach[12], Herman Einsele[13], Jeff Schriber[14], Jian Hou[15], Luciano Costa[16], Mahmoud Aljurf[17], Maria Chaudhry[18], Meral Beksac[19], Miles Prince[20], Mohamad Mohty[21], Murali Janakiram[22], Natalie Callander[23], Noa Biran[24], Pankaj Malhotra[25], Paula Rodriguez Otero[26], Philippe Moreau[27], Rafat Abonour[28], Raheel Iftikhar[29], Rebecca Silberman[30], Sham Mailankody[31], Tara Gregory[32], Yi Lin[33], Paul Carpenter[34], Mehdi Hamadani[1,*], Saad Usmani[31], Shaji Kumar[33]

Transplantation and Cellular Therapy 28 (2022) 75.e1–75.e7

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

Full Length Article

Autologous

Benefits of Autologous Stem Cell Transplantation for Elderly Myeloma Patients in the Last Quarter of Life

Nisha S. Joseph, Vikas A. Gupta, Sarah Wyman, Michael Graiser, Jonathan L. Kaufman, Dhwani Almaula, Joel Andrews, Craig Hofmeister, Madhav Dhodapkar, Leonard T. Heffner, Sagar Lonial, Ajay K. Nooka*

Cancer 2021 November 15;127(22):4133-6.

Editorial

"I Took the Road Less Traveled, and That Has Made All the Difference": Making a Case for High-Dose Therapy and Autologous Stem Cell Transplantation in Elderly Patients With Newly Diagnosed Multiple Myeloma

Ajay K. Nooka, MD, MPH ; Nisha S. Joseph, MD ; and Sagar Lonial, MD

Cancer 2021;127(22):4233-9.

Original Article

Outcomes of Upfront Autologous Hematopoietic Cell Transplantation in Patients With Multiple Myeloma Who Are 75 Years Old or Older

Pashna N. Munshi, MD [1]; David H. Vesole, MD, PhD[1,2]; Andrew St. Martin, MS[3]; Omar Davila, MPH[3]; Shaji Kumar, MD [4]; Muzaffar Qazilbash, MD [5]; Nina Shah, MD [6]; Parameswaran N. Hari, MD, MS[3]; and Anita D'Souza, MD, MS [3]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Blood 2021 July 1;137(26):3604-15.

Regular Article

LYMPHOID NEOPLASIA

Venetoclax sensitivity in multiple myeloma is associated with B-cell gene expression

Vikas A. Gupta,[1] Benjamin G. Barwick,[1] Shannon M. Matulis,[1] Ryosuke Shirasaki,[2] David L. Jaye,[3] Jonathan J. Keats,[4] Benjamin Oberlton,[1] Nisha S. Joseph,[1] Craig C. Hofmeister,[1] Leonard T. Heffner,[1] Madhav V. Dhodapkar,[1] Ajay K. Nooka,[1] Sagar Lonial,[1] Constantine S. Mitsiades,[2] Jonathan L. Kaufman,[1] and Lawrence H. Boise[1]

Blood Cancer Journal

Blood Cancer J 2022 August 4;12(8):115.
www.nature.com/bcj

CORRESPONDENCE OPEN

Check for updates

Venetoclax ex vivo functional profiling predicts improved progression-free survival

Vikas A. Gupta[1] ✉, Shannon M. Matulis[1], Benjamin G. Barwick[1], R. Devin Bog[1], Conrad W. Shebelut[2], Mala Shanmugam[1], Paola Neri[3], Nizar J. Bahlis[3], Madhav V. Dhodapkar[1], Leonard T. Heffner[1], Craig C. Hofmeister[1], Nisha S. Joseph[1], Sagar Lonial[1], Jonathan L. Kaufman[1], David L. Jaye[2], Ajay K. Nooka[1] and Lawrence H. Boise[1] ✉

Natural history of multiple myeloma patients refractory to venetoclax: A single center experience

Kathryn T. Maples[1,2], Ajay K. Nooka[1], Vikas Gupta[1], Nisha S. Joseph[1], Leonard T. Heffner[1], Craig Hofmeister[1], Madhav Dhodapkar[1], Shannon M. Matulis[1], Sagar Lonial[1], Lawrence H. Boise[1], Jonathan L. Kaufman[1]

Am J Hematol 2021 March 1;96(3):E68-71.

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

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

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

What have you observed in terms of toxicity with venetoclax for MM?

 Dr Fonseca	GI side effects	 Dr Lonial	GI side effects
 Dr Kumar	Cytopenias, GI side effects	 Dr Mikhael	Cytopenias
 Dr Landgren	GI side effects	 Dr Richardson	Cytopenias, GI side effects, infection

RTP RESEARCH TO PRACTICE

Case Presentation: 74-year-old man with NDMM receives daratumumab/lenalidomide/dexamethasone in EAA181 clinical trial and develops ileus

Dr Erik Rupard (West Reading, Pennsylvania)

IMS 2022;Abstract OAB-057.

Daratumumab (DARA) + Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients With Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Final Analysis of GRIFFIN

Douglas W. Sborov,[1] Jacob Laubach,[2] Jonathan L. Kaufman,[3] Brandi Reeves,[4] Cesar Rodriguez,[5] Ajai Chari,[5] Rebecca Silbermann,[6] Luciano J. Costa,[7] Larry D. Anderson Jr.,[8] Nitya Nathwani,[9] Nina Shah,[10] Naresh Bumma,[11] Sarah A. Holstein,[12] Caitlin Costello,[13] Andrzej Jakubowiak,[14] Robert Z. Orlowski,[15] Kenneth H. Shain,[16] Andrew J. Cowan,[17] Huiling Pei,[18] Annelore Cortoos,[19] Sharmila Patel,[19] Thomas S. Lin,[19] Paul Richardson,[2] Saad Z. Usmani,[20] Peter M. Voorhees[21]

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Presented at the 19th International Myeloma Society (IMS) Annual Meeting; August 25-27, 2022; Los Angeles, CA, USA.

Scan the QR code.

https://www.congresshub.com/Oncology/IMS2022/Daratumumab/Sborov

RTP RESEARCH TO PRACTICE

ECOG-ACRIN cancer research group
Reshaping the future of patient care

ECOG-ACRIN EAA181 - Effective Quadruplet Utilization After Treatment Evaluation (EQUATE): A Randomized Phase 3 Trial for Newly Diagnosed Multiple Myeloma Not Intended for Early Autologous Transplantation

Shaji Kumar, MD[1], Zihan Wei, MSPH[2], Bradley S. Snyder, MS[3], Michael A. Thompson, MD, PhD, FASCO[4], Matthias Weiss, MD, PhD[5], Lynne Wagner, PhD[6], Lale Kostakoglu, MD, MPH[7], S. Vincent Rajkumar, MD[8]

[1]Mayo Clinic, Rochester, MN; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Brown University - ECOG-ACRIN Biostatistics Center, Providence, RI; [4]Aurora Cancer Care-Milwaukee West, Waukesha, WI; [5]ThedaCare Regional Cancer Center Appleton, WI; [6]Wake Forest University Health Sciences, Winston Salem, NC; [7]University of Virginia Cancer Center, Charlottesville, VA; [8]Mayo Clinic, Rochester, MN

BACKGROUND

- Daratumumab has been approved for treatment of newly diagnosed Multiple Myeloma (MM) in combination with lenalidomide and dexamethasone (DRd) or with bortezomib, melphalan and prednisone (D-VMP) in patients who are not eligible to undergo stem cell transplantation (SCT).[1,2]
- Ongoing trials are examining the role of adding Daratumumab to VRd (GRIFFIN, PERSEUS), but it remains unclear if all patients benefit from a quadruplet regimen.
- Availability of sensitive assays to detect minimal residual disease (MRD) in MM and emerging data demonstrating significant prognostic value for attaining MRD negativity, offers an unprecedented opportunity to develop individualized treatment approaches.[3,4]
- An important question is to identify who benefits from adding a fourth drug to the MoAb-IMiD triplet, thus individualizing therapy based on depth of response.
- We hypothesize that prolonged intensive therapy with the addition of Bortezomib (Btz) for consolidation after Daratumumab SC, lenalidomide and dexamethasone (DRd) induction therapy for newly diagnosed MM will improve survival outcomes with a more pronounced effect when used in MRD positive patients.

OBJECTIVES

Primary Objectives

- Consolidation OS in the MRD+ group

Secondary Objectives

- Consolidation OS in the MRD- group
- PFS
- Safety
- MRD Conversion
- Best Response

PRO Objectives

- Neuropathy and associated physical and functional impairments
- MRD association with QoL
- PRO-CTCAEs
- Compliance

Imaging Objectives

- F-FDG PET/CT association with OS, PFS, and MRD

Venous Thromboembolism (VTE) Risk

- D-dmier and IMPEDE

ELIGIBILITY

- Newly diagnosed multiple myeloma, Not intended for early ASCT
- R-ISS Stage I or II
- Have not received more than 1 cycle of any myeloma therapy
- Have identifiable dominant VDJ sequence for clone tracking
- Measurable disease
- Adequate organ and marrow function
- No peripheral neuropathy ≥ Grade 2 or grade 1 with pain
- ECOG PS of 0-2 (PS 3 allowed if secondary to pain)
- If history of chronic obstructive pulmonary disease must have FEV1 > 50% of predicted normal

DESIGN

- The trial employs a randomized biomarker-stratified design.[5]
- Once enrolled, patients receive 9 cycles of DRd induction
- After induction, patients will undergo MRD testing by Next generation sequencing (ClonoSeq)and will be classified into MRD positive or negative subgroups
- Patients will then be randomized into DRd consolidation followed by DR maintenance (control arm) or DRd + bortezomib consolidation followed by DR maintenance (experimental arm), stratified by MRD status and R-ISS stage
- The primary endpoint is consolidation OS in MRD+ subgroup
- Sample size considerations rest on estimates of MRD subgroup prevalence at the end of induction and center on operating characteristics establishing the treatment effect within the MRD+ subgroup as primary and MRD- subgroup as secondary
- The total accrual goal is 1450 patients

STUDY TIMELINE

Concept Submission to MYSC: Apr 9, 2019
Final Concept Approval by MYSC: Oct 18, 2019
NCI CIRB Approval: Oct 12, 2020
Final NCI Approval: Oct 26, 2020
Activation Date: Oct 27, 2020

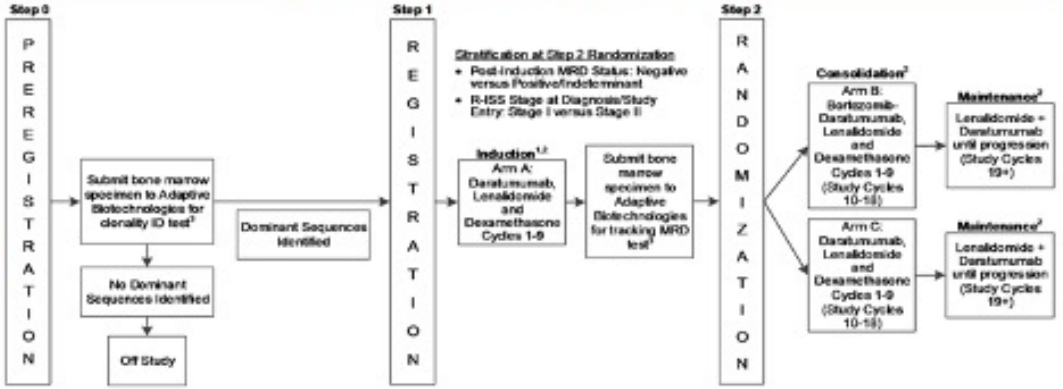
REFERENCES

1. Rajkumar, S.V., et al. 2019 N Engl J Med 380(22): 2104-2115.
2. Moreau, M.V., Dimopoulos, M.A., Cavo M., et al. 2018 N Engl J Med 378:538-539.
3. Yanamandra U, Kumar SK. 2018 Leuk Lymphoma 59:1772-1784
4. Anderson KC, Auclair D, Kelloff GJ, et al. 2017 Clin Cancer Res 23:3980-3985.
5. Freidlin, McShane, Korn. 2010 J Natl Cancer Inst; 102:152-160

ACKNOWLEDGMENTS

This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under the following award numbers: U10CA180794, U10CA180819, U10CA180820, U10CA180888, U10CA189956, UG1CA189140, UG1CA232760. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. government.

SCHEMA & OPERATIONAL CHARACTERISTICS



Accrual Goal:
Step 1 = 1450
Step 2 = 1232
Cycle Duration: 28 days (4 weeks)

1. Patients can mobilize stem cells any time after 4 cycles of induction therapy. If stem cells are harvested, patients can be off treatment for up to 35 days for completion of stem cell collection. While stem cell collection is strongly recommended for patients who are considered eligible for transplant, it is not mandated.
2. Refer to Section 5.1 for detailed dosing instructions.
3. Institutions will be notified of the results of the Clonality ID and tracking MRD tests. Patients for whom dominant sequences were identified must submit bone marrow specimen for MRD test.

Operational Characteristics for Different MRD Distributions within [40%,60%] Range

Group	Prevalence	Sample Size at randomization	Effect Size: HR (Exp/Ctrl)	1-sided alpha	Power	Anticipated accrual (patients per year)	full information events	full information time (year)
Scenario A: Prevalence MRD Positive: 50% (Base Case)								
All		1232	0.640			224		
MRD+	45% - 55%	554 - 678	0.609	2.5%	81%	112	140	6.1
MRD-	55% - 45%	678 - 554	0.667	5.0%	80%	112	161	7.6
Scenario B: Prevalence MRD Positive: 60%								
All		1232	0.640			224		
MRD+	55% - 60%	678 – 740	0.609	2.5%	81%	134	140	5.5
MRD-	45% - 40%	554 - 492	0.667	5.0%	80%	90	161	9
Scenario C: Prevalence MRD Positive: 40%								
All		1232	0.640			224		
MRD+	40% - 45%	492 – 554	0.609	2.5%	81%	90	140	7.1
MRD-	60% - 55%	740 – 678	0.667	5.0%	80%	134	161	6.7

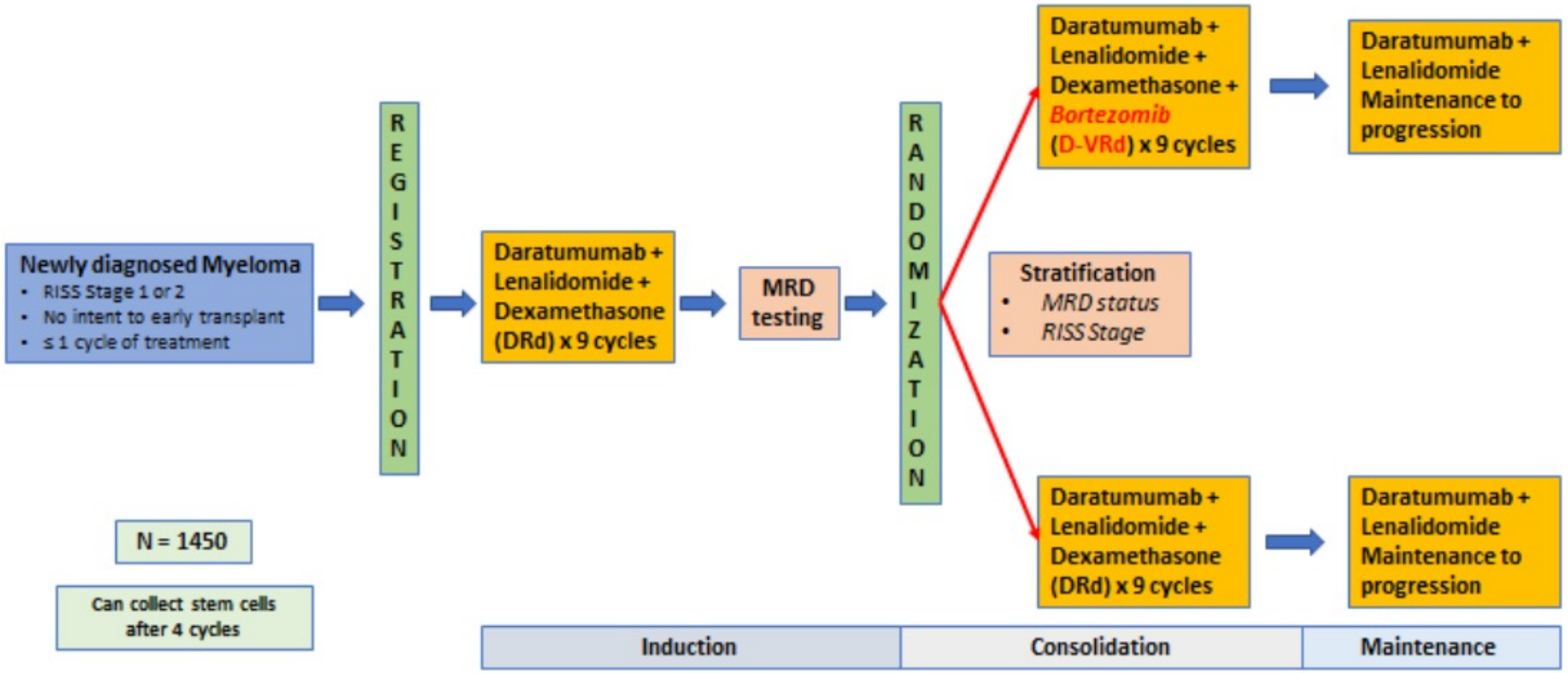
- We will review observed prevalence every 200 patients enrolled on Step 2 up to 600 patients. It is expected that the MRD+ and MRD- distributions will be split 50%/50% as presented in Scenario A
- For a given range of prevalence, a target number of events at full information for both MRD subgroups is set and is intended to be constant within MRD subgroups across scenarios as follow-up times vary
- In each scenario, the effect sizes [hazard ratio (HR)=experimental/control] are constant within subgroups, accrual duration constant at 5.5y for all scenarios
- If MRD+ prevalence ranges exceeding the target upper bound of 60%, only MRD+ patients will be evaluated. If MRD+ prevalence is below 40% at any of the reviews, then the feasibility of the study will be discussed with the NCI

Abstract # TPS8052 | Clinical trial information: NCT04566328. | Questions? kumar.shaji@mayo.edu

Kumar S et al. ASCO 2021;Abstract TPS8052.

RTP RESEARCH TO PRACTICE

Effective Quadruplet Utilization After Treatment Evaluation (EQUATE): A Randomized Phase 3 Trial for Newly Diagnosed Multiple Myeloma



Rajkumar, V [@VincentRK] (2020, October 27) "EQUATE: Our next @eaonc randomized trial for newly diagnosed myeloma is now open." [Tweet]. Retrieved from https://twitter.com/vincentrk/status/1321161816626647043.

Clin Lymphoma Myeloma Leuk 2021 October;21(10):701-10.

Original Study

Daratumumab Plus Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma

Andrzej Jakubowiak,[1] Saad Z. Usmani,[2] Amrita Krishnan,[3] Sagar Lonial,[4] Raymond L. Comenzo,[5] Jianping Wang,[6] Carla de Boer,[7] William Deraedt,[8] Brendan M. Weiss,[9] Jordan M. Schecter,[10] Ajai Chari[11]

UNIVERSITÄTS KLINIKUM HEIDELBERG

Addition of Isatuximab to Lenalidomide, Bortezomib and Dexamethasone as Induction Therapy for Newly-Diagnosed, Transplant-Eligible Multiple Myeloma: The Phase III GMMG-HD7 Trial

Hartmut Goldschmidt[1,2], Elias K. Mai[1], Eva Nievergall[1], Roland Fenk[3], Uta Bertsch[1,2], Diana Tichy[4], Britta Besemer[5], Jan Dürig[6], Roland Schroers[7], Ivana von Metzler[8], Mathias Hänel[9], Christoph Mann[10], Anne Marie Asemissen[11], Bernhard Heilmeier[12], Stefanie Huhn[1], Katharina Kriegsmann[1], Niels Weinhold[1], Steffen Luntz[13], Tobias A. W. Holderried[14], Karolin Trautmann-Grill[15], Deniz Gezer[16], Maika Klaiber-Hakimi[17], Martin Müller[18], Cyrus Khandanpour[19], Wolfgang Knauf[20], Markus Munder[21], Thomas Geer[22], Hendrik Riesenberg[23], Jörg Thomalla[24], Martin Hoffmann[25], Marc-Steffen Raab[1], Hans J. Salwender[26], Katja C. Weisel[11] for the German-speaking Myeloma Multicenter Group (GMMG)

[1]Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany; [2]National Center for Tumor Diseases Heidelberg, Heidelberg, Germany; [3]Department of Hematology, Oncology and Clinical Immunology, University Hospital Düsseldorf, Düsseldorf, Germany; [4]Division of Biostatistics, German Cancer Research Center (DKFZ) Heidelberg, Heidelberg, Germany; [5]Department of Internal Medicine II, University Hospital Tübingen, Tübingen, Germany; [6]Department for Hematology and Stem Cell Transplantation, University Hospital Essen, Essen, Germany; [7]Medical Clinic, University Hospital Bochum, Bochum, Germany; [8]Department of Medicine, Hematology/Oncology, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany; [9]Department of Internal Medicine III, Clinic Chemnitz, Chemnitz, Germany; [10]Department for Hematology, Oncology and Immunology, University Hospital Gießen and Marburg, Marburg, Germany; [11]Department of Oncology, Hematology and BMT, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [12]Clinic for Oncology and Hematology, Hospital Barmherzige Brueder Regensburg, Regensburg, Germany; [13]Coordination Centre for Clinical Trails (KKS) Heidelberg, Heidelberg, Germany; [14]Department of Oncology, Hematology, Immuno-Oncology and Rheumatology, University Hospital Bonn, Bonn, Germany; [15]Department of Internal Medicine I, University Hospital Dresden, Dresden, Germany; [16]Department of Hematology, Oncology, Hemostaseology, and Stem Cell Transplantation, Faculty of Medicine, RWTH Aachen University, Aachen, Germany; [17]Clinic for Hematology, Oncology and Palliative Care, Marien Hospital Düsseldorf, Düsseldorf, Germany; [18]Clinic for Hematology, Oncology and Immunology, Klinikum Siloah Hannover, Hannover, Germany; [19]Medical Clinic A, University Hospital Münster, Münster, Germany; [20]Center for Hematology and Oncology Bethanien, Frankfurt am Main, Germany; [21]Department of Internal Medicine III, University Hospital Mainz, Mainz, Germany; [22]Department of Internal Medicine III, Diakoneo Clinic Schwäbisch-Hall, Schwäbisch-Hall, Germany; [23]Hematology/Oncology Center, Bielefeld, Germany; [24]Hematology / Oncology Center, Koblenz, Germany; [25]Medical Clinic A, Clinic Ludwigshafen, Ludwigshafen, Germany; [26]Asklepios Tumorzentrum Hamburg, AK Altona and AK St. Georg, Hamburg, Germany

UK HD

ASH 2021;Abstract 463.

Case Presentation: 80-year-old man with NDMM, a borderline performance status and multiple medical comorbidities, including DM, CHF and CKD

Dr Ranju Gupta (Bethlehem, Pennsylvania)

Case Presentation: 67-year-old woman with biochemical progression of del(17p) MM, s/p RVd, ASCT and 1 year of maintenance bortezomib/lenalidomide

Dr Warren Brenner (Boca Raton, Florida)

RTP RESEARCH TO PRACTICE

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

VIEWS

PERSPECTIVE

Perspectives on the Risk-Stratified Treatment of Multiple Myeloma

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

BOX 1: THE HIGH-RISK MULTIPLE MYELOMA DISEASE SEGMENT

The challenges of HR disease

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

The biology of HR disease

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

Features of HR disease

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

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

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

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

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

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

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

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

2022 ASCO® ANNUAL MEETING

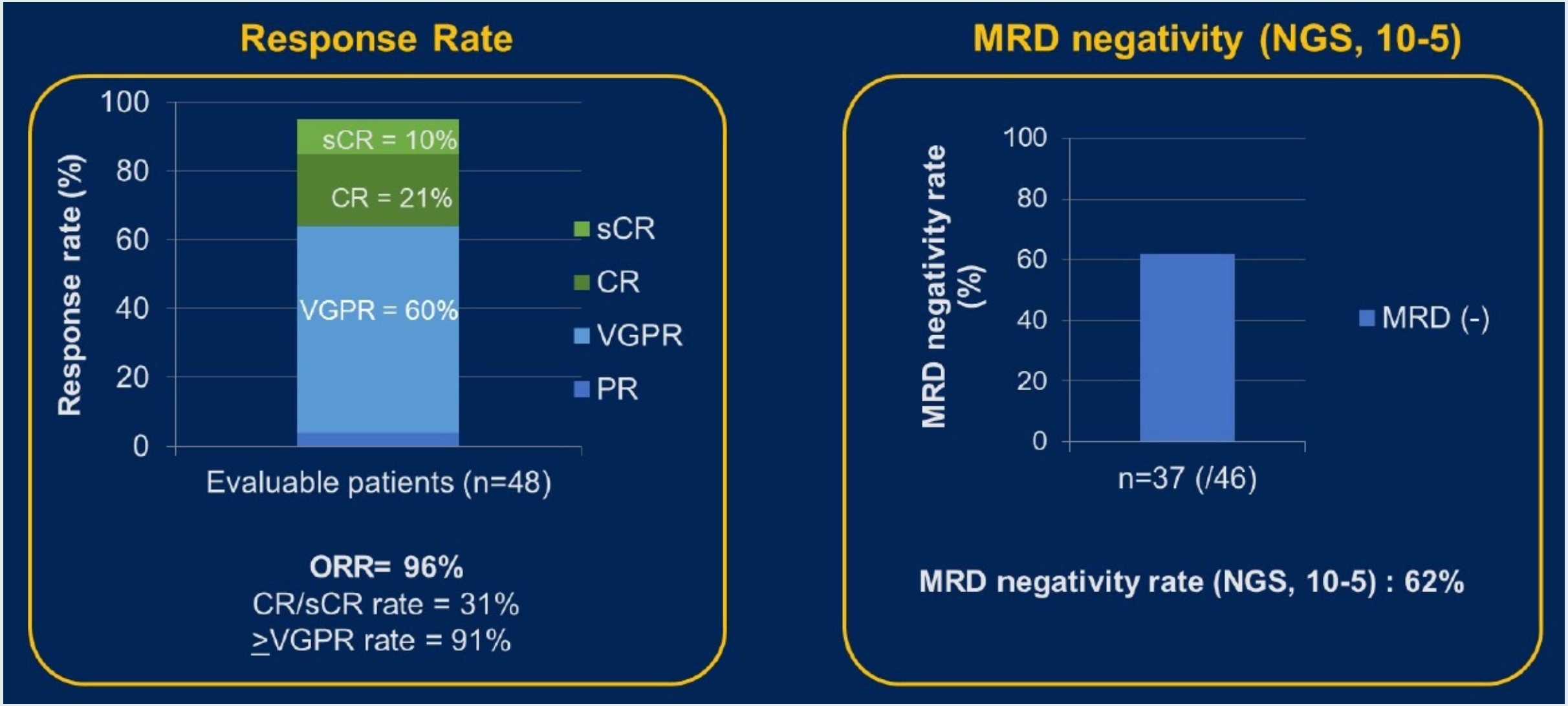
Abstract 8002

Daratumumab Carfilzomib Lenalidomide and Dexamethasone as induction therapy in high-risk transplant eligible newly diagnosed myeloma patients: results of the phase 2 study IFM 2018-04

Cyrille Touzeau[1], Aurore Perrot[2], Cyrille Hulin[3], Salomon Manier[4], Margaret Macro[5], Marie-Lorraine Chretien[6], Lionel Karlin[7], Martine Escoffre[8], Caroline Jacquet[9], Mourad Tiab[10], Xavier Leleu[11], Lucie Planche[12], Hervé Avet-Loiseau[2], Philippe Moreau[1]

RTP RESEARCH TO PRACTICE

IFM 2018-04: Response Rates and MRD with Dara-KRd Induction



Touzeau C et al. ASCO 2022;Abstract 8002.

RTP RESEARCH TO PRACTICE

Case Presentation: Otherwise healthy 75-year-old man with refractory MM, s/p 5 prior lines of therapy

Dr Jeremy Lorber (Beverly Hills, California)

RTP
RESEARCH
TO PRACTICE

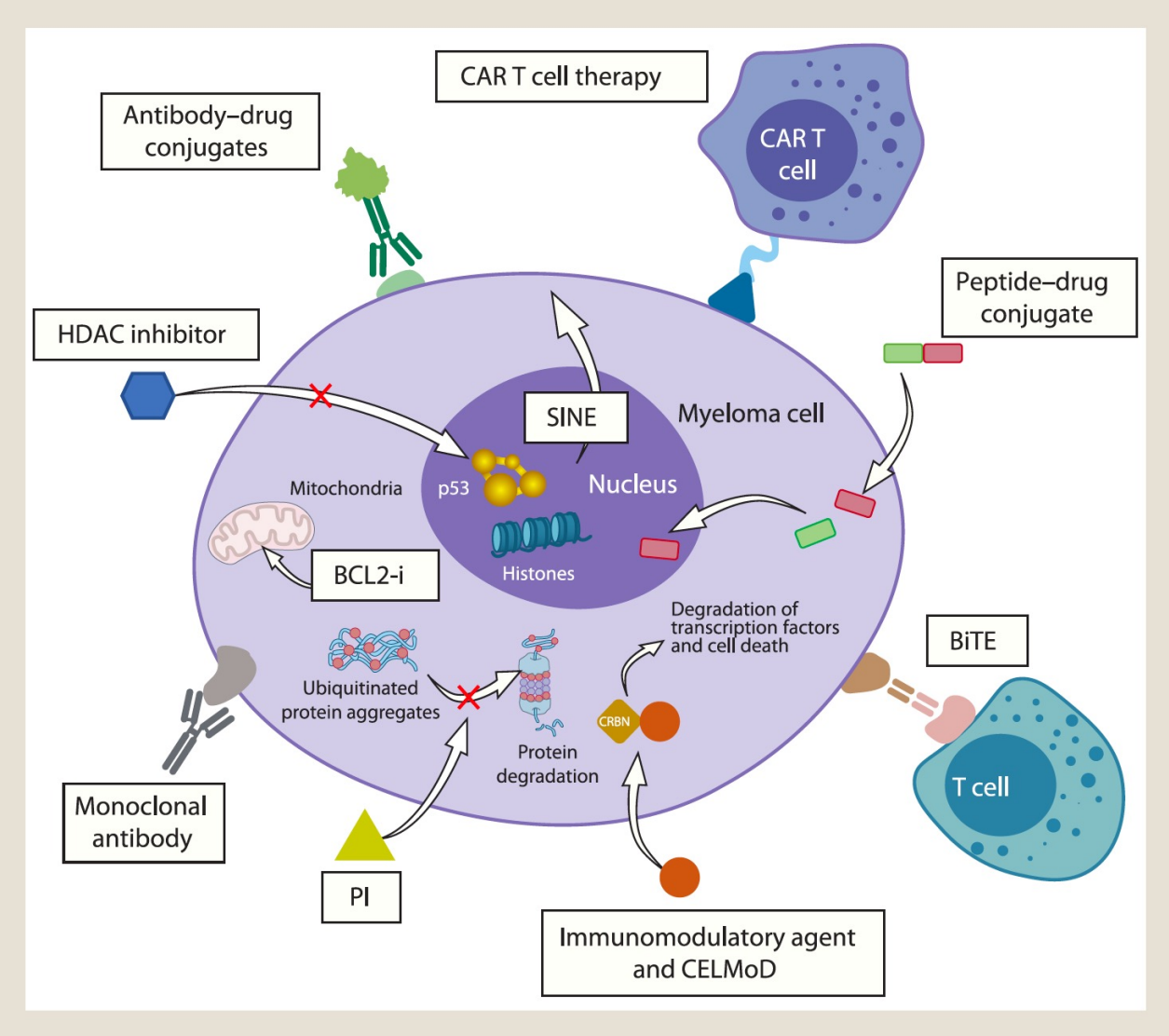
Clin Lymphoma Myeloma Leuk 2022 July;22(7):460-73.

Review Article

Treatment Options for Patients With Heavily Pretreated Relapsed and Refractory Multiple Myeloma

Meletios-Athanasios Dimopoulos,[1] Paul Richardson,[2] Sagar Lonial[3]

Mechanisms of Action of Drug Classes for the Treatment of Refractory Multiple Myeloma



Dimopoulos MA et al. *Clin Lymphoma Myeloma Leuk* 2022 July;22(7):460-73.

Clinical Pharmacology: Advances and Applications

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REVIEW

Novel Approaches to Treating Relapsed and Refractory Multiple Myeloma with a Focus on Recent Approvals of Belantamab Mafodotin and Selinexor

Nisha S Joseph[1]
Yu-Tzu Tai[2]
Kenneth C Anderson[2]
Sagar Lonial[1]

Clin Pharmacol 2021 August 18;13:169-80.

2022 ASCO® ANNUAL MEETING

Abstract 8019

Synergistic Effects of Low-dose Belantamab Mafodotin in Combination with a Gamma-Secretase Inhibitor (Nirogacestat) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): DREAMM-5 Study

Poster No. 443

Speaker: Sagar Lonial, MD, FACP

Acknowledgments

This study was funded by GlaxoSmithKline (GSK Study 208887). Drug linker technology licensed from Seagen, Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa; nirogacestat (gamma-secretase inhibitor) is manufactured and provided by SpringWorks Therapeutics as part of a collaborative agreement with GSK. On behalf of all authors, and with their permission, an audio recording was prepared by Sagar Lonial who did not receive any payment for this recording. Writing assistance was provided by Elisabeth Walsby, PhD and Sharon Bryant, DPT of Fishawack Indicia, part of Fishawack Health and funded by GSK.

Authors and Affiliations

Sagar Lonial, MD, FACP[1], Sebastian Grosicki, MD[2], Marek Hus, MD[3], Kevin Song, MD[4], Thierry Facon, MD[5], Natalie S. Callander, MD[6], Vincent Ribrag, MD[7], Katarina Uttervall, MD[8], Hang Quach, MD[9], Vladimir Vorobyev, MD[10], Chang-Ki Min, MD[11], Shinta Cheng, MD, PhD[12], L. Mary Smith, PhD[12], Jing Yu, PhD[13], Therese Collingwood, PhD[13], Beata Holkova, MD[13], Brandon E. Kremer, MD, PhD[13], Ira Gupta, MD[13], Paul G. Richardson, MD[14], Monique C. Minnema, MD, PhD[15]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Department of Hematology and Cancer Prevention, Medical University of Silesia, Katowice, Poland; [3]Katedra i Klinika Hematoonkologii i Transplantacji Szpiku, Lublin, Poland; [4]Vancouver General Hospital, Vancouver, BC, Canada; [5]Department of Haematology, Lille University Hospital, Lille, France; [6]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [7]Institut Gustave Roussy, Villejuif, France; [8]Karolinska University Hospital, Stockholm, Sweden; [9]University of Melbourne, St. Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [10]S P Botkin City Clinical Hospital, Moscow, Russia; [11]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea; [12]SpringWorks Therapeutics, Stamford, CT, USA; [13]GlaxoSmithKline, Upper Providence, PA, USA; [14]Dana-Farber Cancer Institute, Boston, MA, USA; [15]University Medical Center Utrecht, Utrecht, the Netherlands

Safety and Efficacy of Belantamab Mafodotin in Combination with Rd in Newly Diagnosed, Transplant Ineligible Multiple Myeloma Patients: A Phase 1/2 Study by the Hellenic Society of Hematology

Terpos E et al.

EHA 2022;Abstract S178.

DREAMM-9: Phase I Study of Belantamab Mafodotin plus Standard of Care in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma

Usmani SZ et al.

EHA 2022;Abstract P942.

Lonial et al. *Blood Cancer Journal* (2021)11:103
https://doi.org/10.1038/s41408-021-00494-4

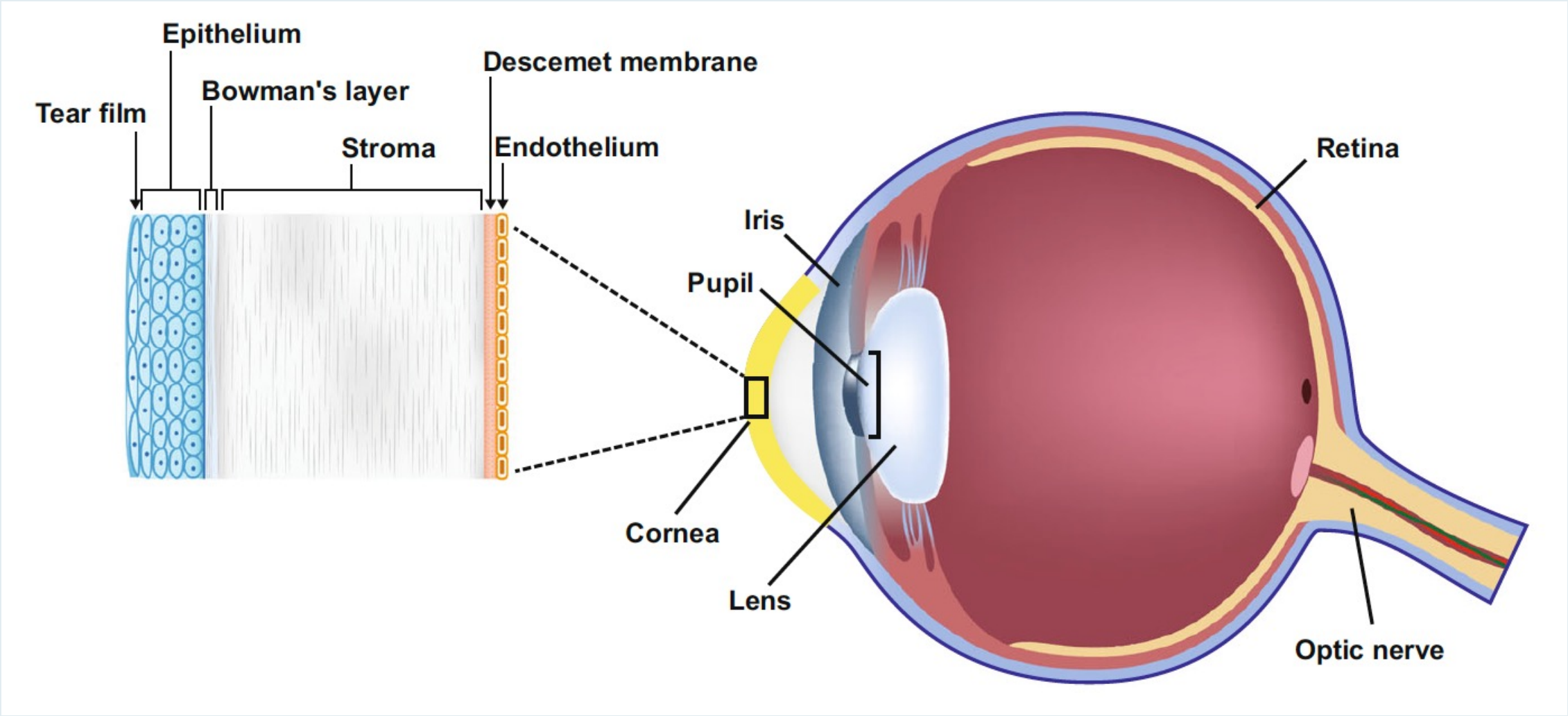
Blood Cancer Journal

ARTICLE Open Access

Management of belantamab mafodotin-associated corneal events 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], Heather A. Potter[6], Douglas Sborov[7], Brian E. Zaugg[8], Rakesh Popat[9], Simona Degli Esposti[10], Julie Byrne[11], Joanna Opalinska[11], January Baron[11], Trisha Piontek[11], Ira Gupta[11], Reza Dana[12], Asim V. Farooq[13], Kathryn Colby[14] and Andrzej Jakubowiak[13]

Anatomy of the Eye, with Focus on the Cornea



Lonial S et al. *Blood Cancer J* 2021;11(5):103.

Example Questions to Ask Patients to Facilitate Reporting of New Corneal-Related AEs with Belantamab Mafodotin Treatment

During conversations with patients regarding the effects of their treatment, it may be helpful to ask the following questions regarding new corneal AEs they may be experiencing with belamaf:

- Are you finding it difficult to read during the day due to your eyesight? Or at night?
- Have you noticed any problems with your eyesight while driving?
- Do you have any problems with your eyes or vision when using a computer/tablet/phone or watching the television?
  - Have you needed to increase the font size on your devices so that you can see the text better?
- Have you noticed any vision changes or other symptoms when you engage in any other activities that are important to you?
- Have you experienced any pain or discomfort in or around your eyes?
- Are your eyes more sensitive than usual to light?
  - Have you needed to turn off the lights or wear sunglasses indoors because you were more sensitive to light?
- Have you noticed any other symptoms related to your eyes or eyesight?
  - Foreign body sensation?
  - Watering eyes?
  - Other (patient to indicate)?

AE adverse event.

Lonial S et al. *Blood Cancer J* 2021;11(5):103.

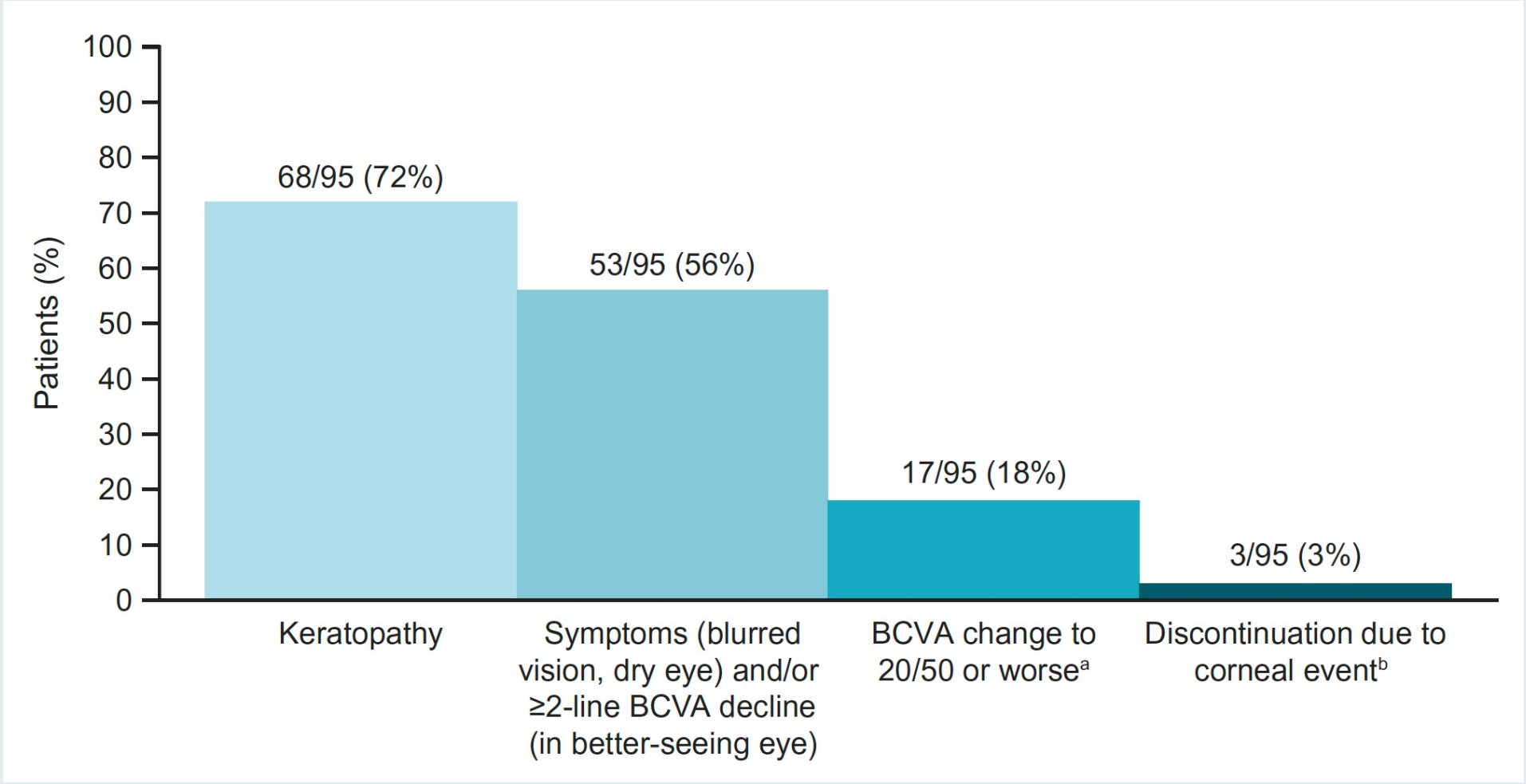
Original Article

Cancer 2021 November 15;127(22):4198-212.

Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study

Sagar Lonial, MD [1]; Hans C. Lee, MD[2]; Ashraf Badros, MD [3]; Suzanne Trudel, MD[4]; Ajay K. Nooka, MD [1]; Ajai Chari, MD [5]; Al-Ola Abdallah, MD[6]; Natalie Callander, MD[7]; Douglas Sborov, MD[8]; Attaya Suvannasankha, MD[9]; Katja Weisel, MD[10]; Peter M. Voorhees, MD[11]; Lynsey Womersley, MSc[12]; January Baron, MS[13]; Trisha Piontek, BSN[13]; Eric Lewis, MD[14]; Joanna Opalinska, MD[13]; Ira Gupta, MD[13]; and Adam D. Cohen, MD[15]

Frequency of Corneal and Vision-Related Events in Patients Who Received 2.5 mg/kg Belantamab Mafodotin in the DREAMM-2 Trial (N = 95)



Lonial S et al. *Cancer* 2021 November 15;127(22):4198-212.

Characterization of Ocular Adverse Events in Patients Receiving Belantamab Mafodotin for ≥12 Months: Post-Hoc Analysis of DREAMM-2 Study in Relapsed/Refractory Multiple Myeloma

Lonial S et al.

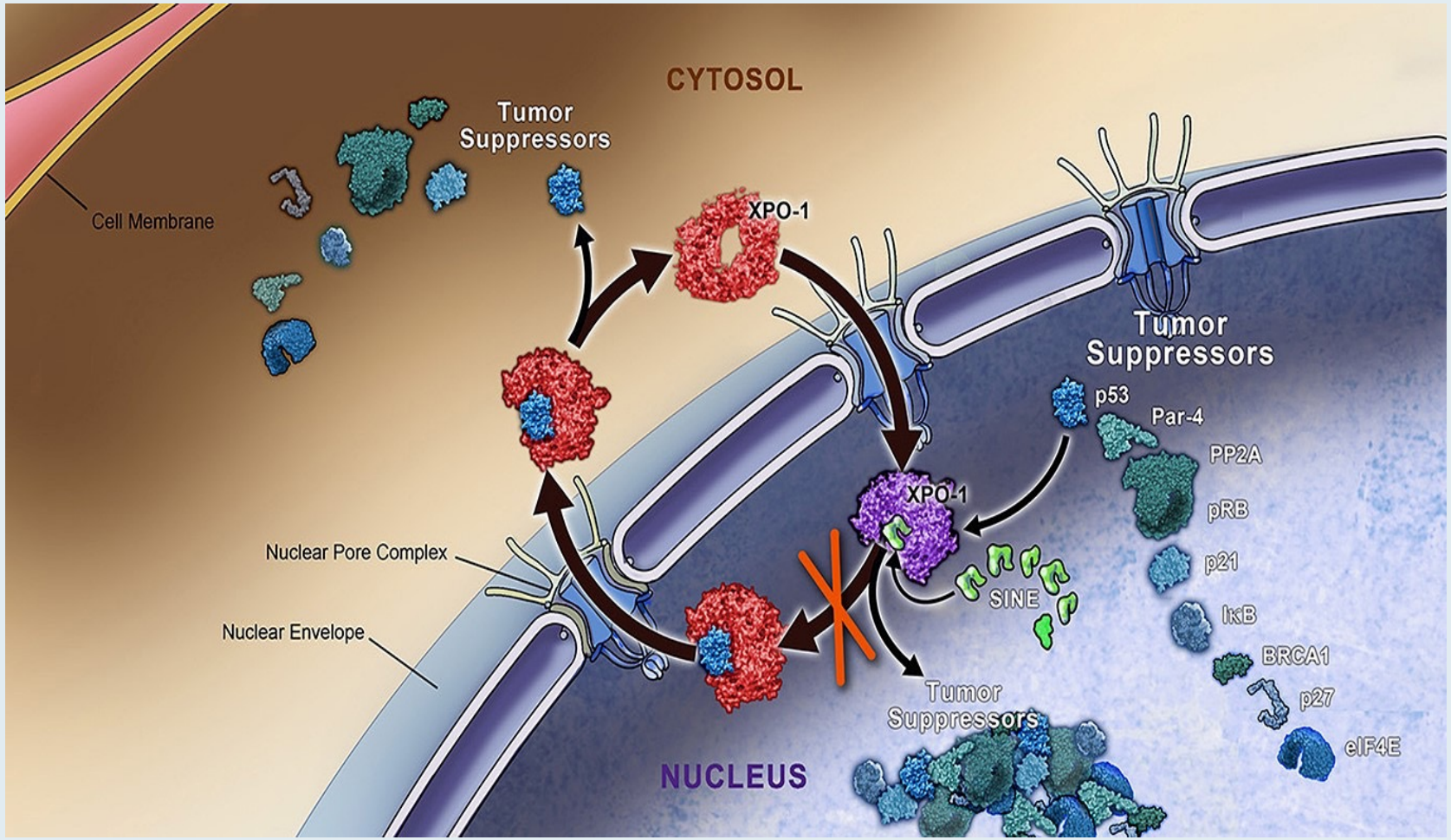
EHA 2021;Abstract EP1026.

Can Patient-Reported Ocular Symptoms Guide Dose Modifications in Patients with Relapsed/Refractory Multiple Myeloma Receiving Belantamab Mafodotin?

Popat R et al.

ASH 2021;Abstract 2746.

Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR) and eIF4E-bound oncoprotein mRNAs (c-myc, Bcl-2, Bcl-xL and cyclins)
- XPO1 is overexpressed in MM and its levels often correlate with poor prognosis
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression

Bahlis N et al. EHA 2016;Abstract P277.

RTP RESEARCH TO PRACTICE

EXPERT REVIEW OF HEMATOLOGY
2021, VOL. 14, NO. 8, 697–706
https://doi.org/10.1080/17474086.2021.1923473

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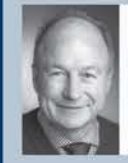
DRUG PROFILE

OPEN ACCESS

Selinexor for the treatment of patients with previously treated multiple myeloma

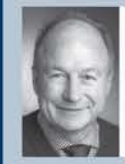
Clifton C. Mo[a], Sundar Jagannath[b], Ajai Chari [b], Ajay K. Nooka[c], Sagar Lonial[c], David Siegel[d], Noa Biran[d], Cristina Gasparetto[e], Nizar J. Bahlis[f] and Paul Richardson[a]

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

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

RTP RESEARCH TO PRACTICE

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

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

Bort/dex = bortezomib/dexamethasone

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

Press Release: August 10, 2022

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

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

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

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

RTP RESEARCH TO PRACTICE

ASCO 2022; Abstract 8020.

Biological Correlative Analyses and Updated Clinical Data of Ciltacabtagene Autoleucel, a BCMA-Directed CAR-T Cell Therapy, in Lenalidomide-Refractory Patients With Progressive Multiple Myeloma After 1–3 Prior Lines of Therapy: CARTITUDE-2, Cohort A

Hermann Einsele[1], Adam Cohen[2], Michel Delforge[3], Jens Hillengass[4], Hartmut Goldschmidt[5], Katja Weisel[6], Marc-Steffen Raab[7], Christoph Scheid[8], Jordan M Schecter[9], Kevin De Braganca[9], Helen Varsos[9], Tzu-Min Yeh[9], Pankaj Mistry[10], Tito Roccia[9], Christina Corsale[9], Muhammad Akram[11], Lida Pacaud[11], Tonia Nesheiwat[11], Mounzer Agha[12], Yael Cohen[13]

[1]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany; [2]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]University Hospitals (UZ) Leuven, Leuven, Belgium; [4]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [5]University Hospital Heidelberg and National Center of Tumor Diseases, Heidelberg, Germany; [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]University Hospital Heidelberg and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center, Heidelberg, Germany; [8]University of Cologne, Cologne, Germany; [9]Janssen Research & Development, Raritan, NJ, USA; [10]Janssen Research & Development, High Wycombe, UK; [11]Legend Biotech USA, Piscataway, NJ, USA; [12]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [13]Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

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

RTP RESEARCH TO PRACTICE

ASCO 2022 | Abstract 8029

Biological Correlative Analyses an Updated Clinical Data of Ciltacabtagene Autoleucel, A BCMA-Directed CAR-T Cell Therapy, in Patients with Multiple Myeloma and Early Relapse After Initial Therapy: CARTITUDE-2, Cohort B

Niels WCJ van de Donk[1] (n.vandedonk@amsterdamumc.nl), Mounzer Agha[2], Adam Cohen[3], Yael Cohen[4], Sébastien Anguille[5], Tessa Kerre[6], Wilfried Roeloffzen[7], Jordan M Schecter[8], Kevin De Braganca[8], Helen Varsos[8], Pankaj Mistry[9], Tito Roccia[8], Enrique Zudaire[10], Christina Corsale[8], Muhammad Akram[11], Dong Geng[11], Tonia Nesheiwat[11], Lida Pacaud[11], Pieter Sonneveld[12], Sonja Zweegman[1]

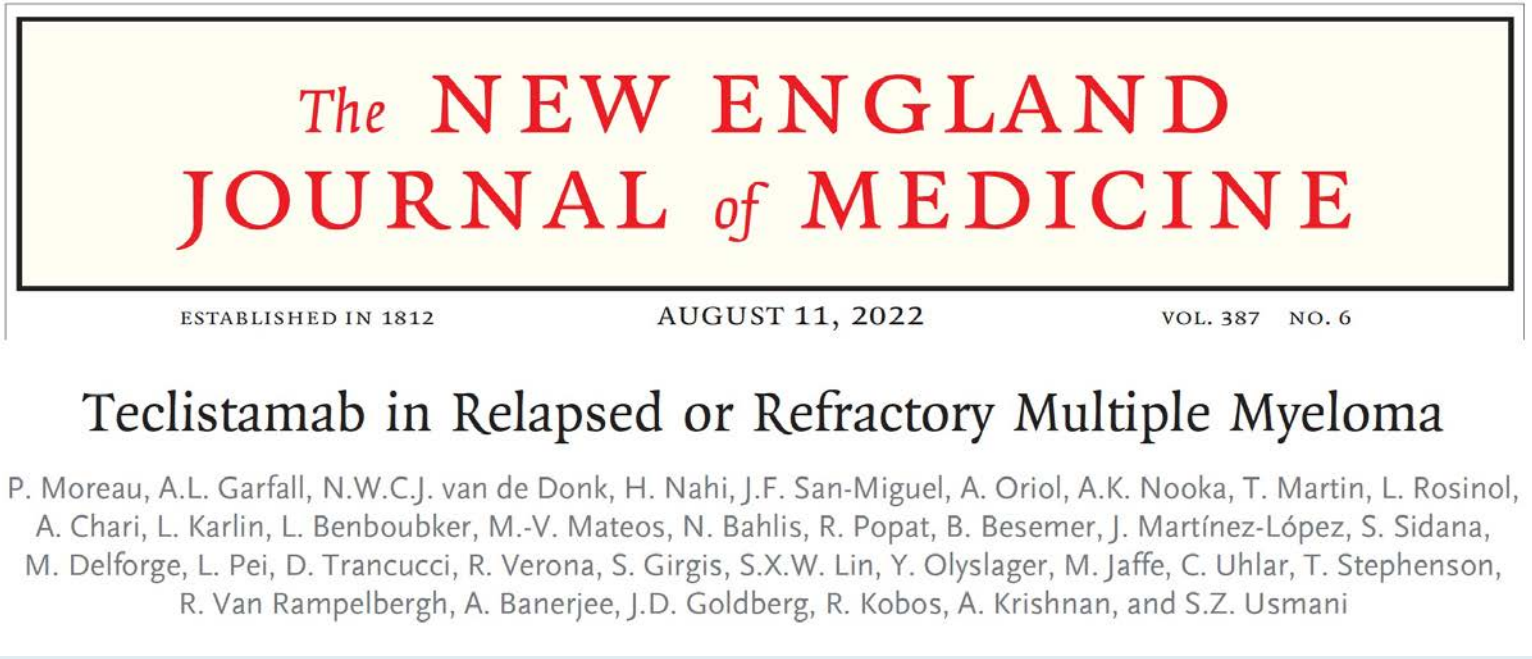
RTP RESEARCH TO PRACTICE

Nat Rev Clin Oncol 2022 August 8;19(10):617-8.

HAEMATOLOGICAL CANCER

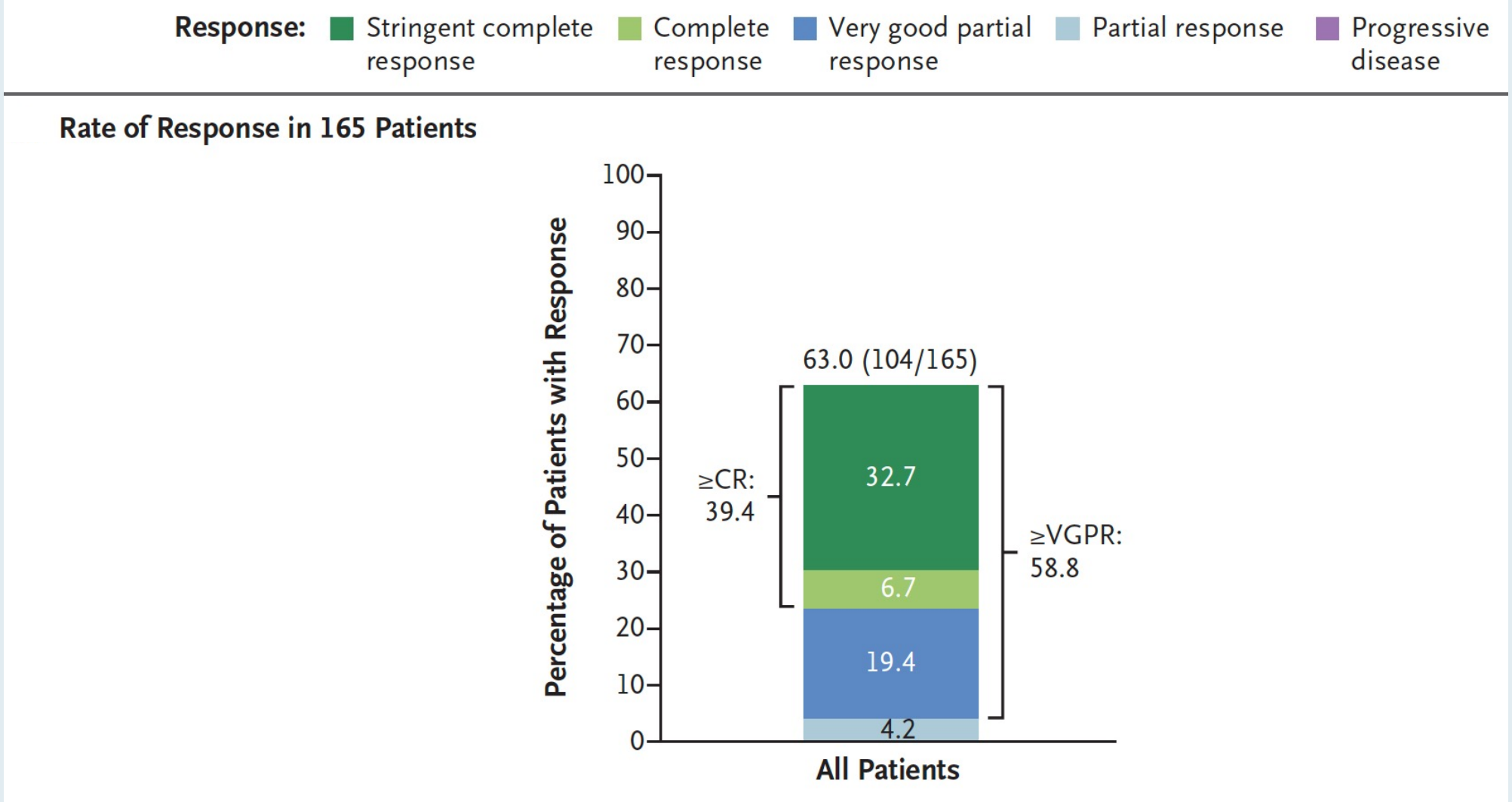
When an embarrassment of riches isn't enough

Krina Patel and Sagar Lonial



JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

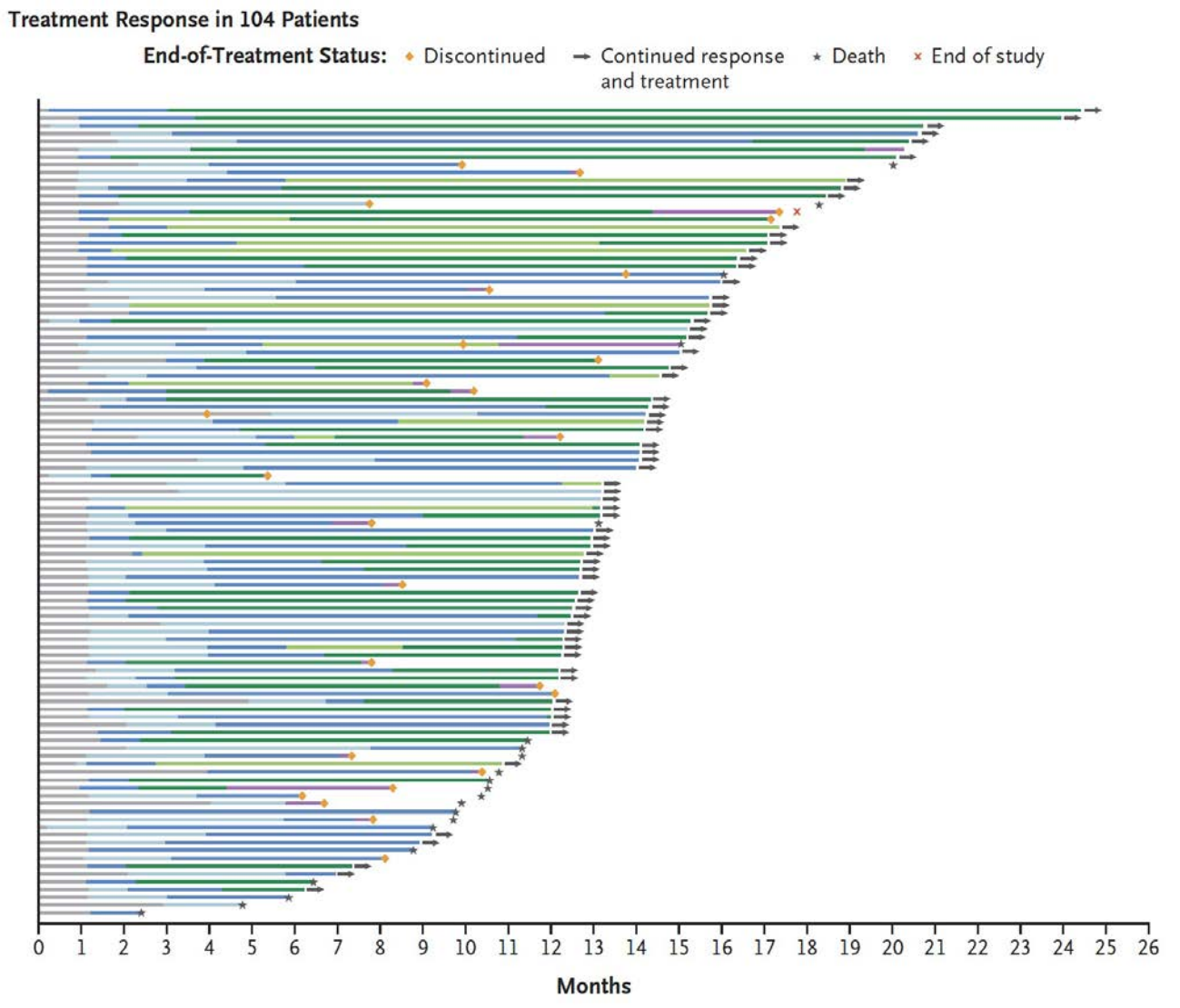
Response to Teclistamab in Patients with Relapsed or Refractory Multiple Myeloma



CR = complete response; VGPR = very good partial response

Moreau P et al. *N Engl J Med* 2022;387(6):495-505.

Response to Teclistamab in Patients with Relapsed or Refractory Multiple Myeloma (Continued)



Moreau P et al. *N Engl J Med* 2022;387(6):495-505.

ASCO 2022;Abstract 8007.

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

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

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

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

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

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

RTP RESEARCH TO PRACTICE

Initial Safety Results for MagnetisMM-3: A Phase 2 Trial of Elranatamab, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients (pts) with Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Lesokhin AM et al.

ASCO 2022;Abstract 8006.

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

Press Release: June 29, 2022

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

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

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

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

RTP RESEARCH TO PRACTICE

Efficacy and Safety of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients With Relapsed/ Refractory Multiple Myeloma: Updated Results From MonumenTAL-1

Monique C Minnema[1], Amrita Krishnan[2], Jesus G. Berdeja[3], Albert Oriol[4], Niels WCJ van de Donk[5], Paula Rodríguez-Otero[6], Daniel Morillo[7], María-Victoria Mateos[8], Luciano J. Costa[9], Jo Caers[10], Deeksha Vishwamitra[11], Joanne Ma[11], Shiyi Yang[11], Brandi W Hilder[11], Jaszianne Tolbert[11], Jenna D Goldberg[12], Ajai Chari[13]

ASCO 2022;Abstract 8015.

RTP RESEARCH TO PRACTICE

EHA 2022;Abstract S183.

Novel Combination Immunotherapy for the Treatment of Relapsed/Refractory Multiple Myeloma: Updated Phase 1b Results for Talquetamab (a GPRC5D x CD3 Bispecific Antibody) in Combination With Daratumumab

Niels WCJ van de Donk[1], Nizar Bahlis[2], Maria-Victoria Mateos[3], Katja Weisel[4], Bhagirathbhai Dholaria[5], Alfred L Garfall[6], Hartmut Goldschmidt[7], Thomas G Martin[8], Daniel Morillo[9], Donna Reece[10], David Hurd[11], Paula Rodríguez-Otero[12], Manisha Bhutani[13], Anita D'Souza[14], Albert Oriol[15], Elham Askari[9], Jesús F San-Miguel[12], K Martin Kortüm[16], Deeksha Vishwamitra[17], Shun Xin Wang Lin[17], Thomas J Prior[17], Lien Vandenberk[18], Marie-Anne Damiette Smit[19], Jenna D Goldberg[20], Ralph Wäsch[21], Ajai Chari[22]

[1]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [2]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Canada; [3]University Hospital of Salamanca/IBSAL/CIC, Salamanca, Spain; [4]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Vanderbilt University Medical Center, Nashville, TN, USA; [6]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]University Hospital Heidelberg and National Center of Tumor Diseases, Heidelberg, Germany; [8]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [9]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [10]Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC, USA; [12]University of Navarra, Pamplona, Spain; [13]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [14]Medical College of Wisconsin, Milwaukee, WI, USA; [15]Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [16]University Hospital of Würzburg, Würzburg, Germany, Würzburg, Germany; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Antwerp, Belgium; [19]Janssen Research & Development, Los Angeles, CA, USA; [20]Janssen Research & Development, Raritan, NJ, USA; [21]Freiburg University Medical Center, Freiburg, Germany; [22]Mount Sinai School of Medicine, New York, NY, USA

Presented at the European Hematology Association (EHA) 2022 Hybrid Congress; June 9–12, 2022; Vienna, Austria.

Meet The Professor with Dr Lonial

INTRODUCTION: Journal Club with Dr Lonial – Part 1

MODULE 1: Case Presentations – Part 1

MODULE 2: Faculty Survey

MODULE 3: Case Presentations – Part 2

MODULE 4: Journal Club with Dr Lonial – Part 2

MODULE 5: Appendix of Key Publications

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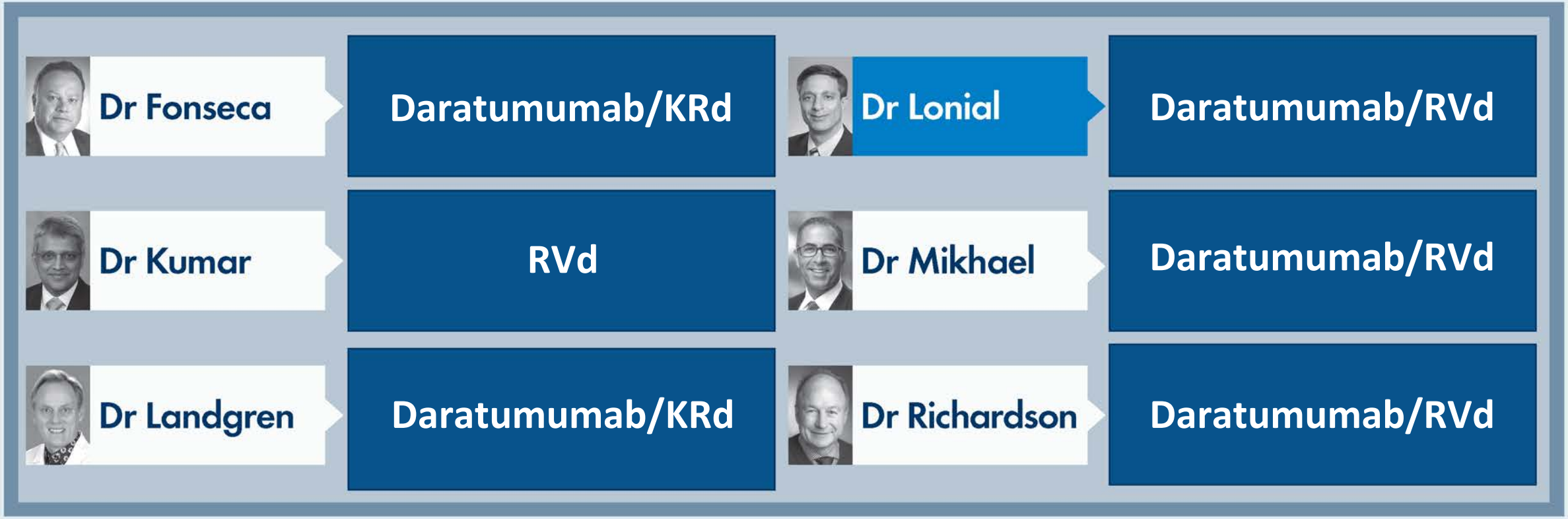
RESEARCH
TO PRACTICE

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



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

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

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

Rd = lenalidomide/dexamethasone; Vd = bortezomib/dexamethasone

In general, what is your preferred initial regimen for an 80-year-old patient with MM who is transplant ineligible with normal renal function and high-risk (del[17p]) MM?

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

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

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

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

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

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

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

 Dr Fonseca	Efficacy is similar with both agents	 Dr Lonial	Efficacy is similar with both agents
 Dr Kumar	Ciltacabtagene autoleucel is more efficacious	 Dr Mikhael	Ciltacabtagene autoleucel is more efficacious
 Dr Landgren	Ciltacabtagene autoleucel is more efficacious	 Dr Richardson	Ciltacabtagene autoleucel is more efficacious

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

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

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

In general, would you feel comfortable adminstering a BCMA-targeted bispecific antibody (eg, teclistamab) to a patient with MM who was not eligible for BCMA-targeted CAR T-cell therapy?

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

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Lonial

MODULE 3: Case Presentations – Part 2

- Dr Lee: 56-year-old woman with smoldering myeloma and t(11;14)
- Dr Rudolph: Noncompliant 72-year-old man and smoker with acute renal failure requiring dialysis and relapsed MM, now on daratumumab with slowly progressive disease

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

Dr Hans Lee (Houston, Texas)

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TO PRACTICE

Blood Cancer Journal

Blood Cancer Journal 2022;12(9):129.

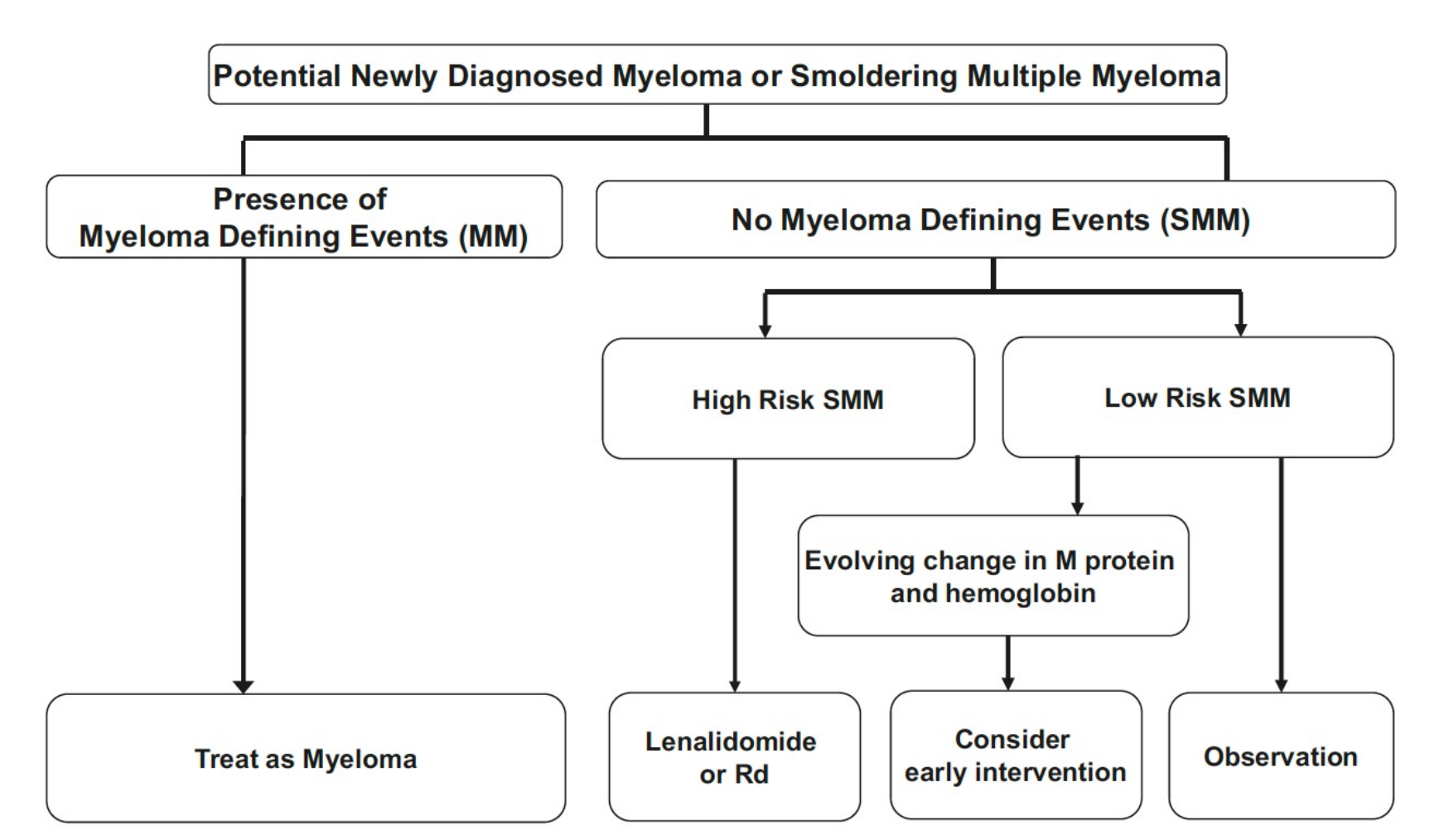
www.nature.com/bcj

CURRENT TREATMENT ALGORITHM OPEN

Smoldering multiple myeloma current treatment algorithms

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

Approach to the Management of Smoldering Multiple Myeloma (SMM)



Rajkumar SV et al. *Blood Cancer J* 2022;12(9):129.

Case Presentation: Noncompliant 72-year-old man and smoker with acute renal failure requiring dialysis and relapsed MM, now on daratumumab with slowly progressive disease

Dr Priya Rudolph (Athens, Georgia)

Meet The Professor with Dr Lonial

INTRODUCTION: Journal Club with Dr Lonial – Part 1

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MODULE 5: Appendix of Key Publications

RTP
RESEARCH
TO PRACTICE

editorials

What The Princess Bride Teaches Us About Outcomes in Multiple Myeloma

Anita D'Souza, MD[1,2] and Sagar Lonial, MD[3]

J Clin Oncol 2021 August 1;39(22):2423-5.

rapid communications

Final Overall Survival Analysis of the TOURMALINE-MM1 Phase III Trial of Ixazomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma

Paul G. Richardson, MD[1]; Shaji K. Kumar, MD[2]; Tamás Masszi, MD, PhD[3]; Norbert Grzasko, MD, PhD[4,5]; Nizar J. Bahlis, MD[6]; Markus Hansson, MD, PhD[7,8]; Luděk Pour, MD[9]; Irwindeep Sandhu, MD[10]; Peter Ganly, BMBCh[11]; Bartrum W. Baker, MBChB[12]; Sharon R. Jackson, MBChB[13]; Anne-Marie Stoppa, MD[14]; Peter Gimsing, MD, DMSc[15]; Laurent Garderet, MD[16]; Cyrille Touzeau, MD, PhD[17]; Francis K. Buadi, MD[2]; Jacob P. Laubach, MD[1]; Michele Cavo, MD[18]; Mohamed Darif, PhD[19]; Richard Labotka, MD[19]; Deborah Berg, RN, MSN[19]; and Philippe Moreau, MD[17]

J Clin Oncol 2021;39(22):2430-42.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Clin Adv Hematol Oncol 2021 March;19(3):166-74.

Antibody Treatment in Multiple Myeloma

Kathryn T. Maples, PharmD,[1,2] Catherine Johnson, PA-C,[1] and Sagar Lonial, MD[1]

HemaSphere EHA 2022;Abstract PB1983.

EHA EUROPEAN HEMATOLOGY ASSOCIATION

PB1983 TRIAL-IN-PROGRESS: PHASE II STUDY OF PHE885, A B-CELL MATURATION ANTIGEN-DIRECTED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY, IN ADULTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

Nikhil Munshi[1], Andrew Spencer[2], Marc S. Raab[3], Aisha Masood[4], Marcela Martinez-Prieto[4], Jufen Chu[4], Shinsuke Iida[5], Sagar Lonial[6], Meletios A. Dimopoulos[7]

Lancet Haematol 2022;9(2):e143-61.

Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group

Noopur S Raje, Elias Anaissie, Shaji K Kumar, Sagar Lonial, Thomas Martin, Morie A Gertz, Amrita Krishnan, Parameswaran Hari, Heinz Ludwig, Elizabeth O'Donnell, Andrew Yee, Jonathan L Kaufman, Adam D Cohen, Laurent Garderet, Ashutosh F Wechalekar, Evangelos Terpos, Navin Khatry, Ruben Niesvizky, Qing Yi, Douglas E Joshua, Tapan Saikia, Nelson Leung, Monika Engelhardt, Mohamad Mothy, Andrew Branagan, Ajai Chari, Anthony J Reiman, Brea Lipe, Joshua Richter, S Vincent Rajkumar, Jesús San Miguel, Kenneth C Anderson, Edward A Stadtmauer, Rao H Prabhala, Phillip L McCarthy, Nikhil C Munshi

nature COMMUNICATIONS

2022;13(1):3750.

ARTICLE

https://doi.org/10.1038/s41467-022-31430-0 OPEN

The genetic heterogeneity and drug resistance mechanisms of relapsed refractory multiple myeloma

Josh N. Vo[1,2,31], Yi-Mi Wu[1,3,31], Jeanmarie Mishler[1], Sarah Hall[1], Rahul Mannan[1,3], Lisha Wang[1], Yu Ning[1], Jin Zhou[1], Alexander C. Hopkins[1], James C. Estill[1], Wallace K. B. Chan[4], Jennifer Yesil[5], Xuhong Cao[1,3,6], Arvind Rao[2,7,8,9], Alexander Tsodikov[10], Moshe Talpaz[11,12], Craig E. Cole[13], Jing C. Ye[11,12], Multiple Myeloma Research Consortium*, P. Leif Bergsagel[14], Daniel Auclair[5], Hearn Jay Cho[5], Dan R. Robinson[1,3,32]✉ & Arul M. Chinnaiyan[1,3,6,12,15,32]✉

Meet The Professor with Dr Lonial

INTRODUCTION: Journal Club with Dr Lonial – Part 1

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RTP
RESEARCH
TO PRACTICE

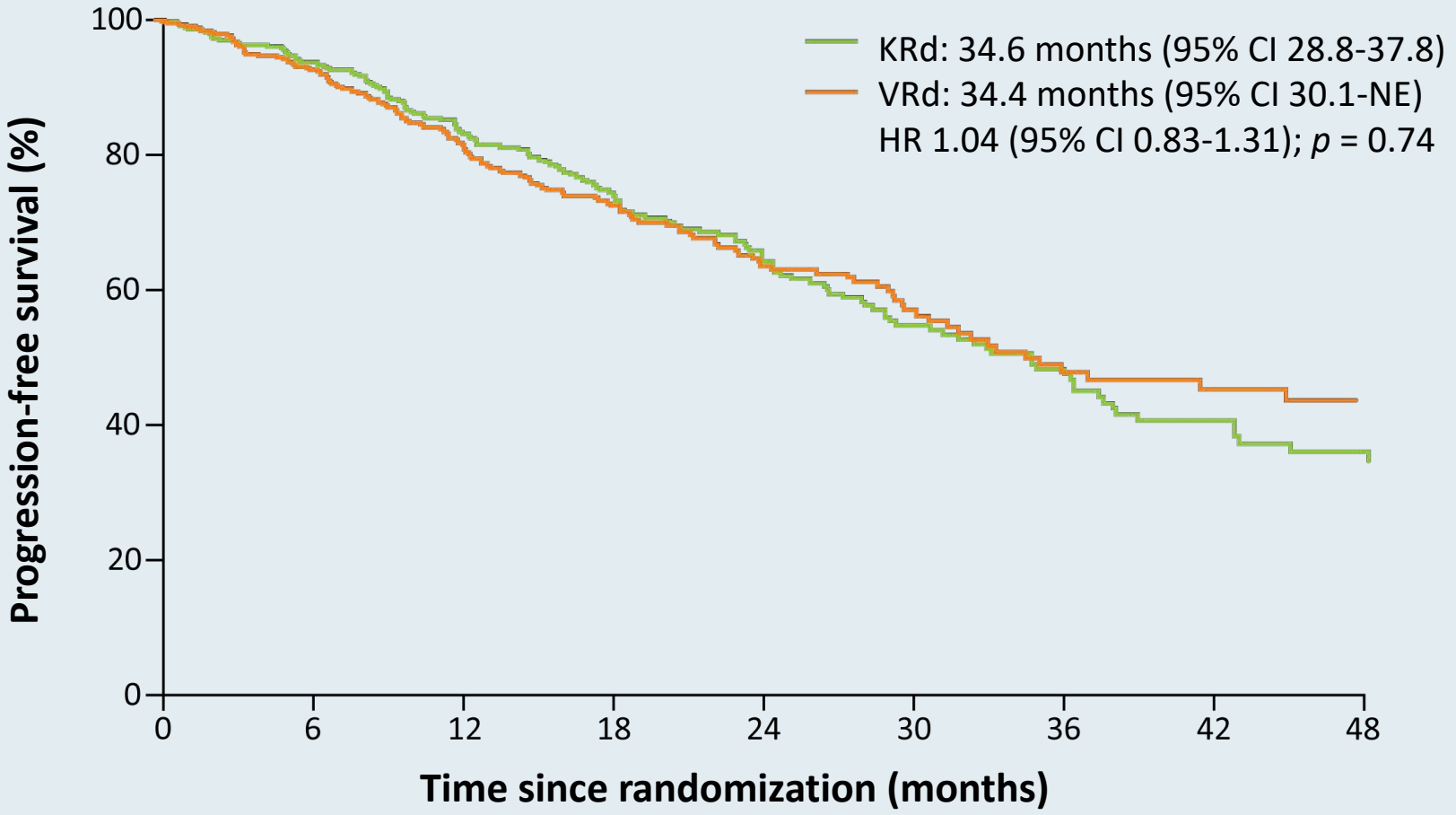
Selection of Front-Line Therapy for Multiple Myeloma (MM)

Lancet Oncol 2020;21(10):1317-30.

Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

Shaji K Kumar, Susanna J Jacobus, Adam D Cohen, Matthias Weiss, Natalie Callander, Avina K Singh, Terri L Parker, Alexander Menter, Xuezhong Yang, Benjamin Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Rosenberg, Jeffrey A Zonder, Edward Faber Jr, Sagar Lonial, Kenneth C Anderson, Paul G Richardson, Robert Z Orlowski, Lynne I Wagner, S Vincent Rajkumar

ENDURANCE (E1A11): Primary Progression-Free Survival Endpoint (Second Interim Analysis)



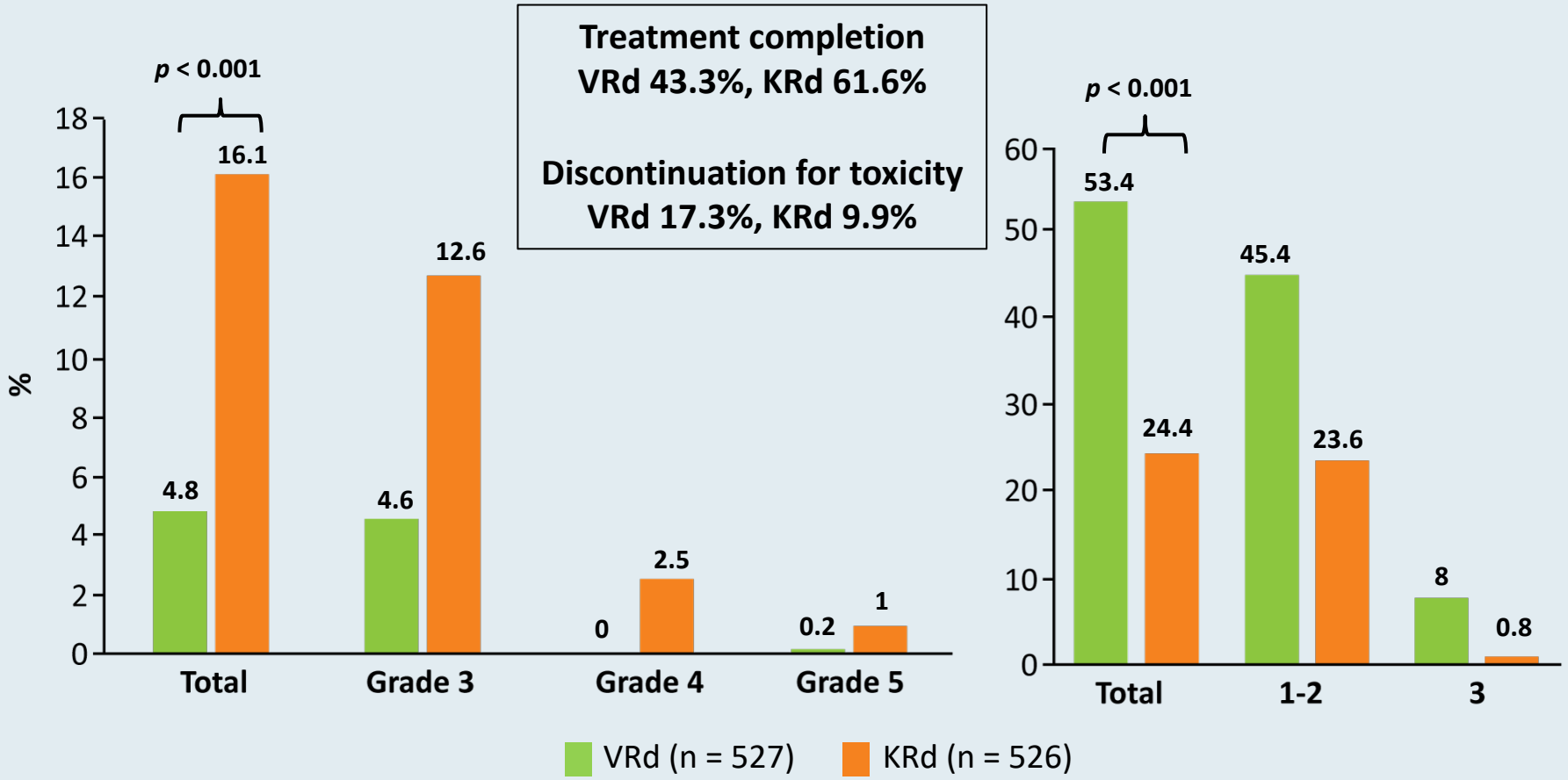
- Median overall survival has not been reached in either group at median follow-up of 24 months; patients will continue on long-term follow-up for overall survival

KRd = carfilzomib, lenalidomide and dexamethasone; VRd = bortezomib, lenalidomide and dexamethasone ; NE = not estimable

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

RTP RESEARCH TO PRACTICE

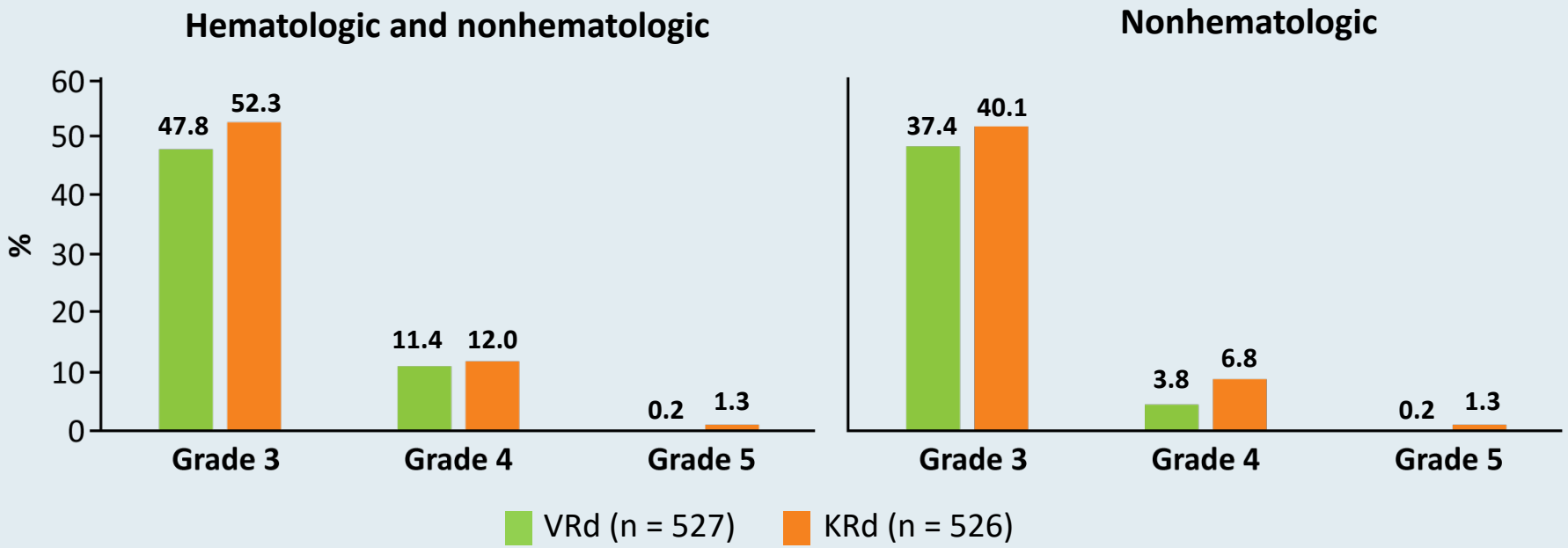
ENDURANCE (E1A11): Treatment-Emergent Adverse Events of Interest



* Grades 1-2 not required reporting

Berdeja JG. ASCO 2020 Discussant.

ENDURANCE (E1A11): Treatment-Related Adverse Events



Step 1 treated patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-VRd	Chi-sq *p*-value
Grade 3-5	313 (59.4)	345 (65.6)	6.2	0.038
(95% CI)	(55.1-63.6)	(61.3-69.6)		
Grade 4-5	61 (11.6)	70 (13.3)	1.7	0.394
(95% CI)	(9.0-14.6)	(10.5-16.5)		

Step 1 treated patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-VRd	Chi-sq *p*-value
Grade 3-5	254 (48.3)	254 (48.3)	6.9	0.024
(95% CI)	(37.1- 45.7)	(44.0-52.6)		
Grade 4-5	21 (4.0)	43 (8.2)	4.2	0.004
(95% CI)	(2.5-6.1)	(6.0-10.9)		

Grade 3 hematologic adverse events were not required reporting

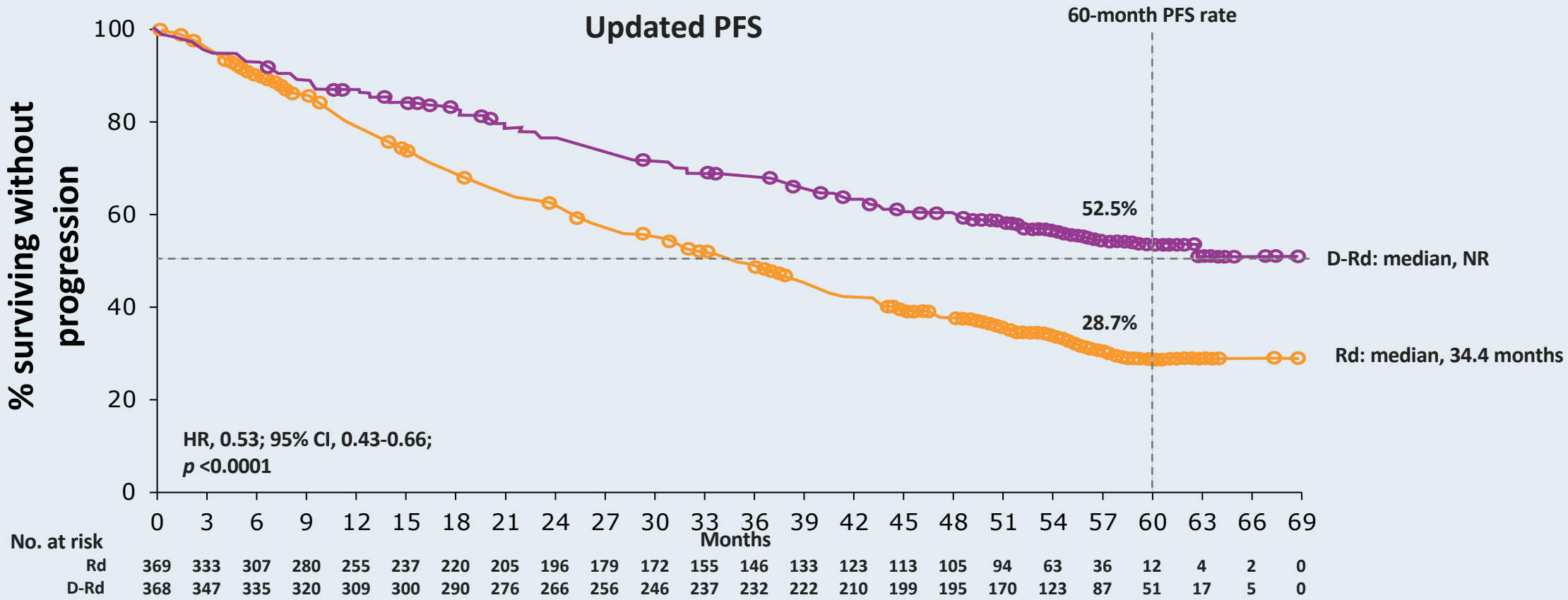
Kumar S et al. ASCO 2020;Abstract LBA3.

Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial

Thierry Facon, Shaji K Kumar, Torben Plesner, Robert Z Orlowski, Philippe Moreau, Nizar Bahlis, Supratik Basu, Hareth Nahi, Cyrille Hulin, Hang Quach, Hartmut Goldschmidt, Michael O'Dwyer, Aurore Perrot, Christopher P Venner, Katja Weisel, Joseph R Mace, Noopur Raje, Mourad Tiab, Margaret Macro, Laurent Frenzel, Xavier Leleu, Tahamtan Ahmadi, Jianping Wang, Rian Van Rampelbergh, Clarissa M Uhlar, Brenda Tromp, Maria Delioukina, Jessica Vermeulen, Saad Z Usmani

***Lancet Oncol* 2021 November;22(11):1582-96.**

MAIA: Progression-Free Survival (60-Month Data)

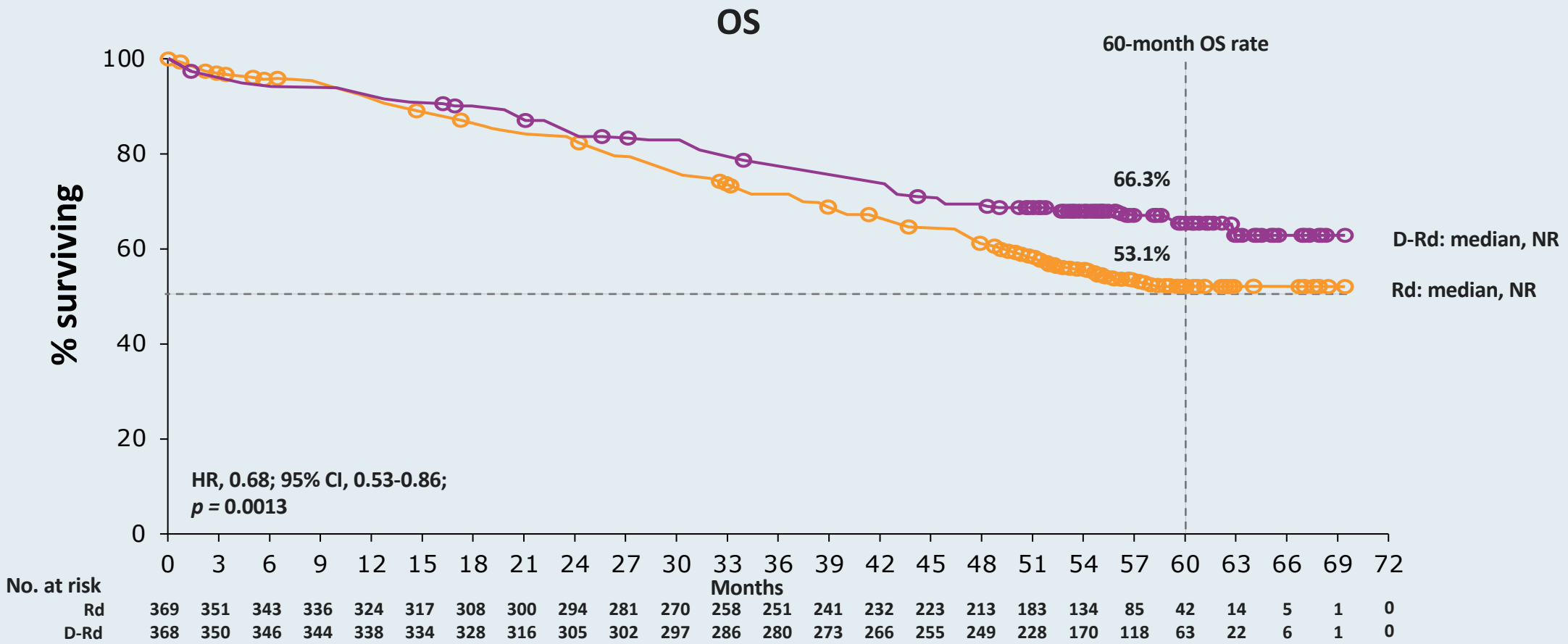


- **D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd**
  - **These data provide a new PFS benchmark for patients with NDMM who are transplant ineligible**

PFS = progression-free survival; D-Rd = daratumumab + lenalidomide + dexamethasone; NR = not reached; Rd = lenalidomide and dexamethasone; HR = hazard ratio; NDMM = newly diagnosed multiple myeloma

Facon T et al. *Lancet Oncol* 2021 November;22(11):1582-96; EHA 2021;Abstract LB1901.

MAIA: Overall Survival (OS)

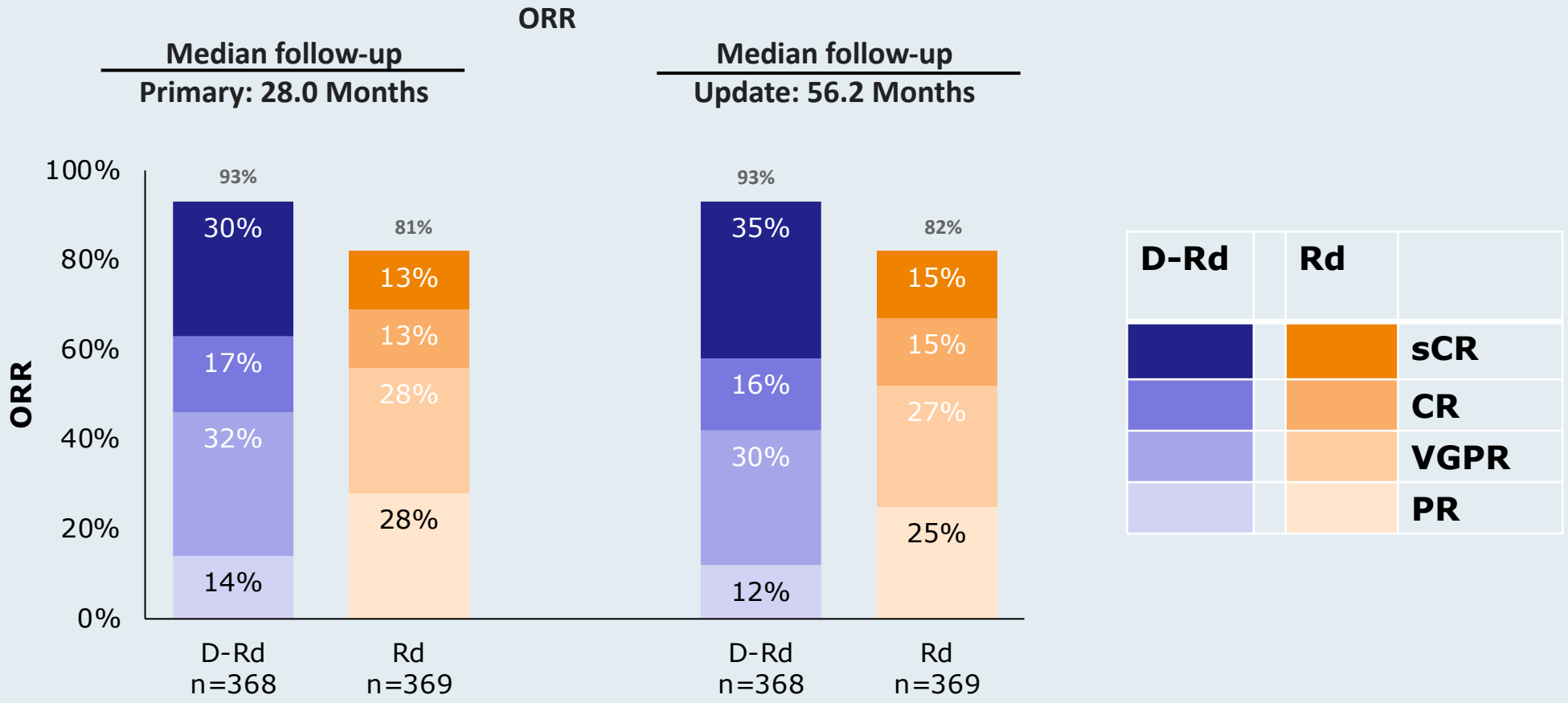


D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, for patients with NDMM who are transplant ineligible

Facon T et al. *Lancet Oncol* 2021 November;22(11):1582-96; EHA 2021;Abstract LB1901.

RTP RESEARCH TO PRACTICE

MAIA: Updated Overall Response Rate (ITT Population)



- D-Rd induced deeper responses with significantly higher rates of ≥CR and ≥VGPR, compared with Rd
  - With >28 months of additional follow-up, responses deepened with continued DARA therapy

sCR = stringent complete response; VGPR = very good partial response

Falcon T et al. *N Engl J Med* 2019:380(22):2104-15; EHA 2021;Abstract LB1901.

IMS 2022;Abstract OAB-057.

Daratumumab (DARA) + Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients With Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Final Analysis of GRIFFIN

Douglas W. Sborov,[1] Jacob Laubach,[2] Jonathan L. Kaufman,[3] Brandi Reeves,[4] Cesar Rodriguez,[5] Ajai Chari,[5] Rebecca Silbermann,[6] Luciano J. Costa,[7] Larry D. Anderson Jr.,[8] Nitya Nathwani,[9] Nina Shah,[10] Naresh Bumma,[11] Sarah A. Holstein,[12] Caitlin Costello,[13] Andrzej Jakubowiak,[14] Robert Z. Orlowski,[15] Kenneth H. Shain,[16] Andrew J. Cowan,[17] Huiling Pei,[18] Annelore Cortoos,[19] Sharmila Patel,[19] Thomas S. Lin,[19] Paul Richardson,[2] Saad Z. Usmani,[20] Peter M. Voorhees[21]

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

Presented at the 19th International Myeloma Society (IMS) Annual Meeting; August 25-27, 2022; Los Angeles, CA, USA.

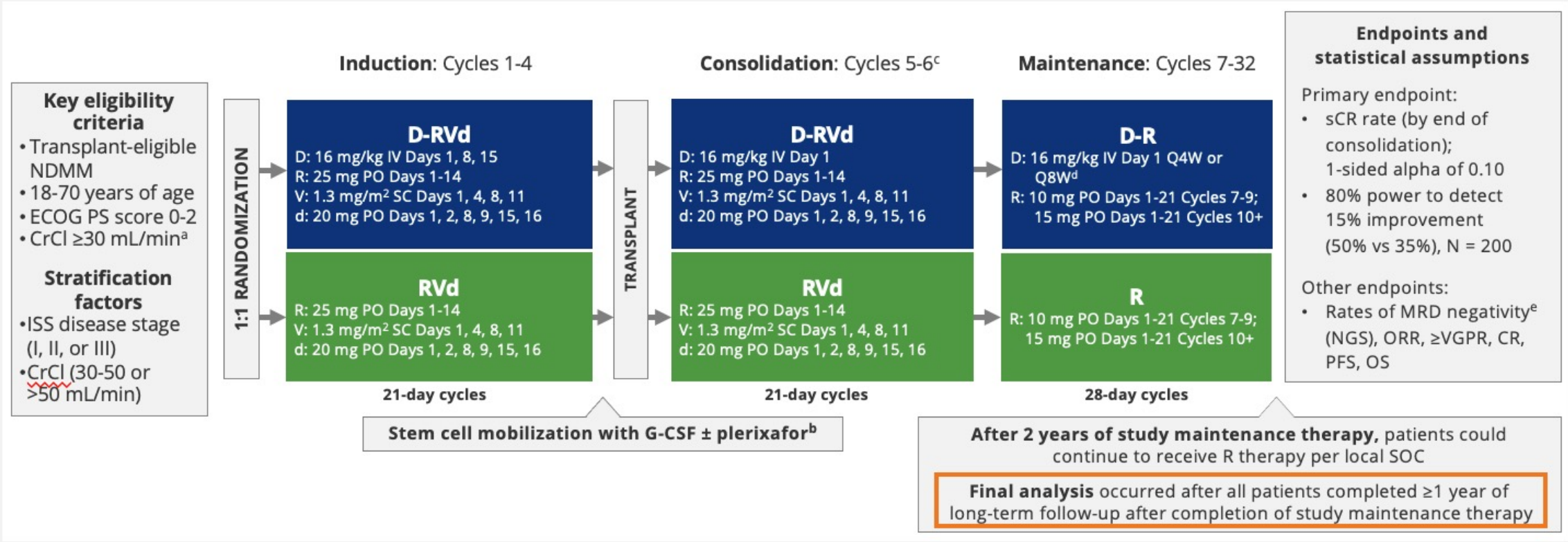
Scan the QR code.

https://www.congresshub.com/Oncology/IMS2022/Daratumumab/Sborov

RTP RESEARCH TO PRACTICE

GRIFFIN Phase II Study Design

- 35 sites in the United States with enrollment between December 2016 and April 2018

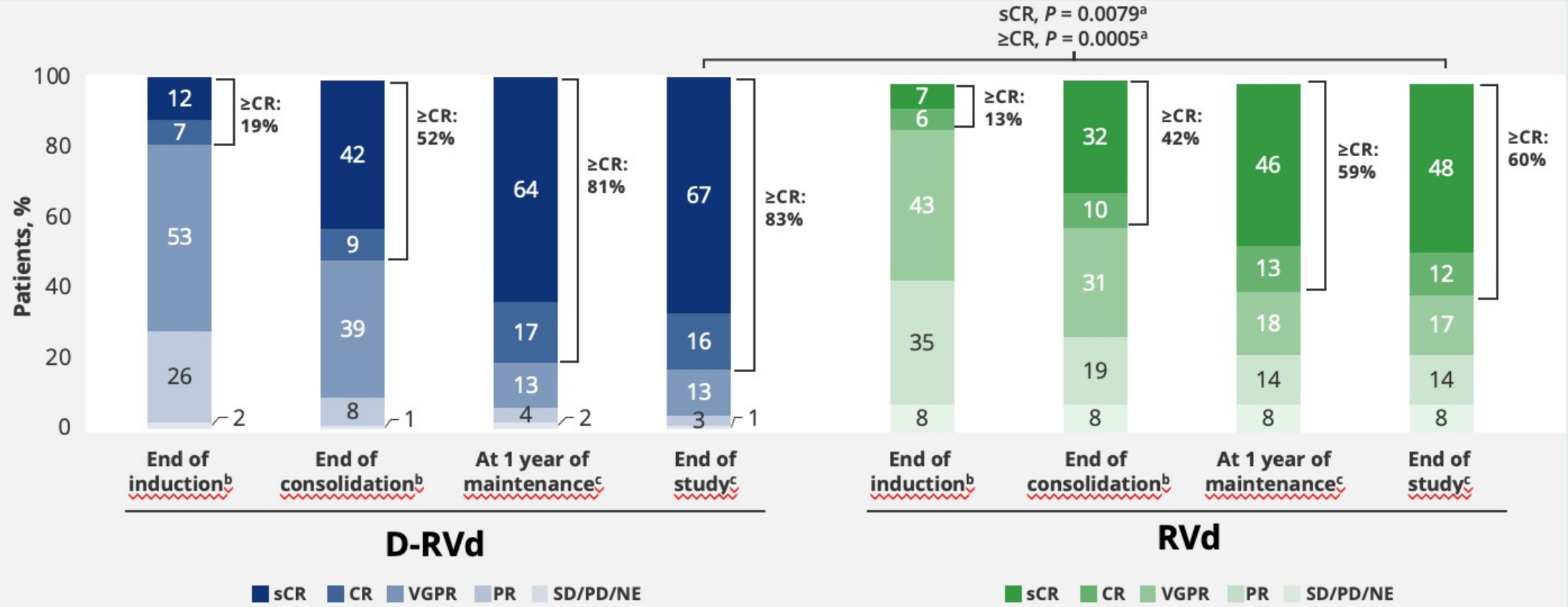


ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; PO, oral; SC, subcutaneous; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab plus lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response; CR, complete response; PFS, progression-free survival; PFS2, PFS on next subsequent line of therapy; OS, overall survival. [a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60 to 100 days post-transplant. [d]Protocol amendment 2 allowed for the option to dose DARA Q4W based on pharmacokinetic results from study SMM2001 (ClinicalTrials.gov Identifier: NCT02316106). [e]To measure MRD negativity at a minimum threshold of 10^{-5}, bone marrow aspirates were collected at first evidence of suspected CR or sCR (including patients with ≥VGPR and suspected DARA interference), after induction but before stem cell collection, at the post-transplant consolidation disease evaluation, and at 12 months and 24 months (±3 weeks) of maintenance therapy.

CrCl,

Sborov DB et al. IMS 2022;Abstract OAB-057.

GRIFFIN Final Analysis: Response Rates over Time



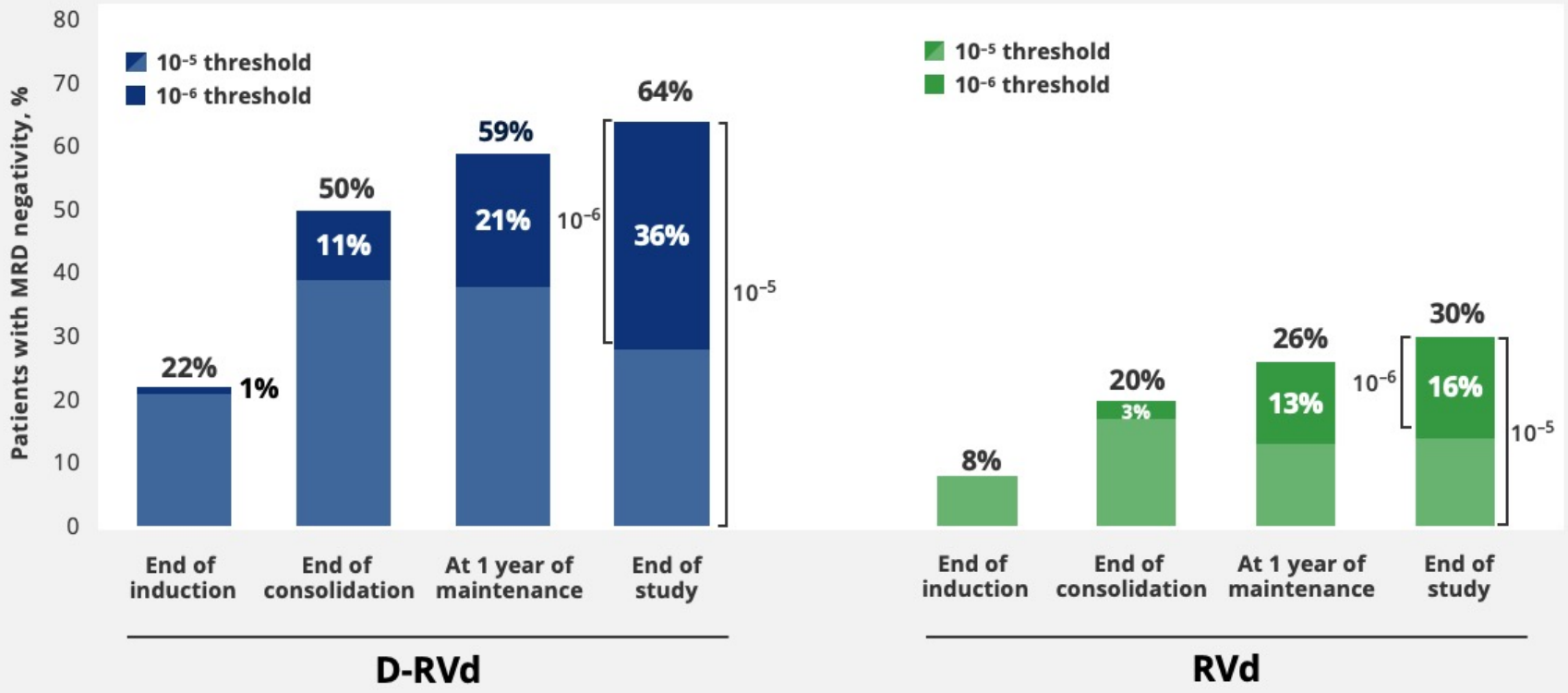
- Rates of ≥CR improved over time and the deepest responses occurred at the end of study maintenance
- At all timepoints, response rates for D-RVd were consistently higher versus RVd

PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable. [a] *P* value was calculated using the Cochran–Mantel–Haenszel chi-squre test. [b]Response rates are from the primary analysis cutoff (median follow-up: 13.5 months), and the response-evaluable population included 196 patients (D-RVd, n = 99; RVd, n = 97). [c]Response rates for the maintenance phase were evaluated at the time of final analysis (median follow-up: 49.6 months), and the response-evaluable population included 198 patients (D-RVd, n = 100; RVd, n = 98).

Sborov DB et al. IMS 2022;Abstract OAB-057.

RTP RESEARCH TO PRACTICE

GRIFFIN Final Analysis: Minimum Residual Disease (MRD) Negativity Rates over Time



MRD-negative (10^{-5}) conversion rate

- 14% (15/104) of D-RVd and 10% (10/103) of RVd patients converted from MRD positive at the end of consolidation to MRD negative by the end of 2 years of study maintenance therapy

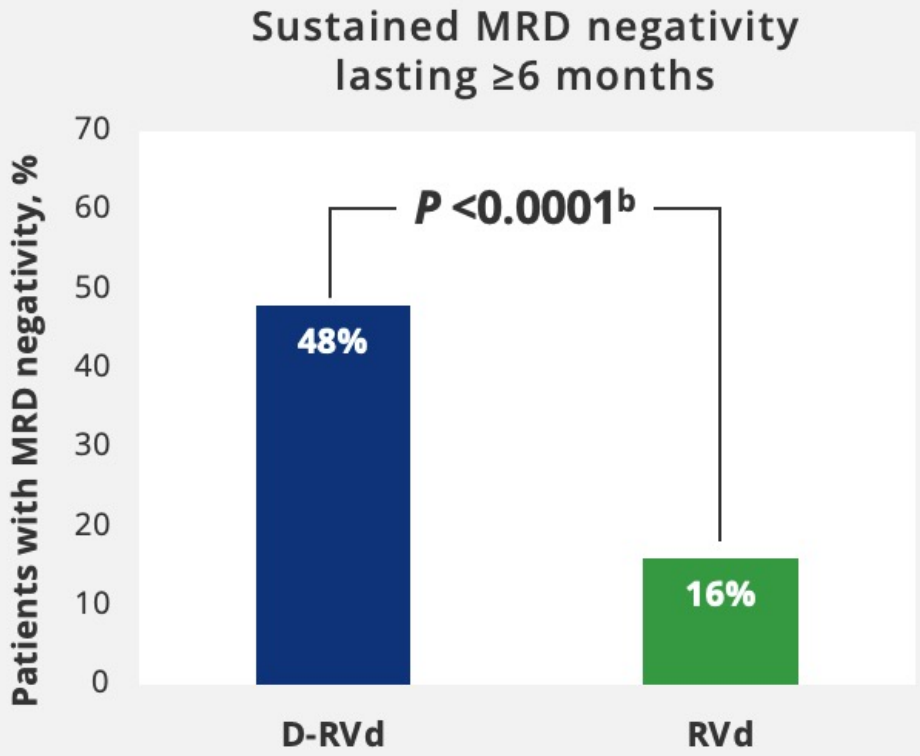
- MRD-negativity rates improved over time and were consistently higher for D-RVd versus RVd
- Rates of MRD negativity continued to deepen throughout the study maintenance period

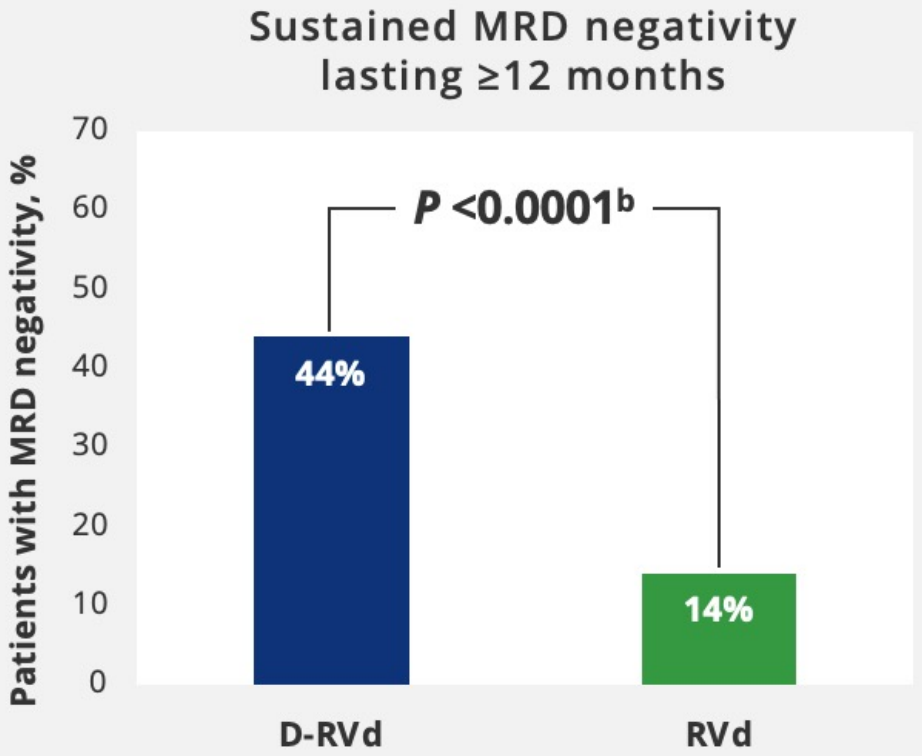
[a]MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Bone marrow aspirates were assessed at baseline, at first evidence of suspected CR or sCR (including patients with VGPR or better and suspected DARA interference), at the end of induction and consolidation, and after 1 and 2 years of maintenance, regardless of response. MRD-negativity rates for all time points were evaluated at the time of final analysis (median follow-up: 49.6 months), and MRD-negativity rates were among the ITT population (D-RVd, n = 104; RVd, n = 103).

Sborov DB et al. IMS 2022;Abstract OAB-057.

RTP RESEARCH TO PRACTICE

GRIFFIN Final Analysis: Rates of Sustained MRD Negativity (10^{-5})

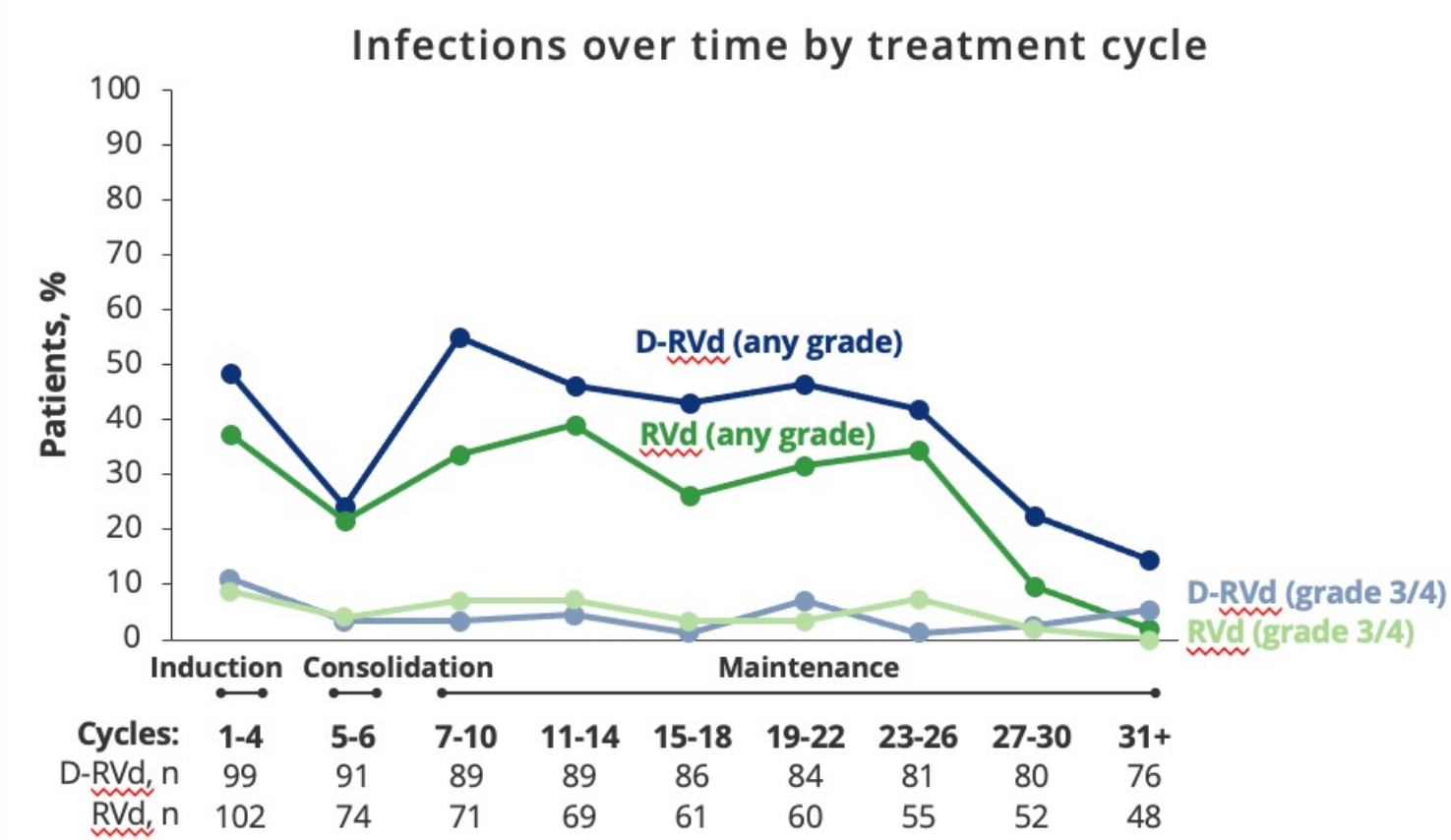




[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 49.6 months, and MRD-negativity rates are among the ITT population (D-RVd, n = 104; RVd, n = 103). Bone marrow aspirates were assessed at baseline, at first evidence of suspected CR or sCR (including patients with VGPR or better and suspected DARA interference), at the end of induction and consolidation, and after 1 and 2 years of maintenance, regardless of response. [b]*P* values were calculated using the Fisher's exact test.

Sborov DB et al. IMS 2022;Abstract OAB-057.

GRIFFIN Final Analysis: Summary of Infections



- The highest incidence of infections occurred in earlier cycles of treatment and maintenance therapy
- The most common infection was upper respiratory tract infection in both groups
- COVID-19 infections occurred in 5 and 2 patients in the D-RVd and RVd groups, respectively
- Rate of infections leading to treatment discontinuation were similar between groups (D-RVd, 2%; RVd, 3%)

Sborov DB et al. IMS 2022;Abstract OAB-057.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 8002

Daratumumab Carfilzomib Lenalidomide and Dexamethasone as induction therapy in high-risk transplant eligible newly diagnosed myeloma patients: results of the phase 2 study IFM 2018-04

Cyrille Touzeau[1], Aurore Perrot[2], Cyrille Hulin[3], Salomon Manier[4], Margaret Macro[5], Marie-Lorraine Chretien[6], Lionel Karlin[7], Martine Escoffre[8], Caroline Jacquet[9], Mourad Tiab[10], Xavier Leleu[11], Lucie Planche[12], Hervé Avet-Loiseau[2], Philippe Moreau[1]

RTP RESEARCH TO PRACTICE

IFM 2018-04: Phase II Study Design

Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p del, t(14;16)
- ECOG 0-2

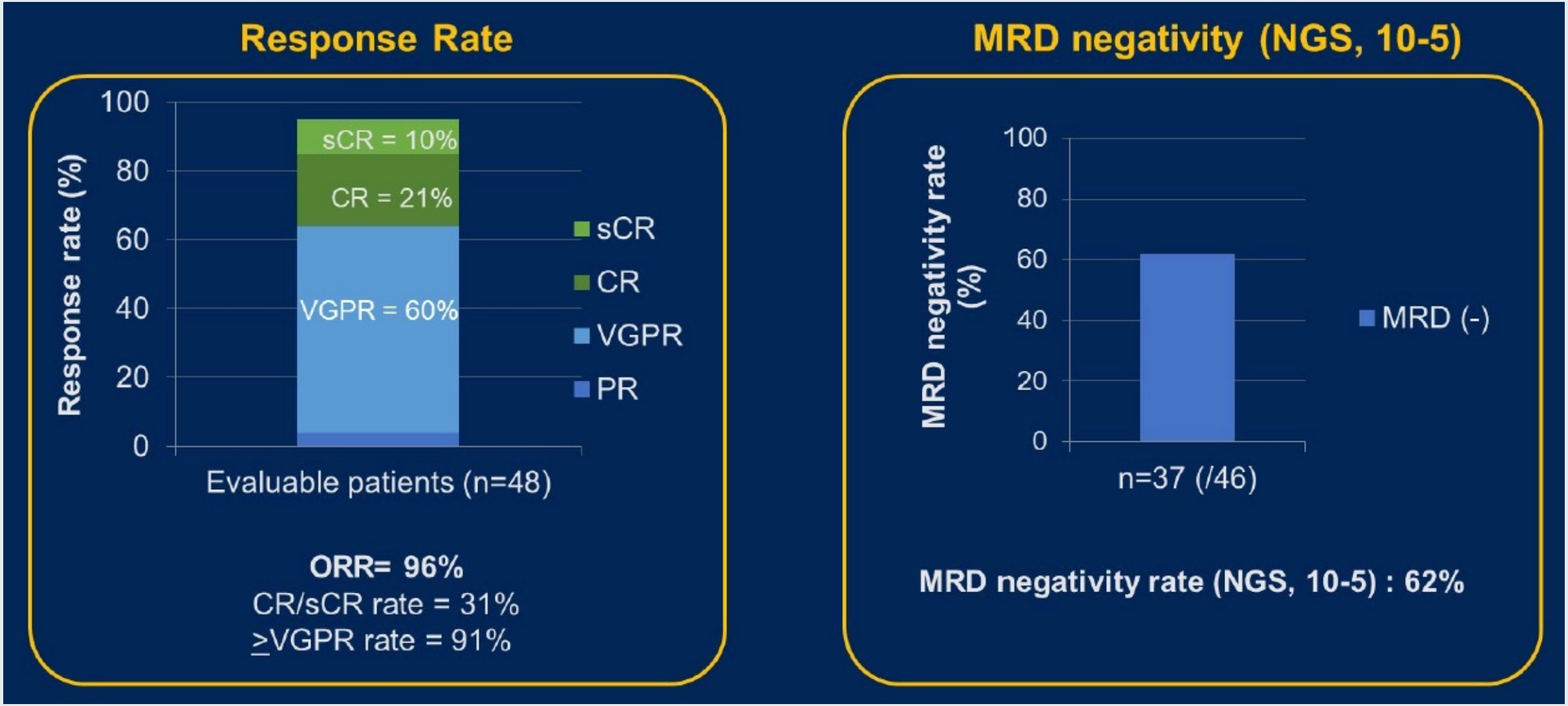
Objectives:

- **Primary Objective :**
  Feasibility (endpoint : >70% patients completed 2nd transplant)
- **Secondary Objectives:**
  Safety, ORR, PFS, OS, stem-cell collection

Induction Dara-KRd x 6	Stem cell collection	ASCT #1	Consolidation Dara KRd x 4	ASCT #2	Maintenance Dara Len 2 years
Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 - 2) D1 D15 (Cycle 3 to 6) **K : (20)36 mg/m2 IV** D1-2, 8-9, 15-16 **Len : 25 mg** D1-21 **Dex : 20 mg** D1-2,8-9,15-16,22-23 **28-day cycles**	Cyclo GCSF +/- Plerix	**Mel 200**	**Dara : 16 mg/kg IV** D1 D15 **K : 56 mg/m2 IV** D1, 8, 15 **Len : 15 mg** D1-21 **Dex : 40 mg** D1, 8, 15, 22 **28-day cycles**	**Mel 200**	**Dara** : 16 mg/kg IV every 8 weeks **Len** : 10 mg 21/28

Touzeau C et al. ASCO 2022;Abstract 8002.

IFM 2018-04: Response Rates and MRD with Dara-KRd Induction



Touzeau C et al. ASCO 2022;Abstract 8002.

RTP RESEARCH TO PRACTICE

IFM 2018-04: Safety of Dara-KRd Induction

Hematologic treatment related AE:

	Any grade N (%)	Grade 3/4 N (%)
Neutropenia	22 (44%)	20 (40%)
Anemia	14 (28%)	7 (14%)
Thrombocytopenia	13 (26%)	4 (8%)

AE leading to treatment discontinuation (n=2)
- COVID-19 infection (n=1)
- tumor lysis syndrome (n=1)

Grade 3/4 infection (n=3)
- COVID 19 infection (n=1)
- CMV infection (n=1)
- Pseudomonas aeruginosa bacteriemia (n=1)

Most common non hematologic treatment related AE:

	Any grade N (%)	Grade 3/4 N (%)
GI disorders	23 (46%)	2(4%)
Infection	20 (40%)	3 (6%)
Skin rash	8 (16%)	0
Deep-vein thrombosis	7 (14%)	3 (6%)
Peripheral neuropathy	6 (12%)	0
Hepatic cytolysis	4 (8%)	2 (4%)
Renal failure	3 (6%)	3 (6%)
Cardiac event	1 (2%)	0

AE = adverse event

Touzeau C et al. ASCO 2022;Abstract 8002.

UNIVERSITÄTS KLINIKUM HEIDELBERG

Addition of Isatuximab to Lenalidomide, Bortezomib and Dexamethasone as Induction Therapy for Newly-Diagnosed, Transplant-Eligible Multiple Myeloma: The Phase III GMMG-HD7 Trial

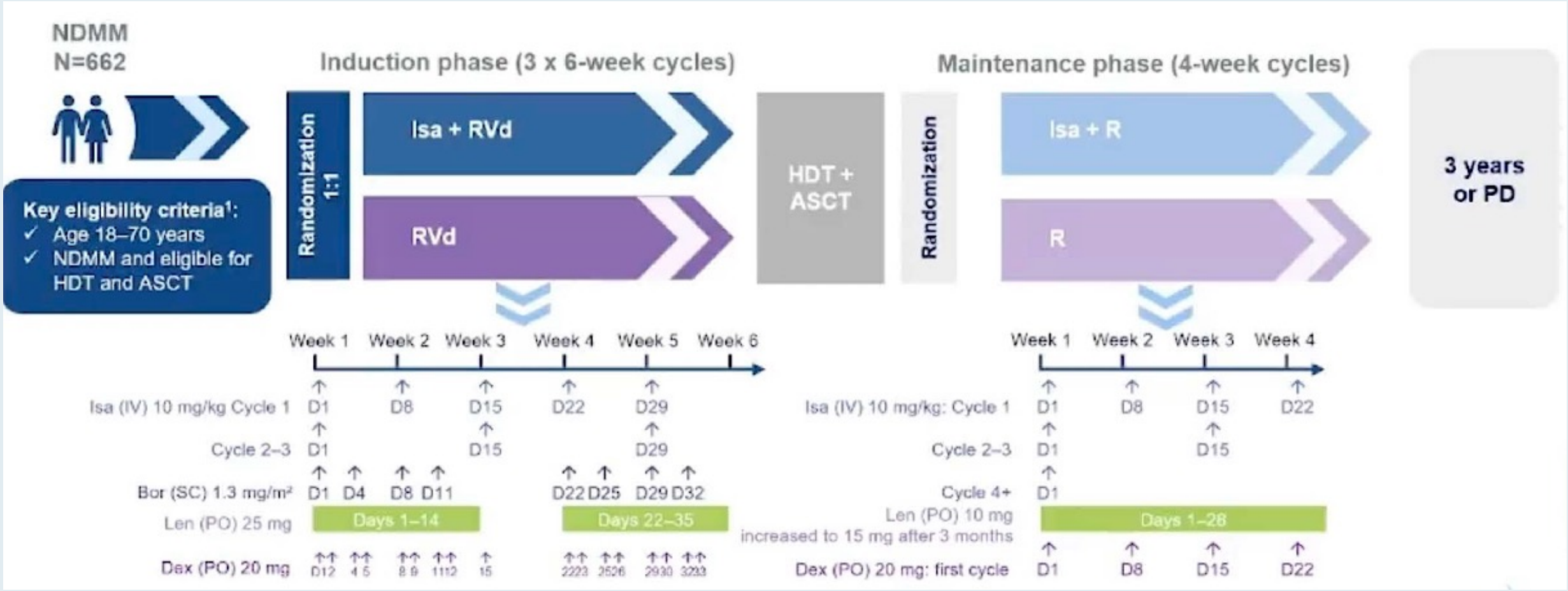
Hartmut Goldschmidt[1,2], Elias K. Mai[1], Eva Nievergall[1], Roland Fenk[3], Uta Bertsch[1,2], Diana Tichy[4], Britta Besemer[5], Jan Dürig[6], Roland Schroers[7], Ivana von Metzler[8], Mathias Hänel[9], Christoph Mann[10], Anne Marie Asemissen[11], Bernhard Heilmeier[12], Stefanie Huhn[1], Katharina Kriegsmann[1], Niels Weinhold[1], Steffen Luntz[13], Tobias A. W. Holderried[14], Karolin Trautmann-Grill[15], Deniz Gezer[16], Maika Klaiber-Hakimi[17], Martin Müller[18], Cyrus Khandanpour[19], Wolfgang Knauf[20], Markus Munder[21], Thomas Geer[22], Hendrik Riesenberg[23], Jörg Thomalla[24], Martin Hoffmann[25], Marc-Steffen Raab[1], Hans J. Salwender[26], Katja C. Weisel[11] for the German-speaking Myeloma Multicenter Group (GMMG)

[1]Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany; [2]National Center for Tumor Diseases Heidelberg, Heidelberg, Germany; [3]Department of Hematology, Oncology and Clinical Immunology, University Hospital Düsseldorf, Düsseldorf, Germany; [4]Division of Biostatistics, German Cancer Research Center (DKFZ) Heidelberg, Heidelberg, Germany; [5]Department of Internal Medicine II, University Hospital Tübingen, Tübingen, Germany; [6]Department for Hematology and Stem Cell Transplantation, University Hospital Essen, Essen, Germany; [7]Medical Clinic, University Hospital Bochum, Bochum, Germany; [8]Department of Medicine, Hematology/Oncology, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany; [9]Department of Internal Medicine III, Clinic Chemnitz, Chemnitz, Germany; [10]Department for Hematology, Oncology and Immunology, University Hospital Gießen and Marburg, Marburg, Germany; [11]Department of Oncology, Hematology and BMT, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [12]Clinic for Oncology and Hematology, Hospital Barmherzige Brueder Regensburg, Regensburg, Germany; [13]Coordination Centre for Clinical Trails (KKS) Heidelberg, Heidelberg, Germany; [14]Department of Oncology, Hematology, Immuno-Oncology and Rheumatology, University Hospital Bonn, Bonn, Germany; [15]Department of Internal Medicine I, University Hospital Dresden, Dresden, Germany; [16]Department of Hematology, Oncology, Hemostaseology, and Stem Cell Transplantation, Faculty of Medicine, RWTH Aachen University, Aachen, Germany; [17]Clinic for Hematology, Oncology and Palliative Care, Marien Hospital Düsseldorf, Düsseldorf, Germany; [18]Clinic for Hematology, Oncology and Immunology, Klinikum Siloah Hannover, Hannover, Germany; [19]Medical Clinic A, University Hospital Münster, Münster, Germany; [20]Center for Hematology and Oncology Bethanien, Frankfurt am Main, Germany; [21]Department of Internal Medicine III, University Hospital Mainz, Mainz, Germany; [22]Department of Internal Medicine III, Diakoneo Clinic Schwäbisch-Hall, Schwäbisch-Hall, Germany; [23]Hematology/Oncology Center, Bielefeld, Germany; [24]Hematology / Oncology Center, Koblenz, Germany; [25]Medical Clinic A, Clinic Ludwigshafen, Ludwigshafen, Germany; [26]Asklepios Tumorzentrum Hamburg, AK Altona and AK St. Georg, Hamburg, Germany

UK HD

ASH 2021;Abstract 463.

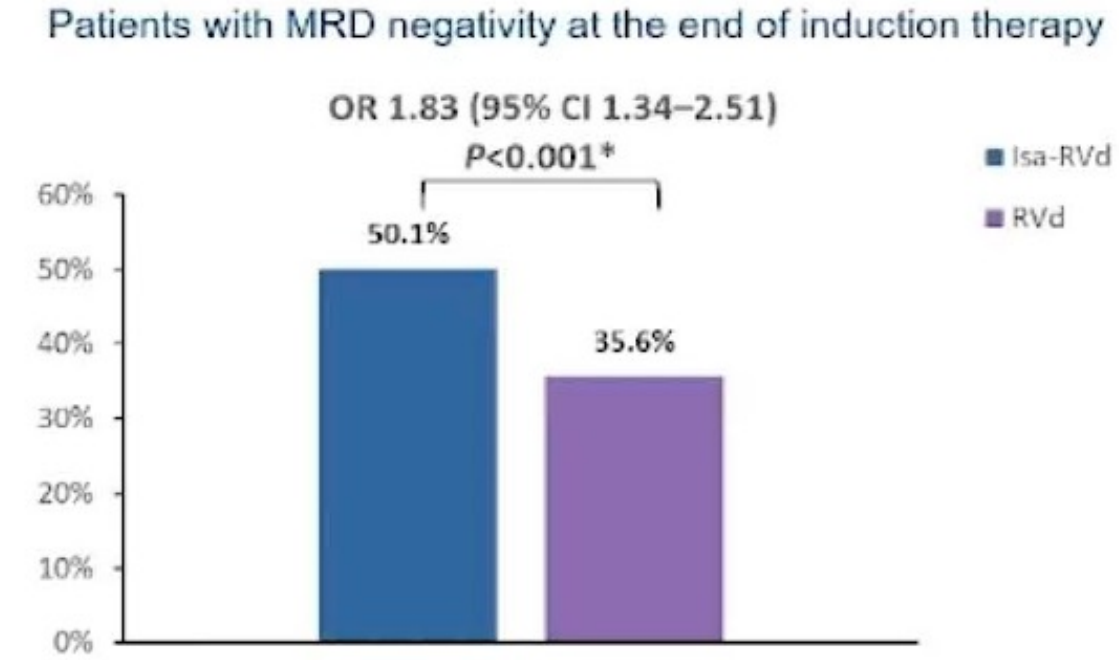
GMMG-HD7 Phase III Trial Design



NDMM = newly diagnosed multiple myeloma; HDT = high-dose treatment; ASCT = autologous stem cell transplantation; Isa = isatuximab; RVd = lenalidomide/bortezomib/dexamethasone; PD = progressive disease

Goldschmidt H et al. ASH 2021;Abstract 463.

GMMG-HD7: MRD Negativity at End of Induction Therapy

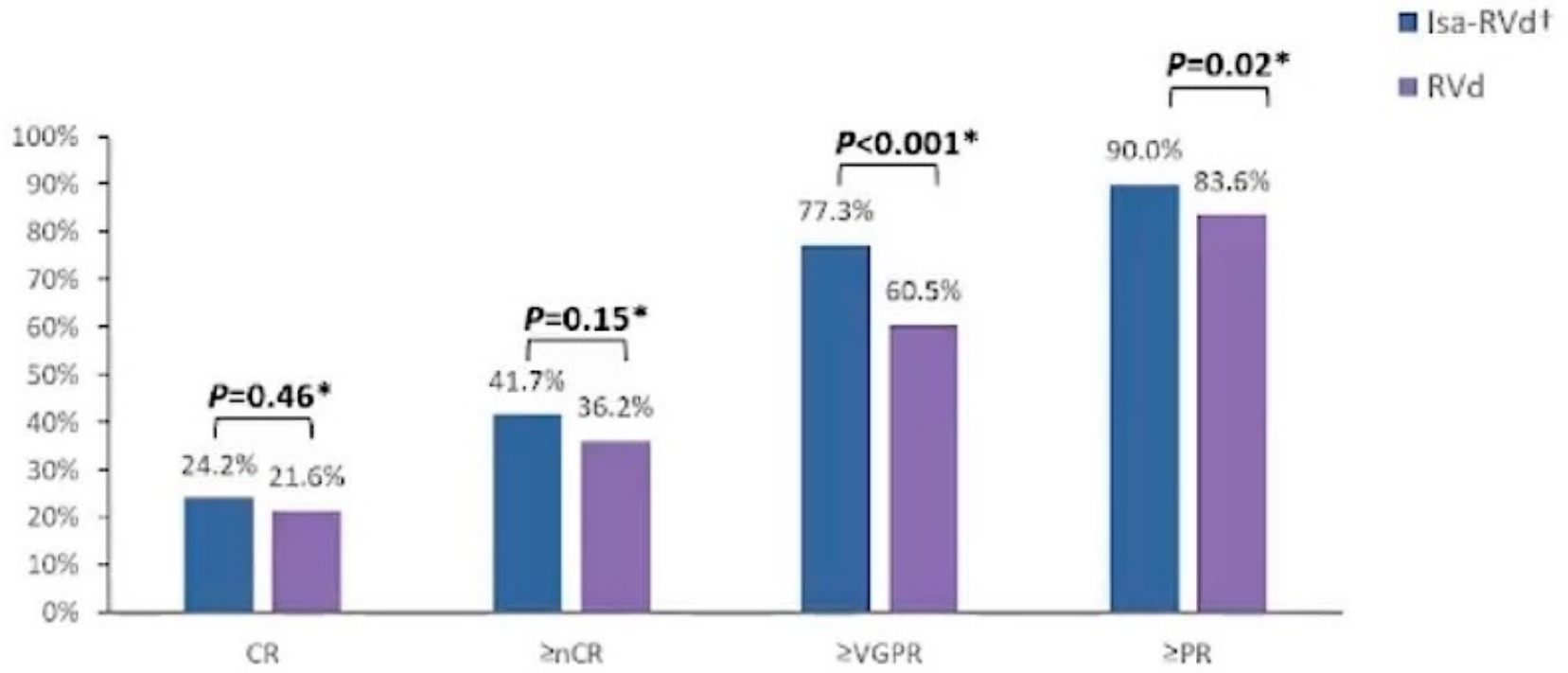


Low number of not assessable/missing† MRD status: Isa-RVd (10.6%) and RVd (15.2%)

Isa-RVd is the first regimen to demonstrate a rapid and statistically significant benefit from treatment by reaching a MRD negativity of 50.1% at the end of induction and to show superiority vs. RVd in a Phase 3 trial

Goldschmidt H et al. ASH 2021;Abstract 463.

GMMG-HD7: Response Rates After Induction Therapy



Although the rates of CR after induction therapy did not differ between the Isa-RVd and RVd arms, there was a significant increase in ≥VGPR rates and ORR with Isa-RVd

Goldschmidt H et al. ASH 2021;Abstract 463.

GMMG-HD7: Safety Profile

AEs CTCAE grade ≥3, n (%)	Isa-RVd (n=330)	RVd (n=328)
Any AE	210 (63.6)	201 (61.3)
Any serious AE (any grade)	115 (34.8)	119 (36.3)
Deaths	4 (1.2)	8 (2.4)
Investigations* (SOC)	79 (23.9)	77 (23.5)
Blood and lymphatic system disorders (SOC)	85 (25.8)	55 (16.8)
Infections and infestations (SOC)	43 (13.0)	34 (10.4)
Nervous system disorders (SOC)	28 (8.5)	33 (10.1)
Gastrointestinal disorders (SOC)	27 (8.2)	31 (9.5)
Metabolism and nutrition disorders (SOC)	12 (3.6)	26 (7.9)

AEs CTCAE grade ≥3, n (%)	Isa-RVd (n=330)	RVd (n=328)
Specific hematologic AE (PT)		
Leukocytopenia/Neutropenia†	87 (26.4)	30 (9.1)
Lymphopenia	48 (14.5)	65 (19.8)
Anemia	13 (3.9)	20 (6.1)
Thrombocytopenia	21 (6.4)	15 (4.6)
Specific non-hematologic AE (PT)		
Peripheral neuropathy	25 (7.6)	22 (6.7)
Thromboembolic events	5 (1.5)	9 (2.7)
Infusion-related reactions‡	4 (1.2)	NA

A comparable number of patients discontinued induction therapy due to AEs in the Isa-RVd arm vs. RVd arm

AE = adverse event

Goldschmidt H et al. ASH 2021;Abstract 463.

2022 ASCO ANNUAL MEETING

Abstract LBA4

RVd ± ASCT and Lenalidomide Maintenance to Progression for NDMM

The Phase 3 DETERMINATION Trial

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

The NEW ENGLAND JOURNAL of MEDICINE

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

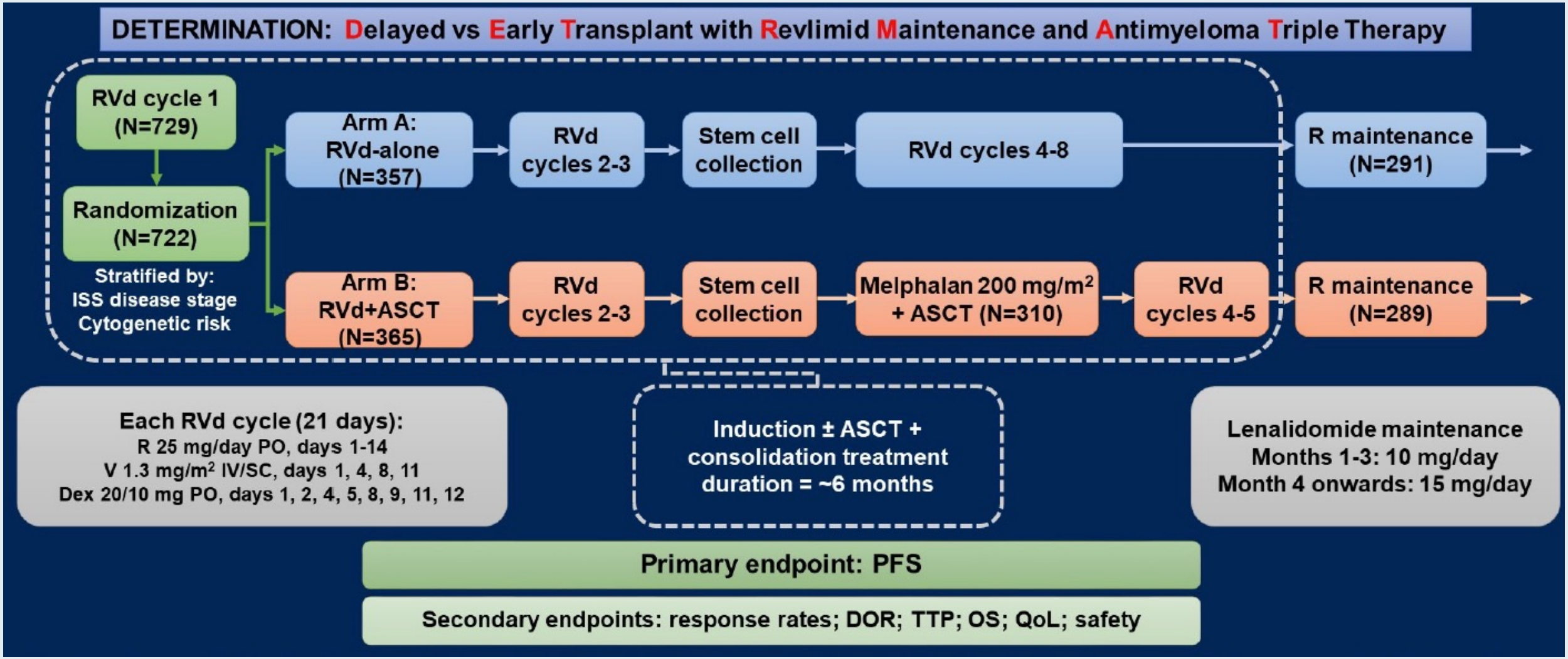
ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

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

RTP RESEARCH TO PRACTICE

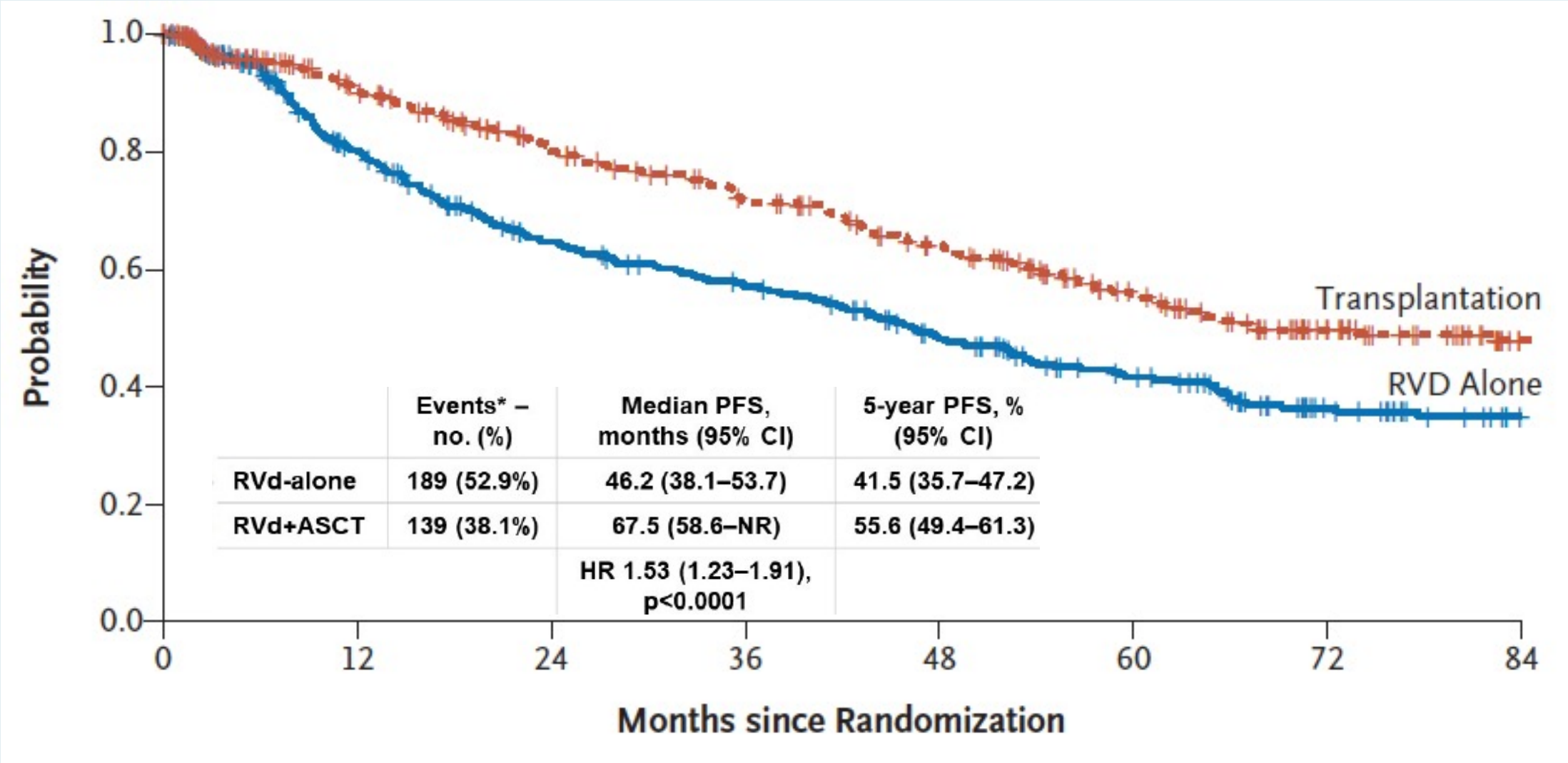
DETERMINATION: Phase III Study Design and Patient Disposition



PFS = progression-free survival; DOR = duration of response; TTP = time to progression; OS = overall survival; QoL = quality of life

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

DETERMINATION: Progression-Free Survival (Primary Endpoint)

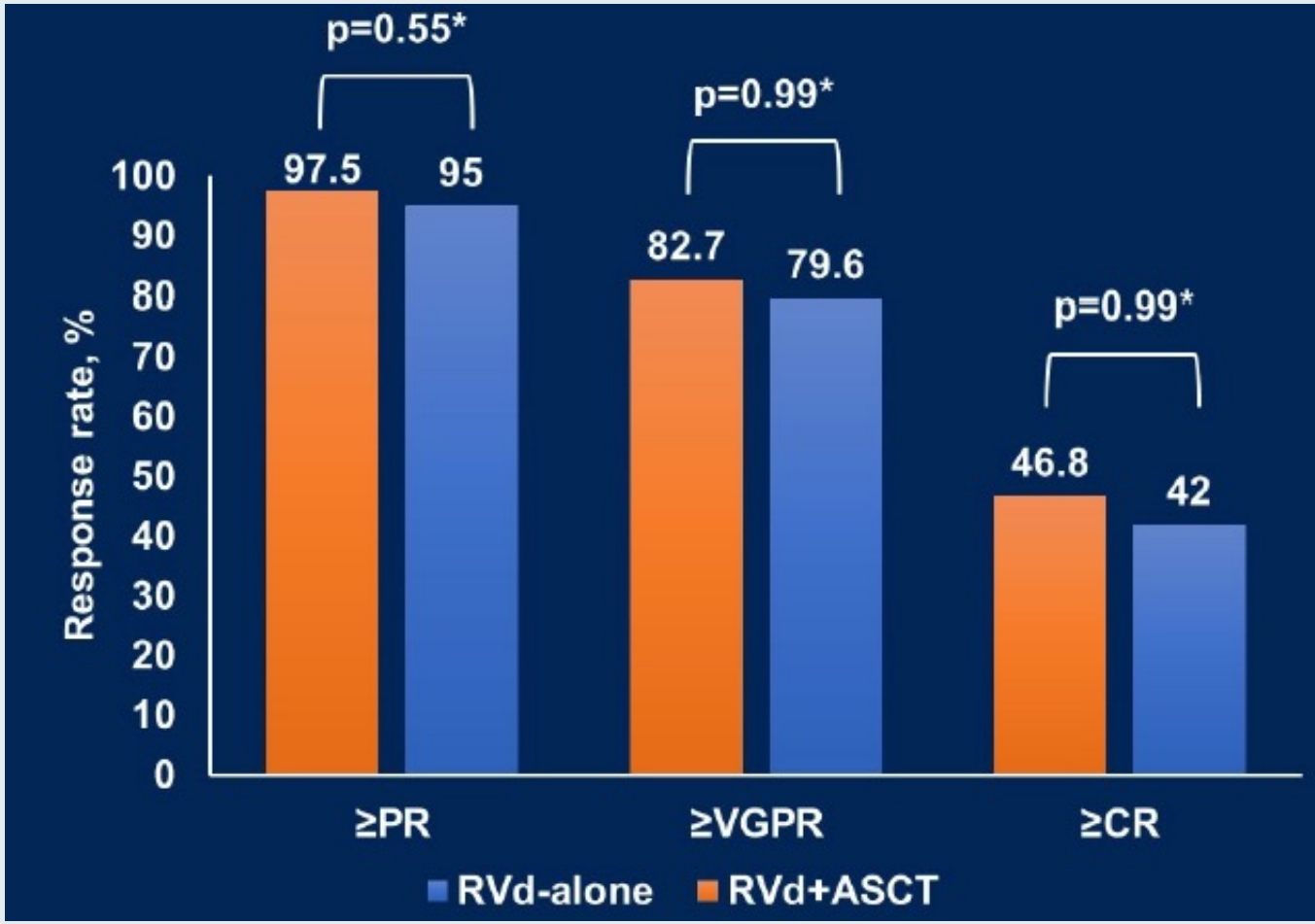


	Events* – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

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

RTP RESEARCH TO PRACTICE

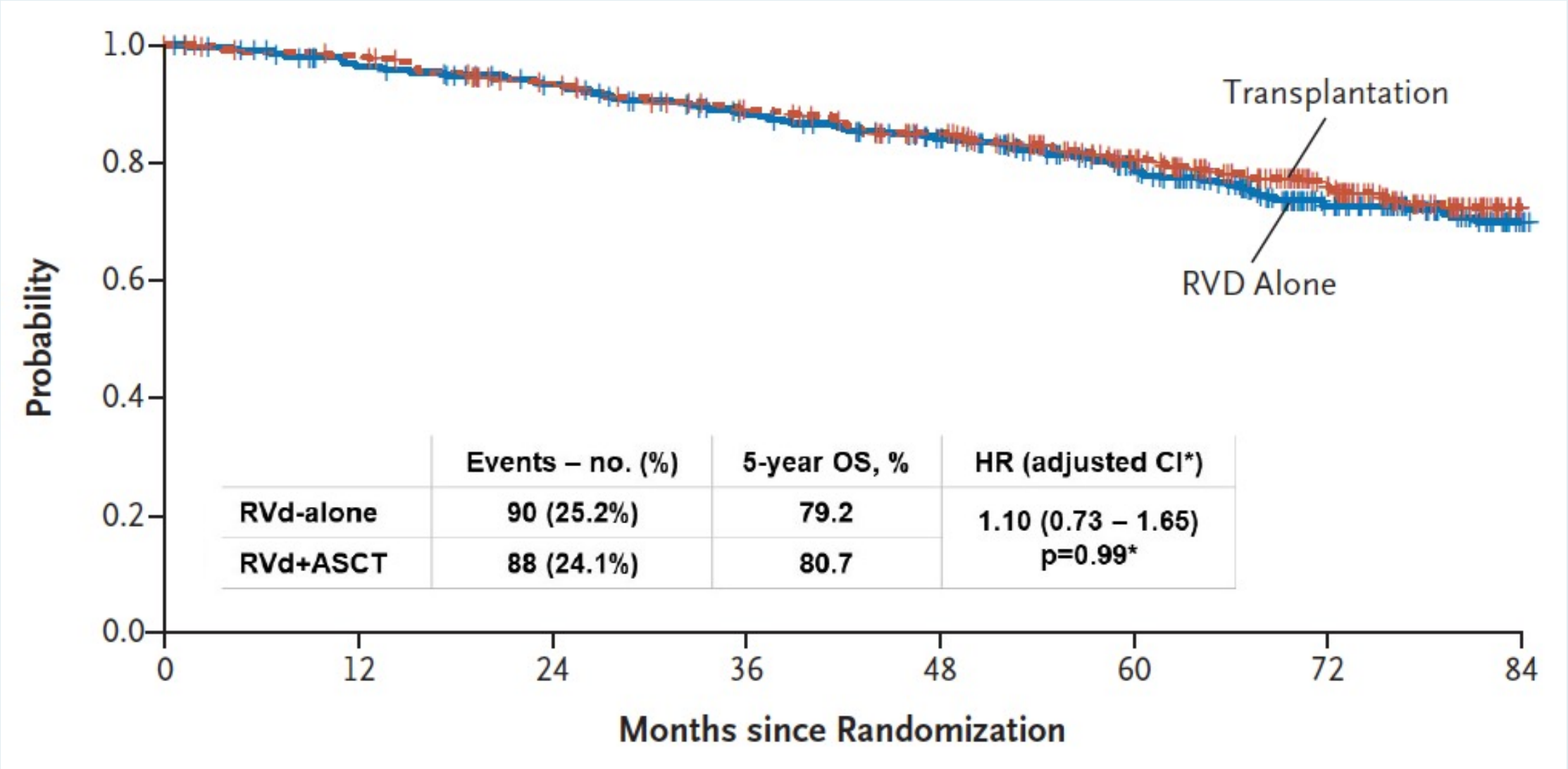
DETERMINATION: Best Response to Treatment and Duration of Response



Duration of response	RVd-alone	RVd+ASCT
Median duration of ≥PR, months	38.9	56.4
	HR 1.45 (Adjusted CI* 1.09–1.93), p=0.003*	
5-year duration of ≥CR, %	52.9	60.6
	HR 1.35 (Adjusted CI* 0.83–2.22), p=0.698*	

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

DETERMINATION: Overall Survival (Key Secondary Endpoint)



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

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

DETERMINATION: Grade ≥3 Treatment-Related Adverse Events (AEs)

AE, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	78.2	94.2
Any hematologic	60.5	89.9
Any grade 5 (fatal) AE	0.3	1.6 *
Neutropenia	42.6	86.3
Thrombocytopenia	19.9	82.7
Leukopenia	19.6	39.7
Anemia	18.2	29.6
Lymphopenia	9.0	10.1
Febrile neutropenia	4.2	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mucositis oral	0	5.2
Fatigue	2.8	6.0
Fever	2.0	5.2
Pneumonia	5.0	9.0
Hypophosphatemia	9.5	8.2
Neuropathy	5.6	7.1

- Rates of all grade ≥3 and of hematologic grade ≥3 treatment-related AEs during all treatment significantly higher with RVd + ASCT (both p<0.001)
  - Rates hematologic grade ≥3 treatment-related AEs during maintenance: 26.1% vs 41.9%
- Related SAEs:
  - Prior to maintenance: 40.3% vs 47.1%
  - During maintenance: 11.3% vs 16.6%

SAE = serious AE

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

RTP RESEARCH TO PRACTICE

VOLUME 35 · NUMBER 29 · OCTOBER 10, 2017

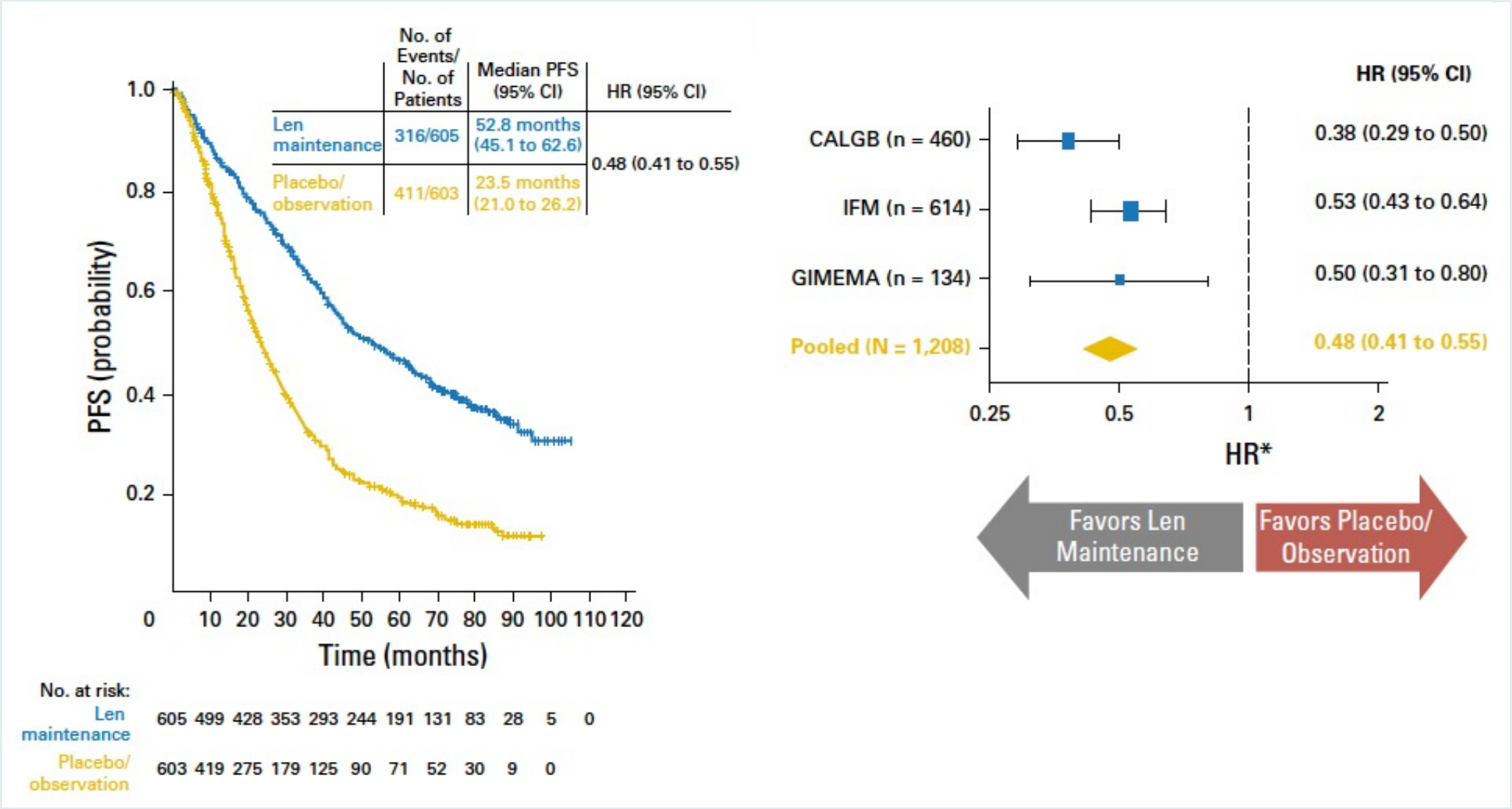
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis

Philip L. McCarthy, Sarah A. Holstein, Maria Teresa Petrucci, Paul G. Richardson, Cyrille Hulin, Patrizia Tosi, Sara Bringhen, Pellegrino Musto, Kenneth C. Anderson, Denis Caillot, Francesca Gay, Philippe Moreau, Gerald Marit, Sin-Ho Jung, Zhinuan Yu, Benjamin Winograd, Robert D. Knight, Antonio Palumbo, and Michel Attal

Meta-Analysis of Maintenance Lenalidomide After ASCT: PFS

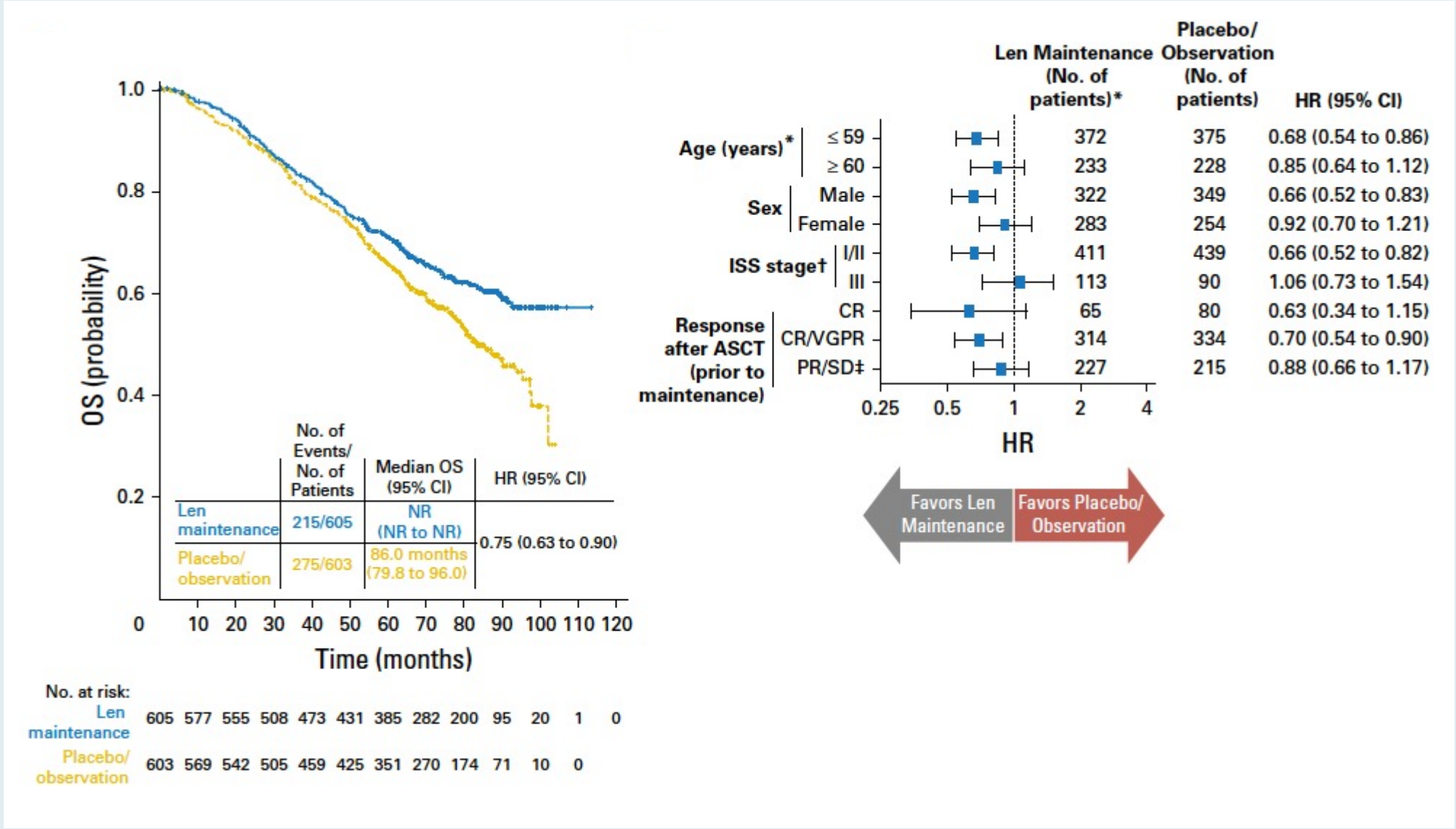


ASCT = autologous stem cell transplantation; PFS = progression-free survival; len = lenalidomide; CALGB = Cancer and Leukemia Group B; IFM = Intergroupe Francophone du Myélome; GIMEMA = Gruppo Italiano Malattie Ematologiche dell'Adulto

McCarthy PL et al. *J Clin Oncol* 2017;35(29):3279-89.

RTP RESEARCH TO PRACTICE

Meta-Analysis of Maintenance Lenalidomide After ASCT: Overall Survival



McCarthy PL et al. *J Clin Oncol* 2017;35(29):3279-89.

Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

*Meletios A Dimopoulos, Francesca Gay, Fredrik Schjesvold, Meral Beksac, Roman Hajek, Katja Christina Weisel, Hartmut Goldschmidt, Vladimir Maisnar, Philippe Moreau, Chang Ki Min, Agnieszka Pluta, Wee-Joo Chng, Martin Kaiser, Sonja Zweegman, Maria-Victoria Mateos, Andrew Spencer, Shinsuke Iida, Gareth Morgan, Kaveri Suryanarayan, Zhaoyang Teng, Tomas Skacel, Antonio Palumbo, Ajeeta B Dash, Neeraj Gupta, Richard Labotka, S Vincent Rajkumar, on behalf of the TOURMALINE-MM3 study group**

***Lancet* 2019;393(10168):253-64.**

original reports

Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial

Meletios A. Dimopoulos, MD[1]; Ivan Špička, MD[2]; Hang Quach, MD[3]; Albert Oriol, MD[4]; Roman Hájek, MD[5]; Mamta Garg, MD[6]; Meral Beksac, MD[7]; Sara Bringhen, MD[8]; Eirini Katodritou, MD[9]; Wee-Joo Chng, MD[10]; Xavier Leleu, MD[11]; Shinsuke Iida, MD[12]; María-Victoria Mateos, MD[13]; Gareth Morgan, MD[14]; Alexander Vorog, MD[15]; Richard Labotka, MD[15]; Bingxia Wang, PhD[15]; Antonio Palumbo, MD[15]; and Sagar Lonial, MD[16]; on behalf of the TOURMALINE-MM4 study group

***J Clin Oncol* 2020;38(34):4030-41.**

Maintenance Ixazomib in Patients Eligible or Ineligible for ASCT: Progression-Free Survival

	Median progression-free survival				
	ASCT	Ixazomib	Placebo	Hazard ratio	*p*-value
TOURMALINE-MM3 (N = 666)	Yes	26.5 mo	21.3 mo	0.72	0.0023
TOURMALINE-MM4 (N = 706)	No	17.4 mo	9.4 mo	0.66	<0.001

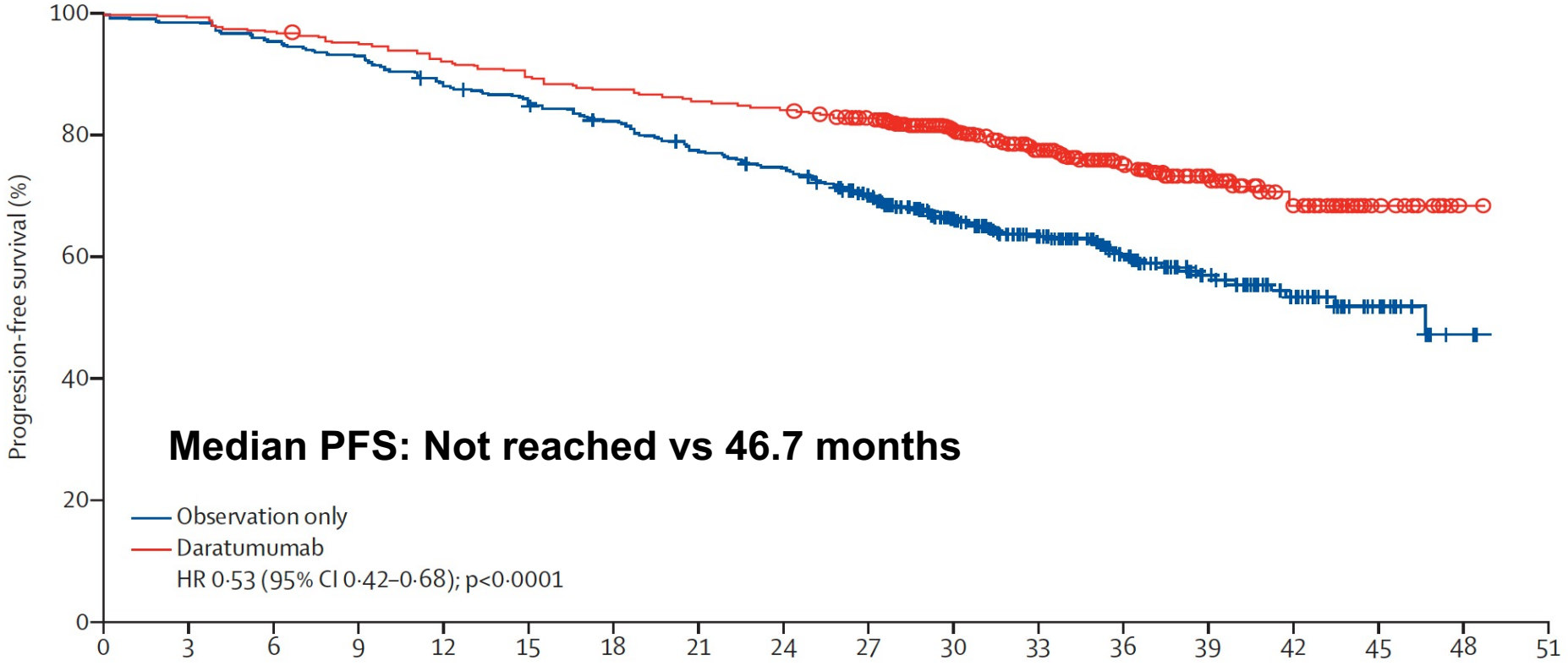
Dimopoulos MA et al. *Lancet* 2019;393(10168):253-64. Dimopoulos MA et al. *J Clin Oncol* 2020;38(34):4030-41.

Lancet Oncol 2021 November;22(10):1378-90.

Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial

Philippe Moreau, Cyrille Hulin, Aurore Perrot, Bertrand Arnulf, Karim Belhadj, Lotfi Benboubker, Marie C Béné, Sonja Zweegman, Hélène Caillon, Denis Caillot, Jill Corre, Michel Delforge, Thomas Dejoie, Chantal Doyen, Thierry Facon, Cécile Sonntag, Jean Fontan, Mohamad Mohty, Kon-Siong Jie, Lionel Karlin, Frédérique Kuhnowski, Jérôme Lambert, Xavier Leleu, Margaret Macro, Frédérique Orsini-Piocelle, Murielle Roussel, Anne-Marie Stoppa, Niels W C J van de Donk, Soraya Wuillème, Annemiek Broijl, Cyrille Touzeau, Mourad Tiab, Jean-Pierre Marolleau, Nathalie Meuleman, Marie-Christiane Vekemans, Matthijs Westerman, Saskia K Klein, Mark-David Levin, Fritz Offner, Martine Escoffre-Barbe, Jean-Richard Eveillard, Réda Garidi, Tahamtan Ahmadi, Maria Krevvata, Ke Zhang, Carla de Boer, Sanjay Vara, Tobias Kampfenkel, Veronique Vanquickelberghe, Jessica Vermeulen, Hervé Avet-Loiseau, Pieter Sonneveld

CASSIOPEIA: PFS in the Maintenance-Specific ITT Population

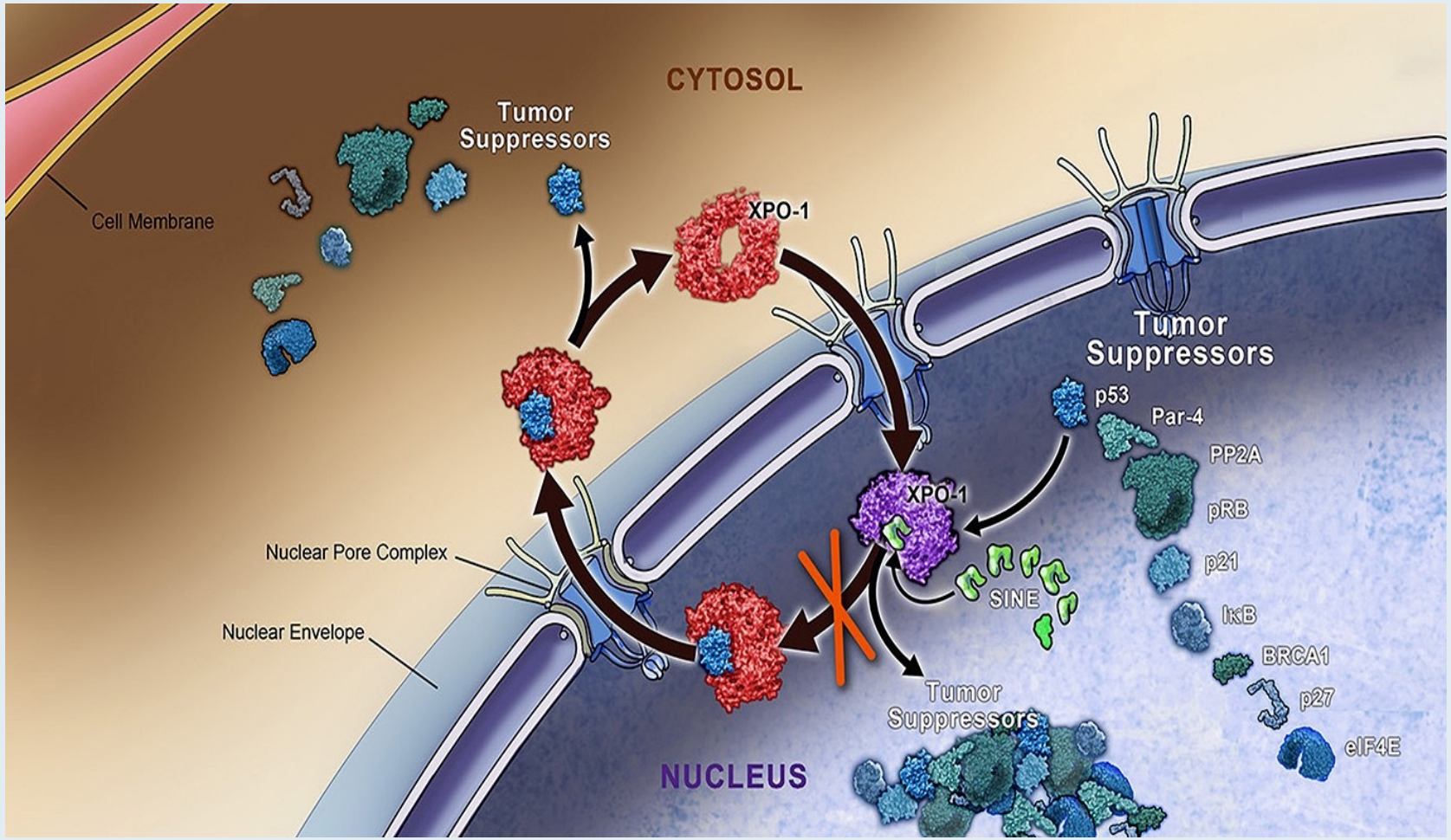


Number at risk (number censored)																		
Observation only	444 (0)	438 (0)	424 (0)	413 (0)	392 (1)	377 (2)	362 (4)	339 (5)	326 (6)	294 (20)	227 (71)	178 (112)	118 (164)	76 (201)	53 (220)	21 (251)	3 (268)	0 (271)
Daratumumab	442 (0)	439 (0)	429 (0)	420 (1)	406 (1)	396 (1)	386 (1)	377 (1)	372 (1)	354 (12)	283 (76)	215 (133)	155 (188)	102 (237)	64 (270)	25 (309)	1 (333)	0 (334)

Moreau P et al. *Lancet Oncol* 2021 November;22(10):1378-90.

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

Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR) and eIF4E-bound oncoprotein mRNAs (c-myc, Bcl-2, Bcl-xL and cyclins)
- XPO1 is overexpressed in MM and its levels often correlate with poor prognosis
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression

Bahlis N et al. EHA 2016;Abstract P277.

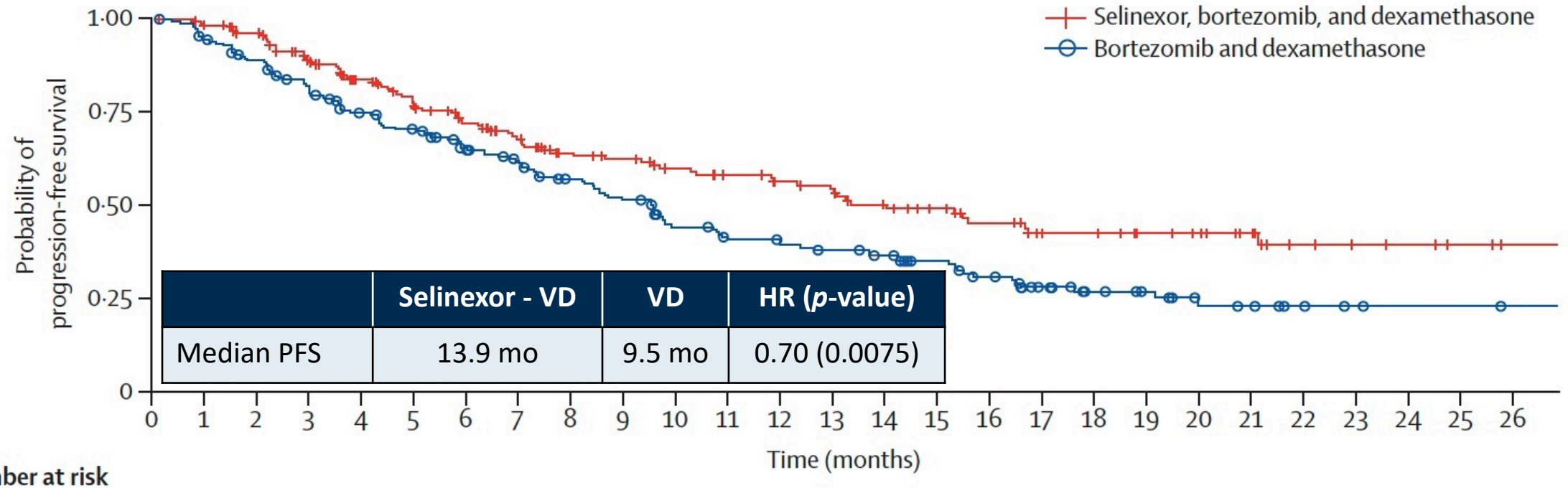
RTP RESEARCH TO PRACTICE

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

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

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

BOSTON: Progression-Free Survival (ITT)



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

Number at risk (number censored)

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

VD = bortezomib and low-dose dexamethasone

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

RTP RESEARCH TO PRACTICE

BOSTON: Response

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

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

BOSTON: Select Adverse Events

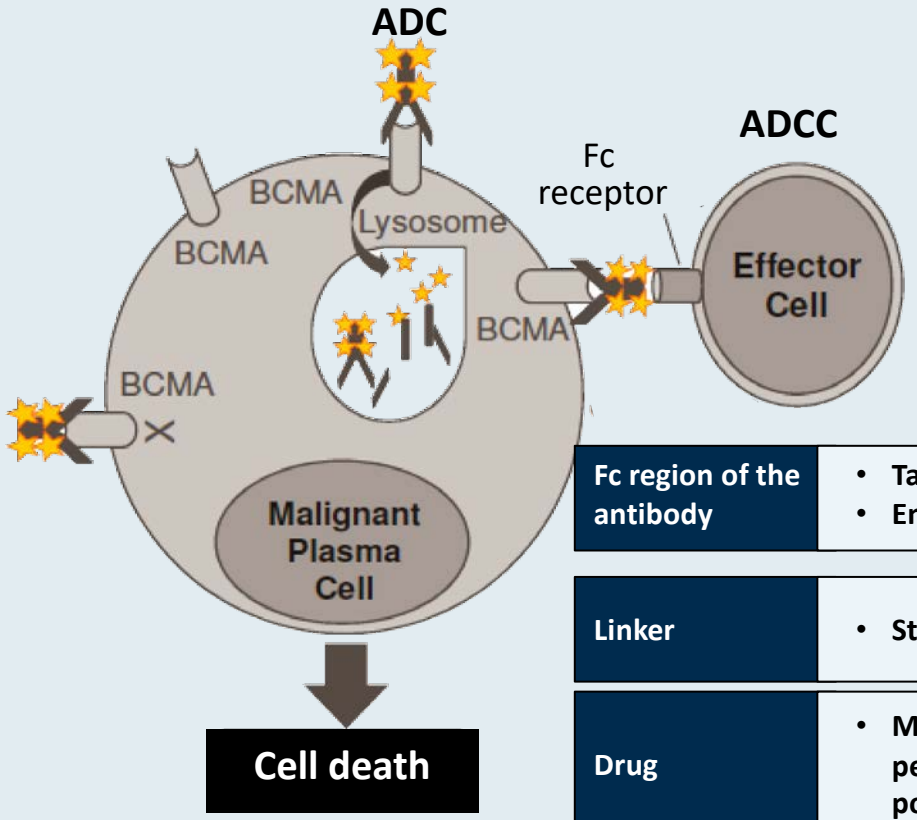
Adverse event	Selinexor + bort/dex (n = 195)		Bort/dex (n = 204)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	60%	39%	27%	17%
Fatigue	42%	13%	18%	1%
Anemia	36%	16%	23%	10%
Peripheral neuropathy	32%	5%	47%	9%
Neutropenia	15%	9%	6%	3%
Treatment discontinuation due to TEAEs	21%		16%	

TEAEs = treatment emergent adverse events

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

Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate

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



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

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

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

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

Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study

Sagar Lonial, MD [1]; Hans C. Lee, MD[2]; Ashraf Badros, MD [3]; Suzanne Trudel, MD[4]; Ajay K. Nooka, MD [1]; Ajai Chari, MD [5]; Al-Ola Abdallah, MD[6]; Natalie Callander, MD[7]; Douglas Sborov, MD[8]; Attaya Suvannasankha, MD[9]; Katja Weisel, MD[10]; Peter M. Voorhees, MD[11]; Lynsey Womersley, MSc[12]; January Baron, MS[13]; Trisha Piontek, BSN[13]; Eric Lewis, MD[14]; Joanna Opalinska, MD[13]; Ira Gupta, MD[13]; and Adam D. Cohen, MD[15]

Cancer 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

DREAMM-2: Single-Agent Belantamab Mafodotin Efficacy Outcomes

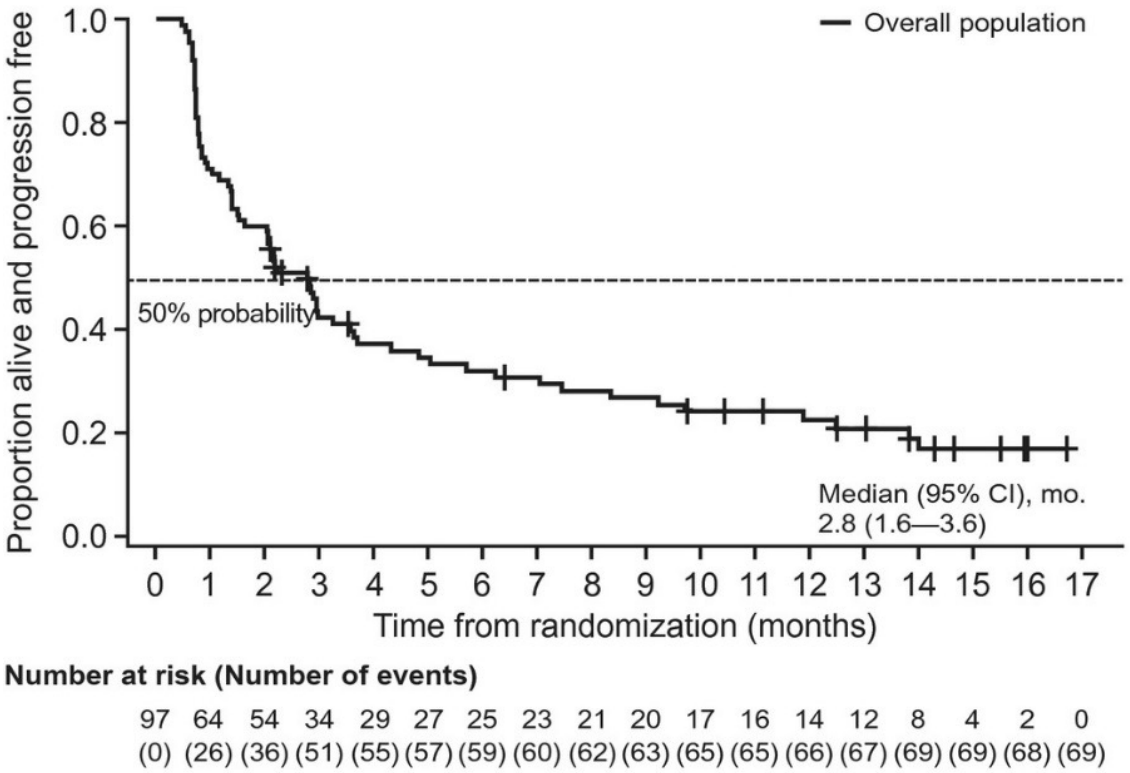
	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	32 (21.7-43.6)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates), months	2.8 (1.6-3.6)	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. *Cancer* 2021;127(22):4198-212; ASH 2020;Abstract 1417.

DREAMM-2: Longitudinal Outcomes

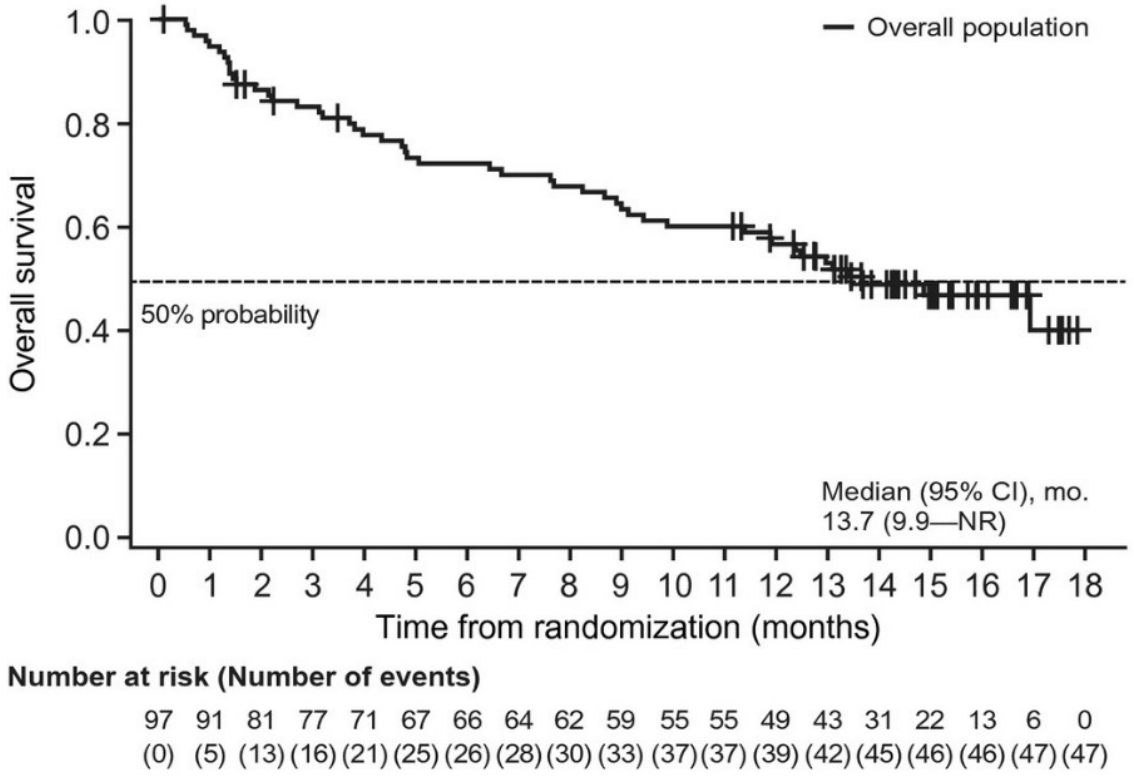
Progression-Free Survival



Number at risk (Number of events)

97	64	54	34	29	27	25	23	21	20	17	16	14	12	8	4	2	0
(0)	(26)	(36)	(51)	(55)	(57)	(59)	(60)	(62)	(63)	(65)	(65)	(66)	(67)	(69)	(69)	(68)	(69)

Overall Survival (OS)



Number at risk (Number of events)

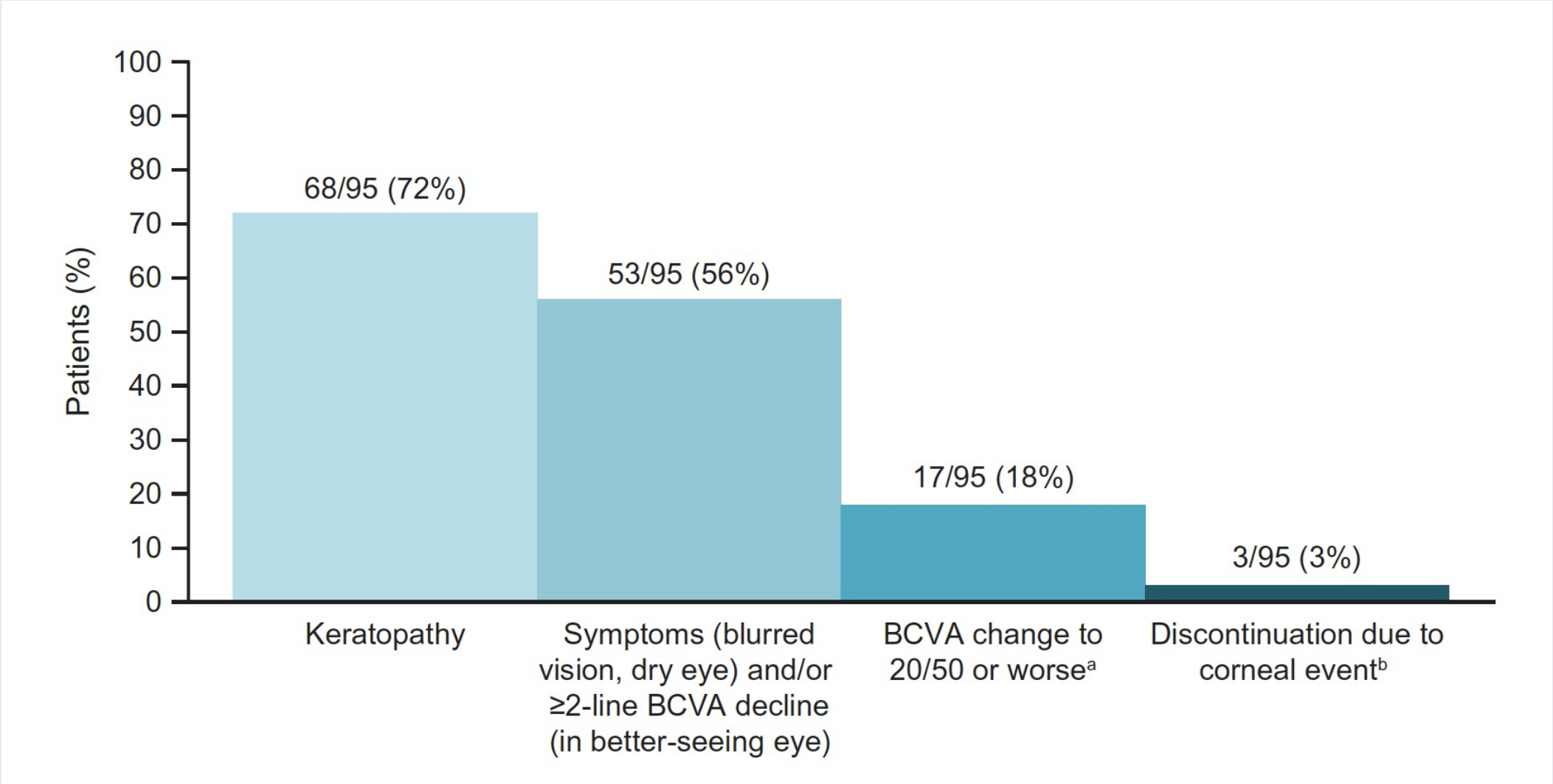
97	91	81	77	71	67	66	64	62	59	55	55	49	43	31	22	13	6	0
(0)	(5)	(13)	(16)	(21)	(25)	(26)	(28)	(30)	(33)	(37)	(37)	(39)	(42)	(45)	(46)	(46)	(47)	(47)

Expected median OS in triple-class refractory myeloma: 8.6 months

Lonial S et al. *Cancer* 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

DREAMM-2: Frequency of Corneal and Vision-Related Events



BCVA = best corrected visual acuity

Lonial S et al. *Cancer* 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

Summary of Select Clinical Trials of Belantamab Mafodotin (Belamaf) Combination Approaches for R/R Multiple Myeloma

Trial	Characteristics	ORR	Safety
DREAMM-6 (NCT03544281)	• Phase I/II • Arm A: belamaf + len/dex (n = 45) • Arm B: belamaf +bor/dex (n = 18)	• Arm A: highest ORR of 75% in the 1.9 mg/kg Q4W dose • Arm B: 78%	Arm A Grade ≥3 AEs: • Thrombocytopenia – 3 (7%) • Keratopathy – 15 (33%) Arm B Grade ≥3 AEs: • Thrombocytopenia – 12 (67%) • Keratopathy – 11 (61%)
DREAMM-4 (NCT03848845)	▪ Phase I/II (N = 34) ▪ Belamaf + pembrolizumab ▪ Dose escalation belamaf 2.5 mg/kg and 3.4 mg/kg	• 47% at RP2D of 2.5 mg/kg	All grades: • Thrombocytopenia – 12 (35%) • Keratopathy – 26 (76%)
ALGONQUIN (NCT03715478)	▪ Phase I/II (N = 56) ▪ Belamaf + pom/dex	• ≥PR/VGPR 89%/72% across all dosing cohorts	Grade ≥3 TEAEs: • Thrombocytopenia – 19 (34%) • Keratopathy – 39 (70%)

ORR = overall response rate; AEs = adverse events; PR = partial response; VGPR = very good partial response; TEAEs = treatment-emergent AEs

Popat R et al. ASH 2020;Abstract 1419; Quach H et al. ASCO 2022;Abstract 8017; Lonial S et al. SOHO 2022;Abstract MM-459; Suvannasankha A et al. EHA 2022;Abstract P940; Trudel S et al. ASH 2021;Abstract 2736.

Ongoing Phase III Trials of Belantamab Mafodotin

Study	N	Setting	Treatment arms	Estimated primary completion
DREAMM-3 (NCT04162210)	380	• Relapsed/refractory multiple myeloma (RRMM) • ≥2 prior lines of treatment, including ≥2 consecutive cycles of both lenalidomide and a proteasome inhibitor (separately or in combination)	• Belantamab mafodotin • Pomalidomide/low-dose dexamethasone	June 2022
DREAMM-8 (NCT04484623)	450	• RRMM • ≥1 prior line of treatment, including a lenalidomide-containing regimen	• Belantamab mafodotin + Pomalidomide/dexamethasone • Bortezomib + Pomalidomide/dexamethasone	March 2023
DREAMM-7 (NCT04246047)	575	• RRMM • ≥1 prior line of treatment	• Belantamab mafodotin + Bortezomib/dexamethasone • Daratumumab + Bortezomib/dexamethasone	April 2023

www.clinicaltrials.gov. Accessed August 2022.

Safety and Efficacy of Belantamab Mafodotin in Combination with Rd in Newly Diagnosed, Transplant Ineligible Multiple Myeloma Patients: A Phase 1/2 Study by the Hellenic Society of Hematology

Terpos E et al.

EHA 2022;Abstract S178.

BelaRd: Results Summary from a Phase I/II Study of Belantamab Mafodotin with Lenalidomide/Dexamethasone for Newly Diagnosed, Transplant-Ineligible MM

Clinical response, n (%)	All patients	Cohort 1 Belamaf 2.5 mg/kg	Cohort 2 Belamaf 1.9 mg/kg	Cohort 3 Belamaf 1.4 mg/kg
Evaluable patients	28	9	9	10
Overall response rate	27 (96.4%)	9 (100.0%)	9 (100.0%)	9 (90%)
CR	4 (14.3%)	2 (22.2%)	2 (22.2%)	—
VGPR	10 (35.7%)	4 (44.4%)	2 (22.2%)	4 (40%)
Select Grade 3/4 AEs	**N = 36**	**n = 12**	**n = 12**	**n = 12**
Leukopenia	2 (5.6%)	2 (16.7%)	—	—
Neutropenia	2 (5.6%)	1 (8.3%)	—	1 (8.3%)
Keratopathy	—	—	—	—
Ocular symptoms	—	—	—	—
Visual acuity reduced	5 (13.9%)	3 (25%)	1 (8.3%)	—

CR = complete response; VGPR = very good partial response

Terpos E et al. EHA 2022;Abstract S178.

DREAMM-9: Phase I Study of Belantamab Mafodotin plus Standard of Care in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma

Usmani SZ et al.

EHA 2022;Abstract P942.

DREAMM-9: Efficacy and Safety Summary with Belantamab Mafodotin and Standard Therapy (VRd) for Newly Diagnosed MM

Clinical response, n (%)	Cohort 1 Belamaf 1.9 mg/kg q3 or 4wk, every cycle of VRd n = 12	Cohort 2 Belamaf 1.4 mg/kg q6 or 8wk, every other cycle of VRd n = 12	Cohort 3 Belamaf 1.9 mg/kg q6 or 8wk, every other cycle of VRd n = 12	Cohort 4 Belamaf 1.0 mg/kg q3 or 4wk, every cycle of VRd n = 15	Cohort 5 Belamaf 1.4 mg/kg q3 or 4wk, every cycle of VRd n = 13
ORR	12 (100%)	11 (92%)	12 (100%)	12 (80%)	12 (92%)
sCR	6 (50%)	1 (8%)	0	3 (20%)	2 (15%)
CR	3 (25%)	0	2 (17%)	2 (13%)	1 (8%)
VGPR	3 (25%)	9 (75%)	7 (58%)	5 (33%)	8 (62%)
Adverse events	**n = 12**	**n = 12**	**n = 12**	**n = 14**	**n = 13**
Grade 3/4 corneal exam findings	9 (75%)	4 (33%)	3 (25%)	7 (50%)	5 (39%)
Grade 3/4 visual acuity changes	10 (83%)	7 (58%)	4 (33%)	3 (21%)	6 (46%)

VRd = bortezomib/lenalidomide/dexamethasone; ORR = overall response rate; CR = complete response; sCR = stringent CR; VGPR = very good partial response

Usmani SZ et al. EHA 2022;Abstract P942.

Corneal Events: Mitigation Strategy

- Corticosteroid eye drops are not beneficial for prophylaxis or treatment
- Lubricating eye drops ≥4 times per day throughout duration of the treatment period
- No contact lens use during treatment period
- Eye examination with BCVA assessment and slit lamp examination with fluorescein staining prior to each planned dose
- Dose delays and dose reductions per recommendations

Lonial S et al. *Blood Cancer J* 2021;11:103.

RTP RESEARCH TO PRACTICE

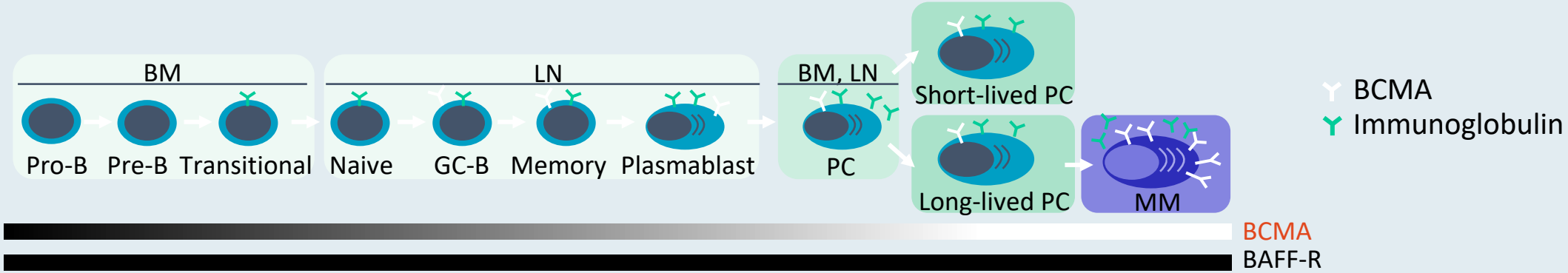
Belantamab Mafodotin Dose Modifications for Corneal Toxicity

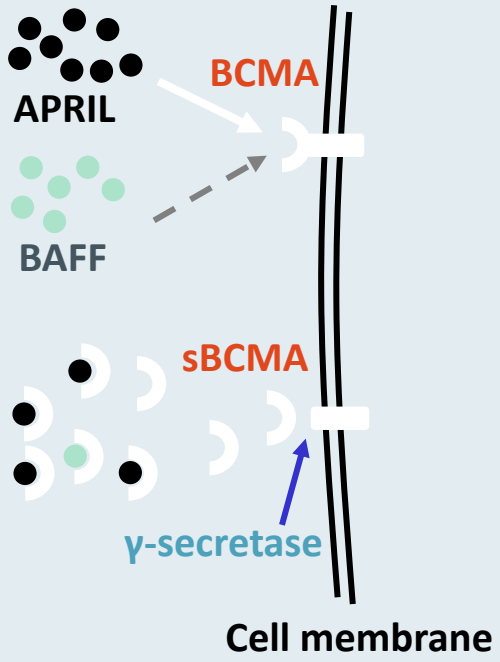
	Exam findings per KVA scale	Recommended dose modifications
Grade 1	Corneal exam: Mild superficial keratopathy	Continue treatment at the current dose
	Change in BCVA: Decline from baseline of 1 line on the Snellen visual acuity chart	
Grade 2	Corneal exam: Moderate superficial keratopathy	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better, and resume at same dose
	Change in BCVA: Decline from baseline of 2 or 3 lines (and Snellen visual acuity not worse than 20/200)	
Grade 3	Corneal exam: Severe superficial keratopathy	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better, and resume at a reduced dose
	Change in BCVA: Decline from baseline by more than 3 lines (and Snellen visual acuity not worse than 20/200)	
Grade 4	Corneal exam: Corneal epithelial defect	Consider treatment discontinuation. Based on a benefit-risk ratio assessment, if continuing belantamab mafodotin is considered, treatment may be resumed at a reduced dose after the event has improved to Grade 1 or better
	Change in BCVA: Snellen visual acuity worse than 20/200	

Farooq AV et al. *Ophthalmol Ther* 2020;9(4):889-911; Lonial S et al. *Blood Cancer J* 2021;11:103.

Incorporation of Chimeric Antigen Receptor (CAR) T-Cell Therapy into the Care of Patients with MM

BCMA as a Target in Myeloma Treatment





- **BCMA: antigen expressed specifically on PCs and myeloma cells**
- **Higher expression on myeloma cells than normal PCs**
- **Not expressed in other tissues**

- **Cell-surface receptor in TNF superfamily**
- **Receptor for APRIL and BAFF**
- **Key role in B-cell maturation and differentiation**
- **Promotes myeloma cell growth, chemotherapy resistance, immunosuppression in bone marrow microenvironment**

Cho S-F et al. *Front Immunol* 2018;9:1821. Moreaux J et al. *Blood* 2004;103(8):3148-57. Sanchez E at al. *Br J Haematol* 2012;158(6):727-38.

Content courtesy of Jesús G Berdeja, MD

RTP RESEARCH TO PRACTICE

FDA Approved CAR T-Cell Therapies for Relapsed or Refractory Multiple Myeloma

February 28, 2022: Ciltacabtagene autoleucel approved for the treatment of relapsed or refractory multiple myeloma in adult patients after 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, based on the CARTITUDE-1 study.

March 26, 2022: Idecabtagene vicleucel approved for the treatment of relapsed or refractory multiple myeloma in adult patients after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma, based on the KarMMA study.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ciltacabtagene-autoleucel-relapsed-or-refractory-multiple-myeloma
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-idecabtagene-vicleucel-multiple-myeloma

RTP RESEARCH TO PRACTICE

Select Clinical Trials of BCMA-Directed CAR T-Cell Therapy for Multi-Agent Refractory Multiple Myeloma: Efficacy Summary

	KarMMa (N = 128)	CARTITUDE-1 (N = 97)	CRB-402 (N = 72)
Phase	II	Ib/II	I/II
Product	Ide-cel	Cilta-cel	BB21217
Median prior lines of therapy	6	6	6
Overall response rate	73%	98%	69%
Complete response	33%	sCR: 83%	sCR/CR: 36%
MRD-negative	26%	92%	67%
Median PFS	8.6 months	Not reached	Not applicable
Median OS	24.8 months	Not reached	Not applicable

Anderson LD et al. ASCO 2021;Abstract 8016. Usmani SZ et al ASCO 2022;Abstract 8028. Martin T et al. *J Clin Oncol* 2022 June 4;[Online ahead of print]. Raje N et al. ASH 2021;Abstract 548. Mateos M-V et al. 2022 ASCO Educational Book.

Select Clinical Trials of BCMA-Directed CAR T-Cell Therapy for Multi-Agent Refractory Multiple Myeloma: CRS and Neurotoxicity

	KarMMa (N = 128)	CARTITUDE-1 (N = 97)	CRB-402 (N = 72)
Product	Ide-cel	Cilta-cel	BB21217
Median prior lines of therapy	6	6	6
CRS	Grade 3: 4%	Grade 3/4: 4%	Grade 3/4: 1%
Neurotoxicity	Grade 3: 3%	Grade 3/4: 11%	Grade 3/4: 4%

CRS = cytokine release syndrome

Anderson LD et al. ASCO 2021;Abstract 8016. Usmani SZ et al ASCO 2022;Abstract 8028. Martin T et al. *J Clin Oncol* 2022 June 4;[Online ahead of print]. Raje N et al. ASH 2021;Abstract 548. Mateos M-V et al. 2022 ASCO Educational Book.

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

Press Release: August 10, 2022

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

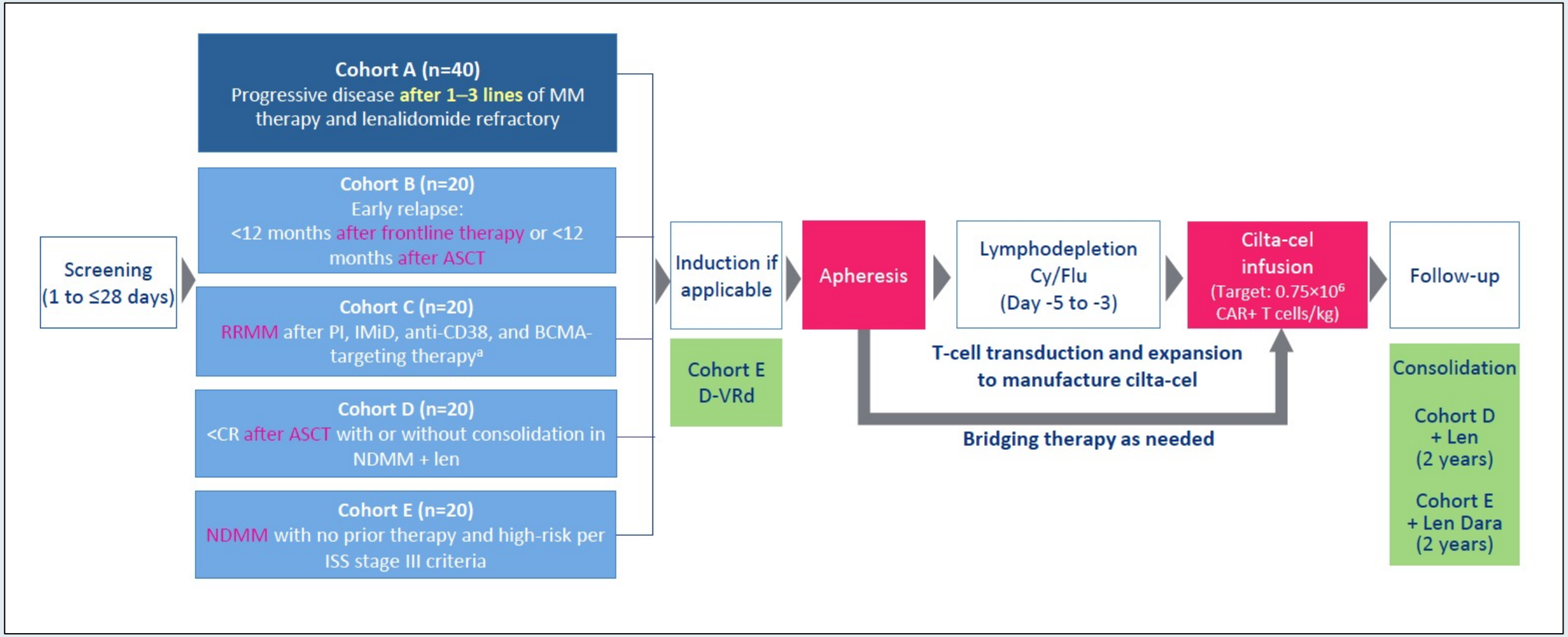
"KarMMa-3 is the first randomized clinical trial to evaluate a CAR T cell therapy in multiple myeloma. Results of a pre-specified interim analysis conducted through an independent review committee showed that KarMMa-3 met its primary endpoint of demonstrating a statistically significant improvement in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

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

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

RTP RESEARCH TO PRACTICE

CARTITUDE-2 Multicohort Overall Trial Design



Agha M et al. EHA 2021;Abstract S190.

ASCO 2022; Abstract 8020.

Biological Correlative Analyses and Updated Clinical Data of Ciltacabtagene Autoleucel, a BCMA-Directed CAR-T Cell Therapy, in Lenalidomide-Refractory Patients With Progressive Multiple Myeloma After 1–3 Prior Lines of Therapy: CARTITUDE-2, Cohort A

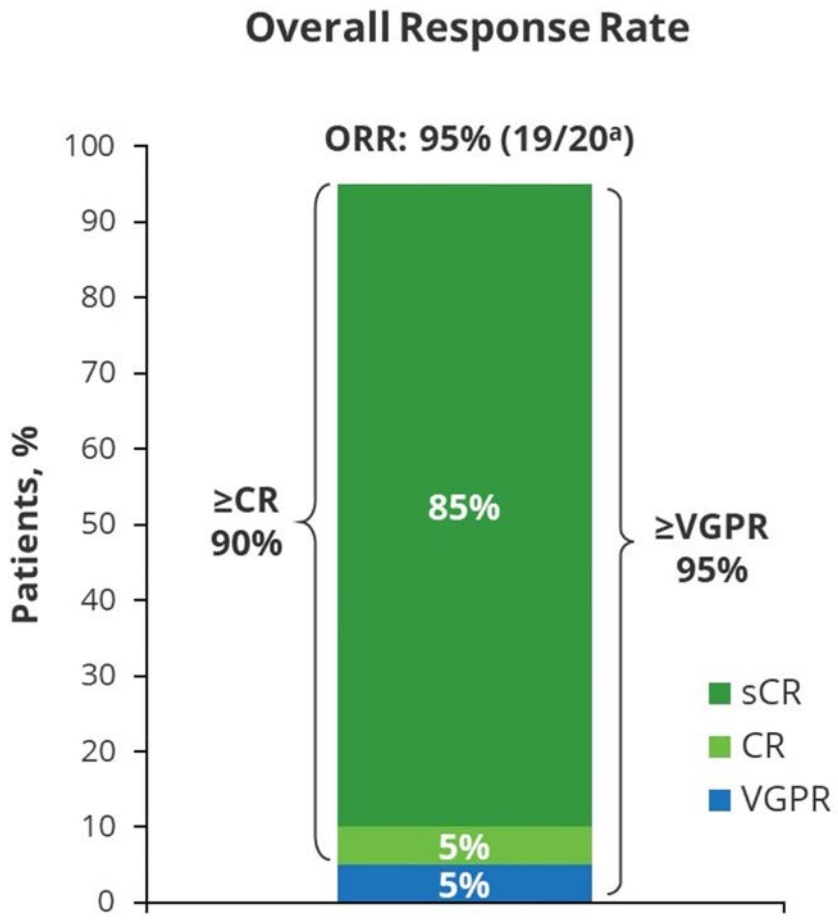
Hermann Einsele[1], Adam Cohen[2], Michel Delforge[3], Jens Hillengass[4], Hartmut Goldschmidt[5], Katja Weisel[6], Marc-Steffen Raab[7], Christoph Scheid[8], Jordan M Schecter[9], Kevin De Braganca[9], Helen Varsos[9], Tzu-Min Yeh[9], Pankaj Mistry[10], Tito Roccia[9], Christina Corsale[9], Muhammad Akram[11], Lida Pacaud[11], Tonia Nesheiwat[11], Mounzer Agha[12], Yael Cohen[13]

[1]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany; [2]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]University Hospitals (UZ) Leuven, Leuven, Belgium; [4]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [5]University Hospital Heidelberg and National Center of Tumor Diseases, Heidelberg, Germany; [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]University Hospital Heidelberg and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center, Heidelberg, Germany; [8]University of Cologne, Cologne, Germany; [9]Janssen Research & Development, Raritan, NJ, USA; [10]Janssen Research & Development, High Wycombe, UK; [11]Legend Biotech USA, Piscataway, NJ, USA; [12]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [13]Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

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

RTP RESEARCH TO PRACTICE

CARTITUDE-2 Cohort A: Ciltacabtagene Autoleucel for Lenalidomide-Refractory MM After 1 to 3 Prior Lines of Therapy



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

Einsele H et al. ASCO 2022;Abstract 8020.

RTP RESEARCH TO PRACTICE

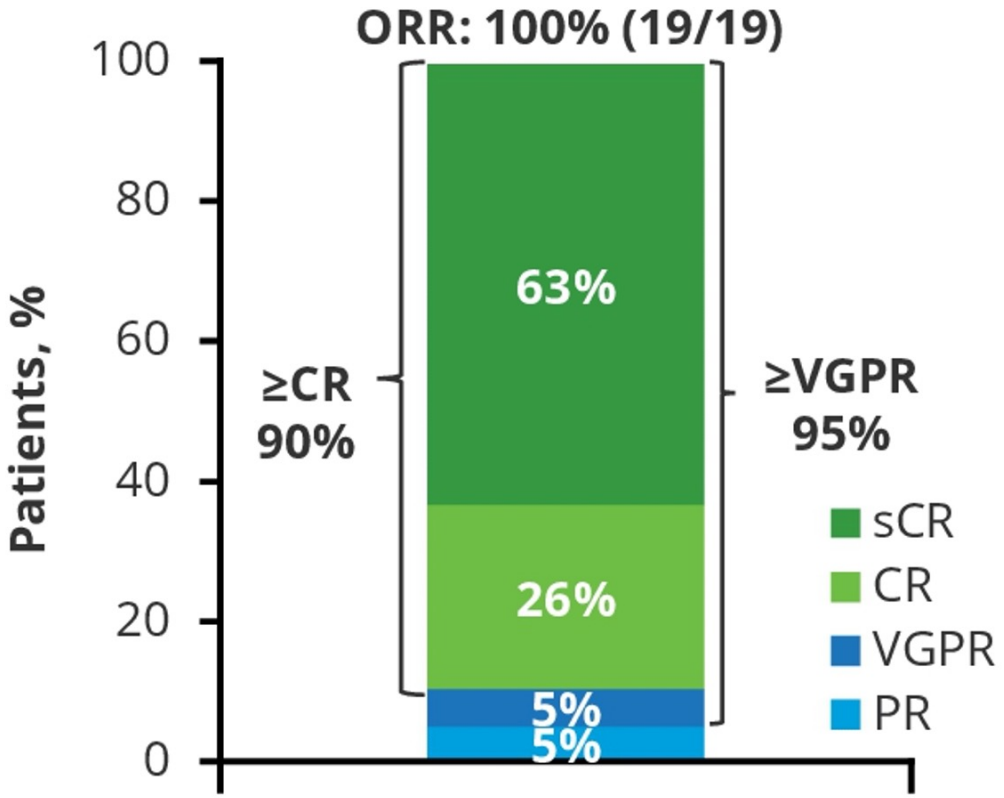
ASCO 2022 | Abstract 8029

Biological Correlative Analyses an Updated Clinical Data of Ciltacabtagene Autoleucel, A BCMA-Directed CAR-T Cell Therapy, in Patients with Multiple Myeloma and Early Relapse After Initial Therapy: CARTITUDE-2, Cohort B

Niels WCJ van de Donk[1] (n.vandedonk@amsterdamumc.nl), Mounzer Agha[2], Adam Cohen[3], Yael Cohen[4], Sébastien Anguille[5], Tessa Kerre[6], Wilfried Roeloffzen[7], Jordan M Schecter[8], Kevin De Braganca[8], Helen Varsos[8], Pankaj Mistry[9], Tito Roccia[8], Enrique Zudaire[10], Christina Corsale[8], Muhammad Akram[11], Dong Geng[11], Tonia Nesheiwat[11], Lida Pacaud[11], Pieter Sonneveld[12], Sonja Zweegman[1]

RTP RESEARCH TO PRACTICE

CARTITUDE-2 (Cohort B): Ciltacabtagene Autoleucel for Patients with Multiple Myeloma and Early Relapse After Initial Therapy



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

van de Donk N WCJ et al. ASCO 2022;Abstract 8029.

CAR T-Cell-Associated Toxicities: Acute and Late Phase

Acute Phase (Days 0-30)

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Cytopenias
- B-cell aplasia and hypogammaglobulinemia
- Tumor lysis syndrome (rare and likely varies by disease burden)

Late Phase (Days 30+)

- Persistent cytopenias
- B-cell aplasia and hypogammaglobulinemia
- T-cell deficiency
- Residual effects of acute toxicity
- Delayed CRS and ICANS is rare but can occur
- Impairment to QoL – fatigue, memory issues not yet well described

Content courtesy of Jesús G Berdeja, MD

Cytokine Release Syndrome Associated with CAR T-Cell Therapy for Multiple Myeloma

- Potentially severe or life-threatening reactions, with the most common manifestations being pyrexia, hypotension, tachycardia, chills, hypoxia, fatigue and headache
- Grade 3 or higher events may include hypotension, hypoxia, hyperbilirubinemia, hypofibrinogenemia, acute respiratory distress syndrome, atrial fibrillation, hepatocellular injury, metabolic acidosis, pulmonary edema, multiple organ dysfunction syndrome and hemophagocytic lymphohistiocytosis/macrophage activation syndrome
- Occurs in about 85%-95% of patients (Grade ≥3: 5%-9%)
- Time to onset: 1-7 days (range 1-23 days)
- Duration: 4-7 days (range 1-63 days)
- Manage with tocilizumab or tocilizumab and corticosteroids

www.carvyktihcp.com/safety; www.abecmahcp.com/safety/

RTP RESEARCH TO PRACTICE

ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome) Associated with CAR T-Cell Therapy for MM

- Potentially severe or life-threatening neurotoxicity, including encephalopathy, tremor, aphasia and delirium.
- Occurs in about 25% of patients (Grade ≥3: 4%-5%)
- Time to onset: 2 to 8 days (range 1-42 days)
- Duration: 6 to 8 days (range 1-578 days)
- Resolved in 77% to 92% of patients
- Manage with supportive care and corticosteroids as needed

www.carvyktihcp.com/safety; www.abecmahcp.com/safety/

Key Select Ongoing Studies of BCMA-Directed CAR T-Cell Therapy with Ide-cel and Cilta-cel

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

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

www.clinicaltrials.gov. Accessed August 2022.

Novel Investigational Agents for MM

BCMA x CD3 Bispecific Antibodies: Summary

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

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

Content courtesy of Noopur Raje, MD

ASCO 2022;Abstract 8007.

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

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

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

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

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

The NEW ENGLAND JOURNAL of MEDICINE

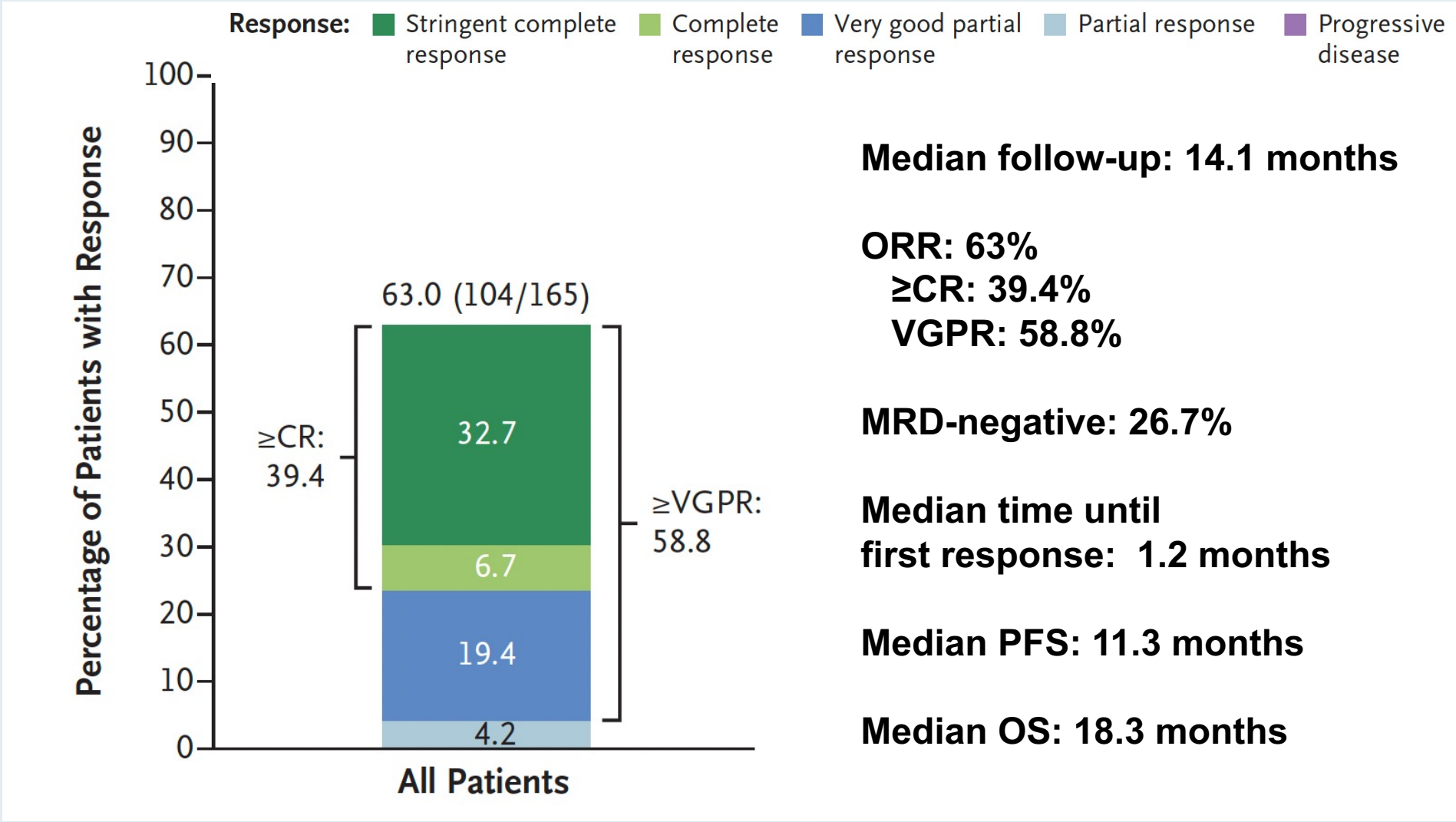
ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

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

RTP RESEARCH TO PRACTICE

MajesTEC-1: Response and Survival



Median follow-up: 14.1 months

ORR: 63%
≥CR: 39.4%
VGPR: 58.8%

MRD-negative: 26.7%

Median time until first response: 1.2 months

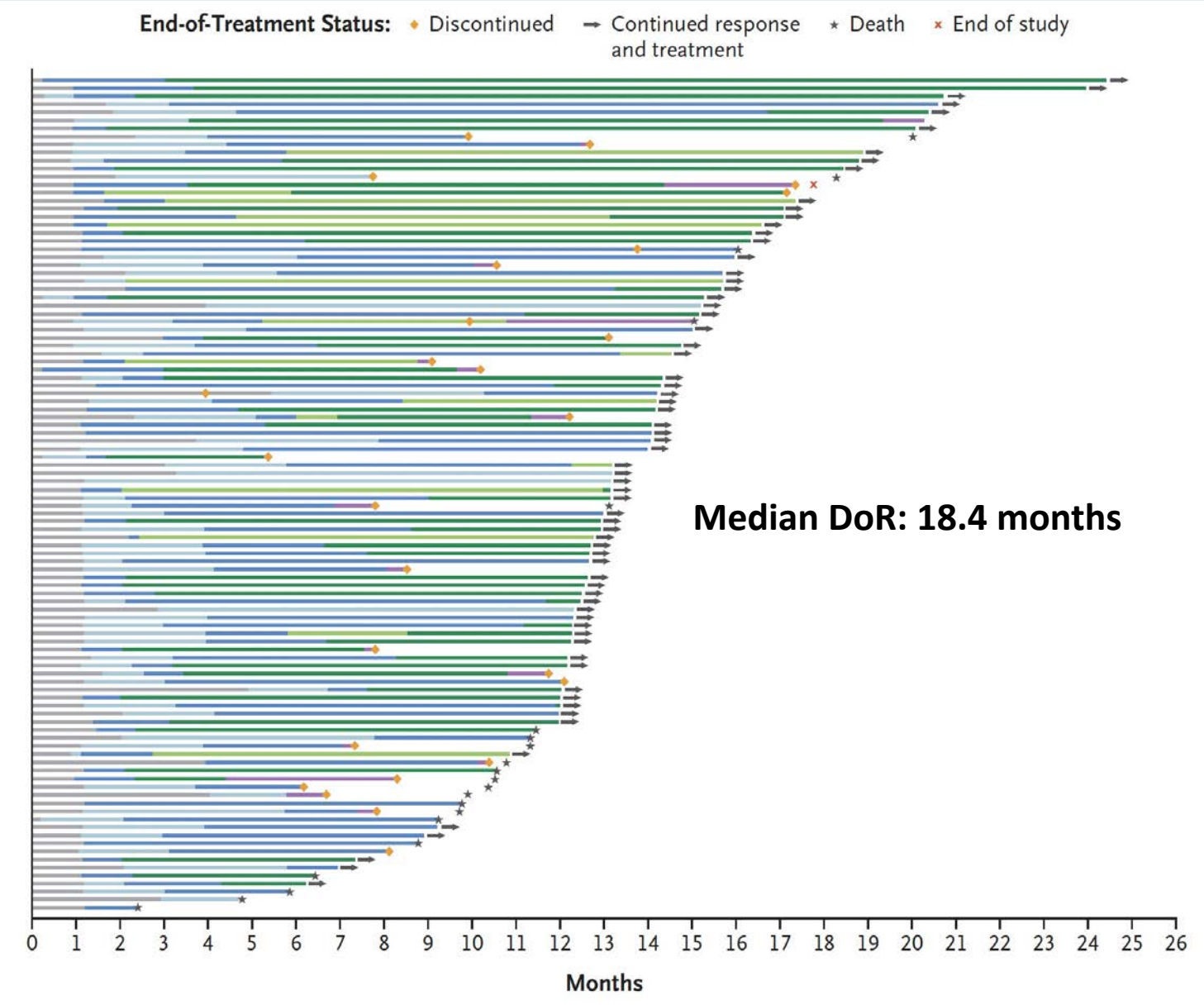
Median PFS: 11.3 months

Median OS: 18.3 months

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

RTP RESEARCH TO PRACTICE

MajesTEC-1: Duration of Response (DoR)



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

MajesTEC-1: Adverse Events

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

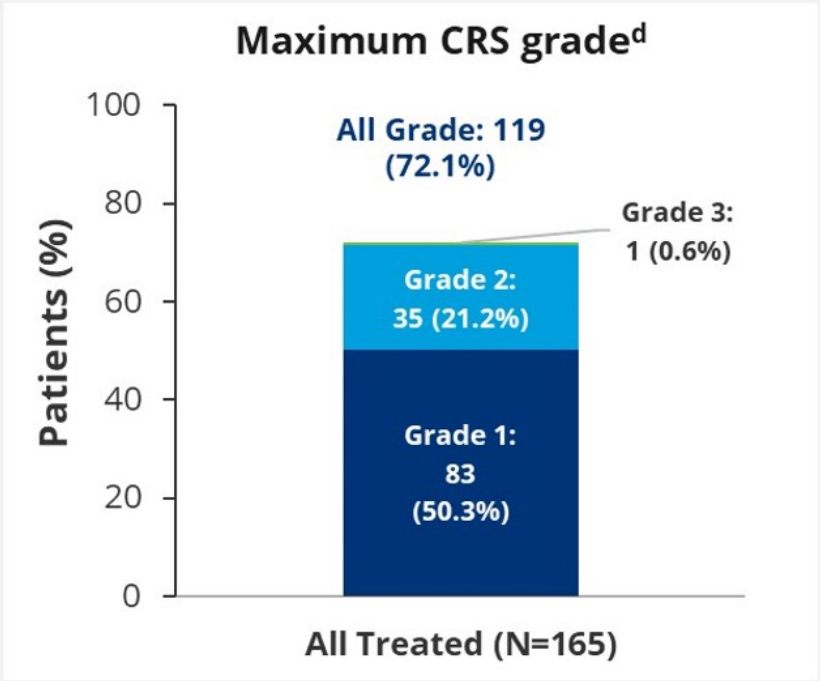
Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Nonhematologic		
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4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

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

RTP RESEARCH TO PRACTICE

MajesTEC-1: Cytokine Release Syndrome

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



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

Nooka AK et al. ASCO 2022;Abstract 8007.

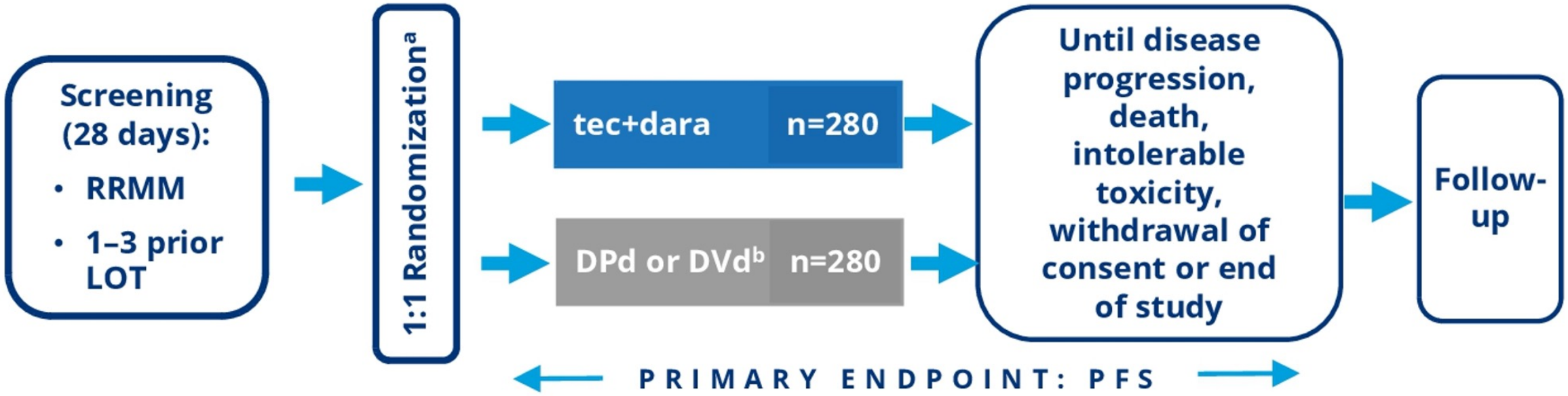
MajesTEC-1: Neurotoxic Events

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

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

Nooka AK et al. ASCO 2022;Abstract 8007.

MajesTEC-3 Ongoing Phase III Study Design



Key Eligibility Criteria:

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

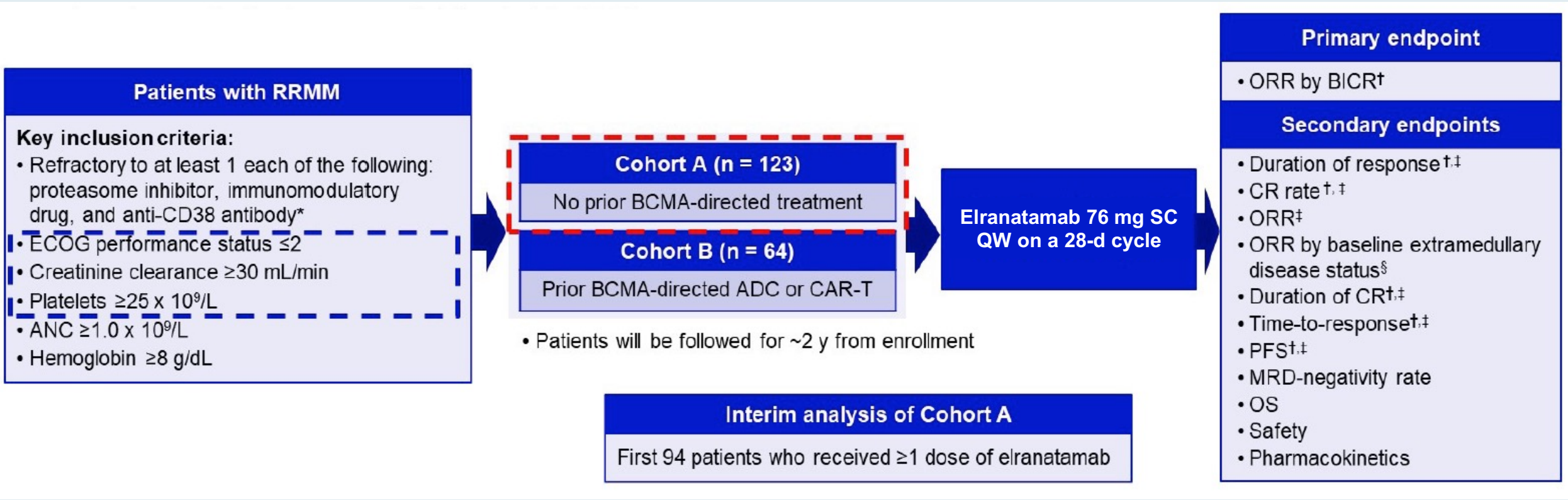
Mateos MV et al. ASCO 2022;Abstract TPS8072.

Initial Safety Results for MagnetisMM-3: A Phase 2 Trial of Elranatamab, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients (pts) with Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Lesokhin AM et al.

ASCO 2022;Abstract 8006.

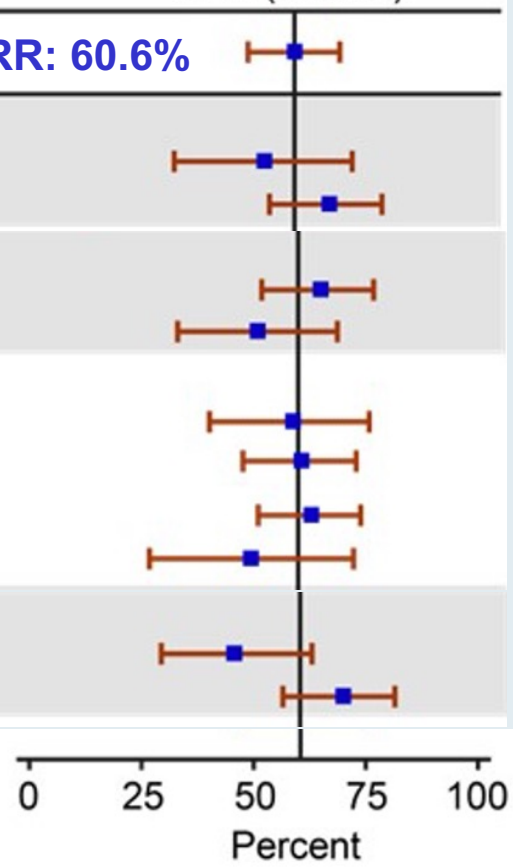
MagnetisMM-3: Phase II Trial Design



Lesokhin AM et al. ASCO 2022;Abstract 8006.

MagnetisMM-3: Overall Response Rate (All and Subgroups)

Subgroup	Patients (N)	ORR (95% CI)
All Patients	94	ORR: 60.6%
Baseline Cytogenetics		
High Risk	26	
Not High-Risk	57	
Number of Prior Lines		
≤5	61	
>5	33	
Age (Years)		
<65	32	
≥65	62	
<75	74	
≥75	20	
Penta Refractory		
Yes	37	
No	57	



Lesokhin AM et al. ASCO 2022;Abstract 8006.

MagnetisMM-3 AEs of Special Interest: Infections

n (%)	Cohort A n = 94	
	Any grade	Grade 3/4
Infection TEAEs in ≥5% of patients		
COVID-related AE	14 (14.9)	8 (8.5)
Upper respiratory tract infection	10 (10.6)	0
Pneumonia	8 (8.5)	4 (4.3)
Urinary tract infection	5 (5.3)	2 (2.1)
TEAEs of interest		
Pneumocystis jirovecii pneumonia	4 (4.3)	3 (3.2)
CMV infection	4 (4.3)	0
CMV infection reactivation	1 (1.1)	0

- Infections reported in 52.1%
  - Grade 3/4: 22.3%
  - Treatment-related: 24.5%
- 1 patient had an infection leading to permanent discontinuation of elranatamab

Lesokhin AM et al. ASCO 2022;Abstract 8006.

MagnetisMM-3 AEs of Special Interest: Peripheral Neuropathy

Peripheral neuropathy, n (%)	Cohort A n = 94	
	Any grade	Grade 3/4
All causality	15 (16.0)	1 (1.1)
Treatment-related	5 (6.4)	1 (1.1)

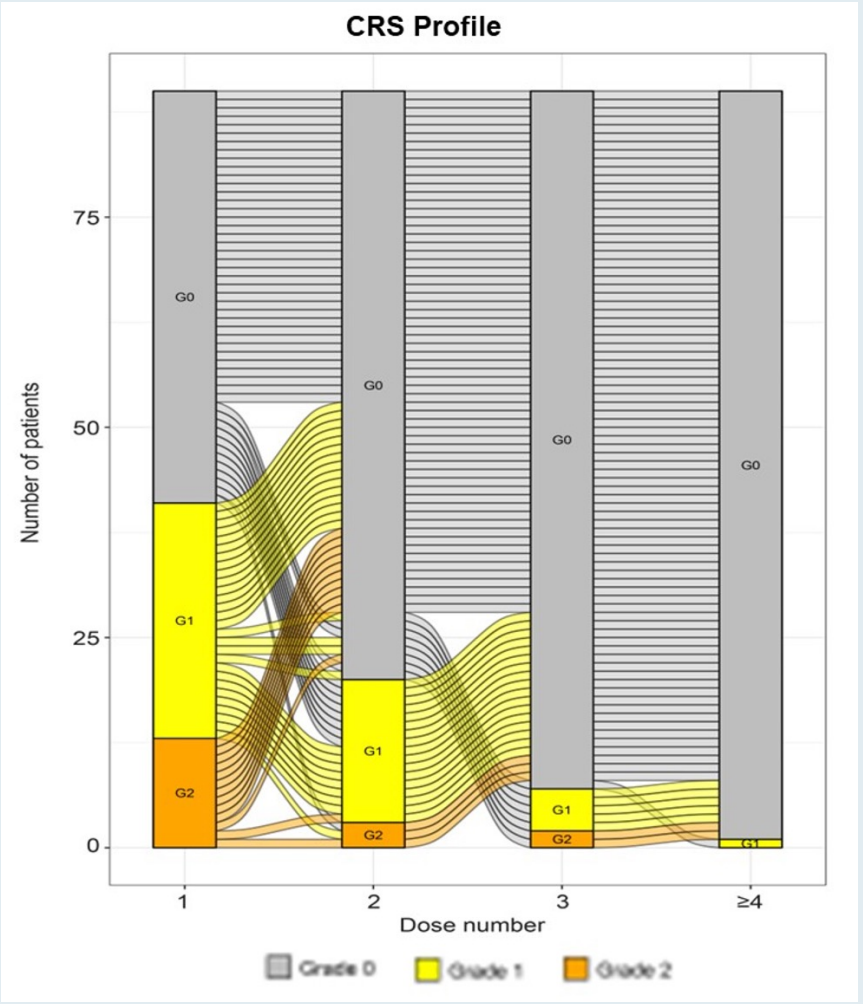
- Most common events (≥2% of patients) were peripheral sensory neuropathy (5.3%) and paresthesia (3.2%). All were grade 1/2, except for 1 patient with grade 3 motor neuropathy
- Two (2.1%) patients had peripheral neuropathy events that led to permanent discontinuation of elranatamab
- A medical history of peripheral neuropathy was reported by 7/15 (46.7%) patients with peripheral neuropathy events

Lesokhin AM et al. ASCO 2022;Abstract 8006.

MagnetisMM-3 AEs of Special Interest: CRS and ICANS

- The 2-step-up priming regimen successfully mitigated the rate and severity of CRS, and the CRS profile was predictable with 88.4% of events after the first 2 doses and 98.6% after the first 3 doses

TEAE of special interest	12/32 mg 2-step-up regimen n = 90*	
	CRS	ICANS
Patients with TEAE, n (%)	53 (58.9)	2 (2.2)
Maximum grade 1	36 (40.0)	0
Maximum grade 2	17 (18.9)	2 (2.2)
Patients with >1 TEAE, n (%)	16 (17.8)	1 (1.1)
Median time to onset of TEAE, days (range)	2.0 (1.0–9.0)	2.5 (1.0–4.0)
Median time to resolution of TEAE, days (range)	2.0 (1.0–19.0)	3.0 (2.0–6.0)
Patients with TEAE who received tocilizumab† or steroids, n (%)	26 (49.1)	2 (100)
Tocilizumab	24 (45.3)	2 (100)
Steroids	7 (13.2)	2 (100)
Permanent discontinuation due to AE, n (%)	0	0



Lesokhin AM et al. ASCO 2022;Abstract 8006.

Novel Non-BCMA Bispecific Antibodies: Summary

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

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

Content courtesy of Noopur Raje, MD

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

Press Release: June 29, 2022

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

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

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

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

RTP RESEARCH TO PRACTICE

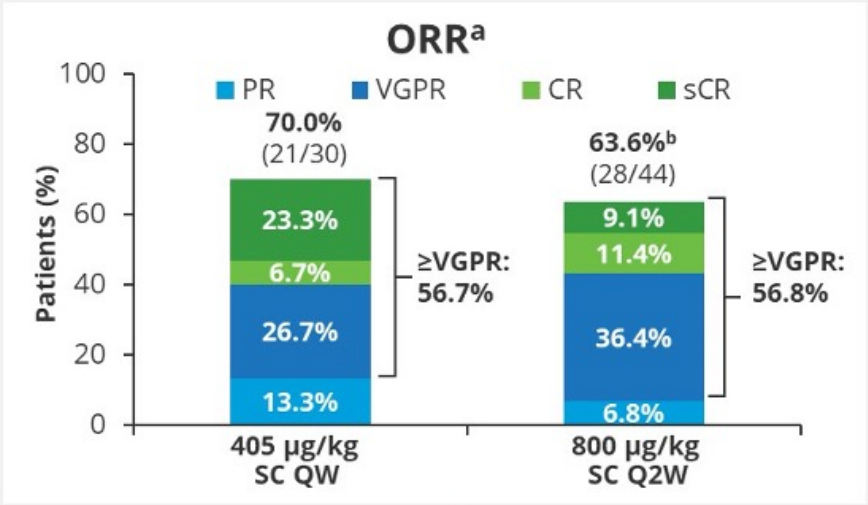
Efficacy and Safety of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients With Relapsed/ Refractory Multiple Myeloma: Updated Results From MonumenTAL-1

Monique C Minnema[1], Amrita Krishnan[2], Jesus G. Berdeja[3], Albert Oriol[4], Niels WCJ van de Donk[5], Paula Rodríguez-Otero[6], Daniel Morillo[7], María-Victoria Mateos[8], Luciano J. Costa[9], Jo Caers[10], Deeksha Vishwamitra[11], Joanne Ma[11], Shiyi Yang[11], Brandi W Hilder[11], Jaszianne Tolbert[11], Jenna D Goldberg[12], Ajai Chari[13]

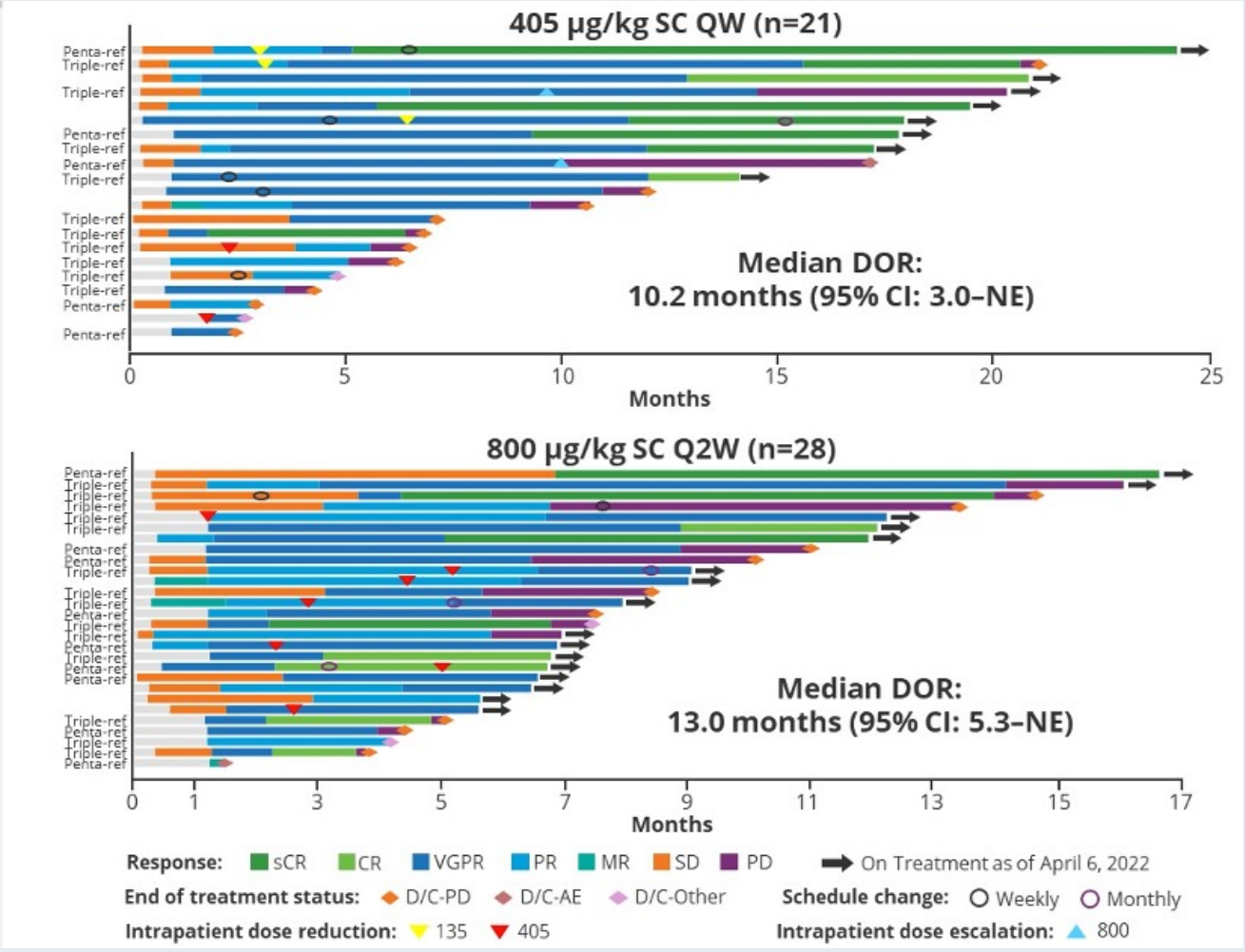
ASCO 2022;Abstract 8015.

RTP RESEARCH TO PRACTICE

MonumenTAL-1: Duration of Response with Talquetamab for R/R MM



Response	405 µg/kg SC QW[c] n=30	800 µg/kg SC Q2W[c] n=44
Median follow-up (months), median (range)	13.2 (1.1–24.0)	7.7 (0.7–16.0)
ORR[a], n (%)	21 (70.0)	28 (63.6)
Triple-class–refractory patients, n/N (%)	15/23 (65.2)	23/34 (67.6)
Penta-drug–refractory patients, n/N (%)	5/6 (83.3)	9/12 (75.0)
Median time to first confirmed response (months), median (range)	0.9 (0.2–3.8)	1.2 (0.3–6.8)



Minnema MC et al. ASCO 2022;Abstract 8015.

MonumenTAL-1: Adverse Events with Talquetamab

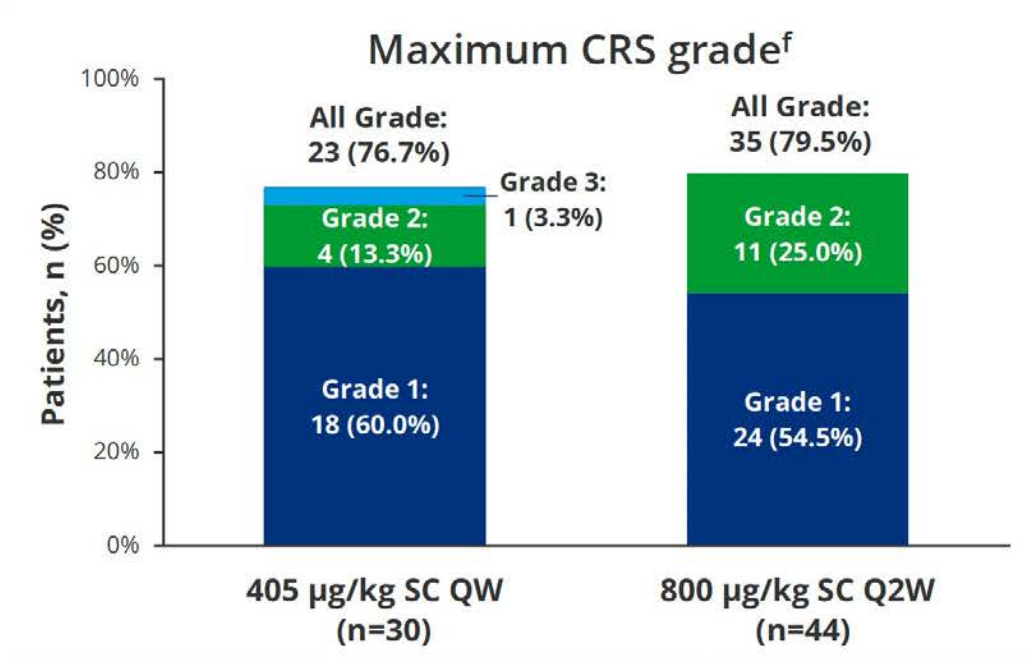
AEs (≥20% of total SC population), n (%)	405 µg/kg SC QW[a] n=30		800 µg/kg SC Q2W[a] n=44	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	20 (66.7)	18 (60.0)	18 (40.9)	15 (34.1)
Anemia	17 (56.7)	9 (30.0)	21 (47.7)	12 (27.3)
Lymphopenia	12 (40.0)	12 (40.0)	18 (40.9)	18 (40.9)
Leukopenia	12 (40.0)	9 (30.0)	10 (22.7)	8 (18.2)
Thrombocytopenia	11 (36.7)	7 (23.3)	10 (22.7)	5 (11.4)
Nonhematologic				
CRS	23 (76.7)	1 (3.3)	35 (79.5)	0
Skin-related AEs[b]	20 (66.7)	0	32 (72.7)	1 (2.3)
Dysgeusia	19 (63.3)	N/A	25 (56.8)	N/A
Nail-related AEs[c]	18 (60.0)	0	15 (34.1)	0
Rash-related AEs[d]	14 (46.7)	1 (3.3)	13 (29.5)	7 (15.9)
Dysphagia	12 (40.0)	0	12 (27.3)	0
Pyrexia	11 (36.7)	0	10 (22.7)	0
Fatigue	10 (33.3)	1 (3.3)	12 (27.3)	0
Dry mouth	9 (30.0)	0	25 (56.8)	0
Weight decreased	9 (30.0)	0	19 (43.2)	1 (2.3)
Nausea	9 (30.0)	0	9 (20.5)	0
Diarrhea	9 (30.0)	0	8 (18.2)	0
ALT increased	6 (20.0)	1 (3.3)	14 (31.8)	3 (6.8)
Decreased appetite	7 (23.3)	1 (3.3)	11 (25.0)	1 (2.3)
Headache	7 (23.3)	0	11 (25.0)	0
AST increased	3 (10.0)	0	14 (31.8)	3 (6.8)

- Overall, the most common adverse events (AEs) were CRS, skin-related events, and dysgeusia
- Cytopenias were mostly confined to step-up and cycle 1–2 doses and generally resolved within 1 week
- Infections occurred in 46.7% of patients at 405 µg/kg QW and 38.6% at 800 µg/kg Q2W (grade 3/4: 6.7%/9.1%)
- CRS events were mostly grade 1/2 and were largely confined to the step-up doses and first full dose
- Dysgeusia was managed with supportive care, and at times with dose adjustments
- No patients died due to drug-related AEs

Minnema MC et al. ASCO 2022;Abstract 8015.

MonumenTAL-1: Cytokine Release Syndrome

Parameter	405 µg/kg SC QW[a] n=30	800 µg/kg SC Q2W[a] n=44
Patients with CRS, n (%)	23 (76.7)	35 (79.5)
Time to onset (days),[b] median (range)	2 (1–22)	2 (1–5)
Duration (days), median (range)	2 (1–3)	2 (1–5)
Patients who received supportive measures,[c] n (%)	23 (76.7)	35 (79.5)
Tocilizumab[d]	19 (63.3)	24 (54.5)
Steroids	1 (3.3)	3 (6.8)
Oxygen	1 (3.3)[e]	2 (4.5)
Single vasopressor	1 (3.3)[e]	0

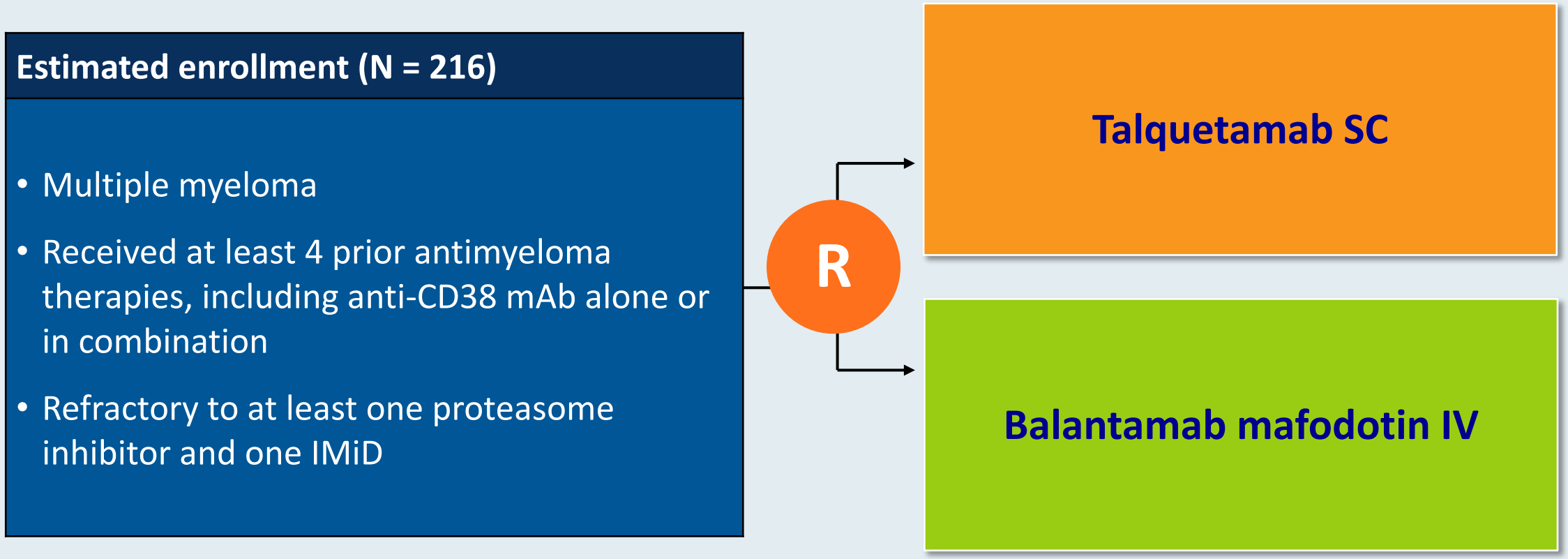


- All CRS events were grade 1/2, except for one grade 3 event
- CRS was largely confined to the step-up doses and first full dose

Minnema MC et al. ASCO 2022;Abstract 8015.

RTP RESEARCH TO PRACTICE

MonumenTAL-5 Phase III Study Design



Primary endpoint: Overall response rate, progression-free survival

www.clinicaltrials.gov. NCT05461209. Accessed August 2022.

EHA 2022;Abstract S183.

Novel Combination Immunotherapy for the Treatment of Relapsed/Refractory Multiple Myeloma: Updated Phase 1b Results for Talquetamab (a GPRC5D x CD3 Bispecific Antibody) in Combination With Daratumumab

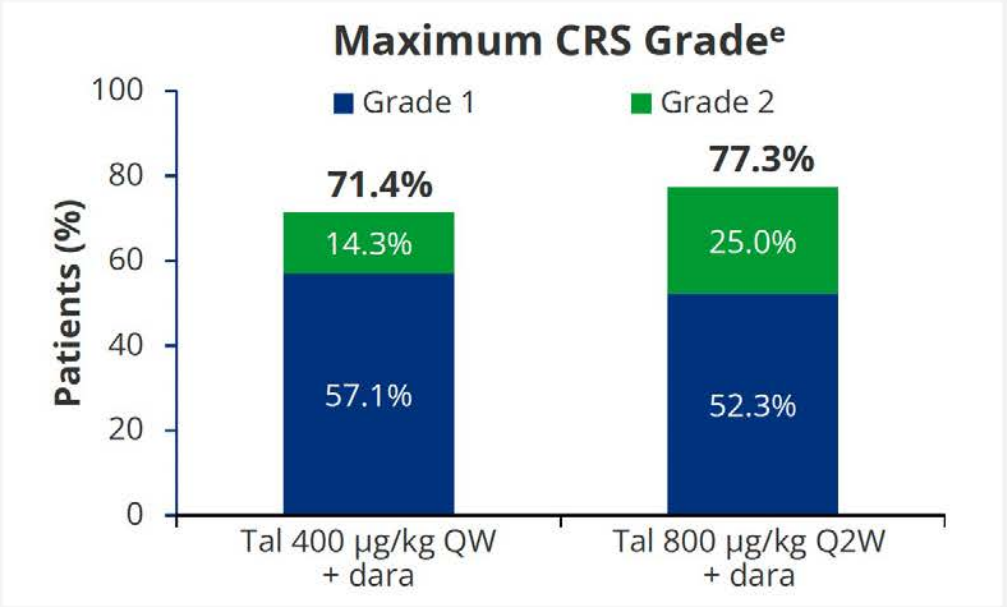
Niels WCJ van de Donk[1], Nizar Bahlis[2], Maria-Victoria Mateos[3], Katja Weisel[4], Bhagirathbhai Dholaria[5], Alfred L Garfall[6], Hartmut Goldschmidt[7], Thomas G Martin[8], Daniel Morillo[9], Donna Reece[10], David Hurd[11], Paula Rodríguez-Otero[12], Manisha Bhutani[13], Anita D'Souza[14], Albert Oriol[15], Elham Askari[9], Jesús F San-Miguel[12], K Martin Kortüm[16], Deeksha Vishwamitra[17], Shun Xin Wang Lin[17], Thomas J Prior[17], Lien Vandenberk[18], Marie-Anne Damiette Smit[19], Jenna D Goldberg[20], Ralph Wäsch[21], Ajai Chari[22]

[1]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [2]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Canada; [3]University Hospital of Salamanca/IBSAL/CIC, Salamanca, Spain; [4]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Vanderbilt University Medical Center, Nashville, TN, USA; [6]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]University Hospital Heidelberg and National Center of Tumor Diseases, Heidelberg, Germany; [8]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [9]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [10]Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC, USA; [12]University of Navarra, Pamplona, Spain; [13]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [14]Medical College of Wisconsin, Milwaukee, WI, USA; [15]Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [16]University Hospital of Würzburg, Würzburg, Germany, Würzburg, Germany; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Antwerp, Belgium; [19]Janssen Research & Development, Los Angeles, CA, USA; [20]Janssen Research & Development, Raritan, NJ, USA; [21]Freiburg University Medical Center, Freiburg, Germany; [22]Mount Sinai School of Medicine, New York, NY, USA

Presented at the European Hematology Association (EHA) 2022 Hybrid Congress; June 9–12, 2022; Vienna, Austria.

TRIMM-2: Cytokine Release Syndrome

Parameter	Tal 400 µg/kg QW + dara (n=14)	Tal 800 µg/kg Q2W + dara (n=44)
Patients with CRS, n (%)	10 (71.4)	34 (77.3)
Time to onset (days)[a], median (range)	3 (2–4)	2 (1–4)
Duration (days), median (range)	2 (1–10)	2 (1–28)
Received supportive measures[b], n (%)	9 (64.3)	30 (68.2)
Tocilizumab[c]	6 (42.9)	14 (31.8)
Corticosteroids	0	2 (4.5)
Oxygen	0	3 (6.8)
Vasopressor	0	0
Other[d]	7 (50.0)	30 (68.2)



- No grade 3/4 CRS events were observed
- CRS events were mostly confined to step-up doses and the first full treatment dose
- No discontinuations due to CRS
- Two patients had ICANS; both ICANS events were grade 1 and resolved within 1 day

van de Donk N WCJ et al. EHA 2022;Abstract S183.

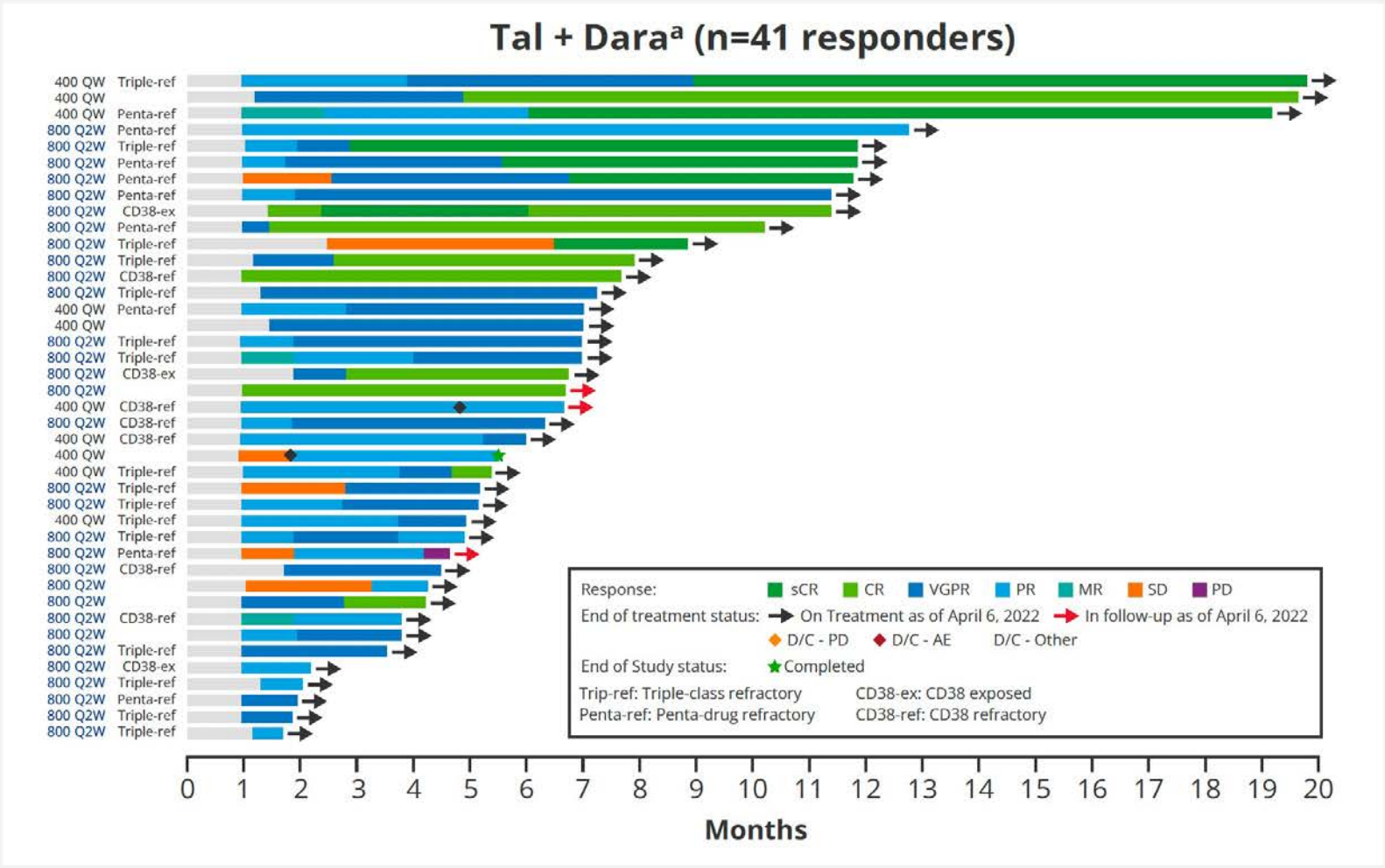
TRIMM-2: Overall Response Rate

Parameter	Evaluable patients[a]	
	Tal 400 µg/kg QW + dara (n=14)	Tal 800 µg/kg Q2W + dara (n=37)
Follow-up, median (range)	**6.7 months** (1.9–19.6)	**4.2 months** (0.2–12.3)
ORR[b], n (%)	**10 (71.4)**	**31 (83.8)**
CR/sCR	4 (28.6)	11 (29.7)
VGPR	4 (28.6)	13 (35.1)
PR	2 (14.3)	7 (18.9)
SD	4 (28.6)	4 (10.8)
PD	0	2 (5.4)
Time to first confirmed response, median (range)	**1.0 month** (0.9–2.4)	**1.0 month** (0.9–6.5)

- With overall median follow-up of 5.1 months, the ORR was **80.4%** (41/51) among all response-evaluable patients
  - VGPR or better: 62.7% (32/51)
  - CR or better: 29.4% (15/51)
- ORR in patients with prior anti-CD38 exposure: 77.3% (34/44)

van de Donk N WCJ et al. EHA 2022;Abstract S183.

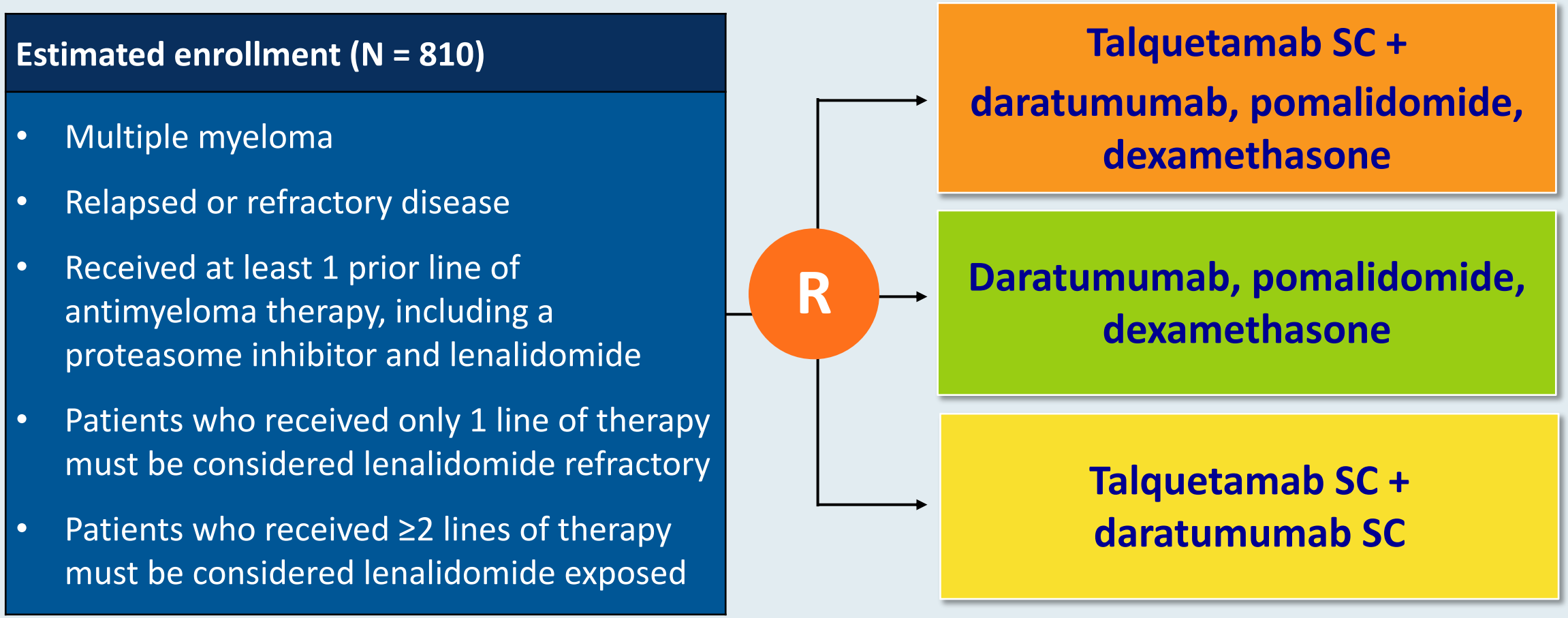
TRIMM-2: Duration of Response



- Responses were observed in heavily pretreated patients, the majority of whom were anti-CD38 refractory
- Responses were durable and deepened over time
- Median duration of response was not reached
- With a median follow-up in responders of 6.5 months (range: 1.6–19.6), 90.2% of responders (37/41) remained on treatment

van de Donk N WCJ et al. EHA 2022;Abstract S183.

MonumenTAL-3 Phase III Study Design



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. NCT05455320. Accessed August 2022.

Cevostamab monotherapy continues to show clinically meaningful activity and manageable safety in patients with heavily pre-treated relapsed/refractory multiple myeloma: updated results from an ongoing Phase I study

ASH 2021;Abstract 157.

Suzanne Trudel,[1] Adam D Cohen,[2] Amrita Krishnan,[3] Rafael Fonseca,[4] Andrew Spencer,[5] Jesus G Berdeja,[6] Alexander Lesokhin,[7] Peter A Forsberg,[8] Jacob P Laubach,[9] Luciano J Costa,[10] Paula Rodriguez-Otero,[11] Rayan Kaedbey,[12] Joshua Richter,[13] Maria-Victoria Mateos,[14] Sheeba K Thomas,[15] Chihunt Wong,[16] Mengsong Li,[16] Voleak Choeurng,[16] Anjali Vaze,[16] Divya Samineni,[16] Teiko Sumiyoshi,[16] James Cooper,[16] Simon Harrison[17]

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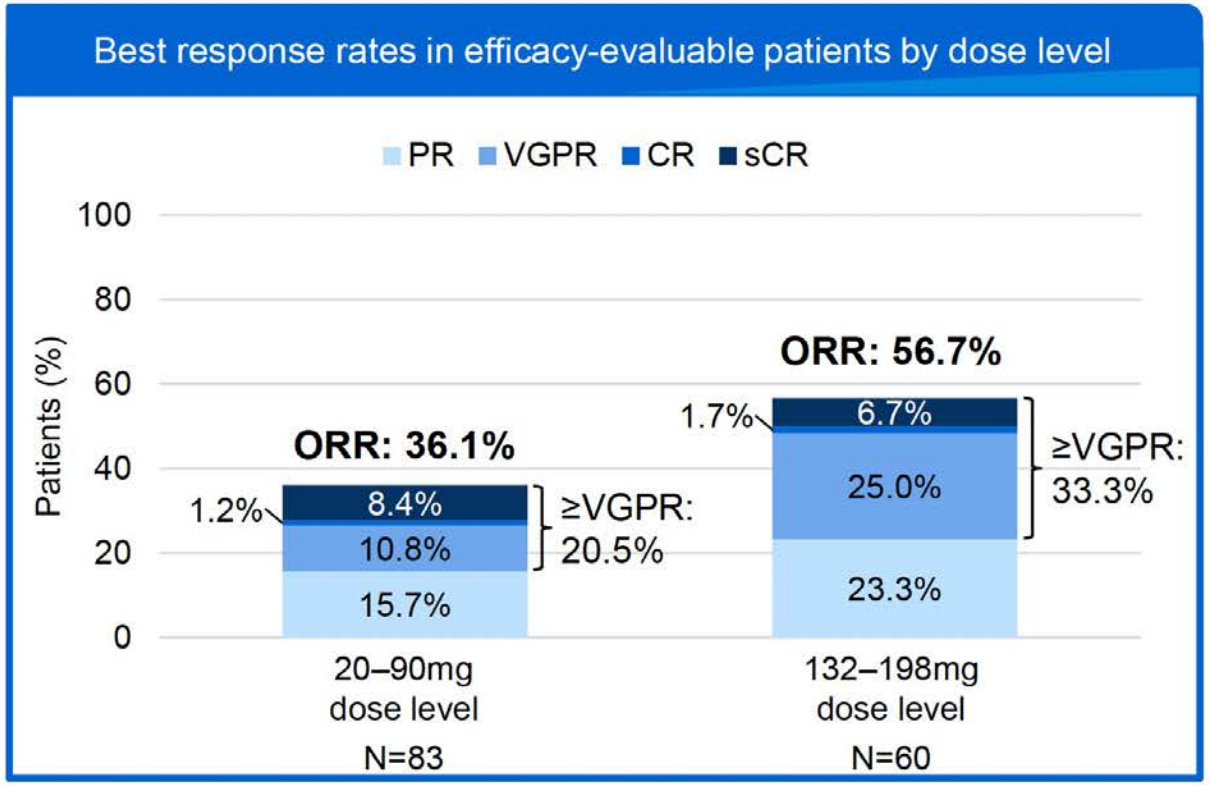
Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition

Response to Cevostamab

- Response observed at the 20mg target dose level and above (N=143 patients)
- ORR increases with target dose
  - ORR in C1 single step-up expansion (3.6/90mg): 29.0%
  - ORR in C1 double step-up expansion (0.3/3.6/160mg): 54.8%
- Response occurs early
  - median time to first response: 1.0 mo (range: 0.7–5.9)
- Response deepens over time
  - median time to best response: 2.1 mo (range: 0.7–11.4)
- MRD negativity by NGS ($<10^{-5}$) detected in 7/10 evaluable patients with ≥VGPR



- Cevostamab was efficacious in patients with heavily pre-treated RRMM. ORR increased with target dose.

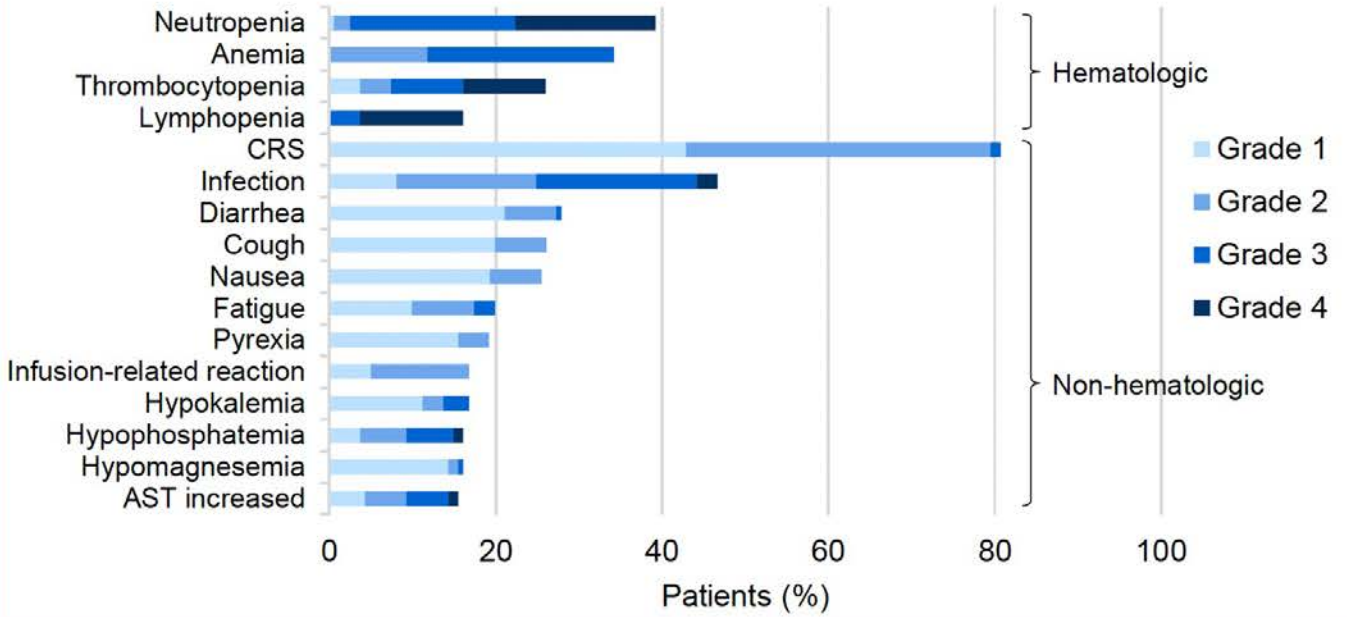
Trudel S et al. ASH 2021;Abstract 157.

Cevostamab Adverse Events Summary

Median time on study: 8.8 months (range: 0.2–37.2)

N (%) of patients	N=161
AE (any Grade)	160 (99.4)
Grade 3	53 (32.9)
Grade 4	46 (28.6)
Serious AE (any Grade)	96 (59.6)
Grade 5 (fatal) AE*†	6 (3.7)
Cevostamab related†	1 (0.6)
AE leading to treatment discontinuation	21 (13.0)
Cevostamab related	7 (4.3)

Common (≥15%) hematologic and non-hematologic AEs in all patients by Grade‡



- Cevostamab had a manageable safety profile. Cevostamab-related AEs leading to discontinuation were uncommon.

Trudel S et al. ASH 2021;Abstract 157.

#84

Final Overall Survival Results from BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination With Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma

ASH 2021;Abstract 84.

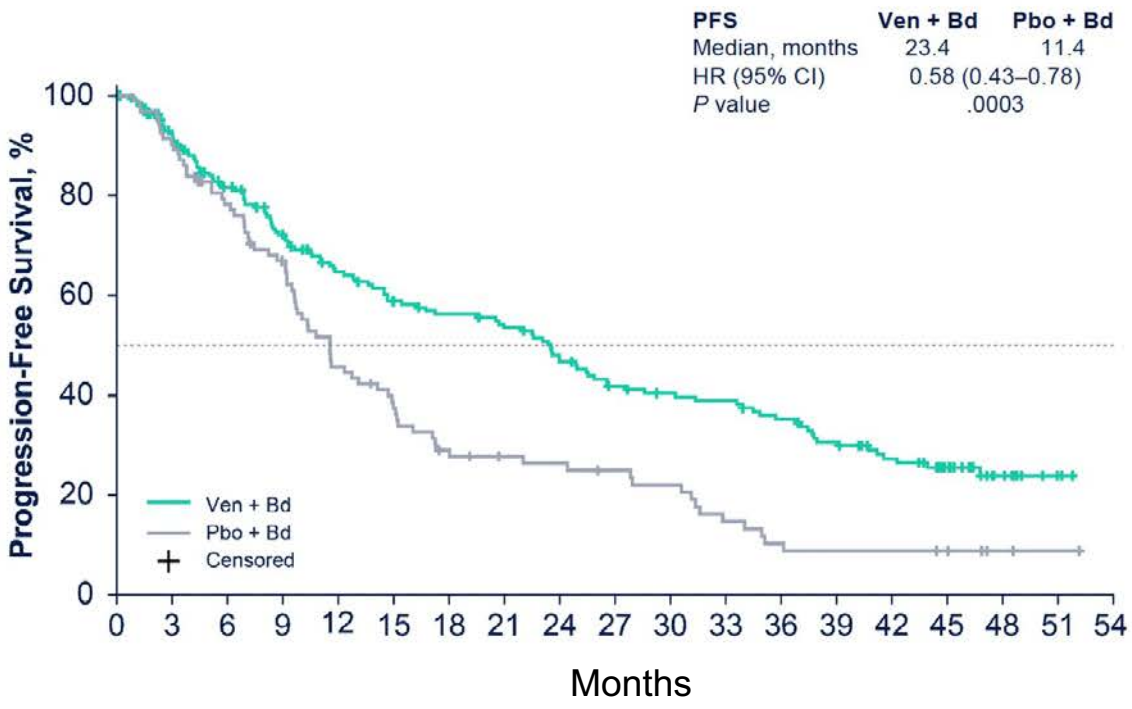
Shaji K. Kumar,[1] Simon J. Harrison,[2] Michele Cavo,[3] Javier de la Rubia,[4] Rakesh Popat,[5] Cristina Gasparetto,[6] Vania Hungria,[7] Hans Salwender,[8] Kenshi Suzuki,[9] Inho Kim,[10] Maika Onishi,[11] Grace Ku,[11] Rajvineeth Pothacamury,[12] Vasudha Sehgal,[12] Abdullah Masud,[12] Jeremy A. Ross,[12] Edyta Dobkowska,[13] and Philippe Moreau[14]

[1]Mayo Clinic, Rochester, MN, USA; [2]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Victoria, Australia; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Seragnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [4]Hematology Service Hospital La Fe and School of Medicine and Dentistry, Catholic University of Valencia, Valencia, Spain; [5]University College Hospitals, London, United Kingdom; [6]Duke University Medical Center, Durham, NC, USA; [7]Clinica São Germano, São Paulo, Brazil; [8]Asklepios Tumorzentrum Hamburg, AK Altona and AK St Georg, Hamburg, Germany; [9]Japanese Red Cross Medical Center, Tokyo, Japan; [10]Seoul National University, Seoul, South Korea; [11]Genentech, Inc, South San Francisco, CA, USA; [12]AbbVie, Inc, North Chicago, IL, USA; [13]Pharmacyclics Switzerland GmbH, An AbbVie Company, Schaffhausen, Switzerland; [14]University Hospital, Nantes, France

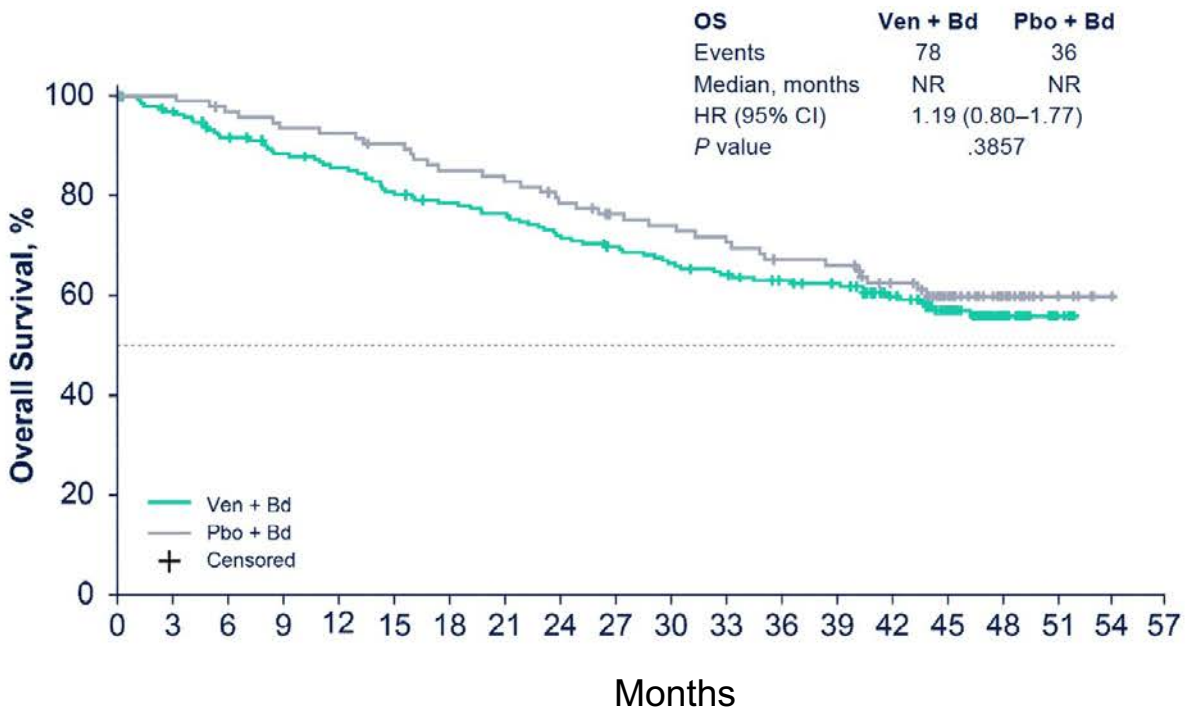
American Society of Hematology Annual Meeting, December 11–14, 2021, Atlanta, Georgia

BELLINI: Investigator-Assessed PFS and OS in All Patients (Median Follow-Up: 45.6 Months)

Investigator-Assessed PFS in All Patients

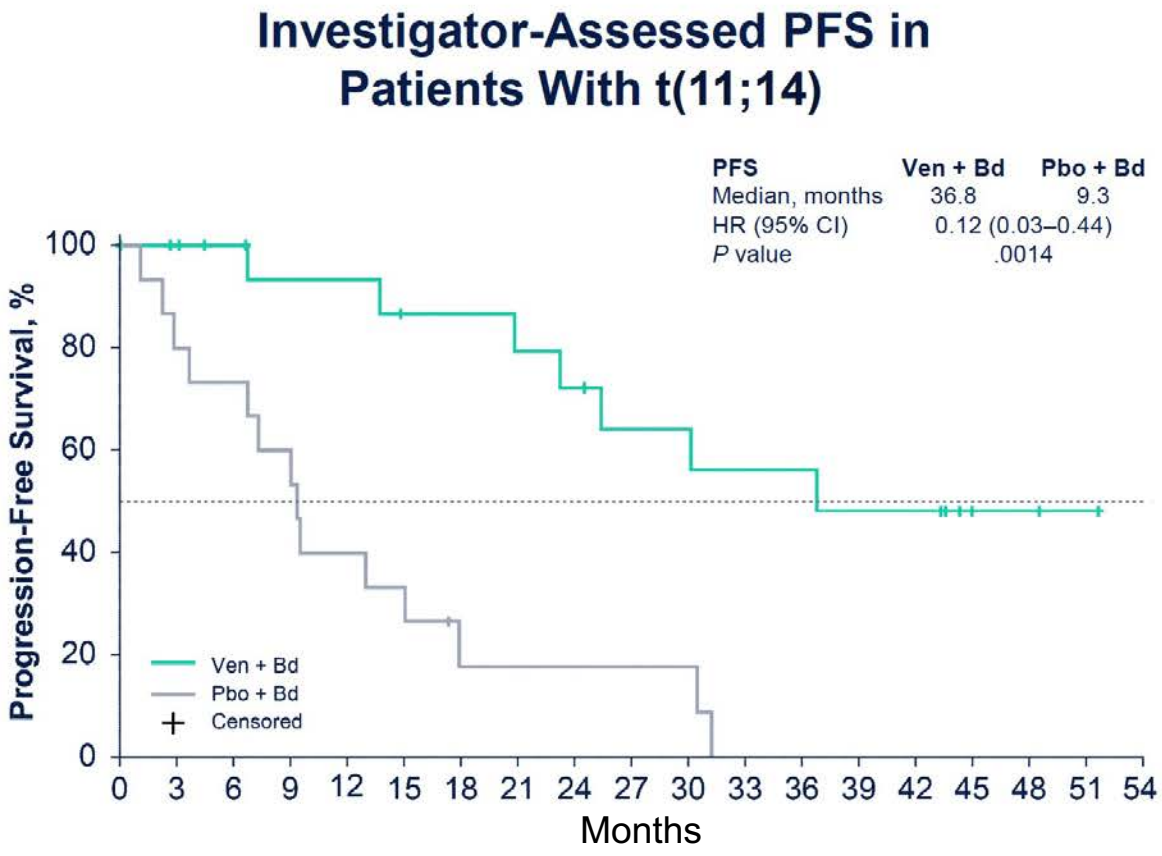


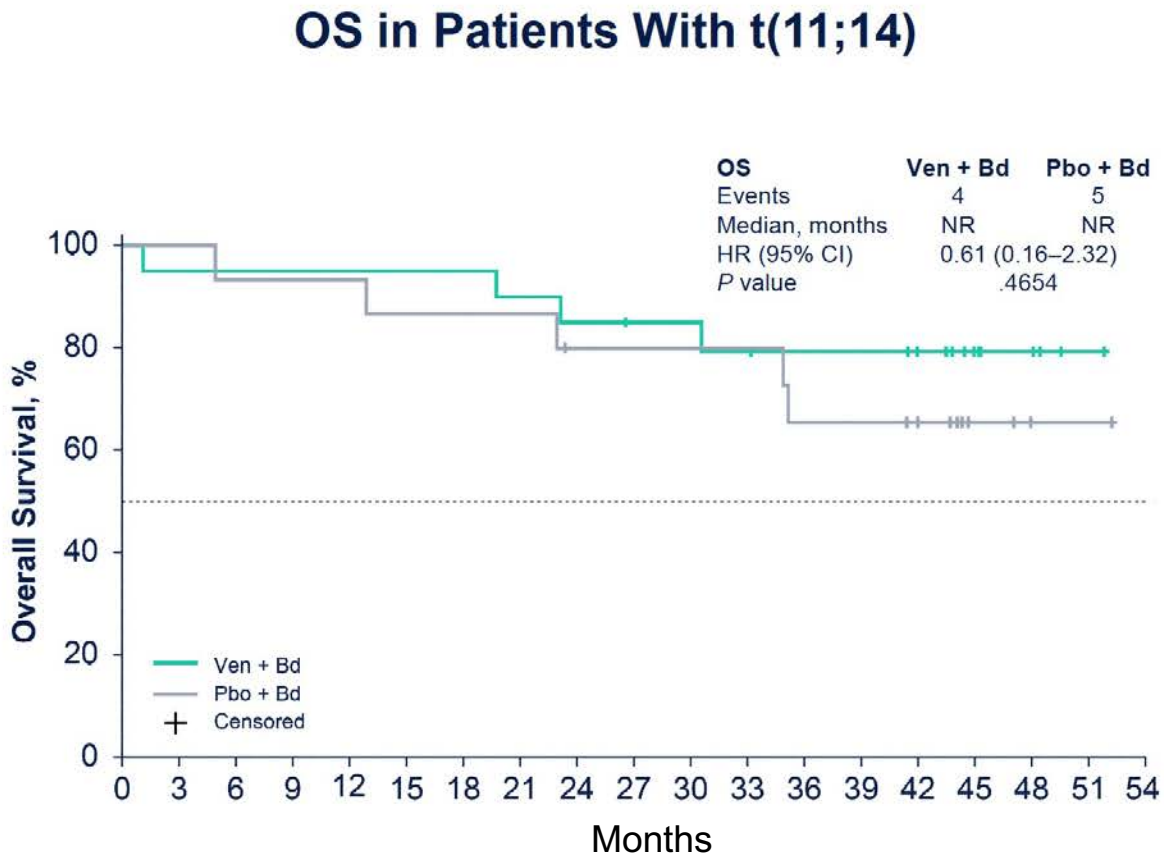
OS in All Patients



Kumar SK et al. ASH 2021;Abstract 84.

BELLINI: Updated PFS and OS in Patients with t(11;14)

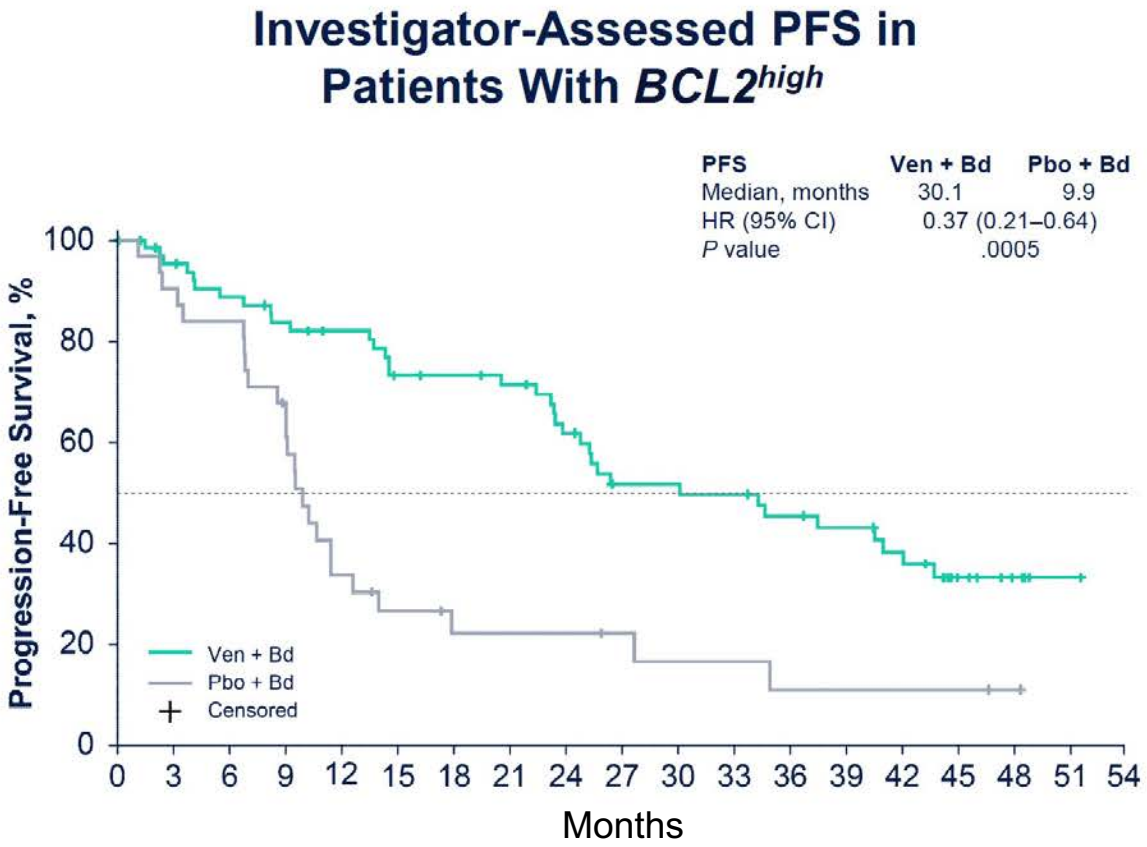


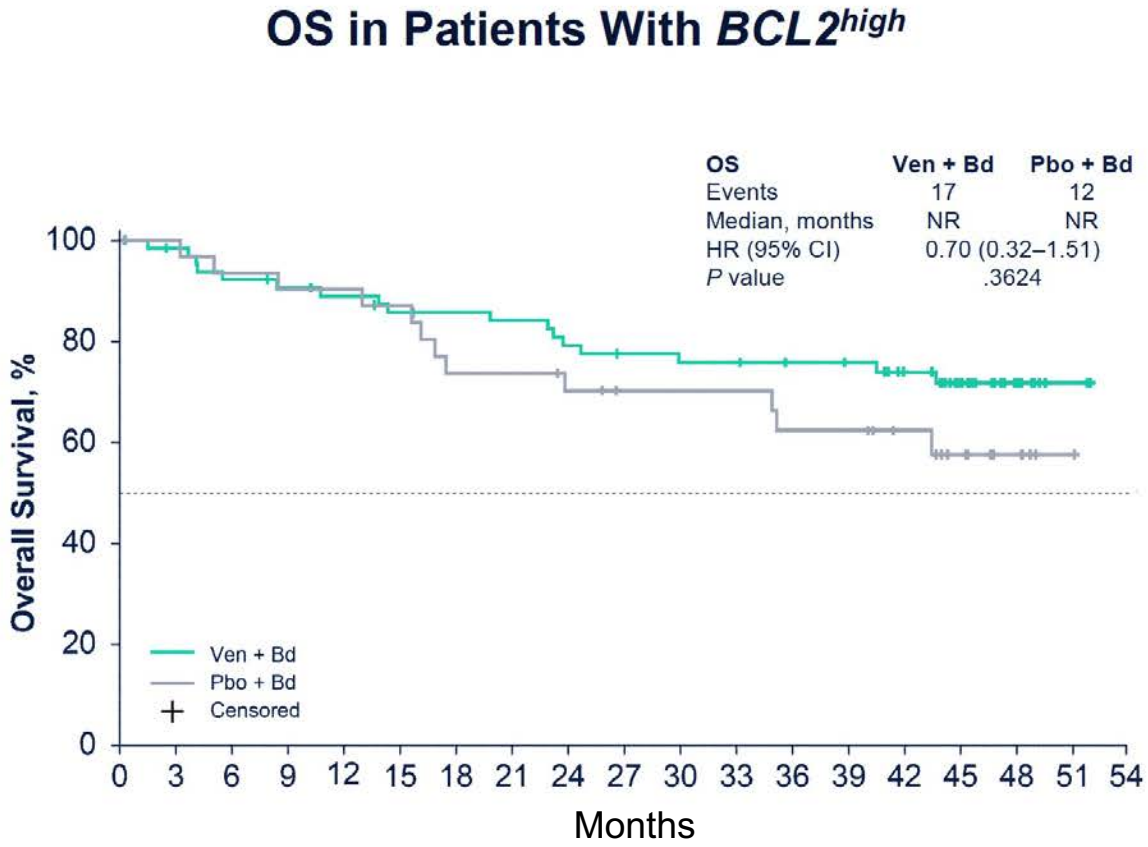


Kumar SK et al. ASH 2021;Abstract 84.

RTP RESEARCH TO PRACTICE

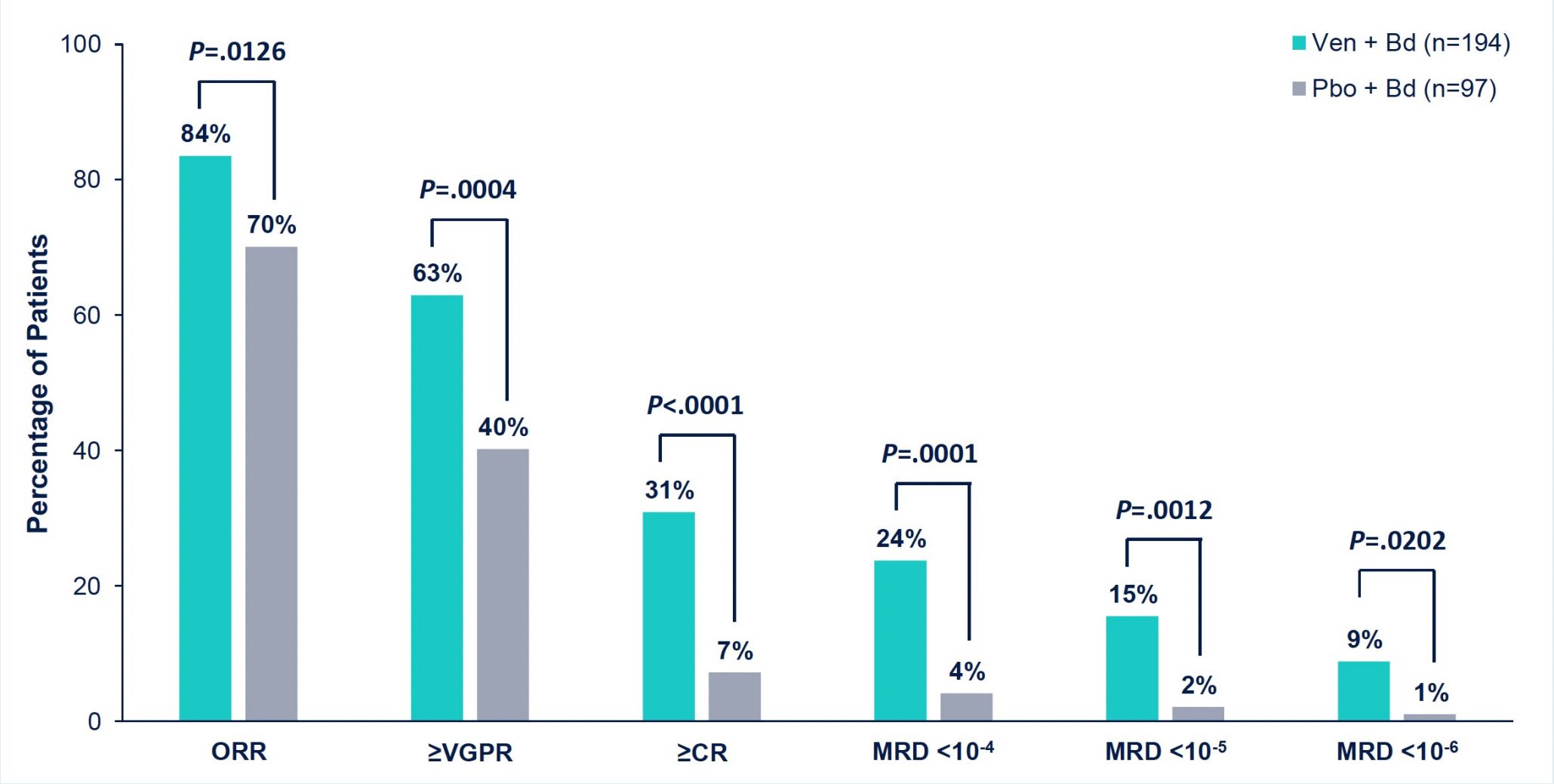
BELLINI: Updated PFS and OS in Patients with High BCL2 Expression





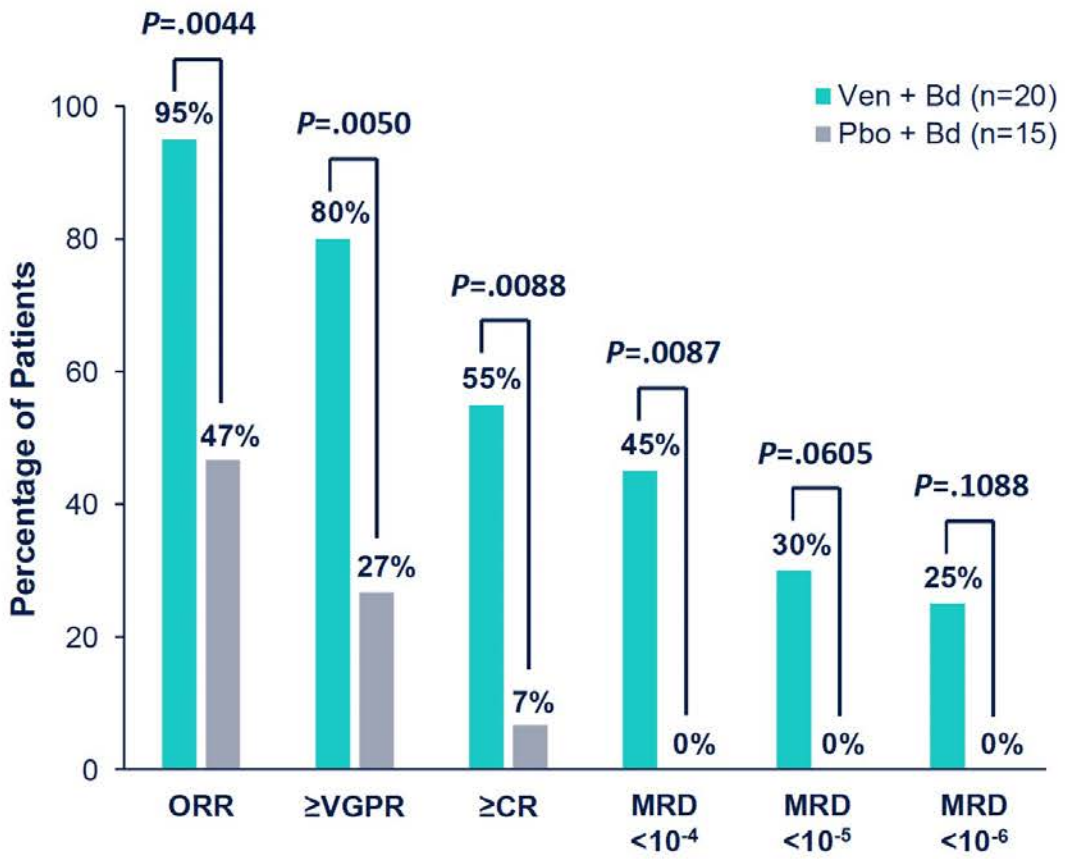
Kumar SK et al. ASH 2021;Abstract 84.

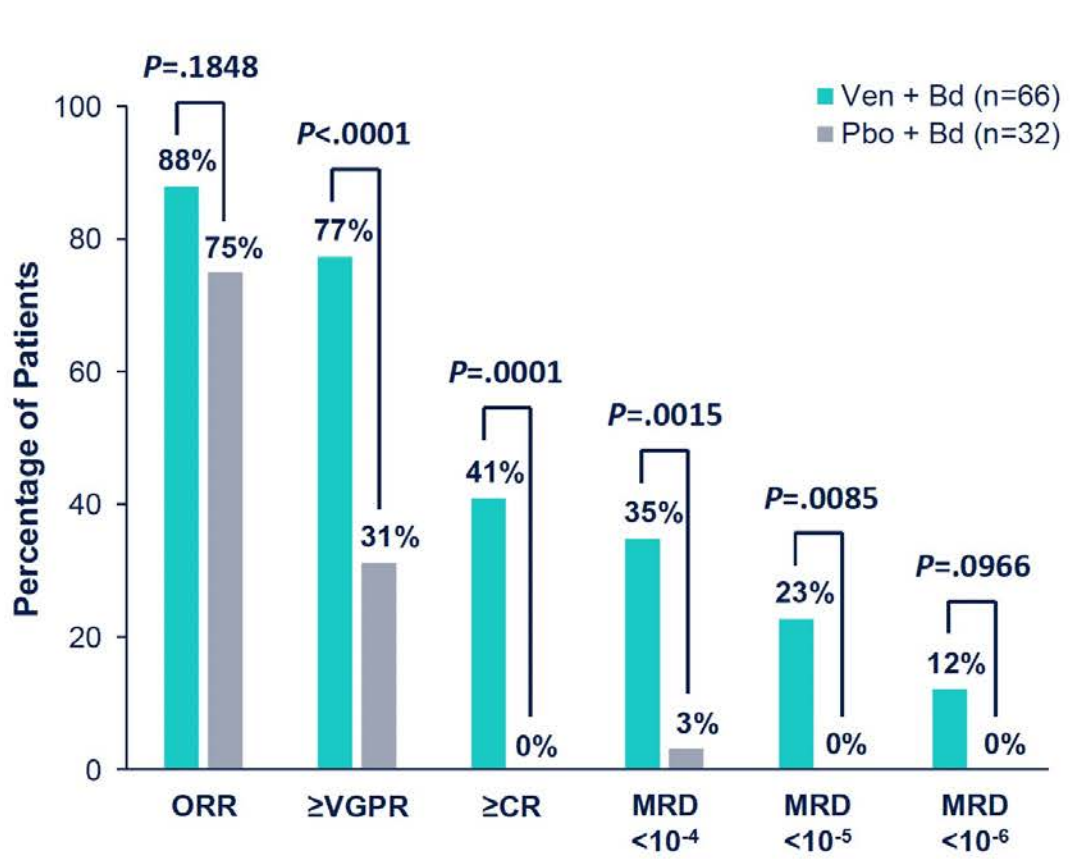
BELLINI: Investigator-Assessed Response Rates and MRD Negativity Rates in All Patients



Kumar SK et al. ASH 2021;Abstract 84.

BELLINI: Response and MRD Negativity Rates in Patients with t(11;14) or High BCL2 Expression





Kumar SK et al. ASH 2021;Abstract 84.

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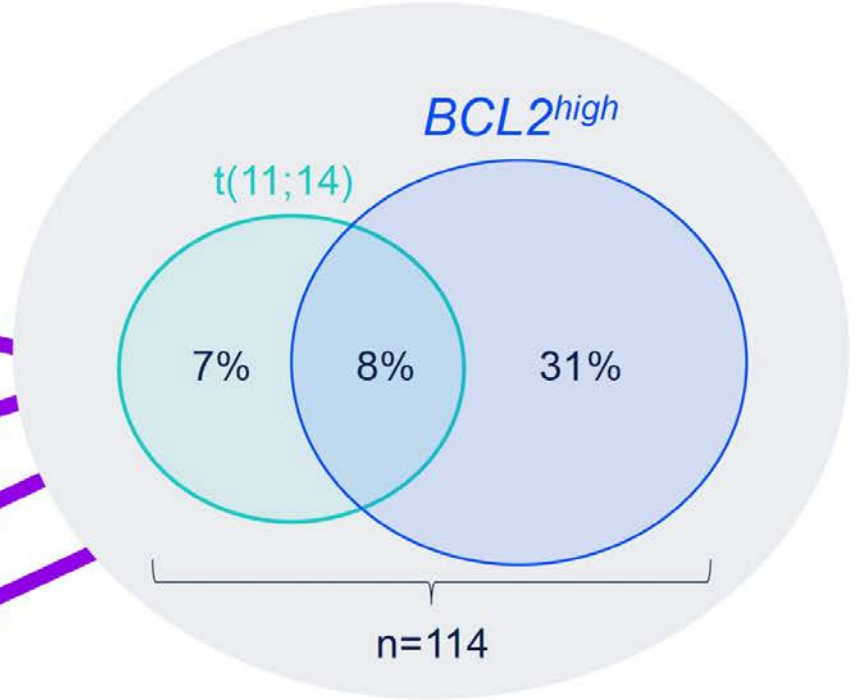
BELLINI: PFS Improvements in Patients with t(11;14) or High BCL2 Expression

Hazard Ratios for PFS and OS by *BCL2* Expression and t(11;14)

	Patients		PFS		OS	
	Ven + Bd (n)	Pbo + Bd (n)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
t(11;14) or *BCL2*^{high}	74	40	0.32 (0.20–0.53)	<.0001	0.82 (0.40–1.70)	NS
t(11;14)	20	15	0.12 (0.03–0.44)	.0014	0.61 (0.16–2.32)	NS
BCL2^{high}	66	32	0.37 (0.21–0.64)	.0005	0.70 (0.32–1.51)	NS
Non-t(11;14) and *BCL2*^{high}	51	24	0.48 (0.26–0.90)	.0215	0.86 (0.35–2.12)	NS

BELLINI Biomarker Subgroups[a] (n=240)



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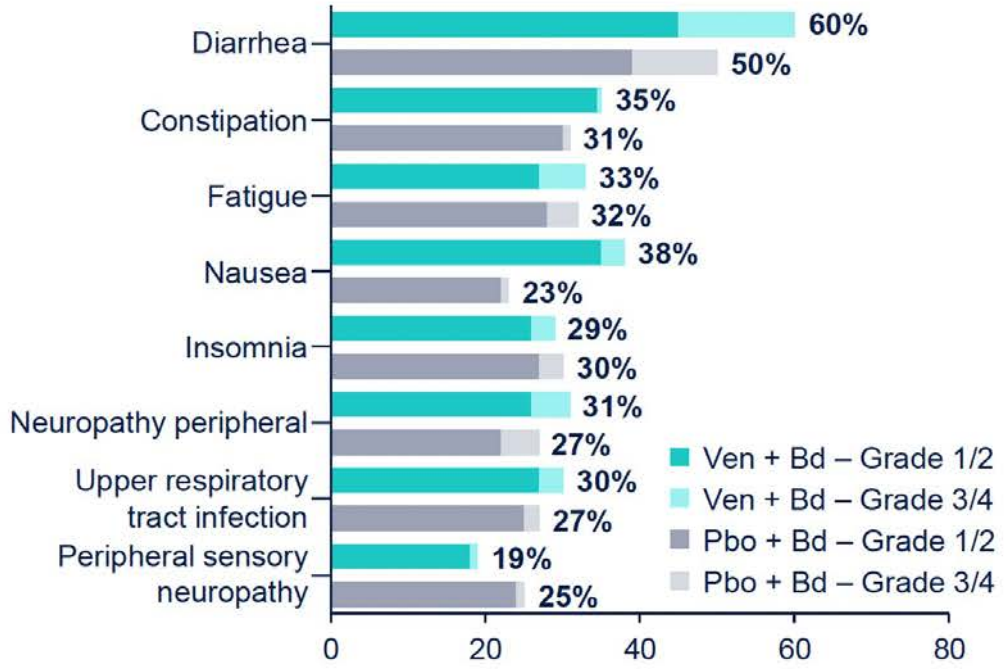
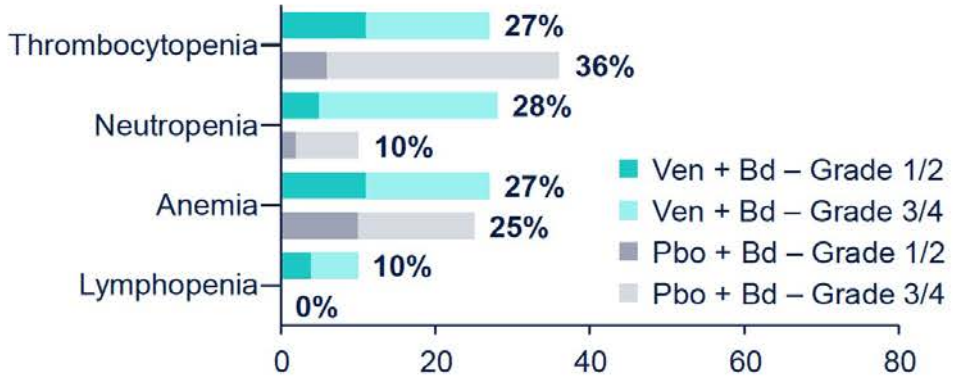
BELLINI: Adverse Event Rates

AEs in ≥25% of Patients in Either Treatment Arm

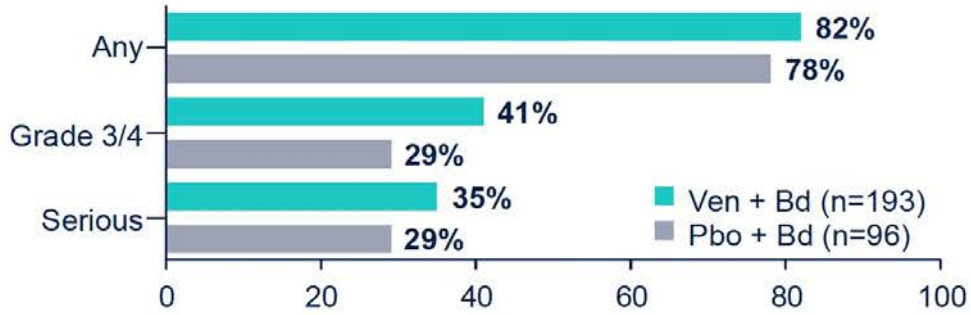


- Overall, 51 patients (26%) in the Ven + Bd arm and 11 patients (11%) in the Pbo + Bd arm discontinued Ven or Pbo due to AEs

Most Common Hematologic AEs



Infections



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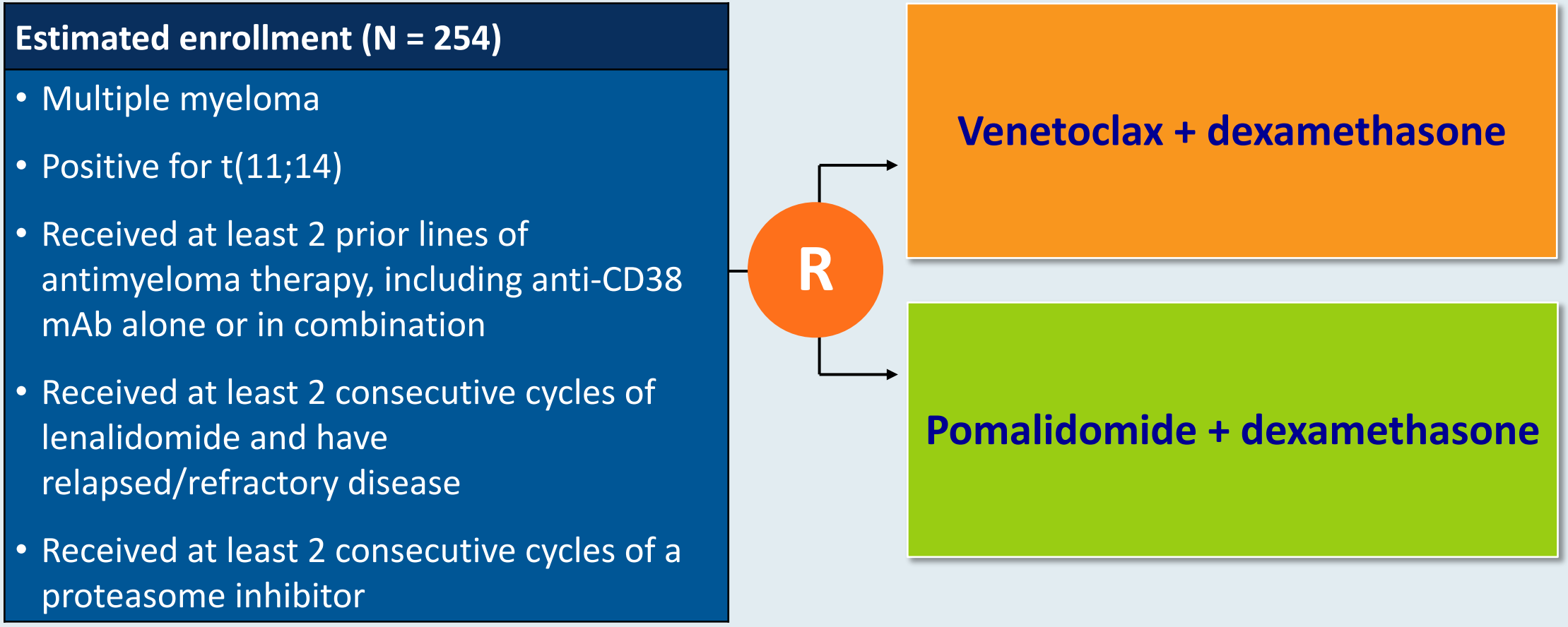
BELLINI: Treatment-Emergent Deaths

Deaths

n (%)	Ven + Bd (n=193)	Pbo + Bd (n=96)
All deaths	77 (40)	36 (38)
Treatment-emergent deaths[a]	14 (7)[b]	2 (2)
Any AE	12 (6)	1 (1)
Deaths occurring while still receiving study drug	0	0
Infection	9 (5)	0
Progressive disease	2 (1)	1 (1)
Non–treatment-emergent deaths	63 (33)	34 (35)

Kumar SK et al. ASH 2021;Abstract 84.

Ongoing Phase III M13-494 Study Design

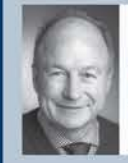


Primary endpoint: Progression-free survival

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

Faculty Survey

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

 Dr Fonseca	Efficacy is similar with both	 Dr Lonial	Efficacy is similar with both
 Dr Kumar	Efficacy is similar with both	 Dr Mikhael	Efficacy is similar with both
 Dr Landgren	Efficacy is similar with both	 Dr Richardson	BCMA-targeted bispecific antibodies are more efficacious*

*More experience with BCMA-targeted bispecific antibodies, and non-BCMA approaches may be as efficacious, but my impression is BCMA-targeted is more active.

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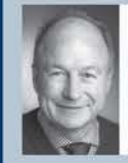
Based on your personal clinical experience and knowledge of available data, how would you compare the tolerability of BCMA-targeted bispecific antibodies (eg, teclistamab) to that of non-BCMA-targeted bispecific antibodies (eg, talquetamab) for patients with R/R MM?

 Dr Fonseca	Tolerability is similar with both	 Dr Lonial	BCMA-targeted bispecific antibodies are more tolerable
 Dr Kumar	Tolerability is similar with both	 Dr Mikhael	BCMA-targeted bispecific antibodies are more tolerable
 Dr Landgren	Tolerability is similar with both	 Dr Richardson	Tolerability is similar with both

RTP RESEARCH TO PRACTICE

Challenging Cases from Junior Investigators — The Application of Available and Emerging Clinical Research in the Care of Patients with Chronic Lymphocytic Leukemia

A CE/NCPD-Accredited Virtual Event in Partnership with the 2022 Pan Pacific Lymphoma Conference

Wednesday, October 12, 2022
5:00 PM – 6:30 PM ET

Faculty

Danielle Brander, MD
Matthew S Davids, MD, MMSc
Anthony R Mato, MD, MSCE
William G Wierda, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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