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

Multiple Myeloma

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

Faculty

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

Moderator

Neil Love, MD

RTP Year in Review 2023

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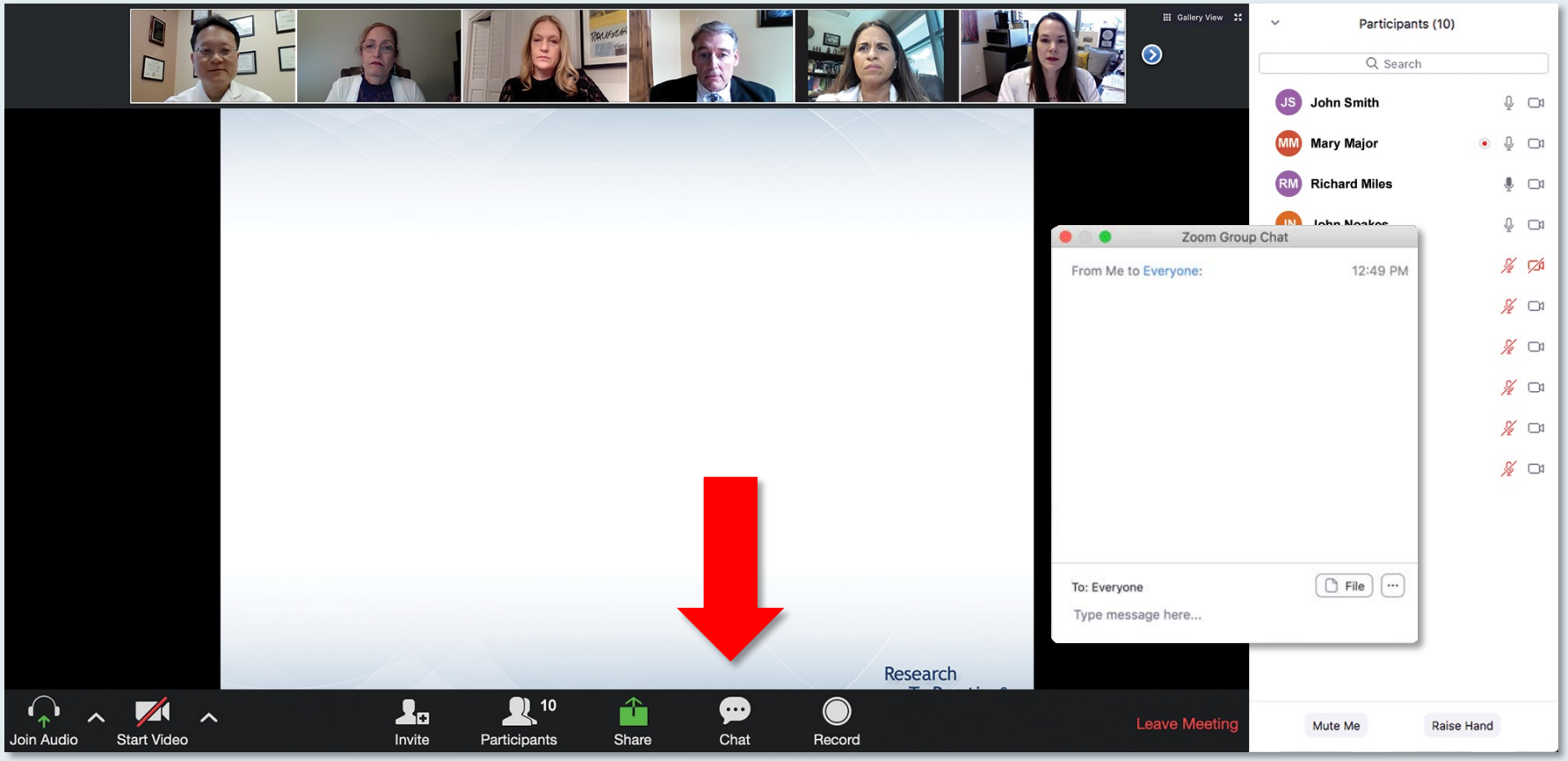
Joseph Mikhael, MD, MEd
Professor, Applied Cancer Research and Drug Discovery
Translational Genomics Research Institute (TGen)
City of Hope Cancer Center
Chief Medical Officer, International Myeloma Foundation
Phoenix, Arizona

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Ajay K Nooka, MD, MPH
Professor, Department of Hematology and Medical Oncology
Medical Director, Winship Data and Technology
Applications Shared Resource
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

We Encourage Clinicians in Practice to Submit Questions



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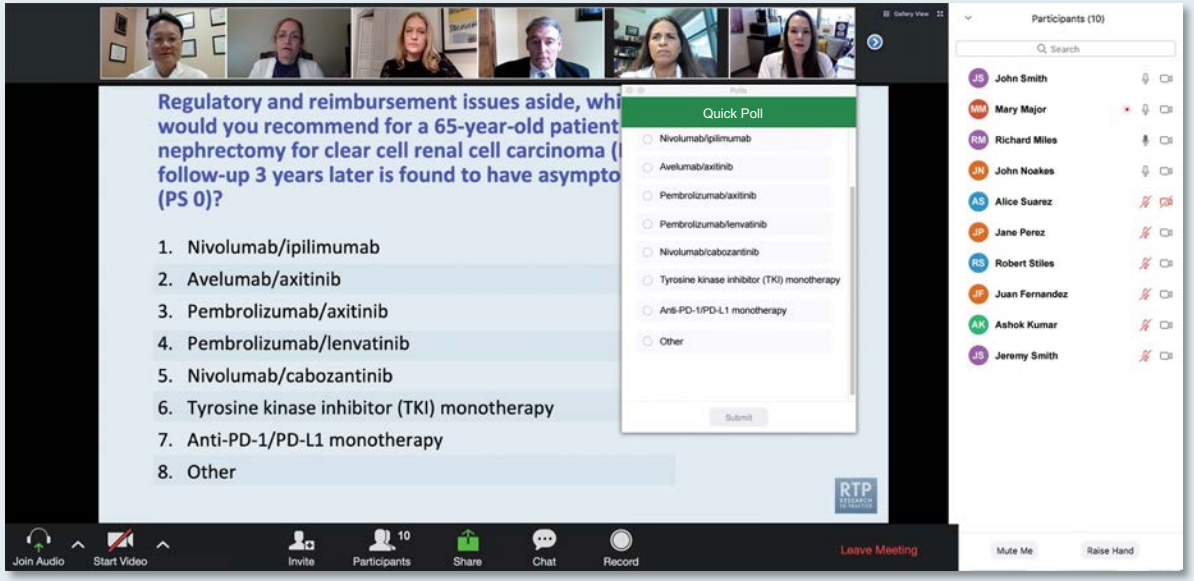

ONCOLOGY TODAY

WITH DR NEIL LOVE

BCMA-Directed Therapies for Multiple Myeloma

DR AMRITA KRISHNAN
CITY OF HOPE CANCER CENTER

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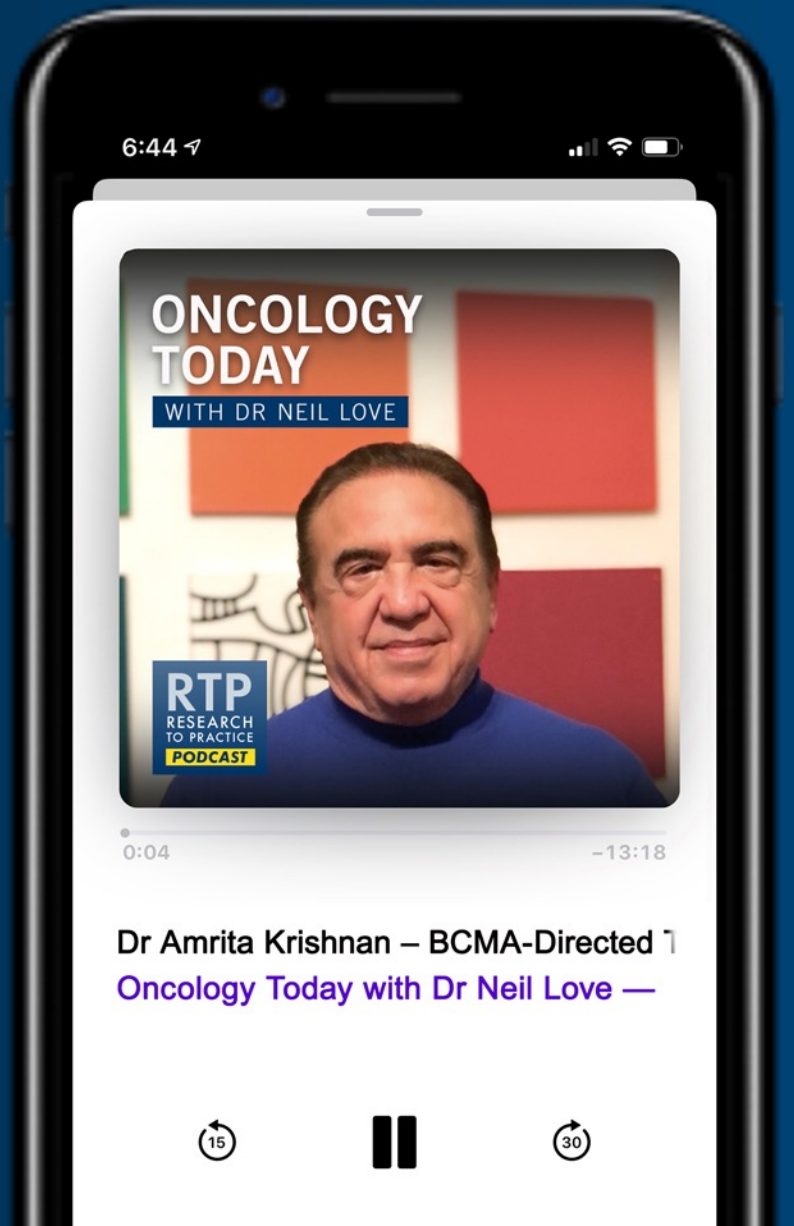

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Dr Love — Disclosures

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Dr Nooka — Disclosures

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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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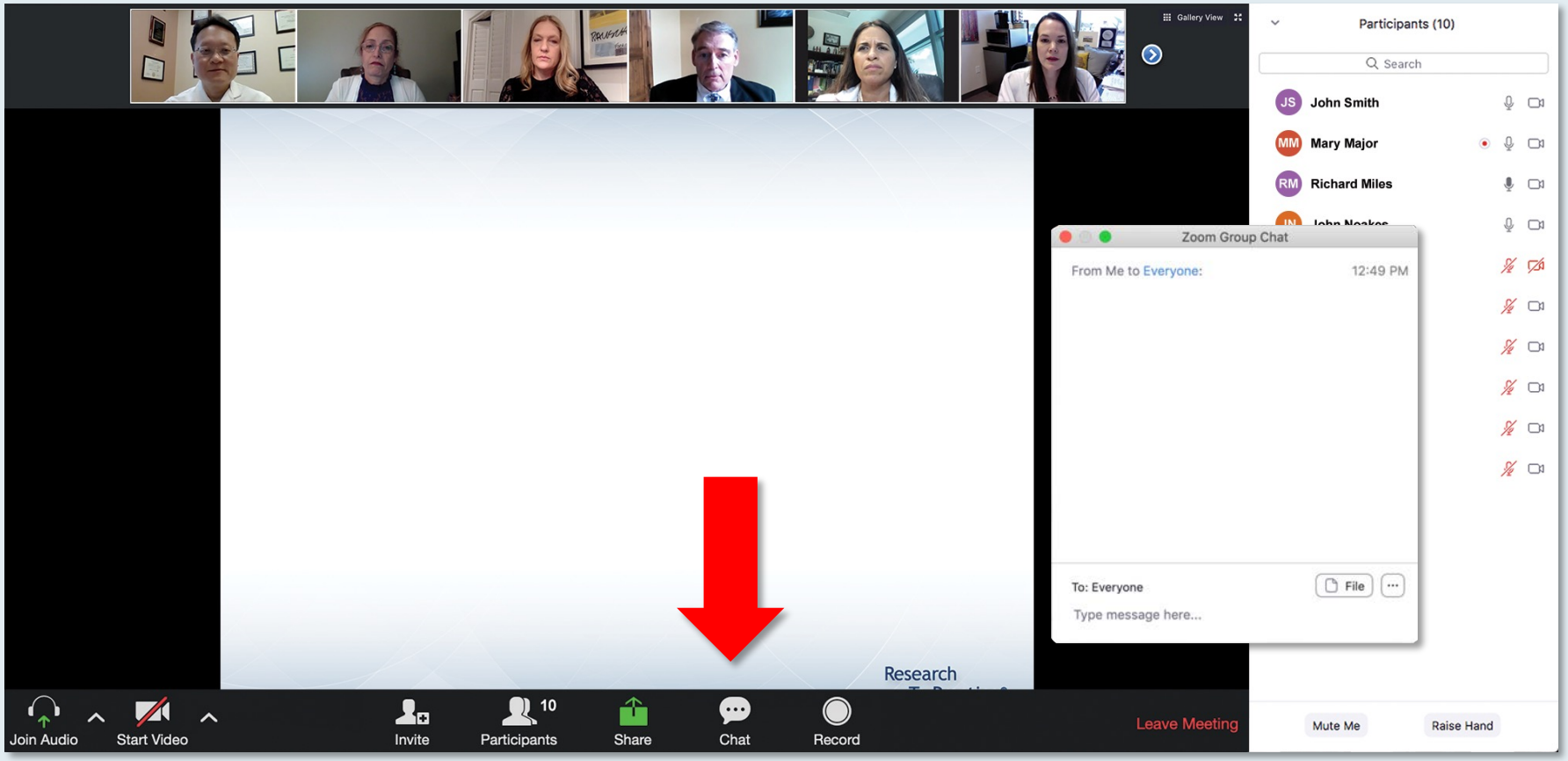

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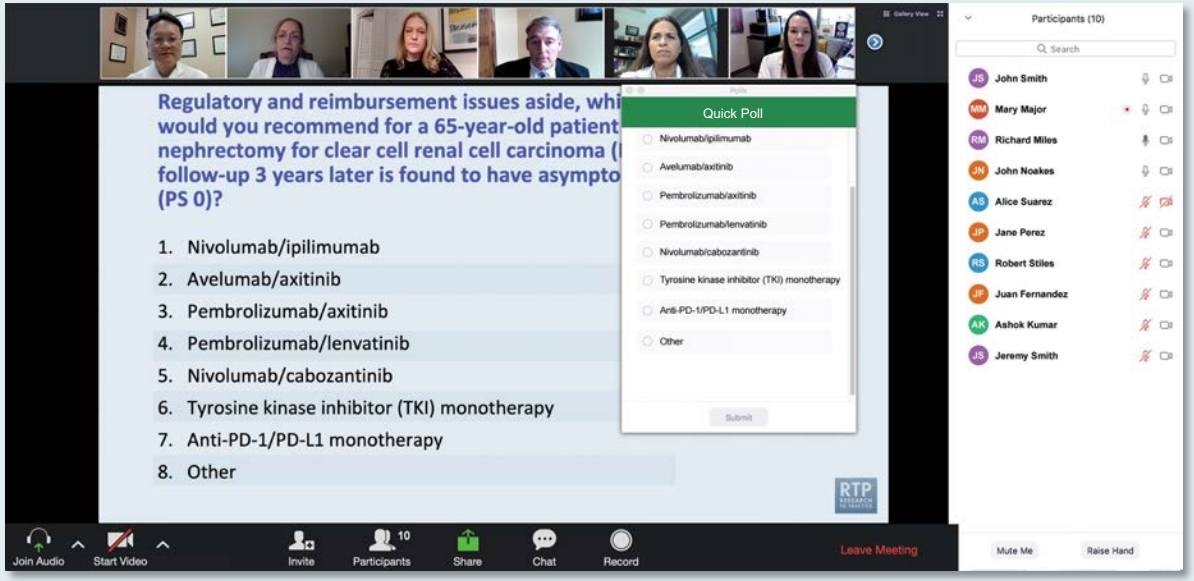

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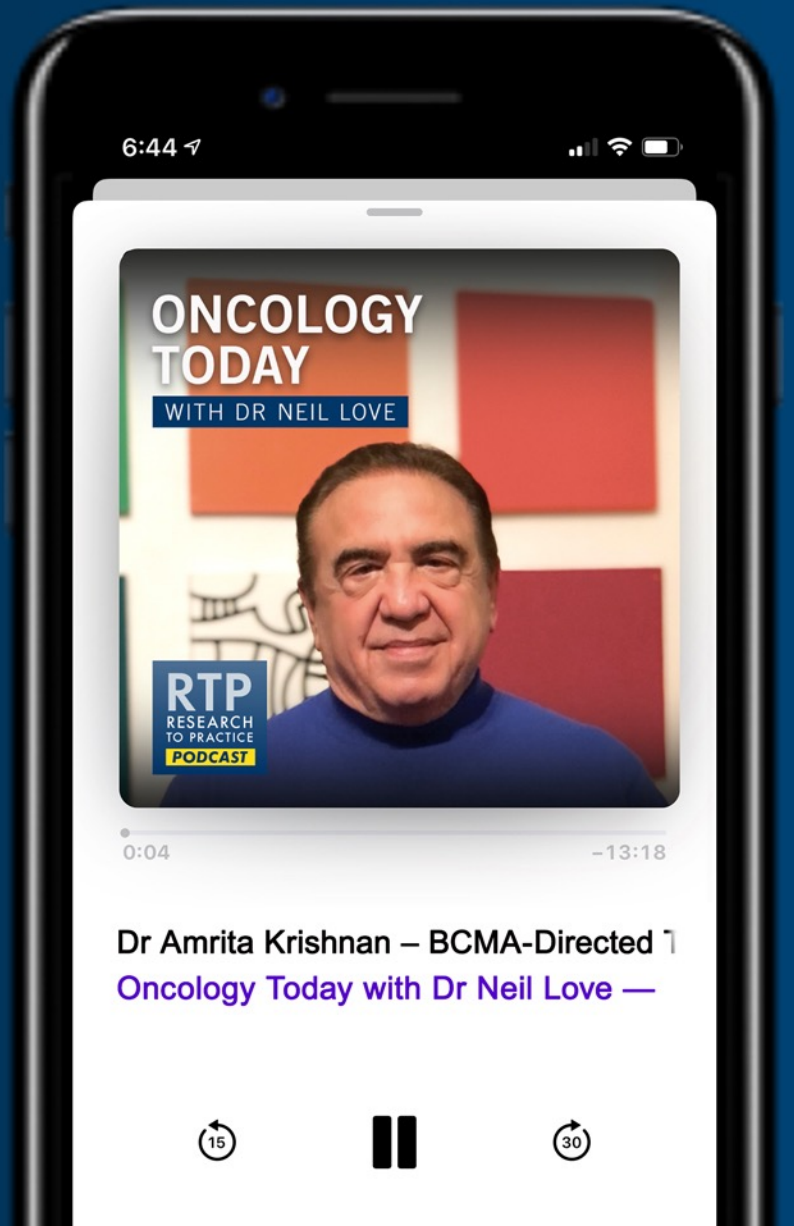

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Optimizing the Current Management of Multiple Myeloma

Research To Practice Year End

December 2022

Joseph Mikhael, MD, MEd, FRCPC
Chief Medical Officer, International Myeloma Foundation
Professor, Translational Genomics Research Institute (TGen)
City of Hope Cancer Center

Chimeric Antigen Receptor T-Cell Therapy, Bispecific Antibodies and Other Novel Approaches

Ajay K Nooka, MD, MPH
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Medical Director
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RTP Year in Review 2023

Key Data Sets

Joseph Mikhael, MD, MEd

- Richardson PG et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med* 2022;387(2):132-47.
- Sborov DW et al. Daratumumab (dara) + lenalidomide, bortezomib, and dexamethasone (RVd) in patients with transplant-eligible newly diagnosed multiple myeloma (NDMM): Final analysis of GRIFFIN. International Myeloma Society Annual Meeting 2022;Abstract OAB-057.
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Key Data Sets

Joseph Mikhael, MD, MEd (continued)

- Weisel K et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in patients with high-risk newly diagnosed multiple myeloma: Planned interim analysis of the GMMG-Concept trial. ASH 2022;Abstract 759.
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- Usmani SZ et al. Final analysis of the phase III non-inferiority COLUMBA study of subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma. *Haematologica* 2022;107(10):2408-17.

Key Data Sets

Joseph Mikhael, MD, MEd (continued)

- Quach H et al. Subcutaneous isatuximab administration by an on-body delivery system (OBDS) in combination with pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma: Phase 1b expansion study results. ASH 2022;Abstract 1923.
- Gasparetto C et al. Once weekly selinexor, carfilzomib and dexamethasone in carfilzomib non-refractory multiple myeloma patients. *Br J Cancer* 2022;126(5):718-25.
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Ajay K Nooka, MD, MPH

- Paiva B et al. Early and sustained undetectable measurable residual disease (MRD) after idecabtagene vicleucel (ide-cel) defines a subset of multiple myeloma (MM) patients in KarMMa achieving prolonged survival. ASH 2022;Abstract 868.
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Key Data Sets

Ajay K Nooka, MD, MPH (continued)

- Einsele H et al. Biological correlative analyses and updated clinical data of ciltacabtagene autoleucel (cilta-cel), a BCMA-directed CAR-T cell therapy, in lenalidomide (len)-refractory patients (pts) with progressive multiple myeloma (MM) after 1–3 prior lines of therapy (LOT): CARTITUDE-2, cohort A. ASCO 2022;Abstract 8020.
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- D'Souza A et al. A Phase I first-in-human study of ABBV-383, a B-cell maturation antigen × CD3 bispecific T-cell redirecting antibody, in patients with relapsed/refractory multiple myeloma. *J Clin Oncol* 2022;40(31):3576-86.

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- Wong SW et al. Alnuctamab (BMS-986349; CC-93269), a B-cell maturation antigen (BCMA) x CD3 2+1 T cell engager (TCE), in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Results from a Phase 1 first-in-human clinical study. ASH 2022;Abstract 162.
- Chari A et al. Talquetamab, a G protein-coupled receptor family C group 5 member D x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): Phase 1/2 results from MonumenTAL-1. ASH 2022;Abstract 157.
- Bahlis N et al. An updated safety and efficacy analysis of venetoclax plus daratumumab and dexamethasone in an expansion cohort of a Phase 1/2 study of patients with t(11;14) relapsed/refractory multiple myeloma. ASH 2022;Abstract 3232.
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- Richardson PG et al. Mezigdomide (CC-92480), a potent, novel cereblon E3 ligase modulator (CELMoD), combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Preliminary results from the dose-expansion phase of the CC-92480-MM-001 trial. ASH 2022;Abstract 568.

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Withdrawal of US Marketing Authorization for Belantamab Mafodotin-blmf for Relapsed/Refractory Multiple Myeloma

Press Release: November 22, 2022

"Today [the manufacturer] has initiated the process for withdrawal of the US marketing authorisation for belantamab mafodotin-blmf following the request of the US Food and Drug Administration (FDA). This request was based on the previously announced outcome of the DREAMM-3 Phase III confirmatory trial, which did not meet the requirements of the FDA Accelerated Approval regulations. Belantamab mafodotin is a monotherapy treatment for adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

As part of the company's efforts to ensure physicians and patients are supported during this important time, patients already enrolled in the belantamab mafodotin Risk Evaluation and Mitigation Strategy (REMS) programme will have the option to enroll in a compassionate use programme to continue to access treatment.

[The company] continues to believe, based on the totality of data available from the DREAMM (DRiving Excellence in Approaches to Multiple Myeloma) development programme, that the benefit-risk profile of belantamab mafodotin remains favourable in this hard-to-treat RRMM patient population. Patients responding to belantamab mafodotin experienced durable clinical benefit, and safety remains consistent with the known safety profile. Sabine Luik, Chief Medical Officer, said, 'We respect the Agency's approach to the accelerated approval regulations and associated process. Multiple myeloma is a challenging disease, with poor outcomes for patients whose disease has become resistant to standard-of-care treatments. We will continue the DREAMM clinical trial programme and work with the US FDA on a path forward for this important treatment option for patients with multiple myeloma.'"

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

RTP RESEARCH TO PRACTICE

FDA Seeks to Withdraw Melphalan Flufenamide for Relapsed/Refractory Multiple Myeloma

Press Release: December 7, 2022

"The US Food and Drug Administration, FDA, has requested a withdrawal of the US marketing authorization for melphalan flufenamide, also called melflufen. The request is based on the outcome of the confirmatory phase 3 OCEAN study, which demonstrated an ITT overall survival HR of 1.1, but with significant survival result differences for both melflufen and the comparator drug pomalidomide for large relevant patient groups.

'We respect FDA's accelerated approval regulations,' says Jakob Lindberg, [company] CEO. 'Multiple myeloma remains an incurable disease, and the treatment options for patients with triple class refractory disease will ultimately become exhausted. The OCEAN study demonstrated clinical benefit for multiple myeloma patients, in particular for non-transplanted elderly patients where the unmet medical need remains very high.'

Melflufen was granted accelerated approval in the US, on February 26, 2021, and is indicated in combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. At the FDA's request, [the company] stopped marketing melflufen in the US on October 22, 2021, and melflufen is currently not commercially available for US patients."

https://www.prnewswire.com/news-releases/oncopeptides-provides-update-on-pepaxto-us-marketing-authorization-301697061.html

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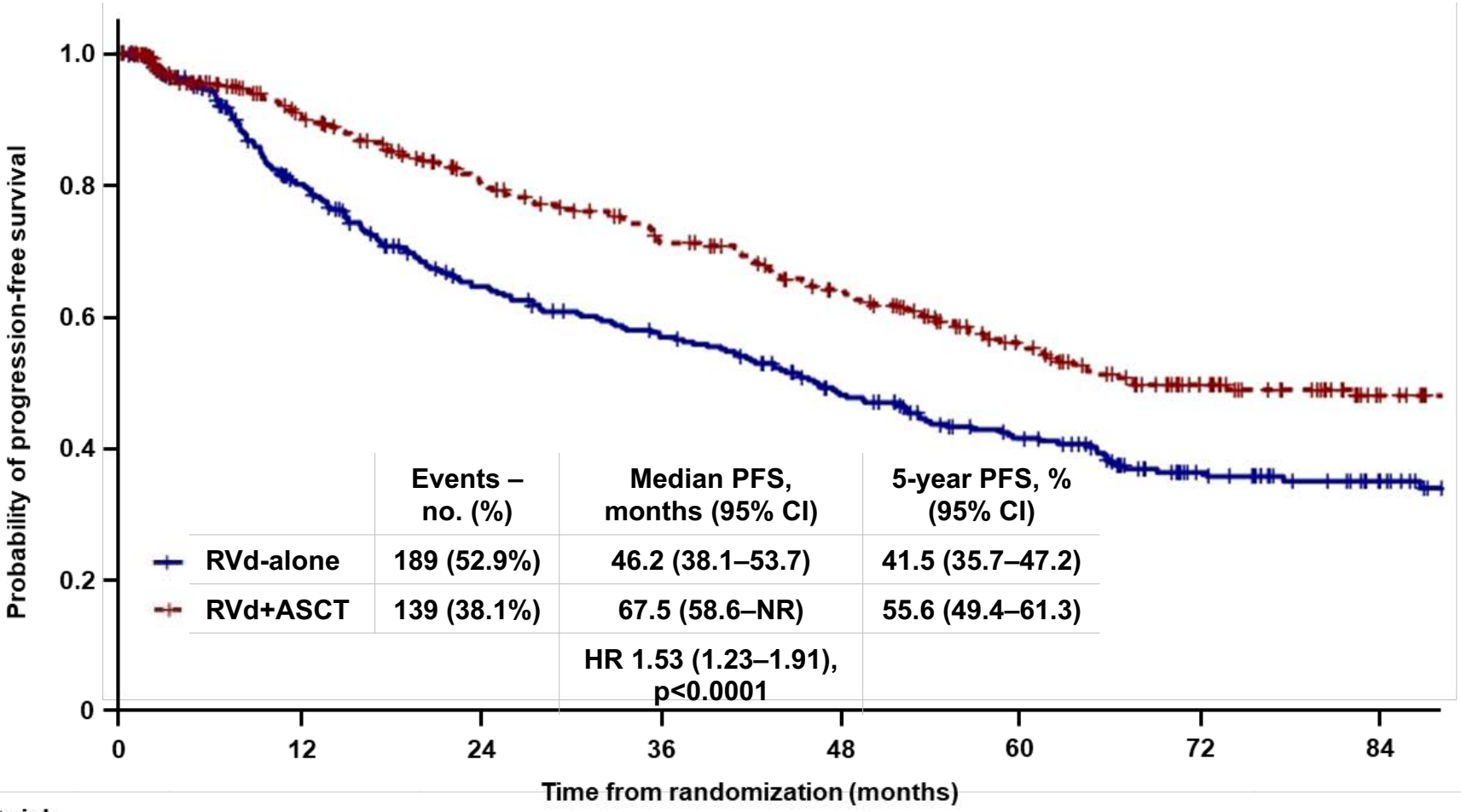
DETERMINATION: Primary endpoint – Progression-free survival

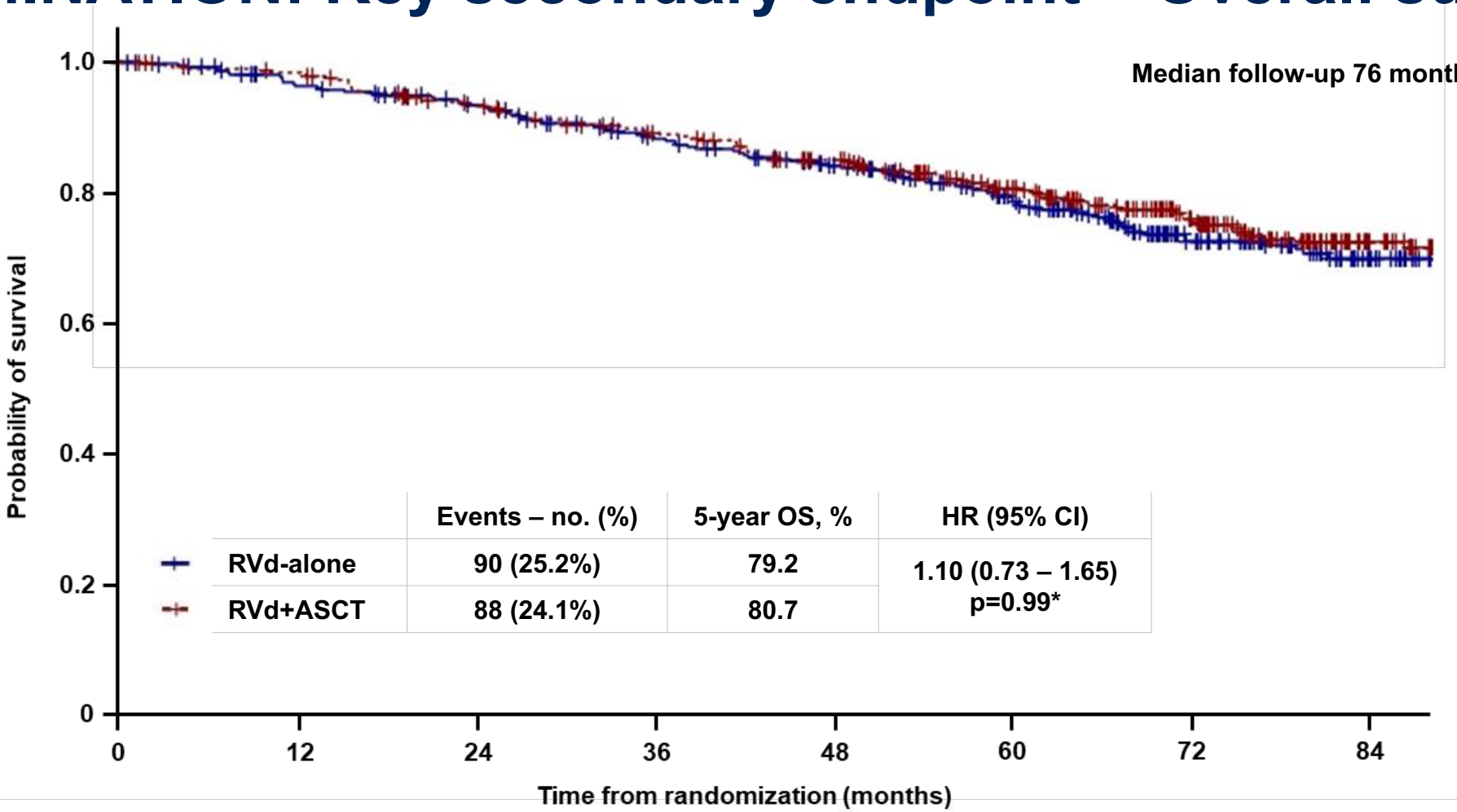


	Events – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cut off: 12/12/21

DETERMINATION: Key secondary endpoint – Overall survival



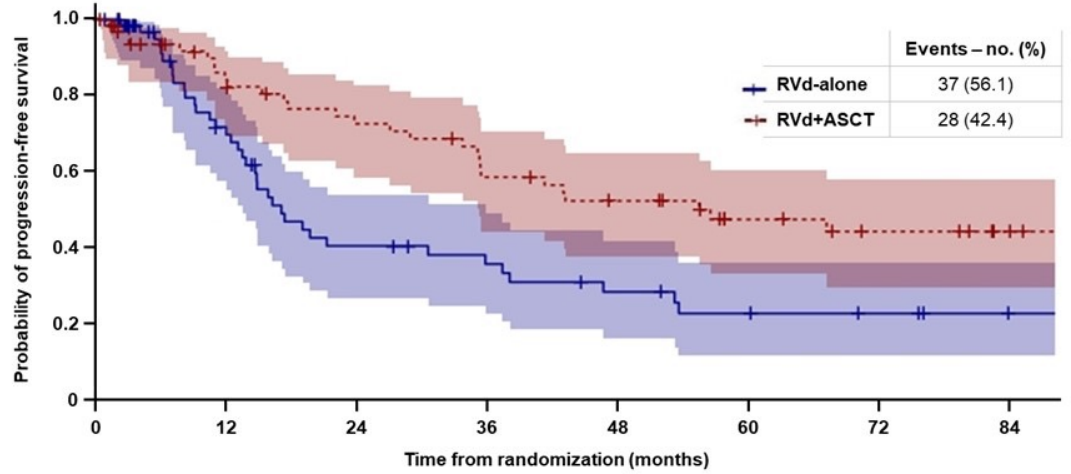
	Events – no. (%)	5-year OS, %	HR (95% CI)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

Patients at risk								
RVd-alone	357	332	313	285	258	214	143	88
RVd+ASCT	365	353	324	300	275	228	165	95

*p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes

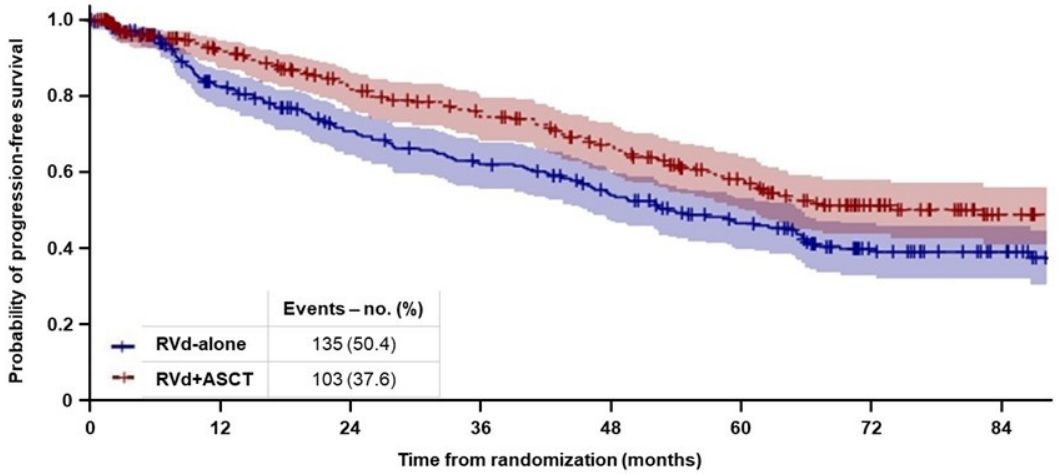
Data cut off:12/12/21

DETERMINATION: PFS by stratification factor – cytogenetic risk



Patients at risk

RVd-alone	66	36	19	16	11	8	6	3
RVd+ASCT	66	45	37	29	24	16	12	8



Patients at risk

RVd-alone	268	197	156	134	109	83	50	34
RVd+ASCT	274	212	175	151	126	94	58	29

Shaded areas indicate 95% CIs

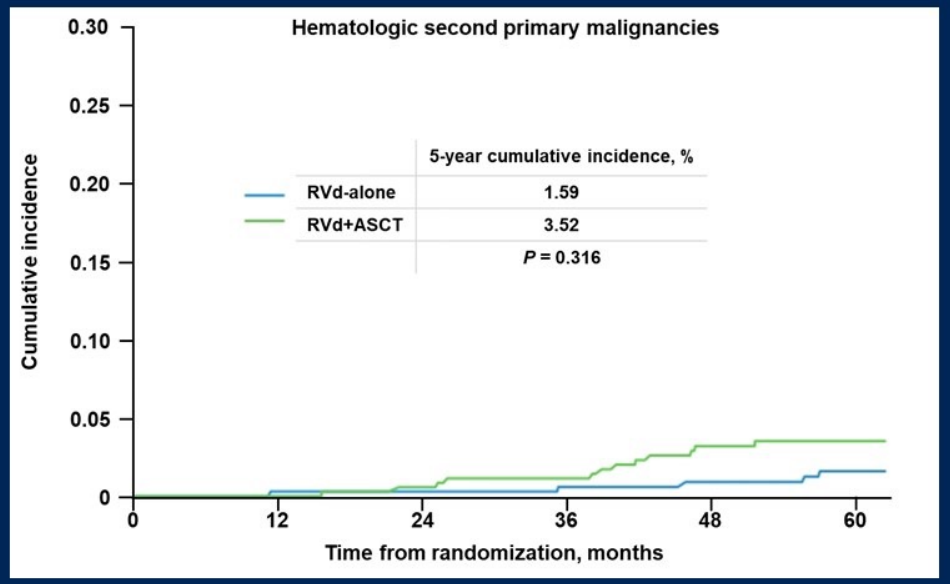
Median PFS, months	RVd-alone	RVd+ASCT
High-risk	17.1	55.5
	HR 1.99 (95% CI 1.21–3.26)	

Median PFS, months	RVd-alone	RVd+ASCT
Standard-risk	53.2	82.3
	HR 1.38 (95% CI 1.07–1.79)	

PRESENTED BY:
Paul G. Richardson, MD

DETERMINATION: Second primary malignancies

- 5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):
  - All : 9.7% vs 10.8%
  - Invasive: 4.9% vs 6.5%
  - Hematologic: 1.59% vs 3.52%



SPMs, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	10.4	10.7
Any invasive SPM	5.3	6.8
Any hematologic SPM	2.5	3.6
ALL, n	7	3
AML/MDS, n	0*	10*
CLL/CML, n	2	0
Any solid tumor SPM	3.4	3.3
Any non-invasive solid tumor SPM	0	0.5
Any non-melanoma skin cancer	5.9	4.1

* p=0.002

DETERMINATION: The debate of To Transplant or Not to Transplant continues:

YES to ASCT

1. The sheer magnitude of the PFS benefit here is staggering – OVER 21 months (And please remember, your honor, that PFS was the PRIMARY endpoint of the trial)
2. Prolonged maintenance (intended until PD) did NOT catch up the PFS benefit
3. We “don’t save the best for last” anymore in MM – early Rx has downstream effect
4. This builds on prior studies and ongoing studies like FORTE
5. You may lose the chance for ASCT if you don’t use it upfront

NO to ASCT

1. OS was not improved, despite only 28% of patients in the non ASCT arm receiving ASCT at relapse – unlike the IFM study where 79% had ASCT at relapse
2. Both IFM and DETERMINATION restricted entry to patients 65 years old and younger – is this really reflective of the ASCT population?
3. The toxicity of ASCT is real - it costs patients 3 months of QOL at minimum
4. The long-term toxicity of ASCT is real – the SPM signal is concerning for MDS/AML
5. With even more enhanced induction options coming (including quadruplets) ASCT may no longer be necessary…

Bottom Line – ASCT remains a standard of care, but ok to delay until 1st relapse

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Courtesy of Joseph Mikhael, MD, MEd

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.

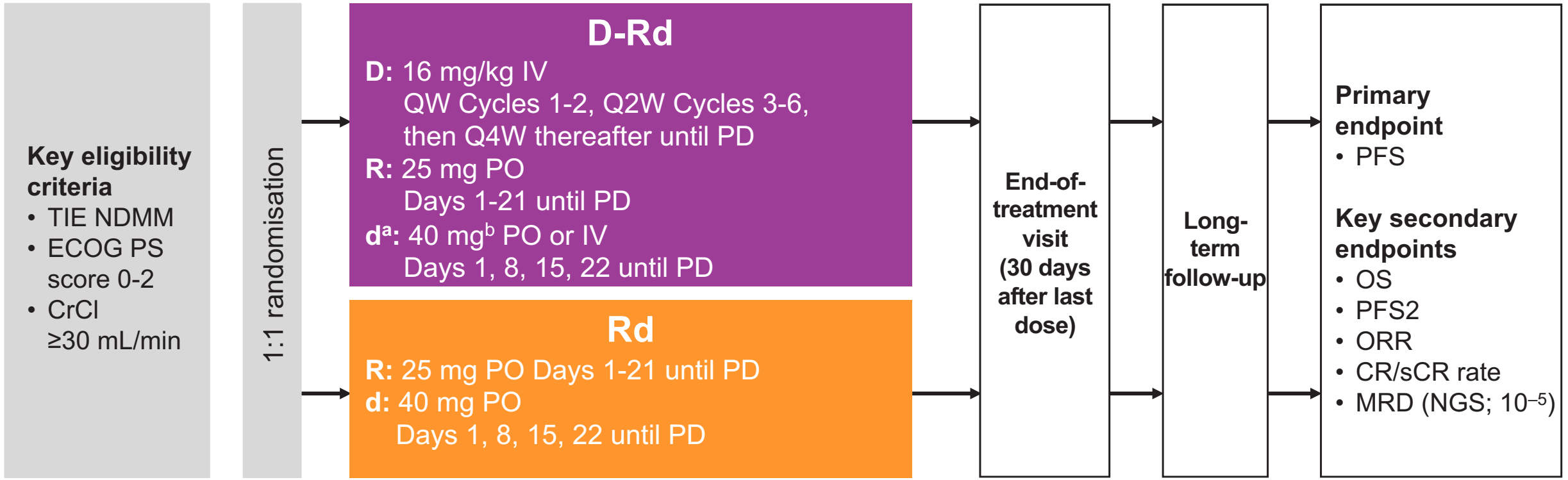
Dr. Joe's Take on GRIFFIN

- Quadruplet therapy is becoming the standard of care
- D-VRD already listed in NCCN
- The deeper responses justify 4 drugs as induction and consolidation post ASCT
- But still unclear if D is needed for maintenance therapy – that will take a phase 3 trial to demonstrate
- Other quads will come using carfilzomib instead of bortezomib and isatuximab instead of daratumumab

Courtesy of Joseph Mikhael, MD, MEd

MAIA

– Patients were enrolled in MAIA from March 2015 through January 2017



Cycles: 28 days

MAIA is a multicentre, randomised, open-label, active-controlled, phase 3 study of D-Rd versus Rd alone in patients with NDMM who are transplant ineligible

Courtesy of Joseph Mikhael, MD, MEd

TIE, transplant-ineligible; ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; PD, progressive disease; PO, oral; ORR, overall response rate; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; BMI, body mass index.

[a]On days when DARA is administered, dexamethasone will be administered to patients in the D-Rd arm and will serve as the treatment dose of steroid for that day, as well as the required pre-infusion medication. [b]For patients >75 years of age or with BMI <18.5 kg/m^2, dexamethasone was administered at a dose of 20 mg QW.

Kumar Update on MAIA

- MAIA is a critical study that has set the new standard of care in pts not going to ASCT
- 5 year PFS (52%) and OS (66%) is remarkable
- DRD is now generally favored over VRD – less toxicity, better outcomes
- Updated results very similar – more information on depth of response with 4 fold increase in MRD negativity with DRD

Courtesy of Joseph Mikhael, MD, MEd

- Touzeau C et al. All-oral triplet combination of ixazomib, lenalidomide, and dexamethasone in newly diagnosed transplant-eligible multiple myeloma patients: Final results of the phase II IFM 2013-06 study. Haematologica 2022;107(7):1693-7.

Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take on Ixa-Len-Dex

- Attractive to use an all oral combination
- Only 42 patients
- Unusual to only have 1 year of maintenance Ixa
- Toxicities are predictable and mangeable
- However, the outcomes are clearly inferior to VRD and DRD
- Ixazomib has consistently not performed well in frontline and maintenance therapy

Courtesy of Joseph Mikhael, MD, MEd

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- Evaluating the risk of treatment complications (eg, infections, cytopenias, SPMs) in uncontrolled trials

MODULE 1: Front-line treatment; autologous stem cell transplant

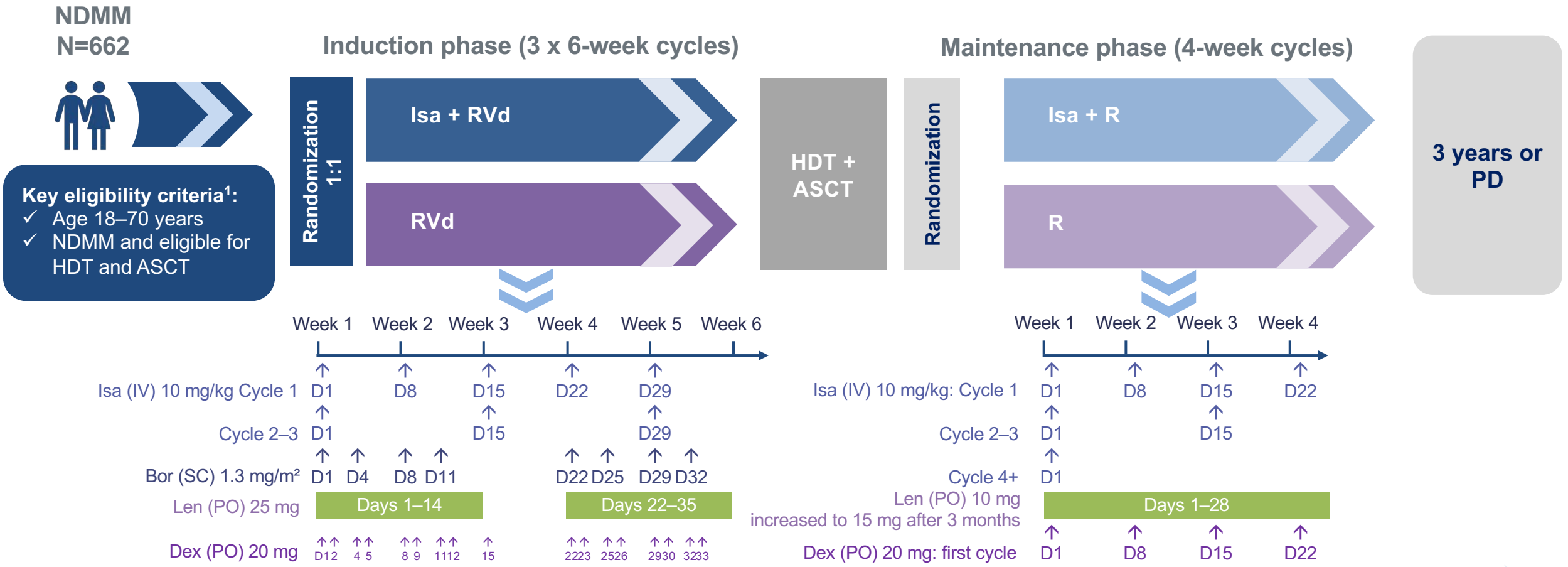
MODULE 2: Anti-CD38 antibodies

MODULE 3: CAR T-cell therapy

MODULE 4: Bispecific antibodies

MODULE 5: Other treatments for relapsed/refractory disease

The first phase 3 study evaluating Isa + RVd for induction and maintenance in Te NDMM patients



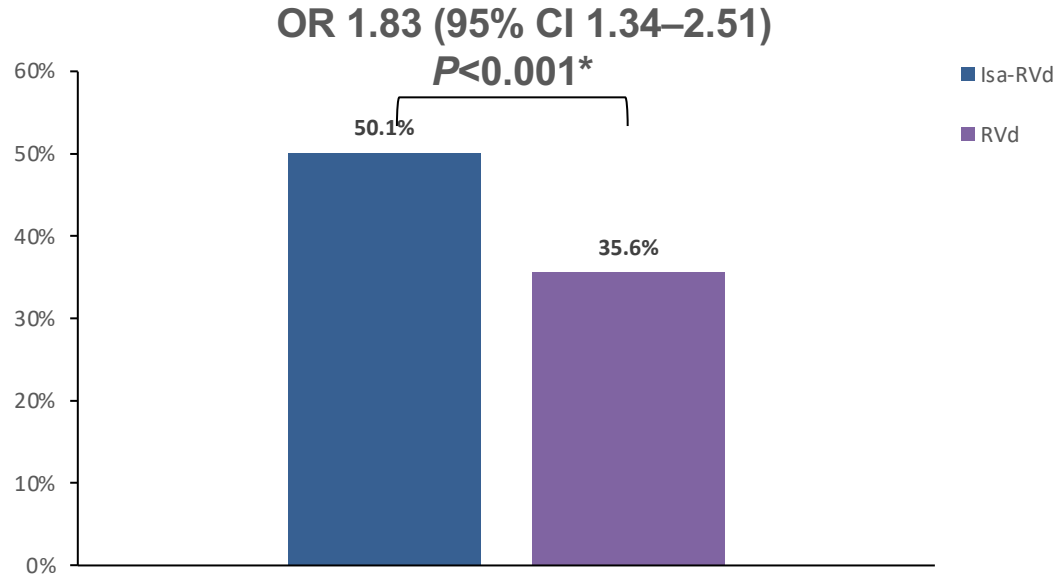
ASCT, autologous stem cell transplant; D, day; d/Dex, dexamethasone; HDT, high-dose therapy; Isa, isatuximab; IV, intravenous; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PO, oral; R/Len, lenalidomide; SC, subcutaneous; Te, transplant eligible; V/Bor, bortezomib; RVd is off label use in some countries according to the lenalidomide summary of product characteristics.

1. ClinicalTrials.gov: NCT03617731

Courtesy of Joseph Mikhael, MD, MEd

First primary endpoint, end of induction MRD negativity by NGF (10^{-5}), was met in ITT analysis

Patients with MRD negativity at the 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

P value derived from stratified conditional logistic regression analysis
†Missing NGF-MRD values were due to either patients' loss to follow-up during induction therapy or to missing bone marrow samples or technical failures in measurement counted as non-responders, i.e. NGF-MRD positive
CI, confidence interval; d, dexamethasone; Isa, isatuximab; ITT, intent-to-treat; MRD, minimal residual disease; NGF, next-generation flow; OR, odds ratio; R, lenalidomide; V, bortezomib

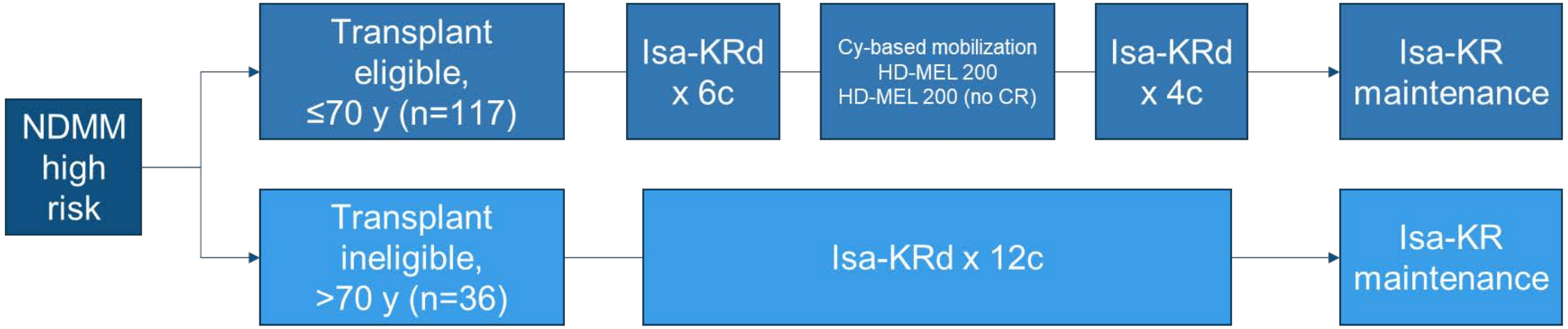
Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take on Isa-VRD

- First phase 3 trial of quad we have seen data for
- First study where MRD is primary endpoint
- Very impressive primary endpoint results with 50% MRD neg after only 18 weeks of therapy
  - Significantly better than VRD
- There seems to be no problem collecting stem cells (that is a problem with DVRD)
- Will be important to see the impact of ASCT after induction
- Further evidence we are moving to quads

Courtesy of Joseph Mikhael, MD, MEd

GMMG CONCEPT: Phase 2, Isatuximab-KRd



Primary endpoint
- MRD-neg (Flow, 10^{-5}) after consolidation

Secondary endpoint
- PFS

Isa-KRd Induction
Cycle 1

Isatuximab	10 mg/kg	day 1, 8, 15, 22
Carfilzomib	20 mg/m²	day 1, 2
Carfilzomib	36 mg/m²	day 8, 9, 15, 16
Lenalidomide*	25 mg	day 1-21
Dexamethasone**	40 mg*	day 1, 8, 15, 22
28-day-cycle		

Isa-KRd Induction
Cycle 2-6

Isatuximab	10 mg/kg	day 1, 15
Carfilzomib	36 mg/m²	day 1, 2, 8, 9, 15, 16
Lenalidomide**	25 mg	day 1-21
Dexamethasone***	40 mg*	day 1, 8, 15, 22
28-day-cycle		

*Cy-based mobilization was moved in an amendment to the time after 3 induction cycles.
**Dose adaption of lenalidomide according to renal function.
***20 mg in patients aged ≥75 years.

Leypoldt LB, et al. *Leukemia*. 2022;36(3):885-888 [Epub ahead of print].

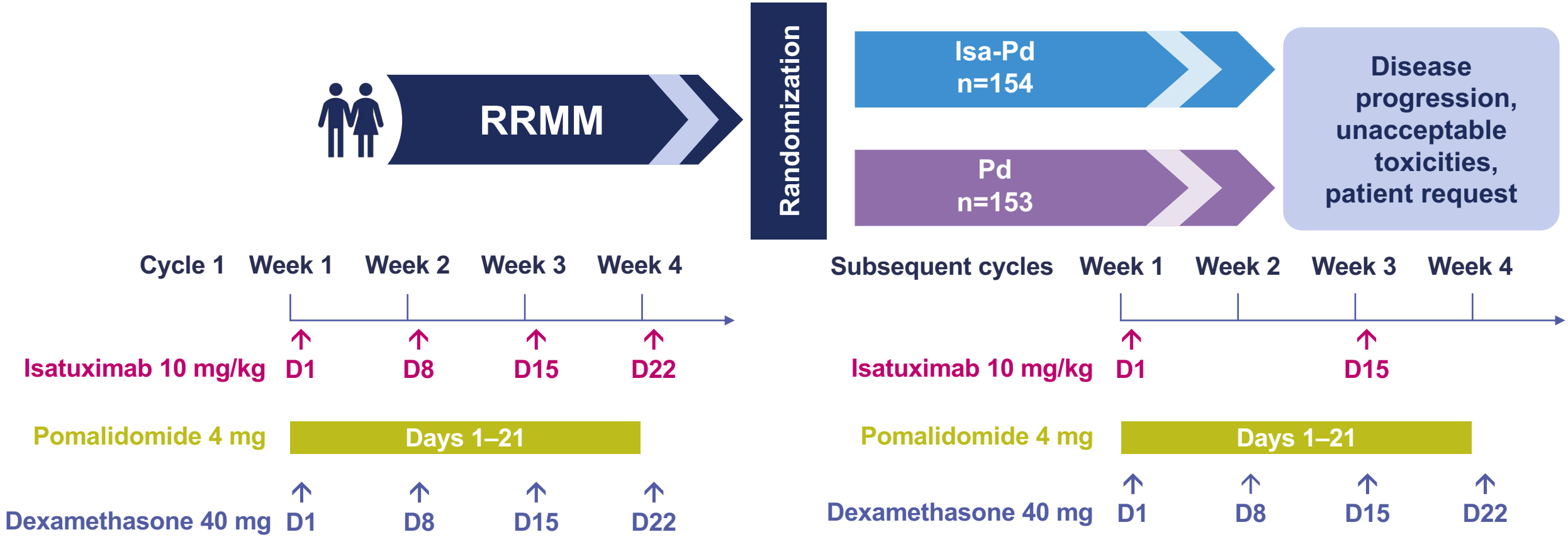
Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take

- We need better options for high risk patients
- quads very much preferred in this group
- Carfilzomib is preferred over bortezomib
- This concept trial demonstrates the feasibility of this quad, even in transplant ineligible patients
- It would require a phase 3 for full proof

Courtesy of Joseph Mikhael, MD, MEd

ICARIA-MM
Study design



NCT02990338.
D, day; Isa-Pd, isatuximab plus pomalidomide and dexamethasone; Pd, pomalidomide and dexamethasone.

Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take on ICARIA

- Good to see an OS advantage in later relapse MM
- 7-month improvement is clinically significant
- No unusual long term safety signals
- We still have a lot to learn about the potential of switching CD38 Abs or re-using them

Courtesy of Joseph Mikhael, MD, MEd

Lymphoma Leukemia & Myeloma Congress
October 18–22 2022

IKEMA

Updated Progression-free Survival (PFS) and Depth of Response in IKEMA, a Randomized Phase 3 Trial of Isatuximab, Carfilzomib and Dexamethasone (Isa-Kd) vs Kd in Relapsed Multiple Myeloma (MM)

Joseph Mikhael, MD, MEd, FRCPC, FACP

Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, AZ, USA

Joseph Mikhael[1], Philippe Moreau[2], Meletios-Athanasios Dimopoulos[3], Kwee Yong[4], Marcelo Capra[5], Thierry Facon[6], Roman Hajek[7], Ivan Špička[8], France Casca[9], Sandrine Macé[10], Marie-Laure Risse[11] & Thomas Martin[12*] on behalf of the IKEMA study group.*

**Co-primary investigators; [1]Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, AZ, USA; [2]Department of Hematology, University Hospital Hôtel-Dieu, Nantes, Pays de la Loire, France; [3]Department of Clinical Therapeutics, The National and Kapodistrian University of Athens, Athens, Greece; [4]Department of Hematology, University College Hospital, London, UK; [5]Centro Integrado de Hematologia e Oncologia, Hospital Mãe de Deus, Porto Alegre, Rio Grande do Sul, Brazil; [6]Department of Hematology, Lille University Hospital, Lille, Hauts-de-France, France; [7]Department of Hemato-Oncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [8]1st Department of Medicine, Department of Hematology, 1st Faculty of Medicine, Charles University and General Hospital, Prague, Czech Republic; [9]Ividata Life Science, Levallois-Perret, Ile-de-France, France, contracted by Sanofi; [10]Sanofi, R&D Translational Medicine, Chilly-Mazarin, Ile-de-France, France; [11]Sanofi, R&D, Vitry-sur-Seine, France; [12]Department of Hematology, University of California at San Francisco, San Francisco, CA, USA.*

Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take on IKEMA

- 3 year PFS in relapsed MM is unprecedented
- Carfilzomib is a very attractive partner in early relapse
  - Giving it indefinitely is key to benefit
- The depth of response, especially MRD, is important in relapsed MM
- The PFS2 was also improved in the intervention arm, so bridges are not being burned

Courtesy of Joseph Mikhael, MD, MEd

- Quach H et al. Subcutaneous isatuximab administration by an on-body delivery system (OBDS) in combination with pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma: Phase 1b expansion study results. ASH 2022;Abstract 1923.

- The on-body delivery system (OBDS), a wearable bolus injector applied to the abdomen by a healthcare professional, is administered SC

Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take on SC Isatuximab

- We have been waiting for this
- It is highly desirable to provide this agent SC – quicker, less reactions, single dose vial, not weight based
- Results of efficacy similar to IV
- Very well tolerated with minimal complications
- Delivery system is unique
- Will facilitate the use of Isatuximab

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Courtesy of Joseph Mikhael, MD, MEd

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- Evaluating the risk of treatment complications (eg, infections, cytopenias, SPMs) in uncontrolled trials

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MODULE 2: Anti-CD38 antibodies

MODULE 3: CAR T-cell therapy

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MODULE 5: Other treatments for relapsed/refractory disease

Paiva B et al. Early and sustained undetectable measurable residual disease (MRD) after idecabtagene vicleucel (ide-cel) defines a subset of multiple myeloma (MM) patients in Karmma achieving prolonged survival. ASH 2022;Abstract 868.

- MRD is prognostic in myeloma. However, among patients receiving CART, whether the marrow based MRD testing, the method of testing (NGF, NGS) or the optimal timing of MRD testing holds the prognostic impact on long term outcomes is unclear.
- Paiva et al. evaluated the prognostic value of the depth of serological responses and the MRD responses among patients that received CAR T cell therapy (Ide-cel) from karMMa-2 trial.
- MRD (NGF, NFS for threshold of 10-6) was analyzed at 1, 3, 6 and 12 months after ide-cel infusion for 125 of 128 patients.
- Concordance between NGF and NGS at 1, 3, 6 and 12 months were of 67%, 75%, 82% and 73%. NGF and NGS showed similar prognostic value at all time points.

Response	Month 1	Month 3	Month 6	Month 12
≥CR	11%	23%	26%	23%
MRD –ve (10-6)	41%	45%	35%	18%
MRD –ve (10-5)	42%	47%	38%	19.5%

Courtesy of Ajay K Nooka, MD, MPH

- MRD +ve (10-6) in eight patients had negative prognostic impact (median PFS 5.5 months).
- At month 1: <CR vs ≥CR – median PFS was 8 vs 11 months, p =0.09). MRD +ve vs MRD –ve (10-6) - median PFS was 2 vs 11.5 months, p < 0.001).
- At months 3, 6 and 12, patients with ≥CR and MRD –ve (10-6) showed significantly longer median PFS vs those in less than CR and undetectable MRD (p ≤ 0.007).
- Reappearance of normal plasma cells, which could be used as a surrogate for loss of CAR T cell persistence and/or functionality.
  - Reappearance of normal plasma cells = inferior PFS
  - absence of normal plasma cells + MRD –ve = improved PFS
- Conclusions:
  - NGF and NGS have higher concordance (discordant samples are hemodilute samples)
  - MRD +ve at 1 month is an early prognostic marker for PFS (not serological response)
  - ≥CR and MRD –ve (10-6) at 12 months are prognostic for improved PFS
  - Reappearance of normal PC could serve as a biomarker for increased risk of progression even among patients MRD-ve
  - Early and sustained MRD-ve patients have improved PFS

Courtesy of Ajay K Nooka, MD, MPH

Topline results from KarMMa-3: Idecabtagene vicleucel significantly improves progression free survival versus standard regimens in relapsed and refractory multiple myeloma

Press Release: August 10, 2022

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

Adapted from Ajay K Nooka, MD, MPH

Martin T et al. Ciltacabtagene autoleucel, an anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. J Clin Oncol 2022 Jun 4;[Online ahead of print].

- Ciltacabtagene autoleucel (cilta-cel),as opposed to Ide-cel is a differentiated CAR-T therapy with two BCMA-targeting single-domain antibodies to confer avidity.
- Approved by the US FDA for the treatment of adult patients with RRMM after ≥4 prior LOT, including a PI, an IMiD, and an anti-CD38 monoclonal antibody based on the CARTITUDE-1, a phase Ib/II study.
- Updated results 2 years after LPI (median follow-up 28 months) was reported in JCO, including high-risk patient subgroups - 66 of the 97 patients remained on study.
- ORR 97.9%; sCR rate: 82.5%. Median PFS and DOR – NE. 27-month PFS and OS rates were 54.9% and 70.4%.
- Of 61 patients, that had evaluable samples for MRD at 10–5 threshold, 56 (91.8%) patients achieved MRD-vity which was sustained for ≥ 6 months in 68%.
- Median TTR – 1.2 months.

Courtesy of Ajay K Nooka, MD, MPH

- Hematologic safety
  - Grade 3/4 thrombocytopenia occurred in 60 patients; 20 (33.3%) had recovered to grade # 2 by day 30, and 35 (58.3%) recovered by day 60.
  - Grade 3/4 neutropenia was reported in 95 patients; 66 (69.5%) had recovered to grade # 2 by day 30 and 85 (89.5%) by day 60.
  - Grade 3/4 lymphopenia occurred in 96 patients; 84 (87.5%) had recovered to grade # 2 by day 30 and 88 (91.7%) by day 60.
- In total, 20 SPMs were reported in 16 patients
  - 11 had hematologic SPM (1 low-grade B-cell lymphoma, 6 cases of MDS, and 4 cases of AML).
  - 9 had solid tumors (4 with squamous cell carcinoma; 1 melanoma, 1 adenocarcinoma, 1 prostate, 1 myxofibrosarcoma, and 1 prostate cancer).
- No further CRS beyond 12 month mark, but 1 case of parkinsonism at day 914.
- Transformative treatment in RRMM. AE profile consistent with what was expected for this refractory patient population.
- Further trials are ongoing to evaluate efficacy of cilta-cel as earlier lines of therapy.

Courtesy of Ajay K Nooka, MD, MPH

Bal S et al. Clinical activity of BMS-986393 (CC-95266), a G protein–coupled receptor class C group 5 member D (GPRC5D)–targeted chimeric antigen receptor (CAR) T cell therapy, in patients with relapsed and/or refractory (R/R) multiple myeloma (MM): First results from a Phase 1, multicenter, open-label study. ASH 2022;Abstract 364.

- GPRC5D, an orphan receptor expressed on MM cells with limited expression in other tissues, is a promising therapeutic target
- MCARH109, a GPRC5D-directed CAR T-cell therapy, demonstrated promising initial safety and efficacy
- Interim results from the dose-escalation (Part A) of study (N=33), median age 63, median prior lines 4, high-risk disease in 48.5%, 54.5% had prior BCMA directed therapy
- 25x106 - 450x106 in 5 cohorts were evaluated for primary endpoint to determine MTD/RP2D
- DLT of prolonged (out to day 42) grade 4 neutropenia and/or thrombocytopenia were reported in 2 patients (25×10^6 and 75×10^6 CAR T cells); MTD has not been exceeded
- CRS 63% (45% grade 1, 6% grade 3), mostly with higher CART dosing
- ICANS grade 1/2 – 6%, low grade toxicities - skin (30%), dysguesia 15%, nails 9%
- ORR of 100% above the dose of 150x106 (N=6), with 90% ORR for all cohorts (N=19) (CRR 47.4%)
- Prior BCMA cohort (N=9) – ORR 77.8%, CRR 45%

Courtesy of Ajay K Nooka, MD, MPH

- At all tested dose levels, BMS-986393 demonstrated a favorable safety profile
    - CRS was mostly grade 1–2; ICANS-type neurotoxicity was infrequent, low-grade, and reversible, and no cerebellar NT was reported across all dose levels tested
    - On-target/off-tumor events occurred in a minority of patients and were grade 1
- Dose-escalation is ongoing; MTD has not been exceeded
- BMS-986393 shows durable responses and promising efficacy at all tested dose levels, including MRD-negative CRs and in BCMA-exposed patients
- These preliminary data support GPRC5D-directed CAR T-cell therapy with BMS-986393 as a new treatment in R/R MM, irrespective of prior BCMA-directed therapy
    - Expansion in Part B is underway to define RP2D

Courtesy of Ajay K Nooka, MD, MPH

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MODULE 3: CAR T-cell therapy

MODULE 4: Bispecific antibodies

MODULE 5: Other treatments for relapsed/refractory disease

Moreau P et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med 2022;387(6):495-505.

- Bispecific antibody teclistamab targets BCMA and CD3
- In the phase I/II MajesTEC-1 trial, 165 heavily pretreated patients (5 prior lines, 26% had high-risk disease) had treatment with weekly subcutaneous injection of teclistamab (at a dose of 1.5 mg/kg) after receiving step-up doses of 0.06 mg and 0.3 mg/kg
- Response rates: ORR - 63%, ≥CR – 39.4%, ≥VGPR rates – 58%. 44 patients (26.7%) were found to be MRD-ve; the MRD-ve rate among the patients with ≥CR was 46%
- Median TTR – 1.2 months
- Median PFS 11.3 months, median DOR 18.4 months

D'Souza A et al. A Phase I first-in-human study of ABBV-383, a B-cell maturation antigen × CD3 bispecific T-cell redirecting antibody, in patients with relapsed/refractory multiple myeloma. J Clin Oncol 2022;40(31):3576-86.

- ABBV-383, a B-cell maturation antigen X CD3 T-cell engaging bispecific antibody
- Safety and efficacy outcomes of phase I dose escalation/ expansion study
- ABBV-383 was administered intravenously over 1-2hours once every 3 weeks, without any step dosing. 3+3 design
- 124 patients (ESC [0.025-120 mg], n=73; ESP [60mg], n=51) have received ABBV-383; median age was 68 years
- AEs: Neutropenia (all grades: 37%) and anemia(29%), CRS (57%) and fatigue (30%)
- ORR was 57% and ≥VGPR was 43%
  - 60 mg EXP (n=49), ORR and ≥VGPR rates were 59% and 39%
  - ≥40 mg ESC and EXP cohorts (n=79) were 68% and 54%, respectively

Courtesy of Ajay K Nooka, MD, MPH

Wong SW et al. Alnuctamab (BMS-986349; CC-93269), a B-cell maturation antigen (BCMA) x CD3 2+1 T cell engager (TCE), in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Results from a Phase 1 first-in-human clinical study. ASH 2022;Abstract 162.

- BCMA x CD3 bispecific antibody in RRMM
- IV ALNUC was associated with a high rate of CRS; any grade, 89%; grade≥3, 5%). SC formulation was explored
- SC ALNUC was given on days 1, 4, 8, 15, and 22 of cycle 1 (28-d cycles), QW in C2–3, Q2W in C4–6, and Q4W in C7 and beyond
  - 2 step-up doses (3 mg on C1D1 and 6 mg on C1D4) and a ≥10 mg target dose on C1D8 and thereafter (Target doses SC dose escalation were 10, 15, 30, and 60 mg)
- 47 pts have received SC ALNUC, ORR was 51% (21/41 pts) across all dosing regimens and 77% (10/13 pts) in pts receiving target doses ≥30mg
- Any grade/grade 3-4: CRS(53%/0%), neutropenia (34%/30%), and anemia (34%/17%)

Courtesy of Ajay K Nooka, MD, MPH

- SC administration widened the therapeutic index with an improved safety profile compared with IV; CRS was limited to grade 1–2 events
- SC ALNUC exhibited promising dose-dependent antitumor activity with a high proportion of MRD responses (100%)
- Another BCMA directed option
- Long term data from the ongoing cohort suggested prolonged PFS of close to 36 months – the highest reported
- No unexpected toxicity seen so far, including ICANS

Courtesy of Ajay K Nooka, MD, MPH

Chari A et al. Talquetamab, a G protein-coupled receptor family C group 5 member D x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): Phase 1/2 results from MonumenTAL-1. ASH 2022;Abstract 157.

- Bispecific antibody talquetamab targets GPRC5D and CD3
- In the phase I/II MonumenTAL-1 trial, 288 heavily pretreated patients (5 prior lines, 60% had high-risk disease) had treatment with a weekly (0.405 mg/kg subcutaneous (SC) weekly) and an every-2-week dose (and 0.8 mg/kg SC every other week) dosing
- Response rates: ORR - 74.1% (weekly dosing) and 73.1% (QOW dosing), ≥CR - 33.6% and 32.4%, ≥VGPR rates - 59.4% and 57.2%
- In 51 patients, who had prior BCMA directed CART/bispecific antibody – ORR 62.7%
- Median TTR – 1.2 months
- Median PFS 7.5 months, median DOR 9.3 months (weekly) and 13 months (QOW)

Courtesy of Ajay K Nooka, MD, MPH

Agenda

INTRODUCTION

- Belantamab mafodotin and melflufen requiems?
- Evaluating the risk of treatment complications (eg, infections, cytopenias, SPMs) in uncontrolled trials

MODULE 1: Front-line treatment; autologous stem cell transplant

MODULE 2: Anti-CD38 antibodies

MODULE 3: CAR T-cell therapy

MODULE 4: Bispecific antibodies

MODULE 5: Other treatments for relapsed/refractory disease

Lonial S et al. Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): A multicentre, multicohort, open-label, phase 1/2 trial. Lancet Haematol 2022;9(11):e822-e832.

- Iberdomide is a novel cereblon E3 ligase modulator (CELMoD) has 20 times higher binding affinity to cereblon with enhanced tumoricidal and immune-stimulatory effects compared with immunomodulatory drugs.
- In the phase 1/2 trial (CC-220-MM-001), patients received escalating doses of oral iberdomide (0.3–1.6 mg on days 1–21/28day cycle) plus oral dexamethasone (40 mg/week), N=197 (90 patients in the dose-escalation cohort and 107 in the dose-expansion cohort at RP2D 1.6 mg). Median age 65, median of 5-6 prior LOT.
- ORR 32% (30% in dose escalation arm and 26% in dose expansion cohort). Median PFS 3 months, median DOR 7 months.
- Safety – hematological and infections.
- Well tolerable, oral agents, likely be used in combinations.

Courtesy of Ajay K Nooka, MD, MPH

Richardson PG et al. Mezigdomide (CC-92480), a potent, novel cereblon E3 ligase modulator (CELMoD), combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Preliminary results from the dose-expansion phase of the CC-92480-MM-001 trial. ASH 2022;Abstract 568

- Mezigdomide (CC-92480), newer CELMoD, similar to Iberdomide, has much more affinity to cereblon and degrades Ikaros and Aiolos more efficiently
- Phase 1/2 trial evaluating MEZI alone or in combination with DEX in pts with RRMM; RP2D of MEZI in combination with DEX was selected at 1 mg once daily for 21/28 days
- 101 pts had received MEZI + DEX. Median age 67, a third had high-risk cytogenetics, median prior LOT 6 (anti-BCMA therapy in 29.7%)
- ORR was 39.6%, with 2 (2.0%) stringent complete responses, 3 (3.0%) complete responses, 18 (17.8%) very good partial responses, and 17 (16.8%) partial responses
- Median PFS was 4.6 months, median DOR 8.3 months

Courtesy of Ajay K Nooka, MD, MPH

- Good as combination therapies with other anti-myeloma agents, likely with bispecific antibodies
  - Given the AE profile likely to be safe with combinations
  - Oral administration makes it more convenient
  - Hematological toxicities of neutropenia are seen in this patient population but may not be as evident in less treated patient population
- Good option as post CART as maintenance as they move forward to earlier LOT
- Good option in Extramedullary disease with ORR of 31% where bispecific antibodies have not shown as much benefit

Courtesy of Ajay K Nooka, MD, MPH

Today's featured article…

Once weekly selinexor, carfilzomib and dexamethasone in carfilzomib non-refractory multiple myeloma patients

Cristina Gasparetto[1✉], Gary J. Schiller[2], Sascha A. Tuchman[3], Natalie S. Callander[4], Muhamed Baljevic[5], Suzanne Lentzsch[6], Adriana C. Rossi[7], Rami Kotb[8], Darrell White[9], Nizar J. Bahlis[10], Christine I. Chen[11], Heather J. Sutherland[12], Sumit Madan[13], Richard LeBlanc[14], Michael Sebag[15], Christopher P. Venner[16], William I. Bensinger[17], Noa Biran[18], Sonia Ammu[19], Osnat Ben-Shahar[19], Andrew DeCastro[19], Dane Van Domelen[19], Tianjun Zhou[19], Chris Zhang[19], Ohad S. Bentur[19], Jatin Shah[19], Sharon Shacham[19], Michael Kauffman[19] and Brea Lipe[20]

A Journal Club Experience

Gasparetto C, et al. *British Jour of Cancer.* 2022 126:718-725

Courtesy of Joseph Mikhael, MD, MEd

• Efficacy Data: Duration of Response and PFS

Outcome Parameter	Month (95% CI)
Median Duration of Response	22.7 (11.8-NE)
Median Progression Free Survival	15 (12.0- NE)

Gasparetto C, et al. *British Jour of Cancer*. 2022 126:718-725

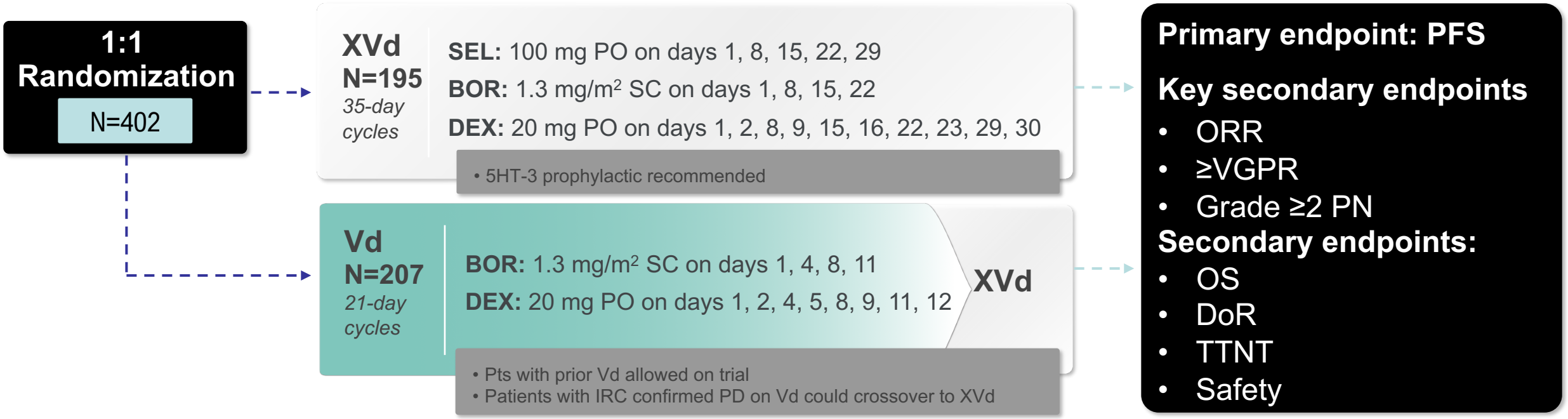
Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take on Weekly Selinexor and Carfilzomib

- Critical to the evolution of seli to be paired with multiple other agents
- Seli is MUCH better tolerated now with weekly dosing and prophylaxis
- This is my favorite combo with seli – highly active
- The 15-month PFS is impressive in this group
- Particularly attractive in high-risk patients

Courtesy of Joseph Mikhael, MD, MEd

BOSTON: A Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with Multiple Myeloma who Had Received 1-3 Prior Therapies



The XVd regimen requires approximately **40% less bortezomib** than Vd which entails **37% fewer clinic visits** over the first 6 months of treatment

Grosicki S, et al. *Lancet*. 2020;396:1563-1573

Courtesy of Joseph Mikhael, MD, MEd

Dr. Joe's Take on BOSTON subgroup renal analysis

- It is expected to see less efficacious results in patients with reduced renal function
  - There is always reduced efficacy in these patients
- This is a feasible regimen as we use both agents in renally impaired patients
- The similarity in AEs in patients independent of renal function is encouraging
- This is a preferred regimen in patients with renal insufficiency

Courtesy of Joseph Mikhael, MD, MEd

Bahlis N et al. An updated safety and efficacy analysis of venetoclax plus daratumumab and dexamethasone in an expansion cohort of a Phase 1/2 study of patients with t(11;14) relapsed/refractory multiple myeloma. ASH 2022;Abstract 3232.

- Phase 1/2 (3-part) study is investigating the combination of VenDd +/- V in RRMM
  - Part 3 evaluated VenDd (Ven400Dd, Ven800Dd) and DVd in pts with t(11;14) RRMM with an ORR of 72.7%, 100% and 31.3%. Updated results of Part 3
- 21, 10, 24 t(11;14) patients enrolled, median age 61, 57, 70, prior LOT 1,1,2
- The ORR was 95%, 100%, and 62%. ≥VGPR was 86%, 100%, and 38% 24-month PFS rate was 94%, 83%, and 47%. The ORR for the combined Ven arms was 98%
- The most common AEs: insomnia (52.4/60.0/29.2), fatigue (47.6/50.0/37.5), diarrhea (33.3/50.0/33.3), and nausea (28.6/30.0/20.8)
- A better biomarker directed therapy for dara naïve patients with t(11;14), with good safety established for the combination of VenDd (Ven400Dd, Ven800Dd)

Courtesy of Ajay K Nooka, MD, MPH

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

A Multitumor CME/MOC-Accredited Live Webinar Series

Targeted Therapy for Non-Small Cell Lung Cancer

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Faculty

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Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2023

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