Inside the Issue: Integrating Bispecific Antibodies into the Management of Multiple Myeloma — Patient Selection and Toxicity Management

A CME/MOC-Accredited Live Webinar

Tuesday, July 18, 2023
5:00 PM – 6:00 PM ET

Faculty

Hans Lee, MD
Saad Zafar Usmani, MD, MBA

Moderator

Neil Love, MD

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Faculty

Hans Lee, MD
Associate Professor
Director, Multiple Myeloma Clinical Research
Department of Lymphoma/Myeloma
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Saad Zafar Usmani, MD, MBA
Chief of Myeloma Service
Memorial Sloan Kettering Cancer Center
New York, New York

Moderator
Neil Love, MD
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Commercial Support

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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

Dr Lee — Disclosures

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Contracted Research	Amgen Inc, Bristol Myers Squibb, GSK, Janssen Biotech Inc, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Data and Safety Monitoring Board/Committee	Allogene Therapeutics

Dr Usmani — Disclosures

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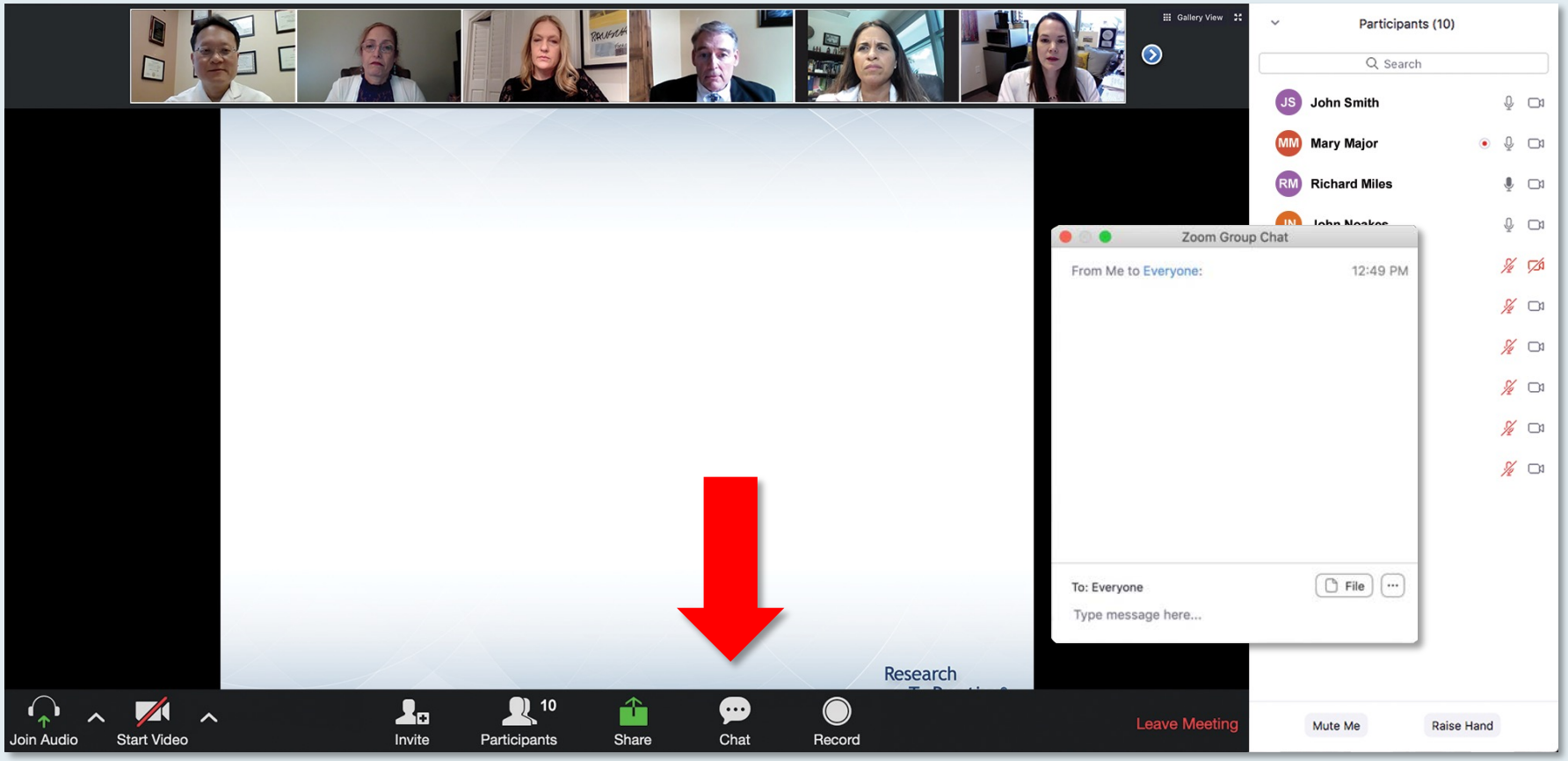
Data and Safety Monitoring Board/Committee	GSK

We Encourage Clinicians in Practice to Submit Questions



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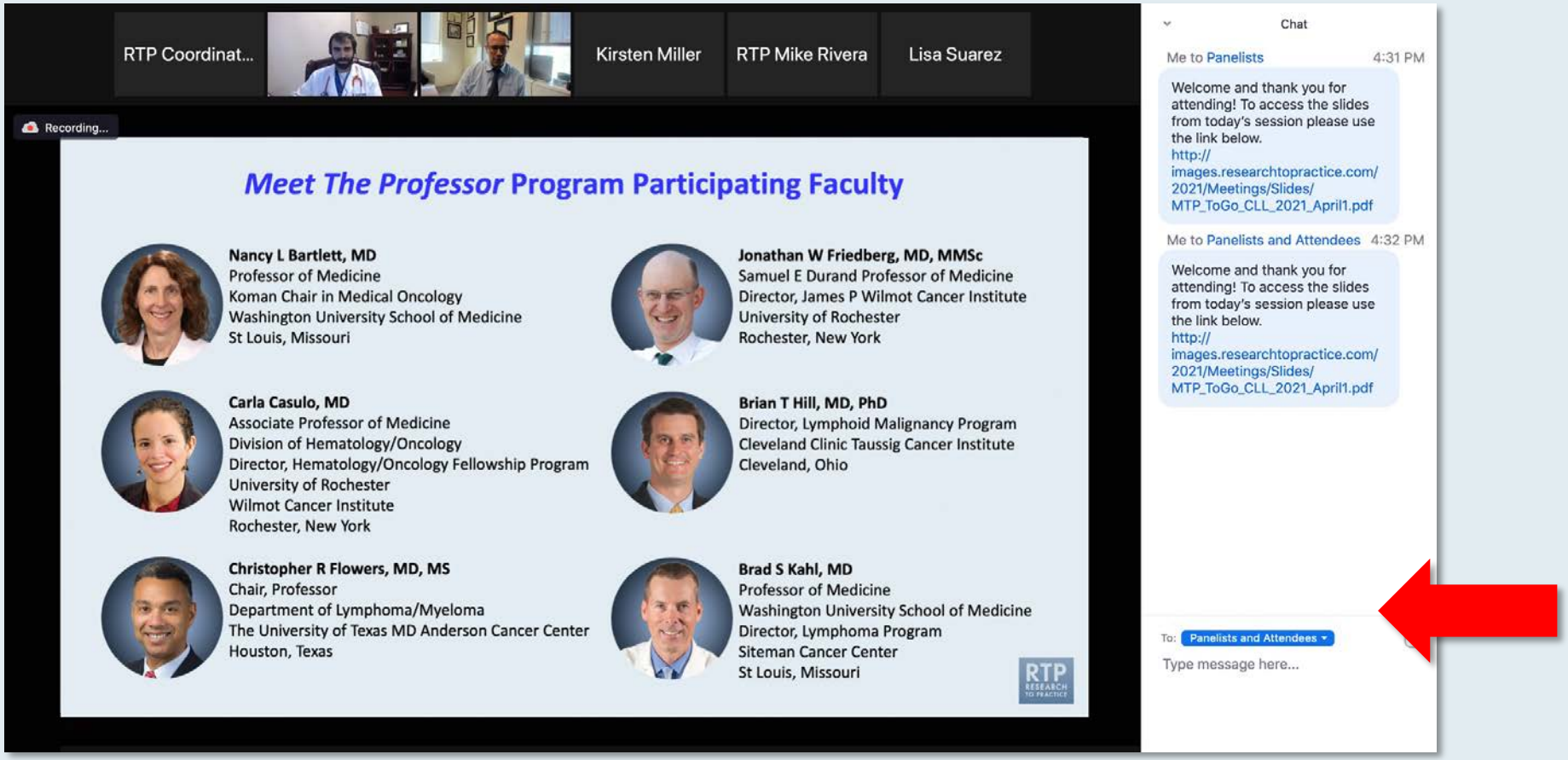

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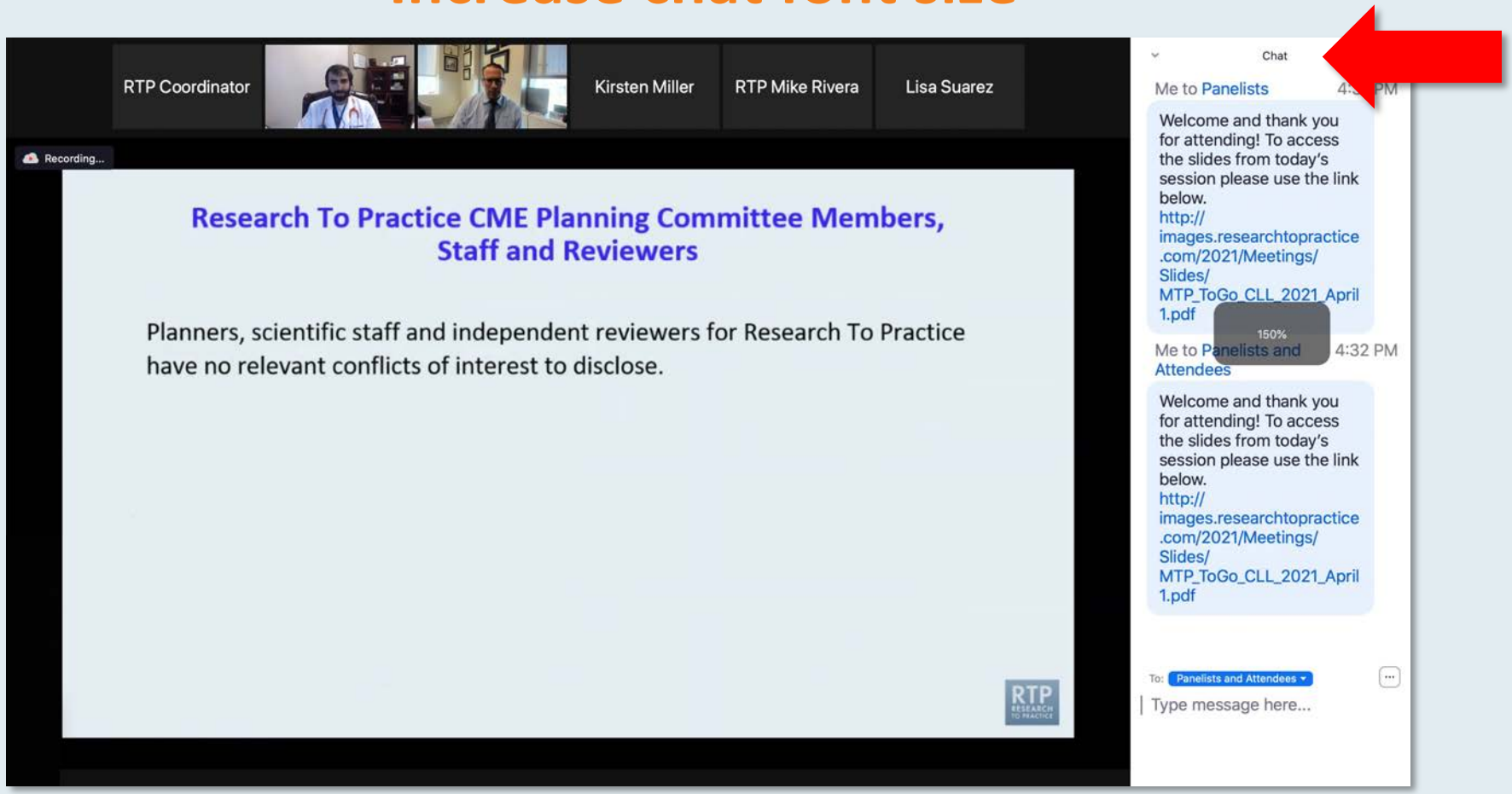

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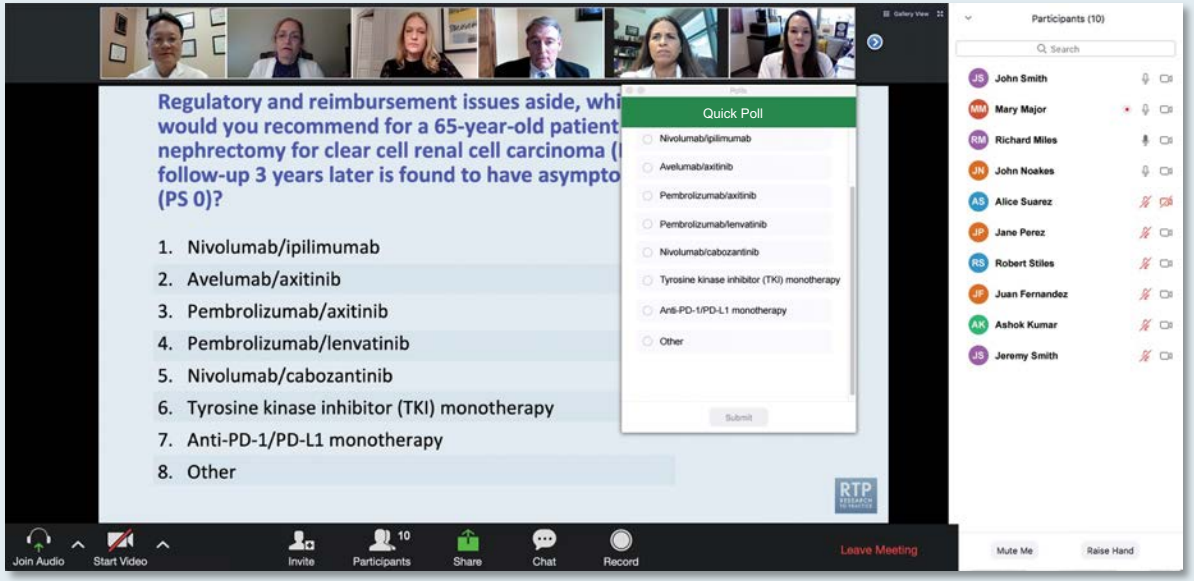

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WITH DR NEIL LOVE

Key Presentations from the 64th American Society of Hematology (ASH) Annual Meeting: Multiple Myeloma Edition

DR JACOB P LAUBACH
DANA-FARBER CANCER INSTITUTE

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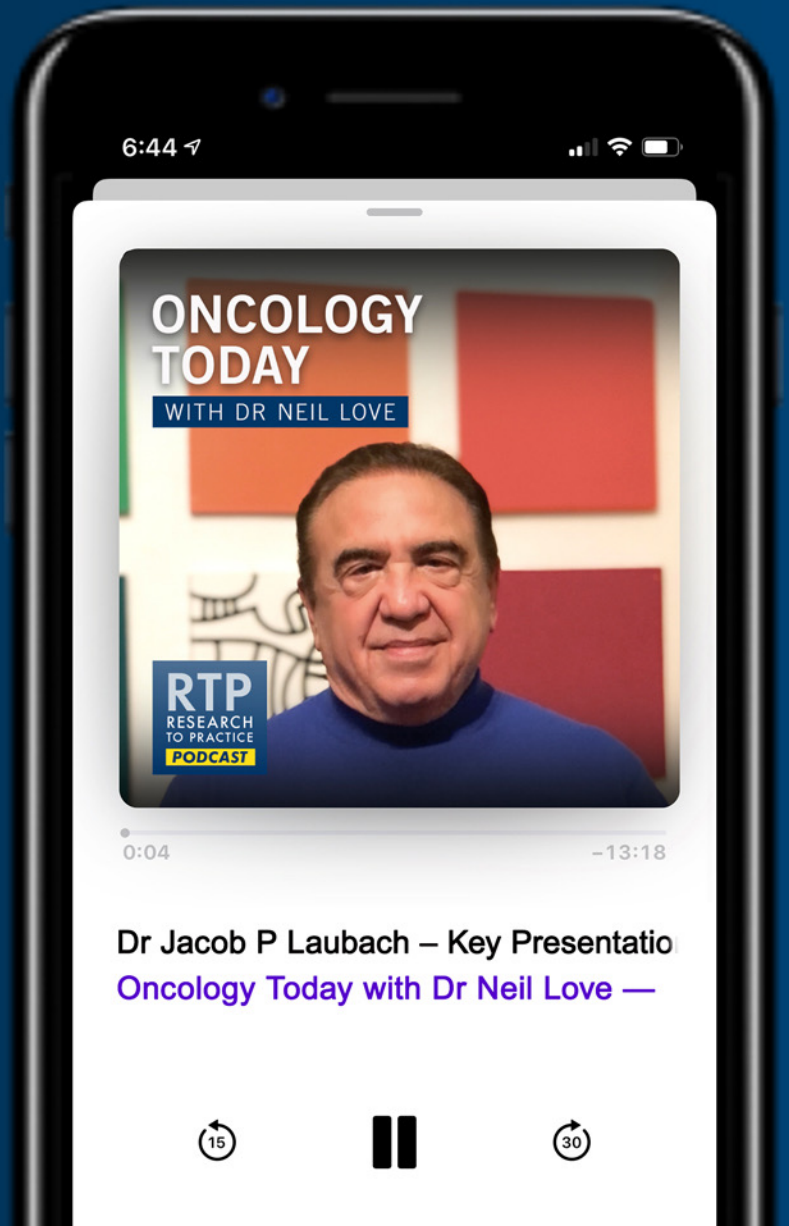

Inside the Issue: Current and Future Management of ER-Positive Metastatic Breast Cancer After Disease Progression on a CDK4/6 Inhibitor

A CME/MOC-Accredited Live Webinar

Thursday, July 20, 2023
5:00 PM – 6:00 PM ET

Faculty

Aditya Bardia, MD, MPH
Erika Hamilton, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

Tuesday, July 25, 2023
5:00 PM – 6:00 PM ET

Faculty

Richard F Riedel, MD

Moderator

Neil Love, MD

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The Implications of Recent Data Sets for the Management of Hepatocellular Carcinoma

A CME/MOC-Accredited Virtual Event

Thursday, July 27, 2023
5:00 PM – 6:00 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA
Daneng Li, MD

Moderator

Neil Love, MD

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Inside the Issue: Exploring the Current and Future Management of High-Risk, Hormone-Sensitive Nonmetastatic Prostate Cancer

A CME/MOC-Accredited Live Webinar

Monday, July 31, 2023
5:00 PM – 6:00 PM ET

Faculty

Neal D Shore, MD
Mary-Ellen Taplin, MD

Moderator

Neil Love, MD

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Inside the Issue: The Current and Future Role of CD20 x CD3 Bispecific Antibodies in the Management of Non-Hodgkin Lymphoma

A CME/MOC-Accredited Live Webinar

Wednesday, August 2, 2023
5:00 PM – 6:00 PM ET

Faculty

Martin Hutchings, MD, PhD
Loretta J Nastoupil, MD

Moderator

Neil Love, MD

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Inside the Issue: Optimizing the Management of Metastatic Pancreatic Cancer

A CME/MOC-Accredited Live Webinar

Tuesday, August 8, 2023
5:00 PM – 6:00 PM ET

Faculty

Eileen M O'Reilly, MD
Zev Wainberg, MD, MSc

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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Survey Participants

Amrita Krishnan, MD
Director of the Judy and Bernard Briskin Center for Multiple Myeloma Research
Professor of Hematology/Hematopoietic Cell Transplantation
City of Hope Cancer Center
Duarte, California

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

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

Jeffrey A Zonder, MD
Professor of Oncology
Leader, Multiple Myeloma and Amyloidosis Multidisciplinary Team
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan

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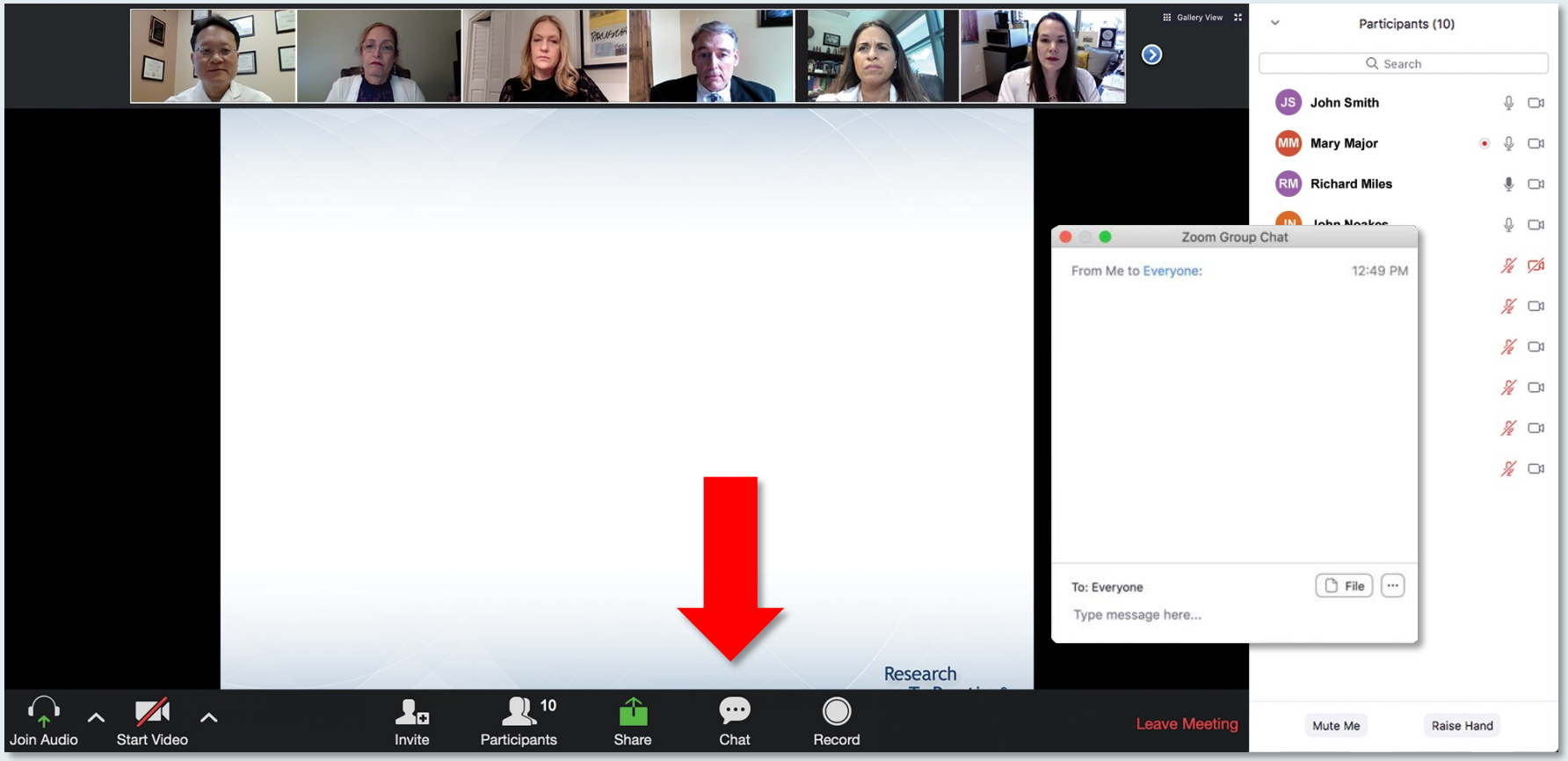

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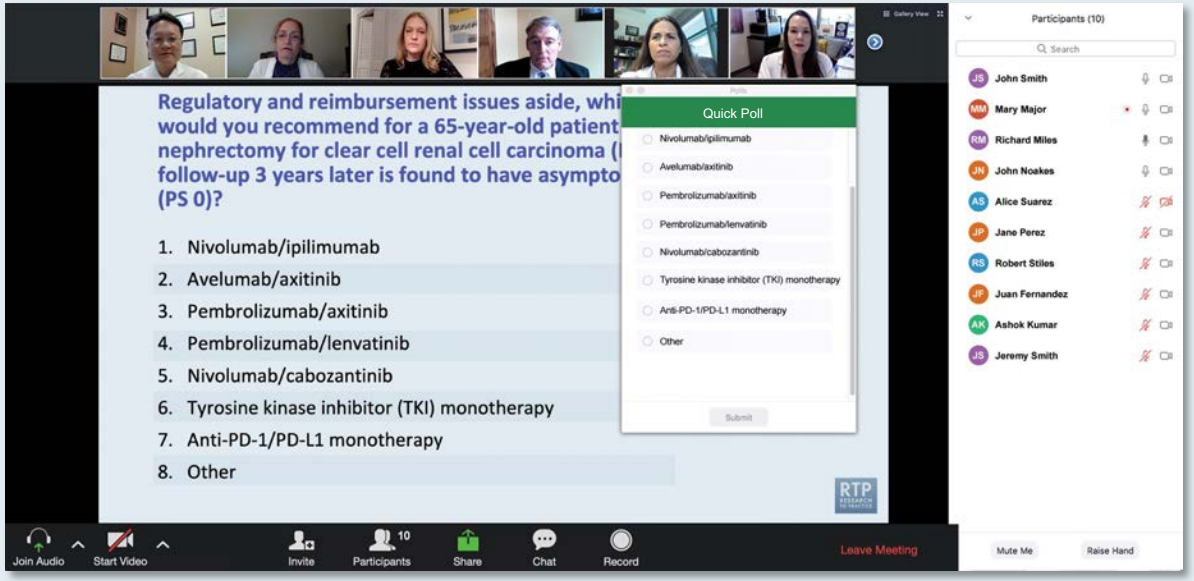

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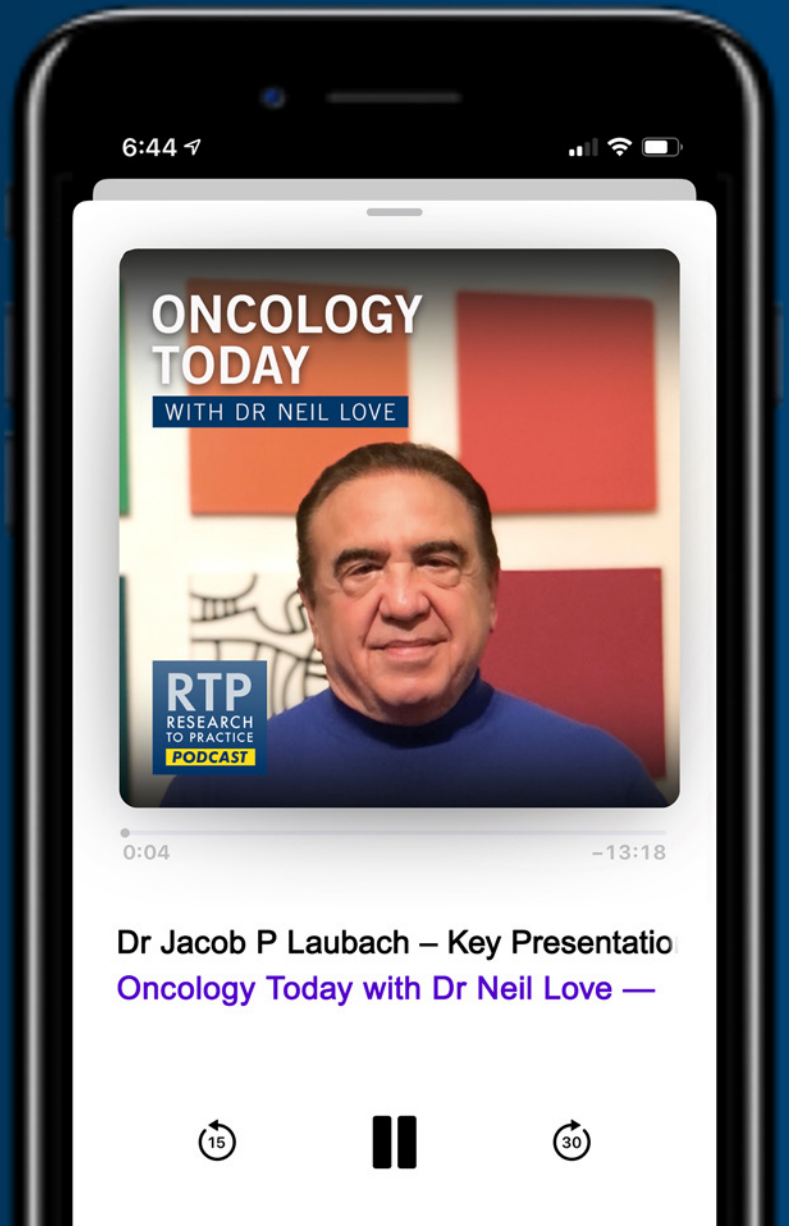

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Data and Safety Monitoring Board/Committee	GSK

Available Data with and Current and Future Role of Bispecific Antibodies in Multiple Myeloma

July 10, 2023

Hans Lee, MD

Associate Professor
Director, Multiple Myeloma Clinical Research
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center

MD ANDERSON

Memorial Sloan Kettering Cancer Center

The Case for Bispecifics in Relapsed/Refractory Multiple Myeloma

Saad Z. Usmani, MD MBA FACP
Chief of Myeloma Service

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Key Data Sets

Hans Lee, MD

- Moreau P et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 2022 August 11;387(6):495-505.
- Moreau P et al. Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). ASCO 2023;Abstract 8011.
- Lee HC et al. LINKER-MM1 study: Linvoseltamab (REGN5458) in patients with relapsed/refractory multiple myeloma. ASCO 2023;Abstract 8006.
- Wong SW et al. Alnuctamab (ALNUC; BMS-986349; CC-93269), a BCMA × CD3 T-cell engager, in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Latest results from a phase 1 first-in-human clinical study. EHA 2023;Abstract P883.
- Mohty M et al. Elranatamab, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, for patients with relapsed/refractory multiple myeloma: Extended follow up and biweekly administration from MAGNETISMM-3. EHA 2023;Abstract S196.

Key Data Sets

Hans Lee, MD (continued)

- Touzeau C et al. Evaluating teclistamab in patients with relapsed/refractory multiple myeloma following exposure to other B-cell maturation antigen (BCMA)-targeted agents. EHA 2022;Abstract S184.
- Nooka AK et al. Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma (RRMM) and prior B-cell maturation antigen (BCMA)-directed therapies: A pooled analysis from MagnetisMM studies. ASCO 2023;Abstract 8008.
- Chari A et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med* 2022 December 15;387(24):2232-44.
- Carlo-Stella C et al. RG6234, a GPRC5D x CD3 T-cell engaging bispecific antibody, is highly active in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Updated intravenous (IV) and first subcutaneous (SC) results from a phase I dose-escalation study. ASH 2022;Abstract 161.
- Lesokhin AM et al. Enduring responses after 1-year, fixed-duration cevostamab therapy in patients with relapsed/refractory multiple myeloma: Early experience from a phase I study. ASH 2022;Abstract 4415.

Key Data Sets

Hans Lee, MD (continued)

- Dholaria BR et al. Talquetamab (tal) + daratumumab (dara) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Updated TRiMM-2 results. ASCO 2023;Abstract 8003.
- Cohen YC et al. First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM). ASCO 2023;Abstract 8002.

Key Data Sets

Saad Zafar Usmani, MD, MBA

- Usmani SZ et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): A multicentre, open-label, single-arm, phase 1 study. *Lancet* 2021 August 21;398(10301):665-74.
- Moreau P et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 2022 August 11;387(6):495-505.
- Voorhees PM et al. A phase 1 first-in-human study of Abbv-383, a BCMA × CD3 bispecific T-cell-redirecting antibody, as monotherapy in patients with relapsed/refractory multiple myeloma. ASH 2022;Abstract 4401.
- Bahlis NJ et al. Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma naïve to B-cell maturation antigen (BCMA)-directed therapies: Results from cohort a of the MagnetisMM-3 study. ASH 2022;Abstract 391.

Key Data Sets

Saad Zafar Usmani, MD, MBA (continued)

- Lesokhin AM et al. Enduring responses after 1-year, fixed-duration cevostamab therapy in patients with relapsed/refractory multiple myeloma: Early experience from a phase I study. ASH 2022;Abstract 4415.
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Agenda

MODULE 1: Biology/Immunology; Overview

MODULE 2: Current Available Data

MODULE 3: Clinical Investigator Survey

MODULE 4: Combinations/Ongoing Trials

MODULE 5: Faculty Cases

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Agenda

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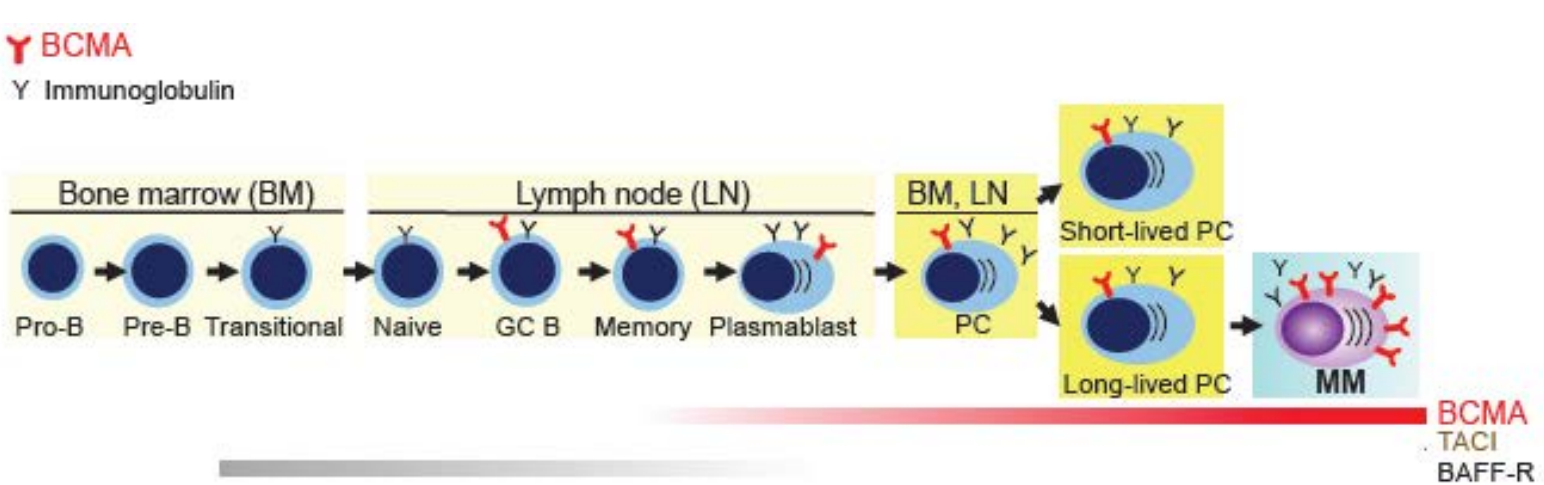
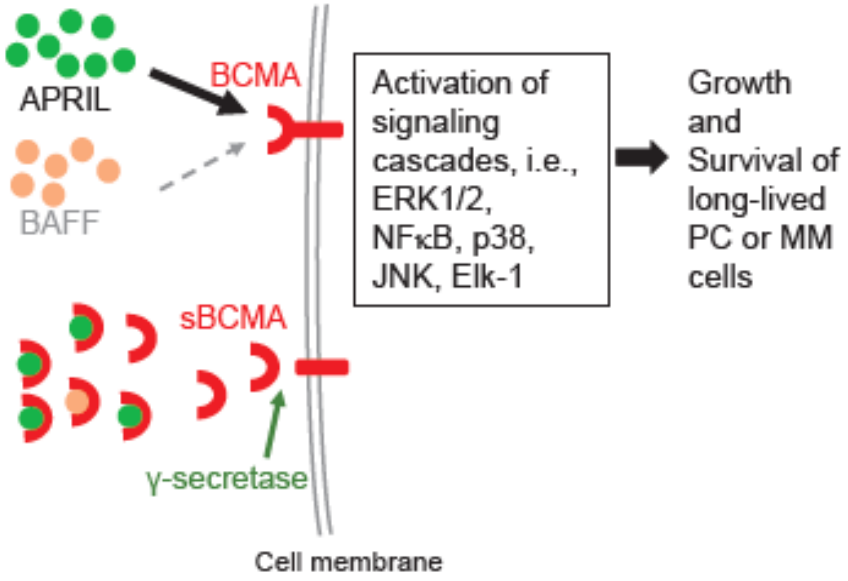
B-cell Maturation Antigen (BCMA)



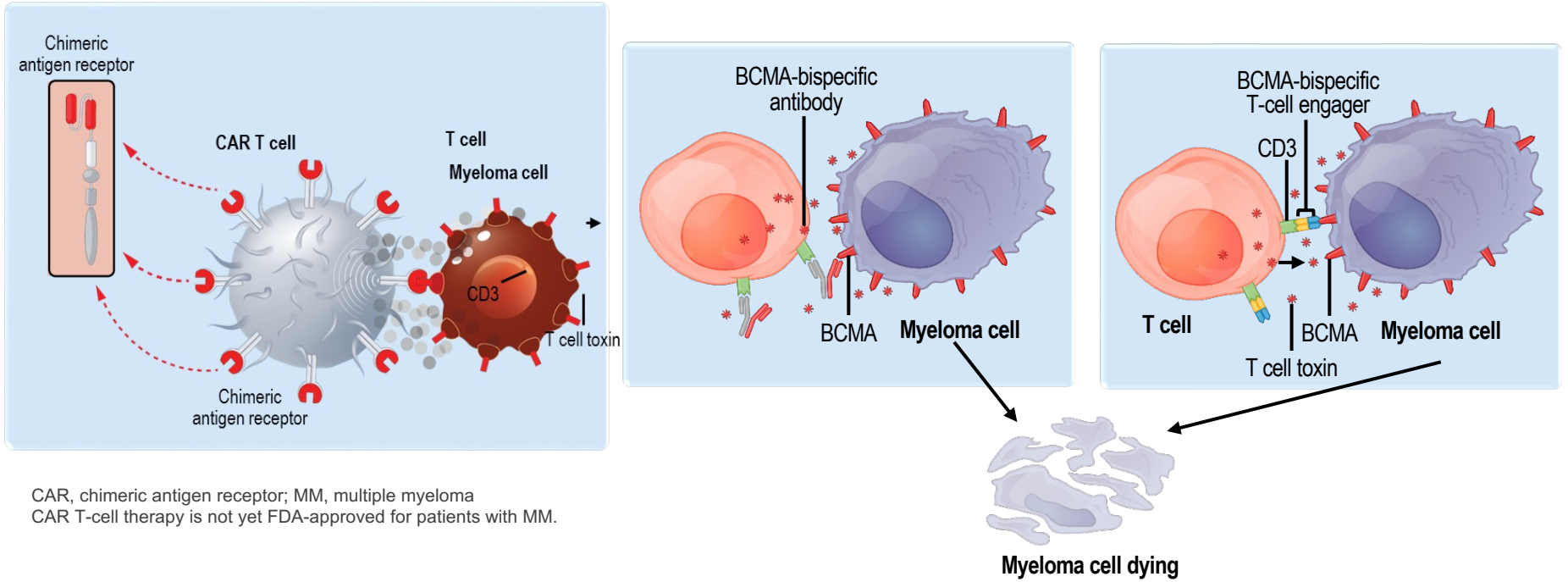


Courtesy of Hans Lee, MD

Cho et al, *Frontiers in Immunology*, 2018

Memorial Sloan Kettering Cancer Center

This is the age of immune therapy in MM therapeutics – our collective aim is cure.



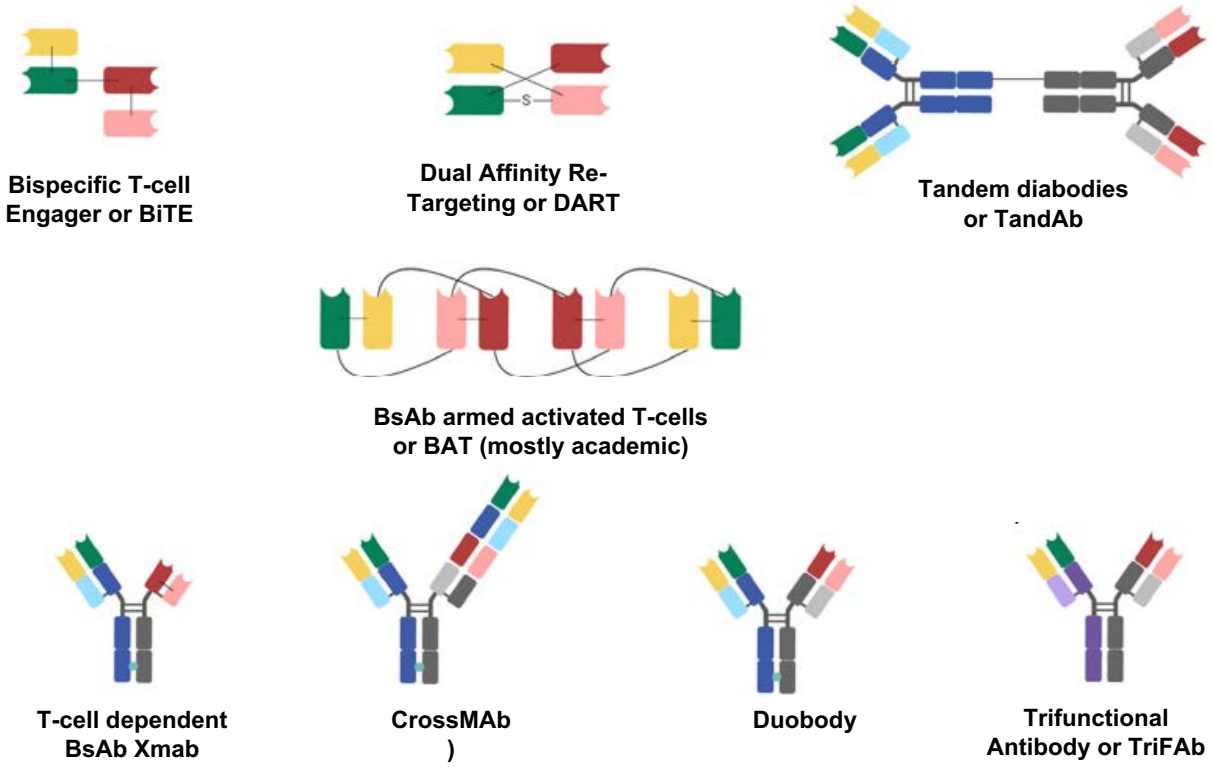
CAR, chimeric antigen receptor; MM, multiple myeloma
CAR T-cell therapy is not yet FDA-approved for patients with MM.

Courtesy of Saad Zafar Usmani, MD, MBA

Adapted from Cho S-F et al. *Front Immunol*. 2018;9:1821.

Memorial Sloan Kettering Cancer Center

Bispecific Antibodies (BsAbs) – Many Different Platforms

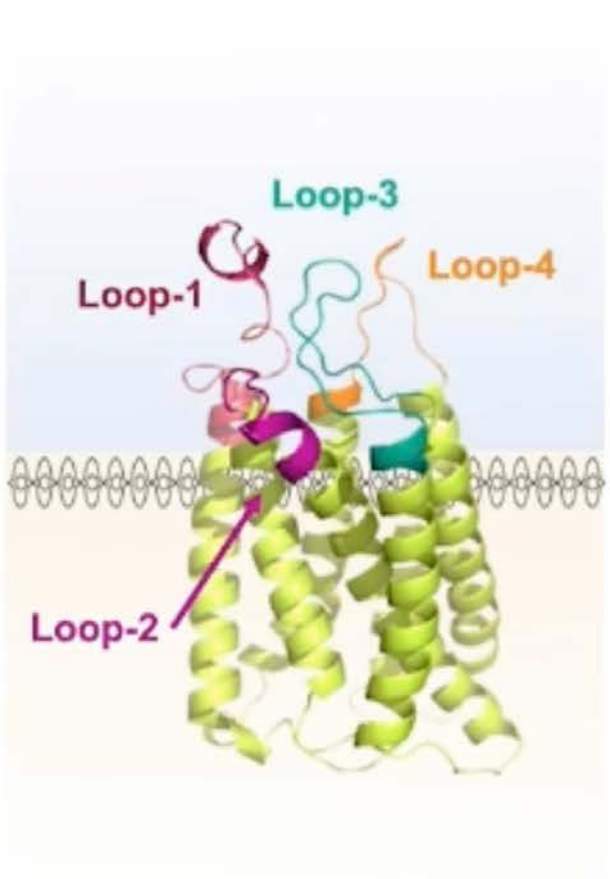


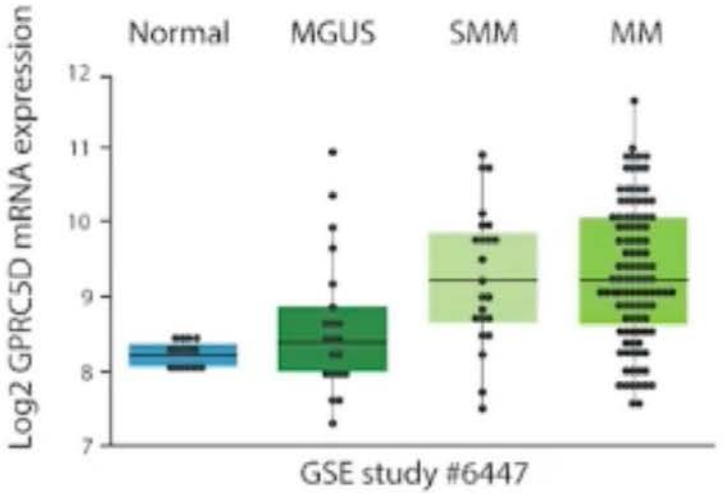
Adapted from Lejeune M et al. Front Immunol 2020 11:762.

Courtesy of Saad Zafar Usmani, MD, MBA

G Protein-Coupled Receptor Class C Group 5 Member D (GPRC5D)

- Orphan G protein-coupled receptor of unknown function
- Limited expression in healthy human tissue, primarily in plasma cells and hair follicles[1-2]
- Highly expressed in myeloma cells and associated with poor prognostic factors in multiple myeloma (MM)[1-3]
- No known shed peptides or extracellular domain shedding (reduced risk for sink effect)
- Ideal target for CD3 redirection



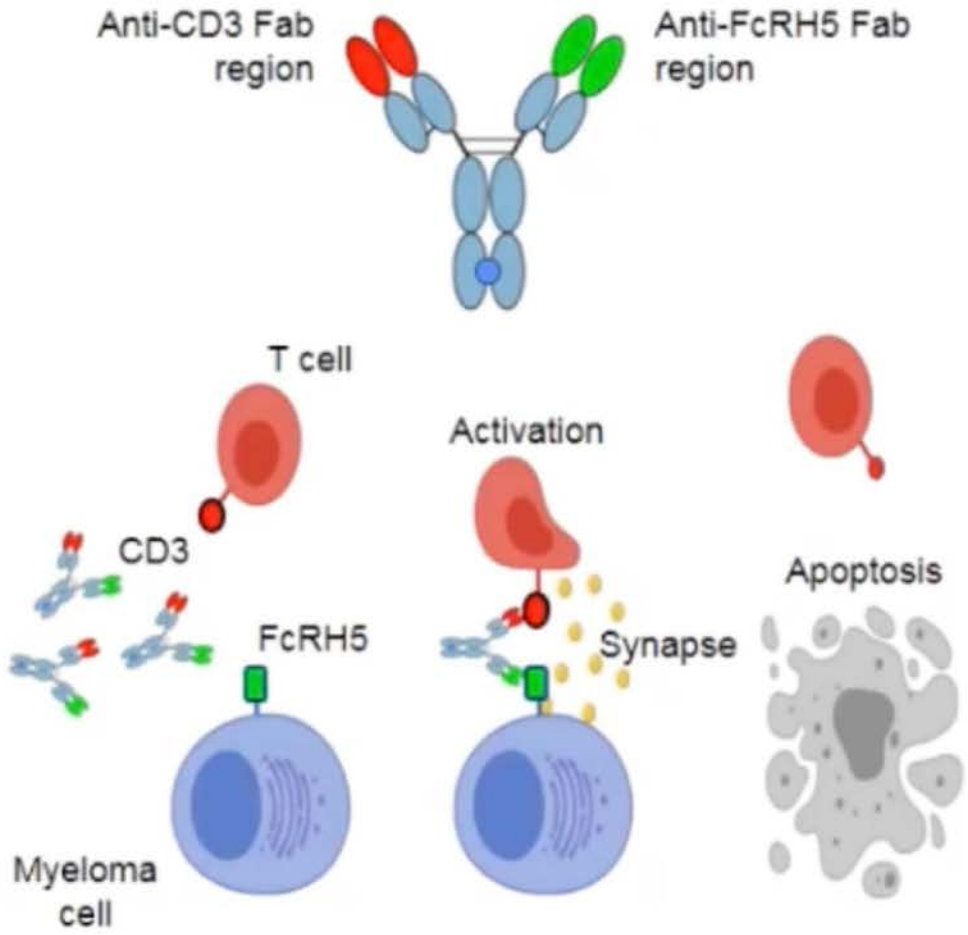


Courtesy of Hans Lee, MD

Chari et al, *ASH Annual Meeting,* 2020

Fc receptor-homolog5 (FcRH5)

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



Courtesy of Hans Lee, MD

Cohen et al, *ASH Annual Meeting,* 2020

BCMA Bispecific T-Cell Antibodies Clinical Data

Drug	N	Route/Schedule	ORR at RP2D or higher doses tested to-date	CRS	Comments
AMG 420	42	4-week continuous IV	70% (400 ug/day, N=10)	All grade (38%), grade 3/4 (2%)	Grade 3 PN (2); 1 death due to hepatic failure (adenovirus)
Alnuctamab	73	SC q week C1-C3, then q2 week C3-6, then q4 week C7+	65%, 57% ≥ VGPR (30 mg, N=26)	All grade (56%), grade 2 (12%), grade 3/4 (0%)	2 BCMA binding domains
Teclistamab	165	SC q week	63%, 59% ≥ VGPR	All grade (72%), grade 2 21%, Grade 3/4 (1%)	Median PFS 12.4 months Median DOR 24 months
TNB-383B (ABBV-383)	75	IV q3 weeks	60%, 43% ≥ VGPR (60 mg, N=60)	All grade (72%), grade 3/4 (2%)	No step-up dosing; 2 BCMA binding domains with attenuated CD3 binding domain
Linvoseltamab	252	IV q week, then q2 weeks starting week 16, then q4 weeks starting week 24 if ≥ VGPR	71%, 59% ≥ VGPR (200 mg cohort, N=117)	All grade (45%), grade 2 (9%), grade 3 (1%), (200 mg cohort, N=227)	6-month median DOR: 84% 6-month median PFS: 73%
AMG 701	85	IV q week	83%, 50% ≥ VGPR (18 mg, N=6)	All grade (65%), grade 3 (9%), grade 4 (0%)	
Elranatamab	123	SC q week, then q2 weeks after 6 cycles with ≥ PR for ≥ 2 months	61%, 55% ≥ VGPR (76 mg SC, N=123) (MagnetisMM-3)	All grade (56%), grade 2 (14%); grade 3/4 (0%)	12 month median DOR: 74% 12-month median PFS: 57%

Topp et al, JCO, 2020; Wong et al, EHA 2023; Mohty et al EHA 2023; D'Souza et al, *JCO,* 2022; Lee et al, ASCO 2023; Harrison et al, ASH 2020; Bahlis et al, ASH 2022

Courtesy of Hans Lee, MD

Non-BCMA Bispecific T-Cell Antibodies in Clinical Development

Drug	N	Route/Schedule	ORR at RP2D or higher doses tested to-date	CRS	Comments
Talquetamab (GPRC5D x CD3)	74	SC q week SC q2 weeks	74%, 59% ≥ VGPR (0.4 mg/kg q week, N=143) 73%, 57% ≥ VGPR (0.8 mg//kg q2 weeks, N=145)	79% All grade, 2% grade 3/4 (0.4 mg/kg q week, N=143) 72% All grade, 1% grade 3/4 (0.8 mg//kg q2 weeks, N=145)	Other unique AEs: dysgeusia, skin exfoliation, nail disorders 50% ORR (8/16) in prior BCMA bispecific or CART
RG6234 (GPRC5D x CD3)	51	IV q2 week x 1 year **(fixed duration)** SC q2 weeks x 1 year **(fixed duration)**	71%, 57% ≥ VGPR (IV, N = 49) 60%, 40% ≥ VGPR (SC, N=48)	82% All grade, 2% grade ≥ 3 (IV) 78% All grade, 2% grade ≥ 3 (IV)	2:1 (GPRC5D:CD3) configuration 56% ORR (10/18) prior BCMA exposed
Cevostamab (FcRH5 x CD3)	161	IV q3 weeks x 17 cycles **(fixed duration)**	57% (132-198 mg, N=60)	All grade (81%) Grade 3/4 (1%)	14% ICANS (all grade 1/2) 33% prior BCMA exposed 8/16 patients maintained response ≥ 6 months after stopping therapy

Chari et al, *NEJM,* 2022; Chari et al, *ASH* 2022; Carlo-Stella et al, *ASH,* 2022; Trudel et al, *ASH* 2021; Lesokhin et al, ASH 2022.

Courtesy of Hans Lee, MD

Agenda

MODULE 1: Biology/Immunology; Overview

MODULE 2: Current Available Data

MODULE 3: Clinical Investigator Survey

MODULE 4: Combinations/Ongoing Trials

MODULE 5: Faculty Cases

Memorial Sloan Kettering Cancer Center

Teclistamab – 1st EMA/FDA Approved BsAb for MM

Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study

Lancet 2021; 398: 665–74

Saad Z Usmani, Alfred L Garfall, Niels W C J van de Donk, Hareth Nahi, Jesus F San-Miguel, Albert Oriol, Laura Rosinol, Ajai Chari, Manisha Bhutani, Lionel Karlin, Lotfi Benboubker, Lixia Pei, Raluca Verona, Suzette Girgis, Tara Stephenson, Yusri Elsayed, Jeffrey Infante, Jenna D Goldberg, Arnob Banerjee, María-Victoria Mateos, Amrita Krishnan

The NEW ENGLAND JOURNAL of MEDICINE

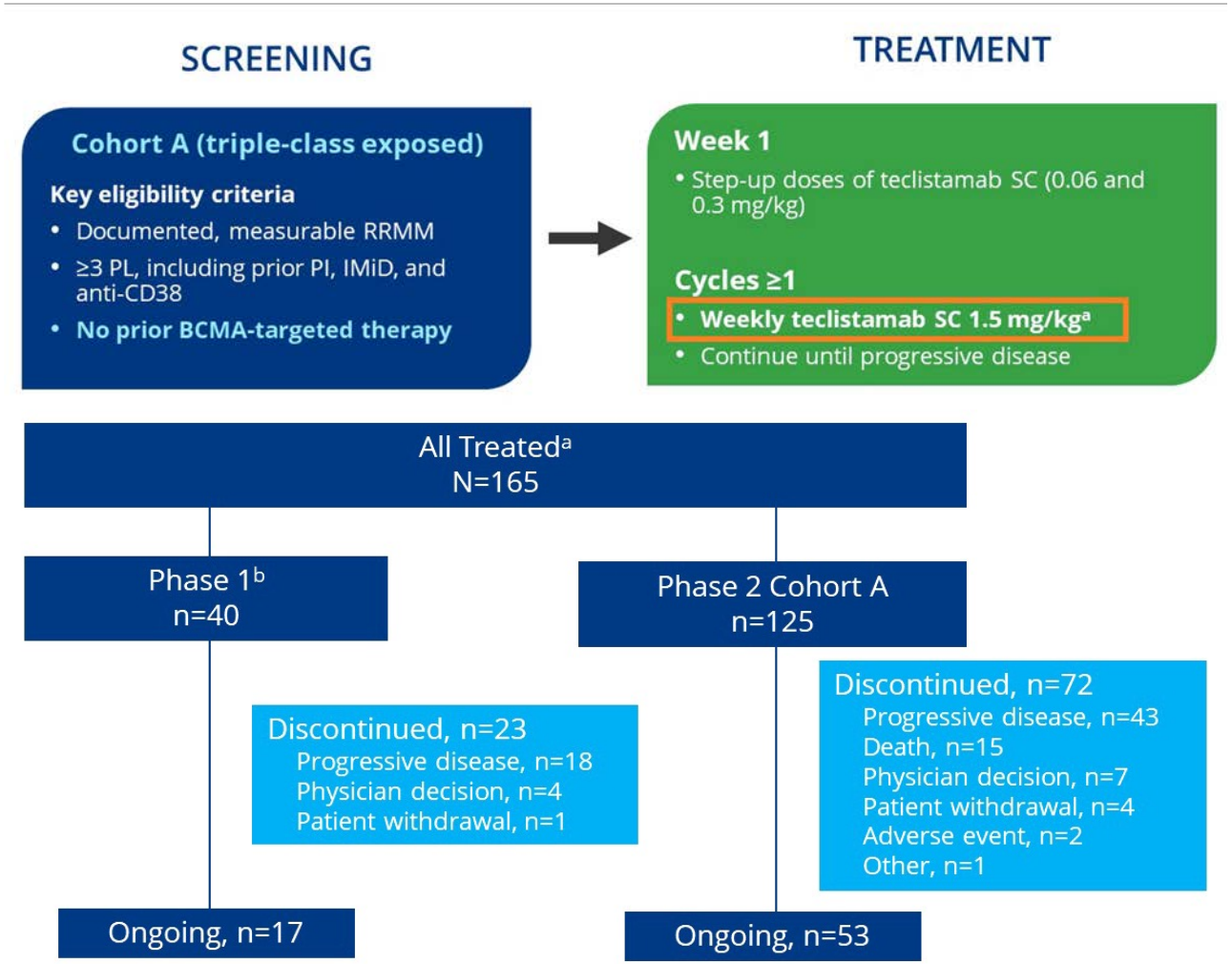
ESTABLISHED IN 1812 AUGUST 11, 2022 VOL. 387 NO. 6

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

Courtesy of Saad Zafar Usmani, MD, MBA

Teclistamab – MajesTEC-1

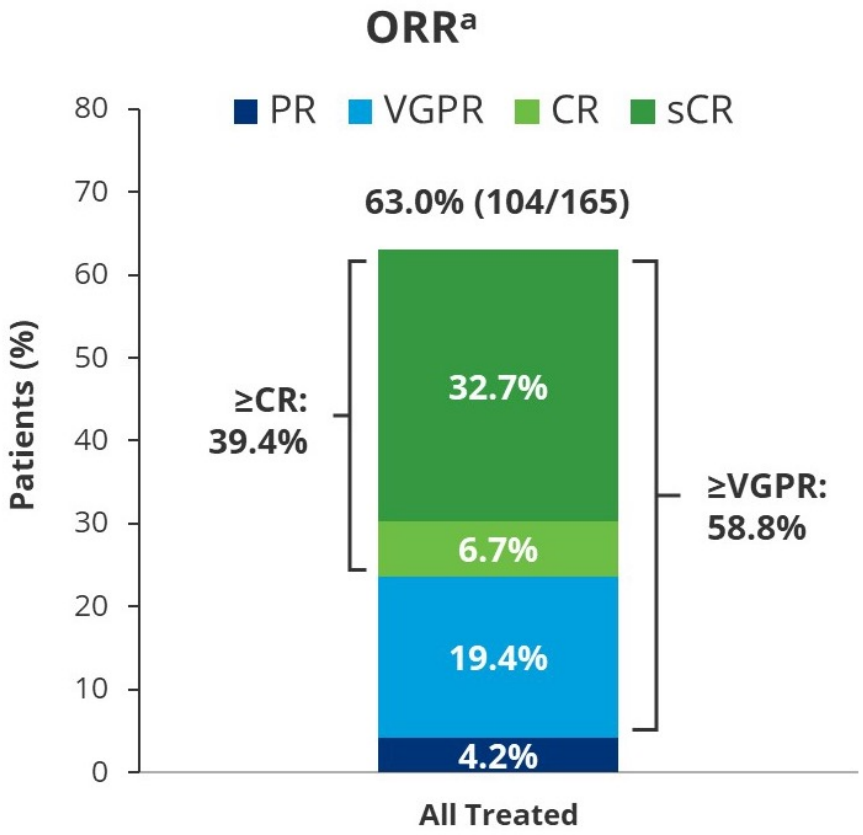


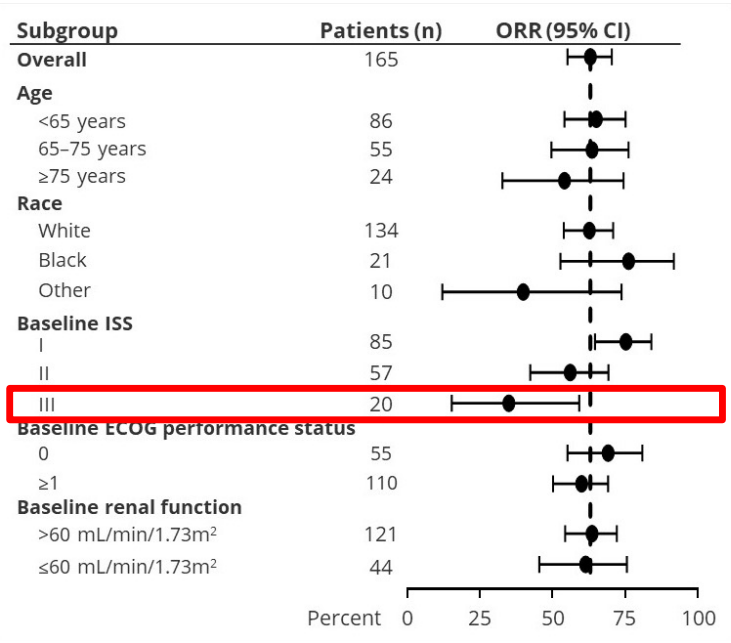
Patients with confirmed complete response (CR) or better for ≥6 months (phase 2) could switch to q2 week dosing

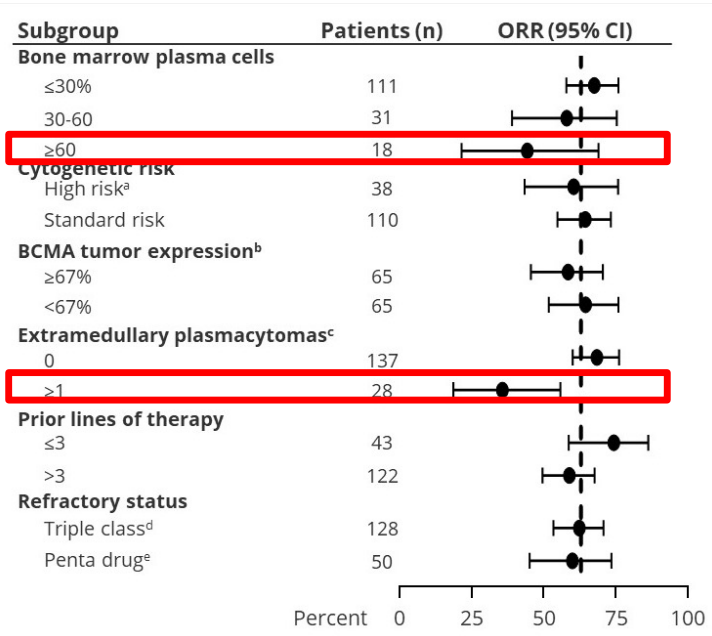
Courtesy of Hans Lee, MD

Nooka et al, *ASCO* 2022; Moreau et al, *NEJM*, 2022

Teclistamab – MajesTEC-1 (Efficacy)



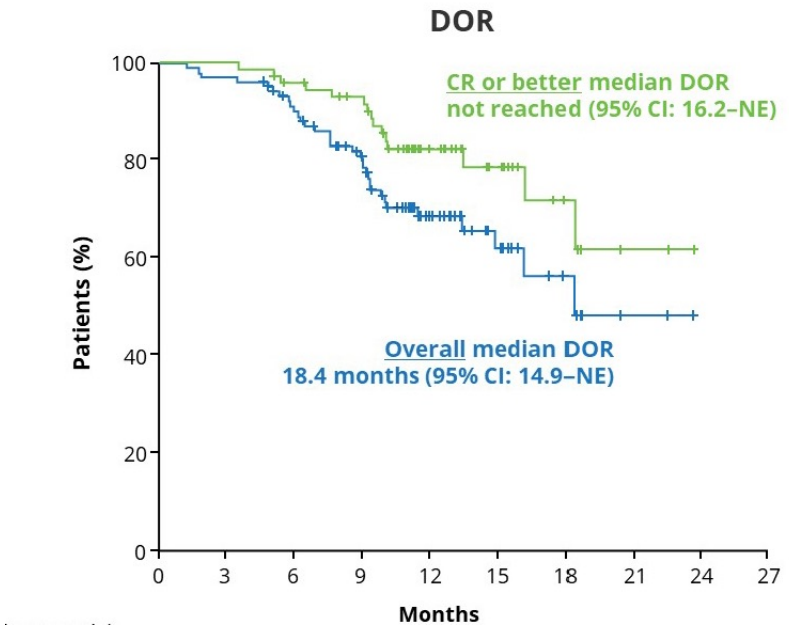


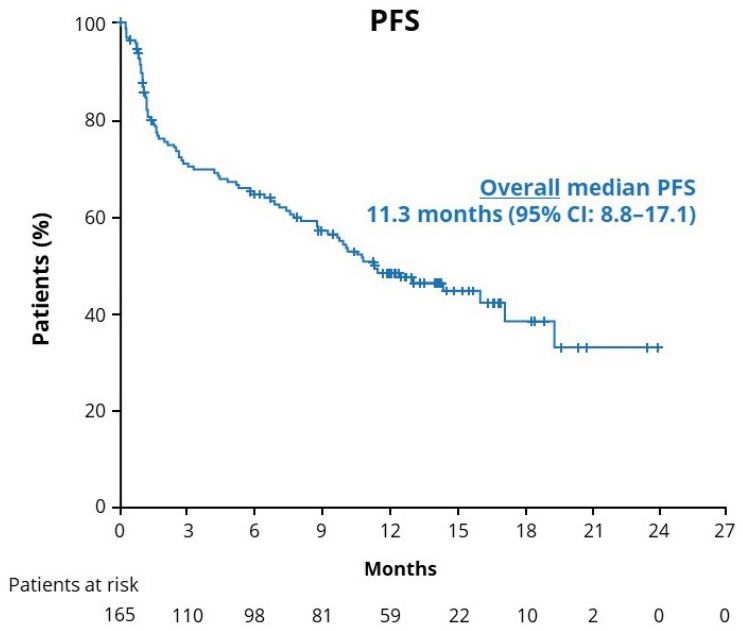


Courtesy of Hans Lee, MD

Nooka et al, *ASCO* 2022; Moreau et al, *NEJM*, 2022

Teclistamab – MajesTEC-1 (Efficacy)





Updated ASCO 2023 Data (22-month follow-up)

Median DOR: 24 months

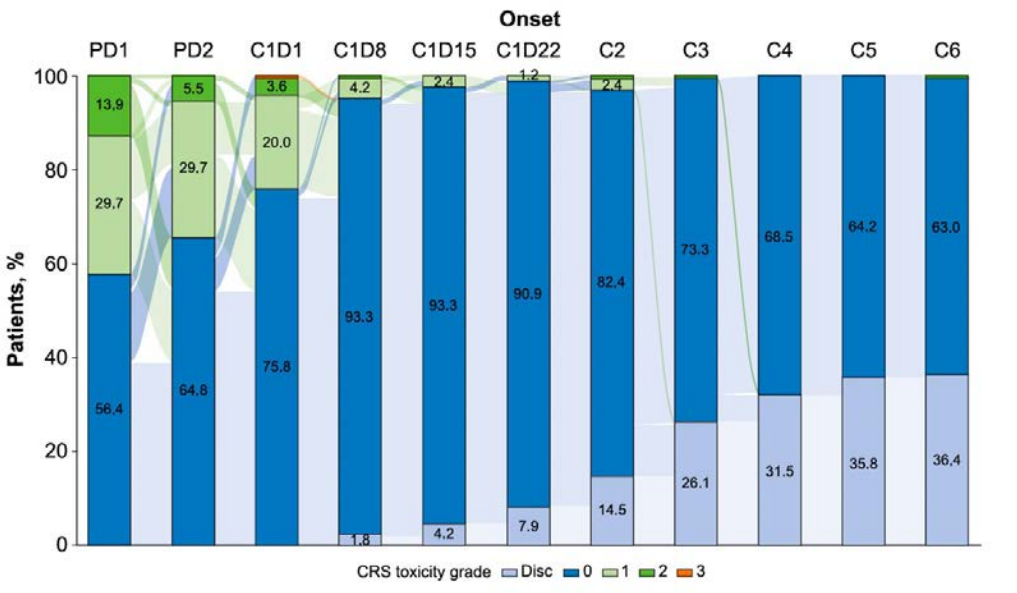
Median PFS: 12.5 months

Patients who transitioned from QW to Q2W dosing: median DOR of 20.5 months from the date of switch.

Courtesy of Hans Lee, MD

Nooka et al, *ASCO* 2022; Moreau et al, *NEJM*, 2022, Moreau et al, *ASCO,* 2023 , Bhutani et al, ASCO 2023.

CRS Onset and Management in Patients Receiving Teclistamab on the MajesTEC-1 Study



CRS events, No. (%)	CRS events managed with tocilizumab (*N* = 68)	CRS events not managed with tocilizumab (*N* = 127)
CRS events, any grade	68 (100)	127 (100)
Subsequent CRS events	13 (19.1)	63 (49.6)
Grade 1 CRS events	31 (45.6)	122 (96.1)
Subsequent CRS events (any grade)[a]	4 (12.9)	61 (50.0)
Subsequent CRS events (grade ≥2)[a]	1 (3.2)	3 (2.5)
Grade ≥2 CRS events	37 (54.4)	5 (3.9)
Subsequent CRS events (any grade)[b]	9 (24.3)	2 (40.0)
Subsequent CRS events (grade ≥2)[b]	6 (16.2)	0

Note: Table shows numbers of events (overall, 119 patients experienced 195 CRS events in the study). CRS was graded according to American Society for Transplantation and Cellular Therapy criteria.[6]

Abbreviation: CRS, cytokine release syndrome.

[a]Percentages based on the number of grade 1 CRS events as denominator.

[b]Percentages based on the number of grade ≥2 CRS events as denominator.

Martin TG et al. *Cancer* 2023;129(13):2035-46.

Teclistamab: Step-Up Dosing

Step-up doses

Step-up dose 1
(0.06 mg/kg)

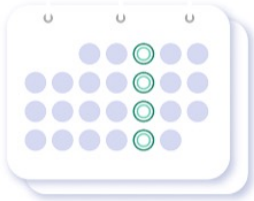
Step-up dose 2
(0.3 mg/kg)

First treatment dose
(1.5 mg/kg)

*Step-up dose 2 may be given between 2 to 4 days after step-up dose 1 and may be given up to 7 days after step-up dose 1 to allow for resolution of adverse reactions.
†First treatment dose may be given between 2 to 4 days after step-up dose 2 and may be given up to 7 days after step-up dose 2 to allow for resolution of adverse reactions.

Due to the risk of CRS and neurologic toxicity, including ICANS, patients should be hospitalized for 48 hours after administration of all doses within the TECVAYLI™ step-up dosing schedule.

After step-up doses, once weekly dosing



(1.5 mg/kg)

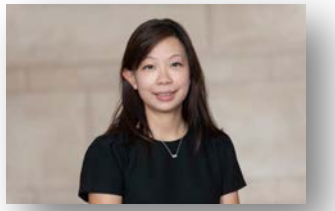
Until disease progression or unacceptable toxicity

Remember: Dose is based on actual body weight. Dose reductions are not recommended, and dose delays may be required to manage toxicities.

https://tecvaylirems.com/#Main

RTP RESEARCH TO PRACTICE

Memorial Sloan Kettering Cancer Center



Commercial Teclistamab Use at MSKCC

- Oct-Nov 2022: P/T Committee packet for institutional approvals, SOP development, staff training, REMS registration, etc.
- Phase I (Nov 2022-March 2023): Inpatient monitoring , assess safety data.
- Phase II (April 2023-onwards): Early discharge after step-up dosing all pts, early intervention with Toci for persistent fevers.
- Phase III (June 2023-onwards): All outpatient dosing for selected pts
- Dosing schedule: Response adapted reduction in dosing frequency.

Courtesy of Saad Zafar Usmani, MD, MBA

Linvoseltamab – LINKER-MM1 study

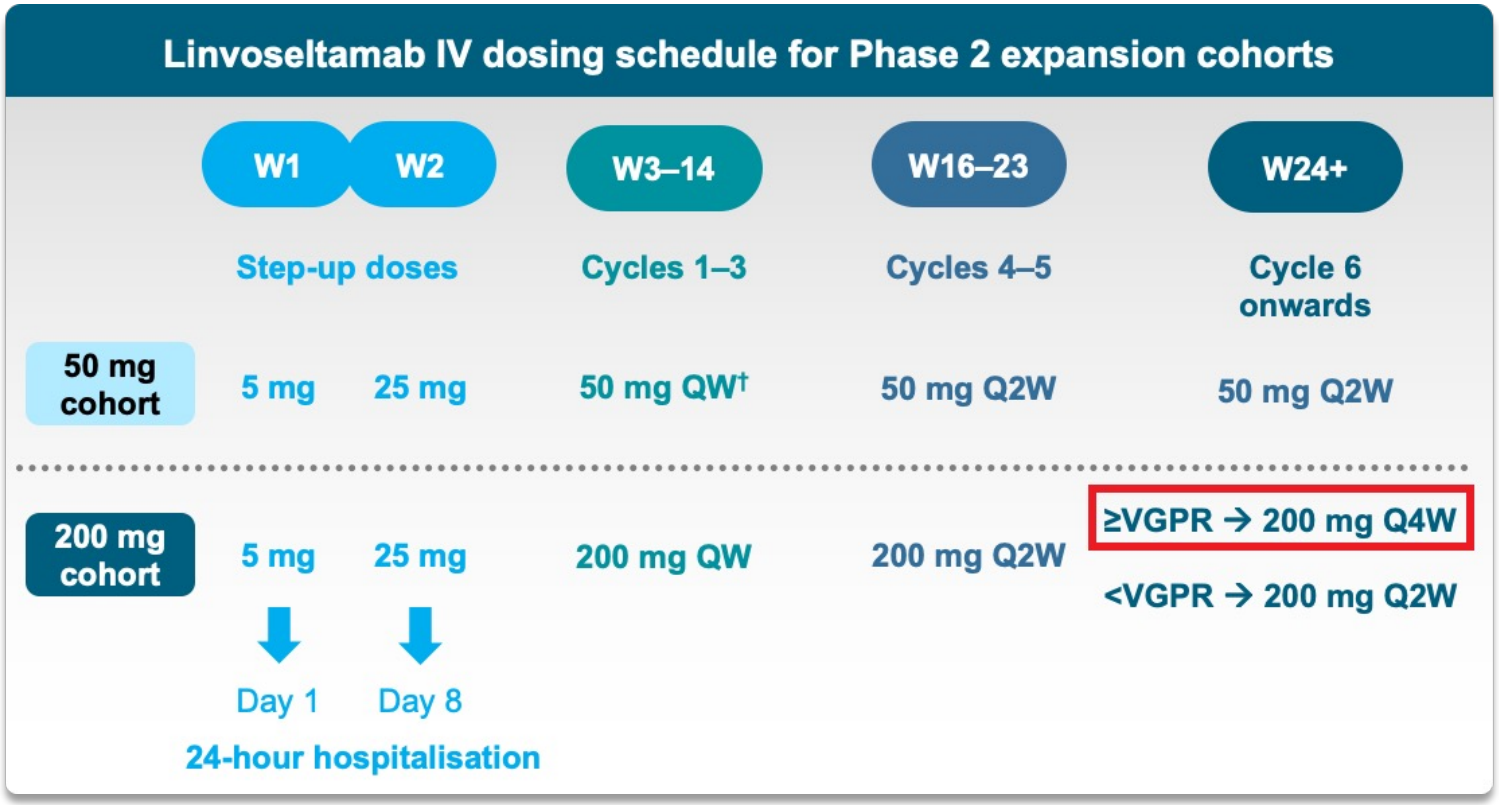
Key eligibility criteria for Phase 2

- Active MM by IMWG criteria
- Progression on or after at least three lines of therapy, including an IMiD, a PI and an anti-CD38 Ab, or triple-refractory disease (refractory to at least one IMiD + one PI + one anti-CD38 Ab)

Key Phase 2 objectives

- Primary: to assess the antitumour activity as measured by ORR as determined by a blinded IRC (IMWG criteria)
- Secondary: ORR by investigator assessment, DOR, PFS, MRD status and OS

Linvoseltamab IV dosing schedule for Phase 2 expansion cohorts



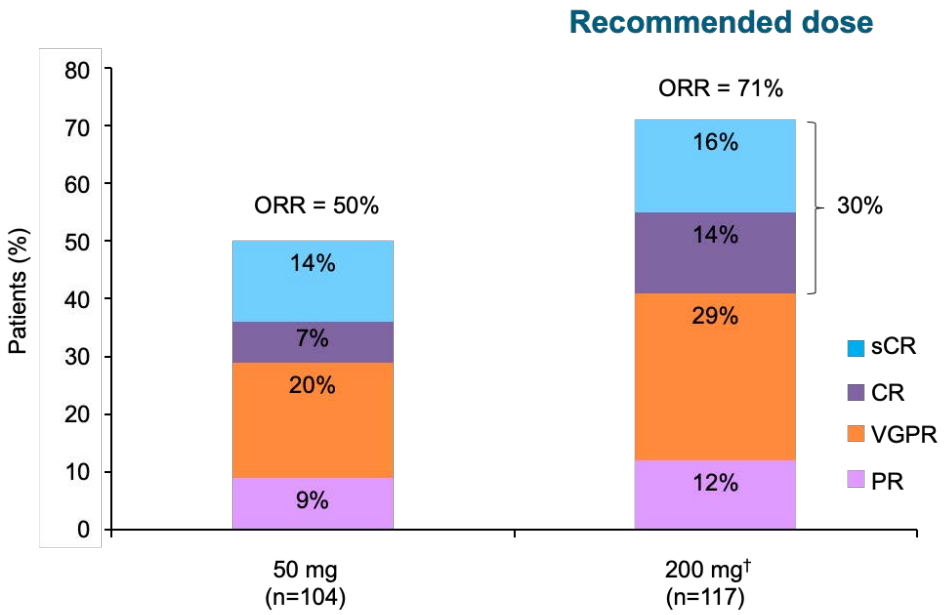
†Patients in the 50 mg cohort who progress within 4–12 weeks of treatment were allowed to escalate to 200 mg dosing.

Ab, antibody; CD, cluster of differentiation; DOR, duration of response; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IRC, independent review committee; IV, intravenous; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; QW, once every week; Q2W, once every 2 weeks; Q4W, once every 4 weeks; VGPR, very good partial response; W, week.

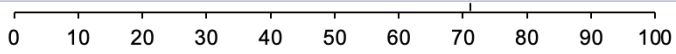
Courtesy of Hans Lee, MD

Lee et al, *ASCO* 2023

Linvoseltamab – LINKER-MM1 study (Efficacy)



Subgroup		Responders	Total (N)	ORR (95% CI)
Age	18–64	29	44	65.9 (50.1, 79.5)
	65–74	33	42	78.6 (63.2, 89.7)
	≥75	21	31	67.7 (48.6, 83.3)
Race	White	61	83	73.5 (62.7, 82.6)
	Non-White	20	31	64.5 (45.4, 80.8)
ISS stage	I	33	45	73.3 (58.1, 85.4)
	II	32	44	72.7 (57.2, 85.0)
	III	13	22	59.1 (36.4, 79.3)
EMP status	Without EMP	73	100	73.0 (63.2, 81.4)
	With EMP	9	16	56.3 (29.9, 80.2)
Cytogenetic risk	Standard	55	71	77.5 (66.0, 86.5)
	High	26	42	61.9 (45.6, 76.4)
Baseline BMPC	<50%	48	62	77.4 (65.0, 87.1)
	≥50%	13	26	50.0 (29.9, 70.1)
Baseline soluble BCMA	<400 ng/mL	48	57	84.2 (72.1, 92.5)
	≥400 ng/mL	28	51	54.9 (40.3, 68.9)
Refractory status (mutually exclusive categories)	Triple-refractory	13	19	68.4 (43.4, 87.4)
	Quad-refractory	30	39	76.9 (60.7, 88.9)
	Penta-refractory	17	28	60.7 (40.6, 78.5)



Data cut-off: 28 Feb 2023.

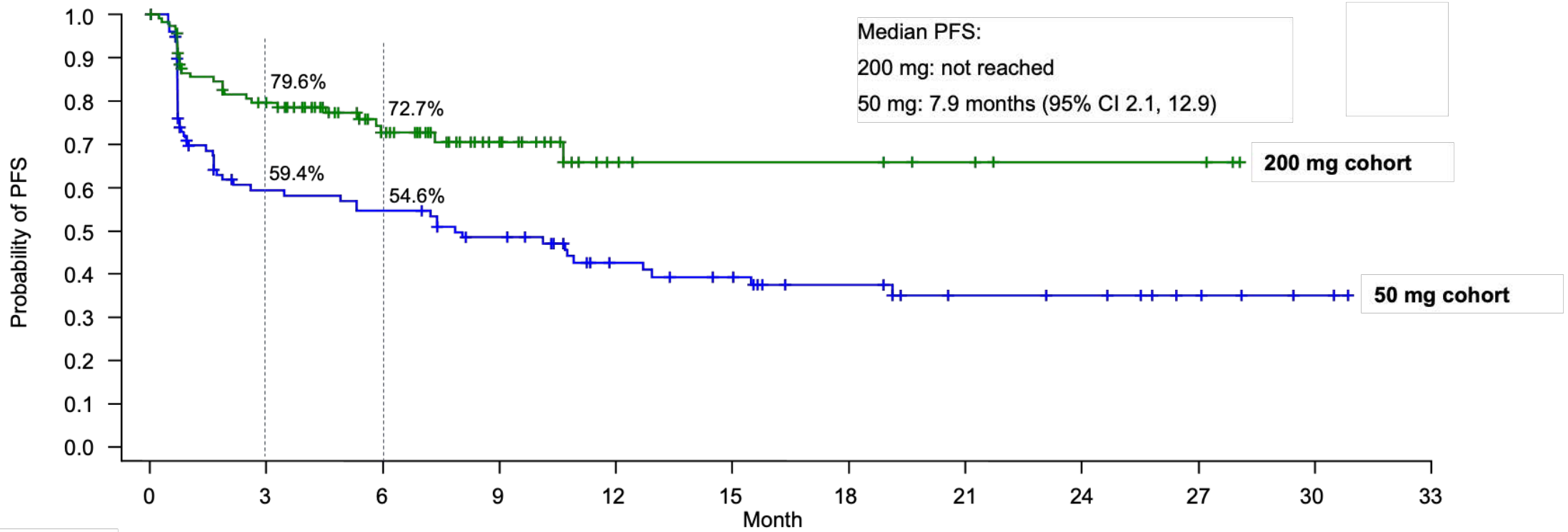
†Includes patients from dose escalation and dose expansion parts of the study.

BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; CI, confidence interval; EMP, extramedullary plasmacytoma; ISS, International Staging System; ORR, objective response rate.

Courtesy of Hans Lee, MD

Lee et al, *ASCO* 2023

Linvoseltamab – LINKER-MM1 study (Efficacy)



50 mg cohort, n	104	50	46	38	26	22	16	10	9	5	2	0
200 mg cohort, n	117	79	43	24	9	7	7	5	3	3	0	0

Data cut-off: 28 Feb 2023. Median duration of follow-up for 50 mg was 7.7 months (range 0.3–31.3) and for 200 mg was 5.6 months (range 0.2–28.2).

†PFS as measured using the IMWG criteria[1]

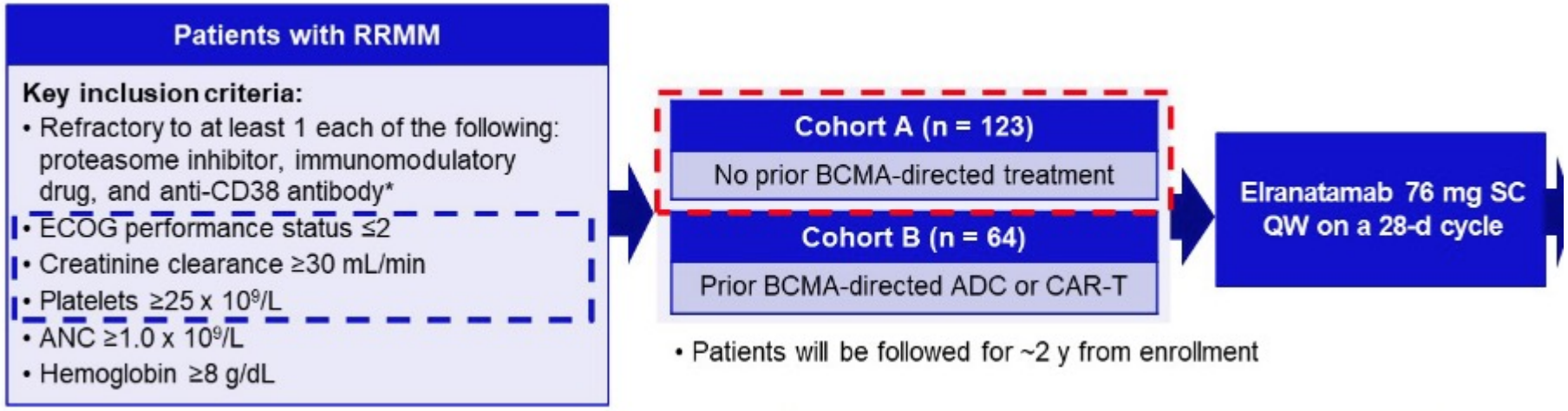
[1]Kumar S, et al. *Lancet Oncol*. 2016;17:8,E328-E346

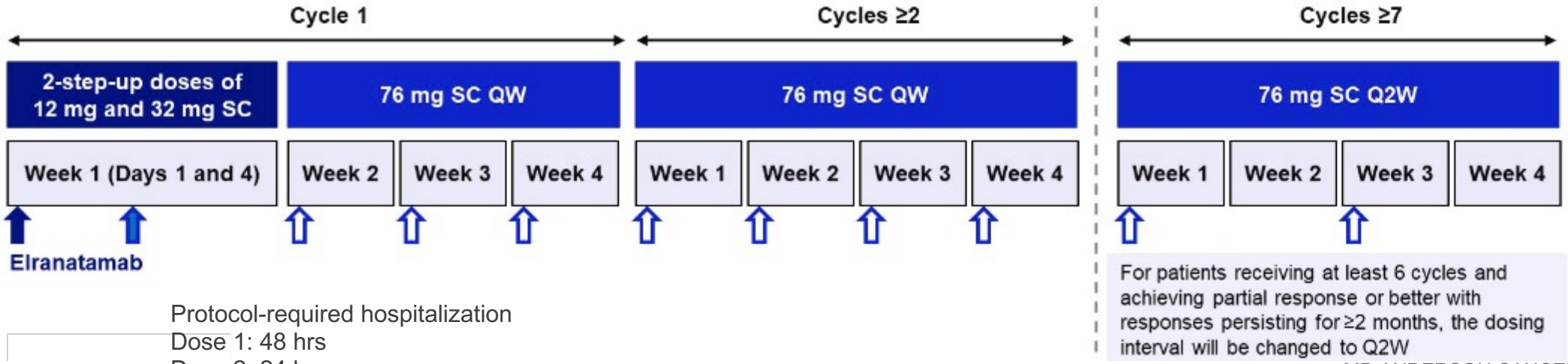
CI, confidence interval; IMWG, International Myeloma Working Group; PFS, progression-free survival.

Courtesy of Hans Lee, MD

Lee et al, *ASCO* 2023

Elranatamab - MagnetisMM-3 Study - Schema





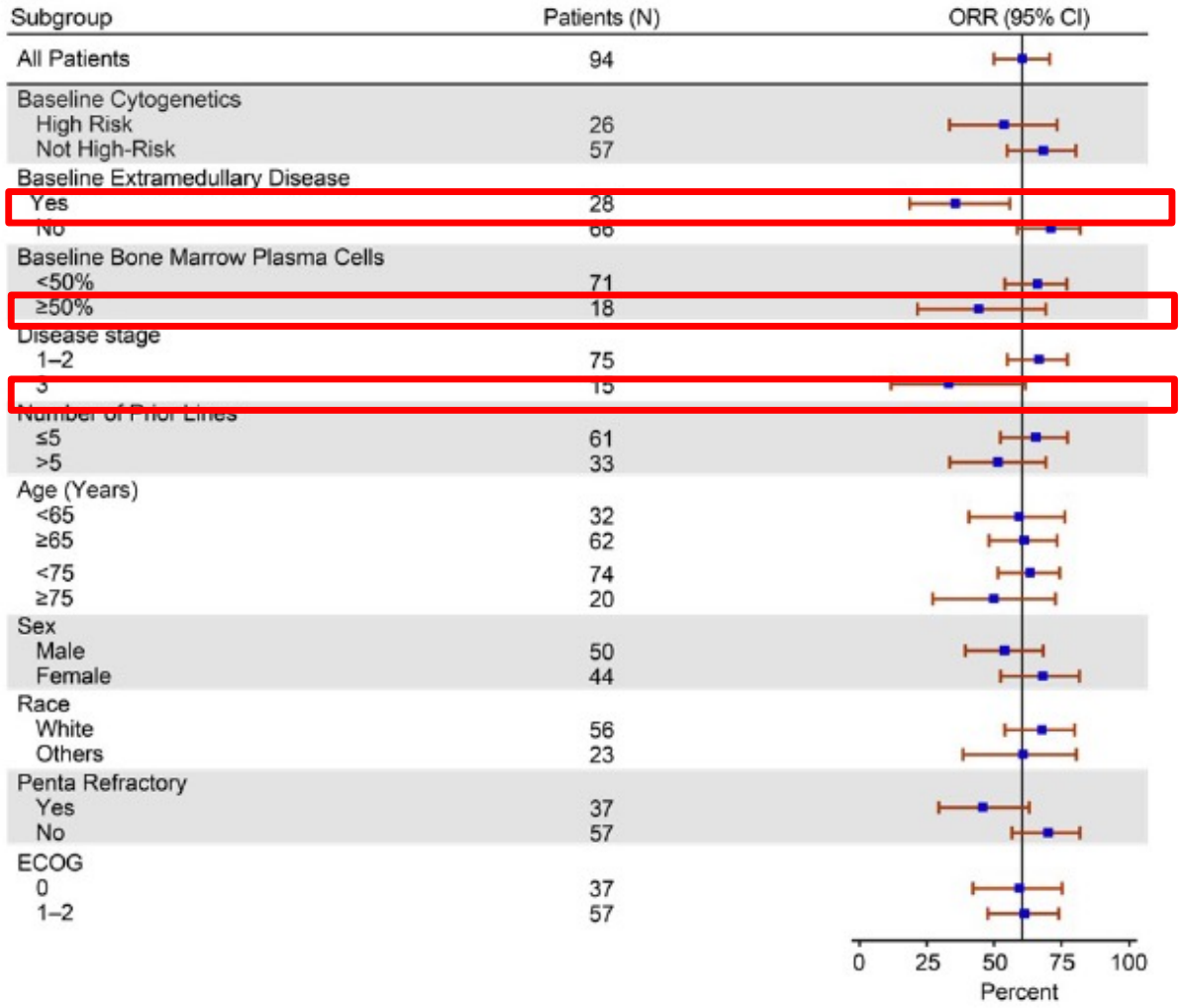
Protocol-required hospitalization
Dose 1: 48 hrs
Dose 2: 24 hrs

Courtesy of Hans Lee, MD

Mohty et al, EHA 2023

Elranatamab - MagnetisMM-3 (Efficacy)

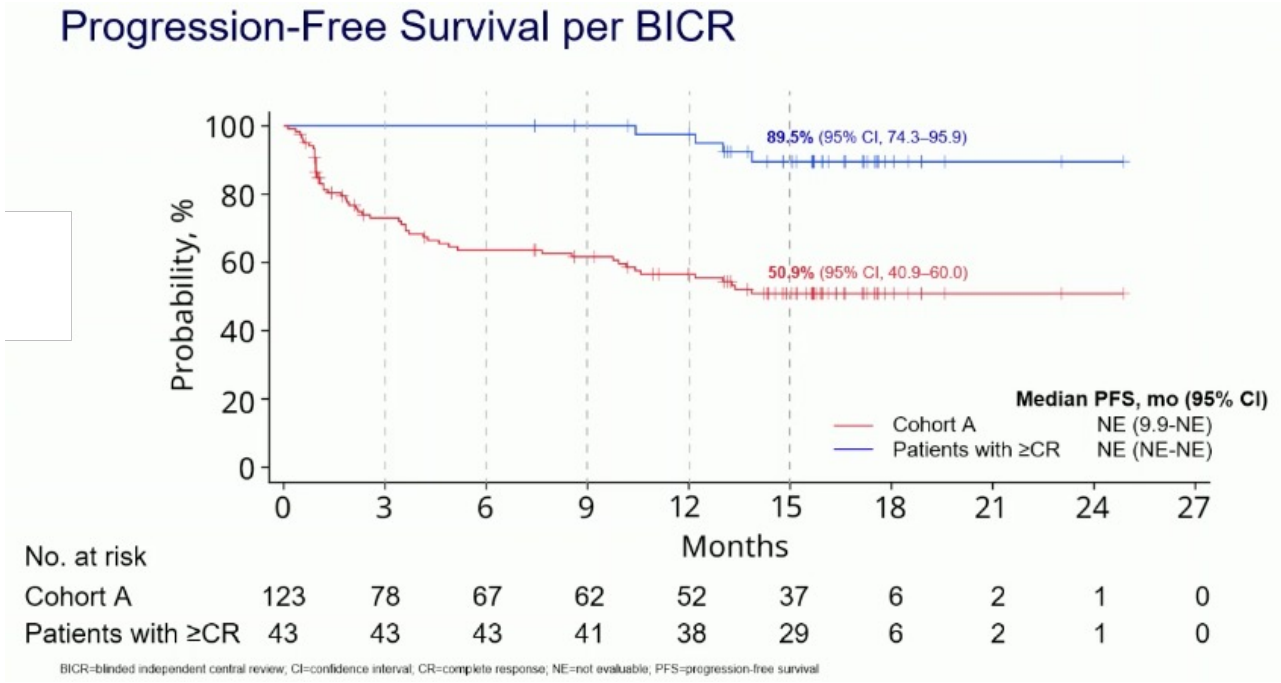
ORR: 61%, 55% ≥ VGPR



Courtesy of Hans Lee, MD

Bahlis et al, ASH 2022; Mohty et al, EHA 2023

Elranatamab - MagnetisMM-3 (Efficacy)



Updated EHA 2023 Data (14.7-month follow-up)

12-month median: DOR: 74%

12-month median: PFS: 57%

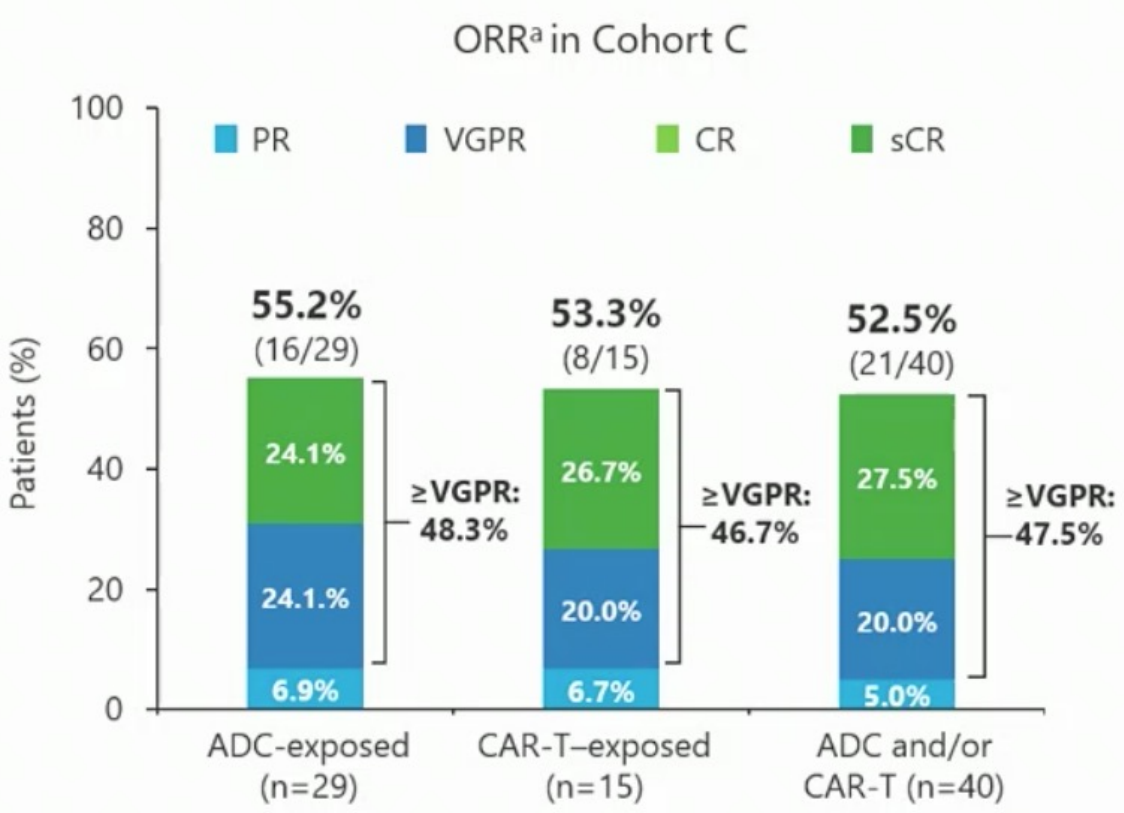
Patients that transitioned to q2 week dosing: 40 (80%) patients switched to q2 week dosing and maintained or improved response ≥ 6 months after switch

Mohty et al, EHA 2023

Sequencing BCMA-Directed Immunotherapies CART and/or ADC -> Bispecific

Teclistamab Cohort C of MagesTEC-1 Study

Characteristic	N=40
Prior lines of therapy, median (range)	6 (3–14)
Prior stem cell transplantation, n (%)	36 (90.0)
Exposure status, n (%)	
Triple-class[d]	40 (100)
Penta-drug[e]	32 (80.0)
BCMA-targeted treatment	40 (100)[f]
ADC	29 (72.5)
CAR-T	15 (37.5)
Refractory status, n (%)	
Triple-class[d]	34 (85.0)
Penta-drug[e]	14 (35.0)
To last line of therapy	34 (85.0)

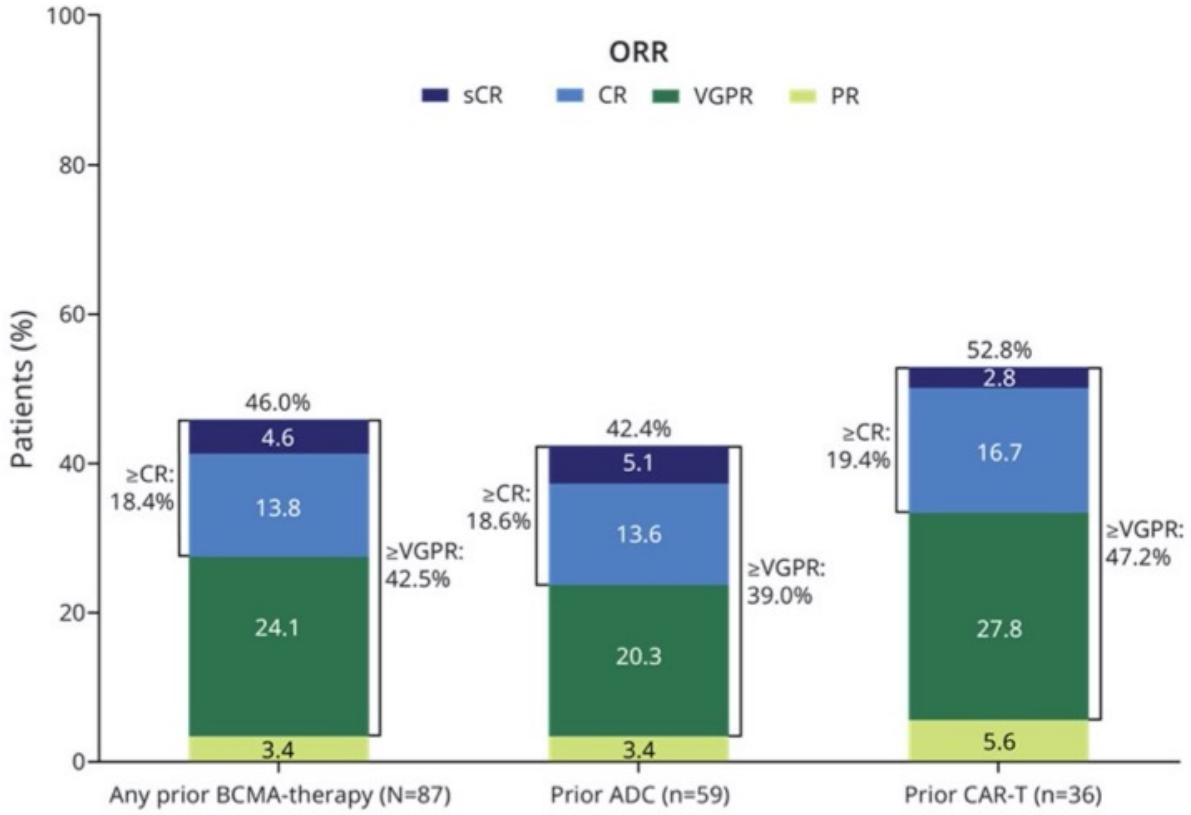


Courtesy of Hans Lee, MD

Tozeau et al, *EHA*, 2022

Sequencing BCMA-Directed Immunotherapies
CART and/or ADC -> Bispecific

Pooled Analysis of Elranatamab in MagnetisMM-1, MagnetisMM-2, MagnetisMM-3, MagnetisMM-9 studies



Median PFS: 5.5 months
- **Prior ADC PFS: 3.9 months**
- **Prior CAR-T PFS: 10.0 months**

Median DOR: 17.1 months
- **Prior ADC DOR: 13.6 months**
- **Prior CAR-T DOR: NE**

Courtesy of Hans Lee, MD

Nooka et al, *ASCO*, 2023

Memorial Sloan Kettering Cancer Center

Summary of BCMA Bispecific Antibodies

	Teclistamab (n=165)	Linvoseltamab (n=167)	ABBV-383 (n=118)	Elranatamab (n=123)	Alnuctamab (n=68)
Route	SC	IV	IV	SC	SC
Dose and schedule	1.5mg/kg/QW	Q1W x 16w W≥16: Q2W	Q3W	76mg/Q1W C≥7: Q2W if PR	Q1W x 8 w Q2W C3-C7 C≥7 Q4W
Median prior LoT	5 (2-14)	6 (2-17)	5 (1-15)	5 (2-12)	4 (3-11)
Triple refractory	77.6%	90%	61%	96%	63%
CRS, G≥3	72.1%, 0.6%	47.9%, 0.6%	54%, 3%	57.7%, 0%	53%, 0%
Neurotoxicity, G≥3	3%, 0	4%, 0	NR, 6 pts	4, 3.4	2 pts, 3%
Infections, G≥3	76.4%, 44.8%	NR	32%, 17%	66.7%, 35%	34%, 9%
ORR (%)	63%	75% 200-800 mg	60%/81%* *at ≥40 mg	61%	53%
≥CR (%)	39.4%	16%	20%/30%*	27.6%	23%
Median PFS (m) (95% CI)	11.3 m (8.8-17.1)	Not reported	Not reported	NE (10.4-NE)	Not reported
Median DoR (m) (95% CI)	18.4 m (14.9-NE)	Not reached	Not reported	NE (12.0-NE)	Not reported
MRD – (10^{-5})	26.7%	4/10	Not reported	90.9% (n=22)	16/20

Moreau P et al. NEJM 2022; Bahlis N et al. ASH 2022; Wong S et al. ASH 2022; Voorhees PM et al. ASH 2022 ;

Courtesy of Saad Zafar Usmani, MD, MBA

Talquetamab (GPRC5d x CD3 Bispecific) - MonumenTAL-1

Phase I: progression on or intolerance to all established therapies; ECOG PS 0-1

Phase II: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody; ECOG PS 0–2

→ Talquetamab 0.4 mg/kg SC QW* (n = 143)

→ Talquetamab 0.8 mg/kg SC Q2W* (n = 145)

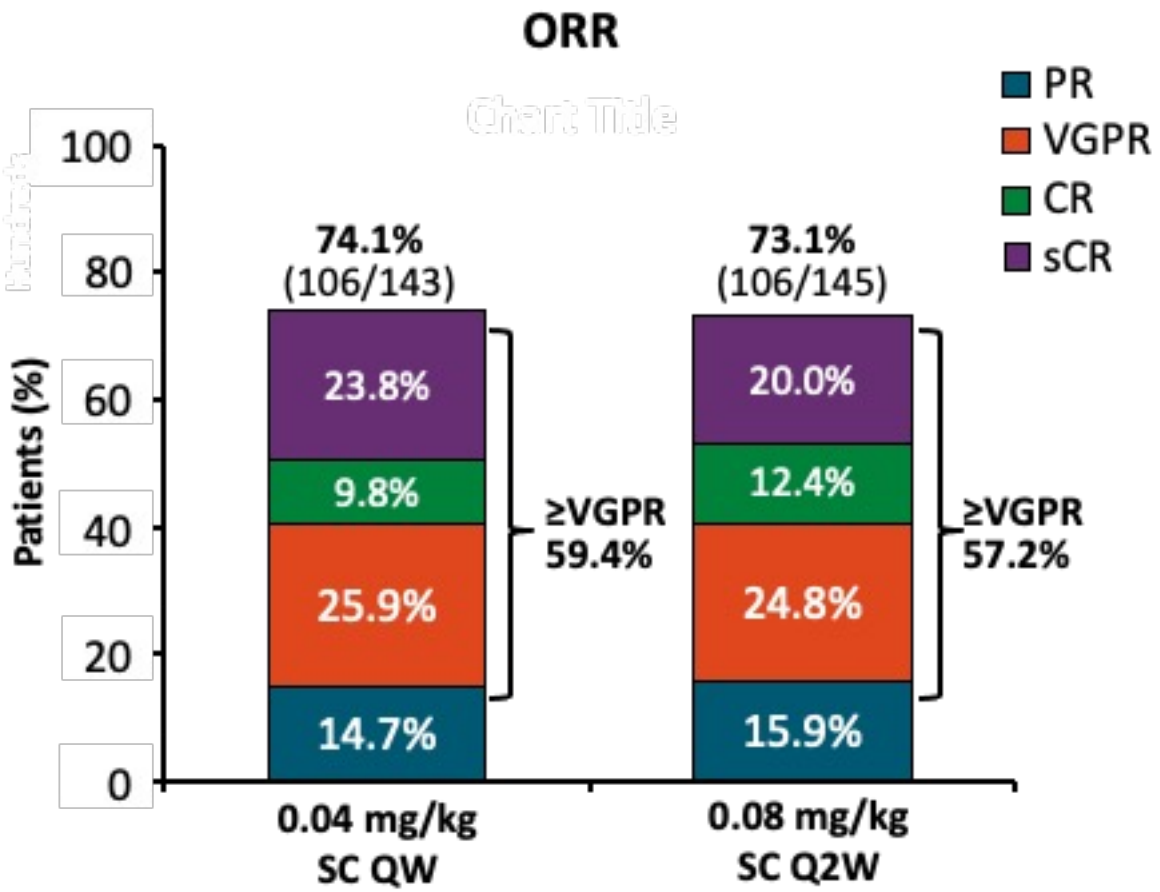
→ Prior T-Cell Redirection Group: Talquetamab Either 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W (n = 51)

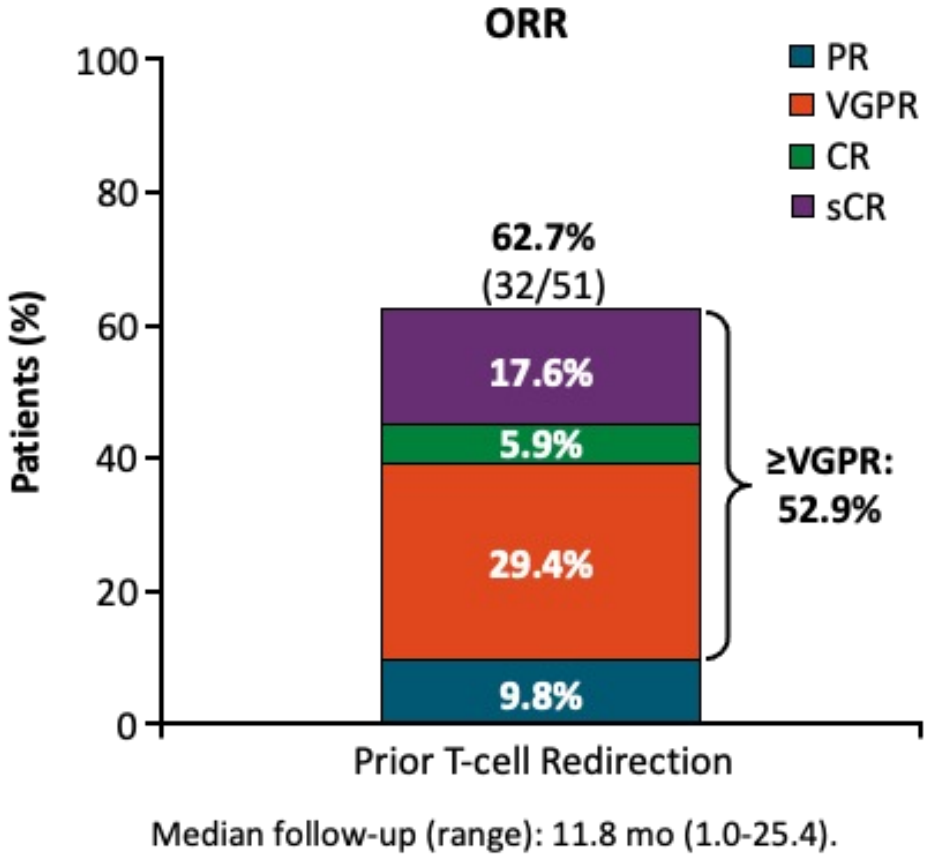
*Previous anti-BCMA therapy allowed; T-cell redirection therapy naive.

Courtesy of Hans Lee, MD

Chari et al, *ASH,* 2022, *NEJM*, 2022.

Talquetamab (MonumenTAL-1) - Efficacy





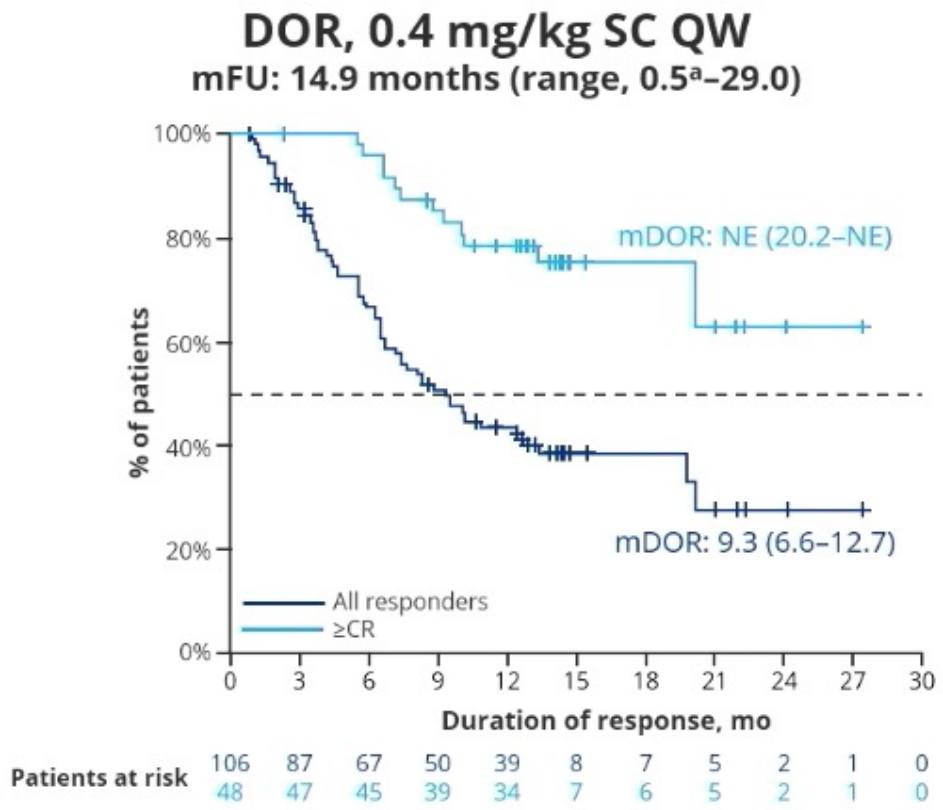
Median follow-up (range): 11.8 mo (1.0-25.4).

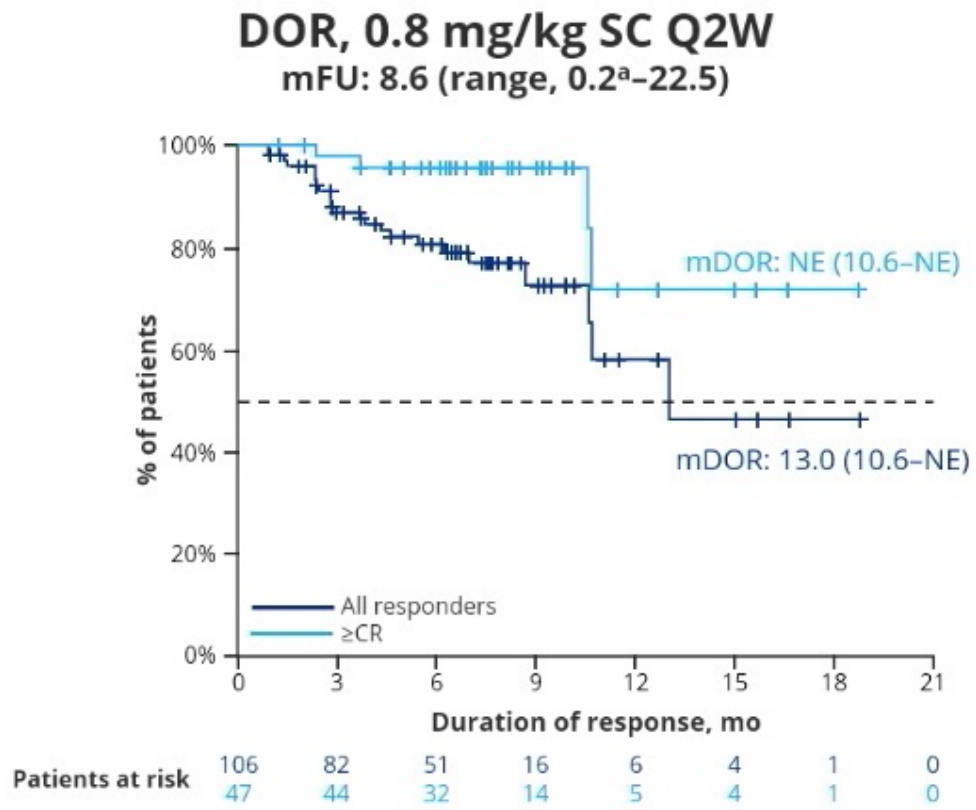
71% received CAR-T therapy, 35% received a BsAb, and 6% received both

Courtesy of Hans Lee, MD

Chari et al, *ASH,* 2022; Chari et al, *NEJM*, 2022.

Talquetamab (MonumenTAL-1) - Efficacy





mPFS: 7.5 months (95% CI: 5.7–9.4; 33% censored)

11.9 months (95% CI: 8.4–NE; 61% censored)

Courtesy of Hans Lee, MD

Chari et al, *ASH,* 2022; Chari, et al *NEJM*, 2022.

Memorial Sloan Kettering Cancer Center

Summary of non-BCMA Bispecific Antibodies

	Talquetamab (n=288)		Forimtamig (n=57)	Cevostamab (n=157)
Target	GPRC5d-CD3		2+1 GPRC5d-CD3	FcRH5-CD3
Route	SC (n=143)	SC (N=145)	SC	IV
Dose and schedule	0.4 mg/kg QW	0.8mg/kg Q2W	1200-7200 mcg/kg Q2W	Q3W
Median prior LoT	5 (2-13)	5 (2-17)	4 (2-14)	6 (2-18)
Triple refractory	74.1%	69%	71.9%	85%
CRS, G≥3	79%, 2.1%	72.4%, 0.7%	78.9%, 1.8%	81%, 1.2%
Neurotoxicity, G≥3	13.9%, 1.6%	10%, 1.8%	12.3%, .6%	14.3%, 0.6%
Infections, G≥3	57.3%, 16.8%-	50.3%, 11.7%	45.6%, 26.4%	45%, ND
ORR (%)	74.1%	73.1%	63.6%	56.7% 132-198mg
≥CR (%)	33.6%	32.4%	25.5%	8.4%
Median PFS (m) (95% CI)	7.5 (5.7-9.4)	11.9 (8.4-NE)	NR	NR
Median DoR (m) (95% CI)	9.3 (6.6-12.7)	13.0 (10.6-NE)	12.5 (1.2-12.5)	11.5 (6-18.4)
MRD – (10^{-5})	NR	NR	10/14	7/10

Chari A et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel S et al. ASH 2021.

Courtesy of Saad Zafar Usmani, MD, MBA

Memorial Sloan Kettering Cancer Center

Summary of Bispecific Antibodies - Infections

	Teclistamab n=165	Elranatamab n=123	Alnuctamab n=68 (sc)	ABBV-838 n=118	Talquetamab n=288 [0.4-0.8mg/kg]*	Cevostamab n=161	Forimtamig n=57 (SC)
Median FUP (months, m)	14.1 m	10.4 m	4.1 m	4.3 – 8.0m	14.9 – 8.6 m	8.8 m	8.0m
Overall, n (%)	126 (76.4)	82 (66.7)	23 (34)	38 (32)	57.3%-50.3%	45%	26 (45.6)
Grade 3-4, n (%)	74 (44.8)	43 (35)	6 (9)	20 (17)	16.8%-11.7%	ND	15 (26.4)
Bacterial	ND	ND	ND	ND		ND	ND
Fungal	ND	ND	ND	ND		ND	ND
Viral	ND	ND	ND	ND		ND	ND
Opportunistic infections 1. PJP 2. CMV	6 patients NR (*1 patients with Adenoviral pneumonia)	6 (4.9) 10 (8.1)	ND ND	ND ND	5(3.5%)–4(2.8%) ND 3 patients	ND	ND
COVID infections, n (%) Overall Grade 3-4	29 (17.6) 20 (12.1)	31 (25.2) 14 (11.4)	ND ND	ND ND	13(9.1) – 16(11) 0.7% - 2.1%	ND	12 (24.6) 2 (3.6)
Infectious death, n (%)	16/27	NR	ND	4 pts	NR	ND	ND

Moreau P et al. NEJM 2022; Lesokhin A et al. ASH 2022. ; Wong S et al. ASH 2022; Voorhees PM et al. ASH 2022; Chari A et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel S et al. ASH 2021

Courtesy of Saad Zafar Usmani, MD, MBA

Myeloma Bispecific Antibodies Summary

- **ADVANTAGES**
  - "**Off-the-shelf"** format provides immediate **ACCESS** to patients in immediate need of therapy
  - **Strong efficacy** (comparable to some autologous CART products)
- **DISADVANTAGES**
  - **Continuous dosing (vs. CART)**
  - **Adverse events**
    - CRS common; Grade 3/4 CRS and neurotoxicity rare; severe CRS is mitigated by step-up dosing strategy (still requires inpatient monitoring)
    - Drug- or target-specific AEs
      - Infection risk
      - GPRC5D: dysgeusia, skin exfoliation, nail disorders

Courtesy of Hans Lee, MD

Memorial Sloan Kettering Cancer Center

Pros/Cons of Bispecifics

- Pros:
  - Off the shelf
  - Low grade cytokine release syndrome (CRS)
  - Low incidence of neurotoxicity (NT)
  - Many targets: BCMA, GPRC5D, FCRH5
  - Ability to combine with other mechanisms of actions
- Cons:
  - Not every patient is responding to BsAbs.
  - Continuous therapy model associated with infection risk
    - Hypogammaglobulinemia requiring IVIg administration
    - VZV/PJP Prophylaxis
  - Logistic challenges for community at large during first cycle of monitoring and managing CRS/NT

Courtesy of Saad Zafar Usmani, MD, MBA

Agenda

MODULE 1: Biology/Immunology; Overview

MODULE 2: Current Available Data

MODULE 3: Clinical Investigator Survey

MODULE 4: Combinations/Ongoing Trials

MODULE 5: Faculty Cases

RTP
RESEARCH
TO PRACTICE

Based on your personal clinical experience and knowledge of available data, in general how would you compare the antitumor activity (response, duration of response, etc) of BCMA-targeted bispecific antibodies to that of BCMA-targeted chimeric antigen receptor (CAR) T-cell therapy for patients with standard-risk relapsed/refractory (R/R) multiple myeloma (MM)?

 Dr Lee	BCMA-targeted CAR T-cell therapy has somewhat greater antitumor activity
 Dr Usmani	BCMA-targeted CAR T-cell therapy has somewhat greater antitumor activity
 Dr Krishnan	BCMA-targeted CAR T-cell therapy has somewhat greater antitumor activity
 Dr Nooka	BCMA-targeted CAR T-cell therapy has somewhat greater antitumor activity
 Dr Raje	BCMA-targeted CAR T-cell therapy has significantly greater antitumor activity
 Dr Zonder	BCMA-targeted CAR T-cell therapy has somewhat greater antitumor activity

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, in general how would you compare the cytokine release syndrome (CRS) and related toxicity with BCMA-targeted bispecific antibodies to that with BCMA-targeted CAR T-cell therapy for patients with R/R MM?

 Dr Lee	BCMA-targeted CAR T-cell therapy has somewhat more CRS and related toxicity
 Dr Usmani	BCMA-targeted CAR T-cell therapy has significantly more CRS and related toxicity
 Dr Krishnan	BCMA-targeted CAR T-cell therapy has somewhat more CRS and related toxicity
 Dr Nooka	BCMA-targeted CAR T-cell therapy has significantly more CRS and related toxicity
 Dr Raje	BCMA-targeted CAR T-cell therapy has somewhat more CRS and related toxicity
 Dr Zonder	BCMA-targeted CAR T-cell therapy has somewhat more CRS and related toxicity

Based on your personal clinical experience and knowledge of available data, in general how would you compare the quality of life (QoL) (eg, inconvenience, related considerations) with BCMA-targeted bispecific antibodies to that with BCMA-targeted CAR T-cell therapy for patients with R/R MM?

 Dr Lee	BCMA-targeted CAR T-cell therapy has somewhat better QoL
 Dr Usmani	BCMA-targeted bispecific antibodies have somewhat better QoL
 Dr Krishnan	BCMA-targeted CAR T-cell therapy has somewhat better QoL
 Dr Nooka	BCMA-targeted bispecific antibodies have somewhat better QoL
 Dr Raje	BCMA-targeted CAR T-cell therapy has somewhat better QoL
 Dr Zonder	QoL is similar with both

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, in general how would you compare the antitumor activity of the FDA-approved BCMA-targeted bispecific antibody teclistamab to that of unapproved BCMA-targeted bispecific antibodies (eg, elranatamab, linvoseltamab or alnuctamab) for patients with standard-risk R/R MM?

 Dr Lee	Antitumor activity is similar with both
 Dr Usmani	Antitumor activity is similar with both
 Dr Krishnan	Antitumor activity is similar with both
 Dr Nooka	Antitumor activity is similar with both
 Dr Raje	Antitumor activity is similar with both
 Dr Zonder	Antitumor activity is similar with both

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, in general how would you compare the CRS and related toxicity of the FDA-approved BCMA-targeted bispecific antibody teclistamab to that of unapproved BCMA-targeted bispecific antibodies (eg, elranatamab, linvoseltamab or alnuctamab) for patients with R/R MM?

 Dr Lee	Teclistamab has somewhat more CRS and related toxicity
 Dr Usmani	CRS and related toxicity is similar with both
 Dr Krishnan	Teclistamab has somewhat more CRS and related toxicity
 Dr Nooka	CRS and related toxicity is similar with both
 Dr Raje	CRS and related toxicity is similar with both
 Dr Zonder	CRS and related toxicity is similar with both

RTP RESEARCH TO PRACTICE

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

 Dr Lee	Antitumor activity is similar with both
 Dr Usmani	Antitumor activity is similar with both
 Dr Krishnan	Antitumor activity is similar with both
 Dr Nooka	Non-BCMA-targeted bispecific antibodies have somewhat greater antitumor activity
 Dr Raje	Antitumor activity is similar with both
 Dr Zonder	Antitumor activity is similar with both

RTP RESEARCH TO PRACTICE

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

 Dr Lee	Ciltacabtagene autoleucel has somewhat greater antitumor activity
 Dr Usmani	Ciltacabtagene autoleucel has significantly greater antitumor activity
 Dr Krishnan	Ciltacabtagene autoleucel has somewhat greater antitumor activity
 Dr Nooka	Ciltacabtagene autoleucel has significantly greater antitumor activity
 Dr Raje	Ciltacabtagene autoleucel has significantly greater antitumor activity
 Dr Zonder	Ciltacabtagene autoleucel has somewhat greater antitumor activity

RTP RESEARCH TO PRACTICE

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

 Dr Lee	Ciltacabtagene autoleucel has somewhat more CRS and related toxicity
 Dr Usmani	CRS and related toxicity is similar with both
 Dr Krishnan	Ciltacabtagene autoleucel has somewhat more CRS and related toxicity
 Dr Nooka	Ciltacabtagene autoleucel has significantly more CRS and related toxicity
 Dr Raje	CRS and related toxicity is similar with both
 Dr Zonder	Ciltacabtagene autoleucel has somewhat more CRS and related toxicity

RTP RESEARCH TO PRACTICE

Please provide an example of a patient with R/R MM to whom you would administer a bispecific antibody but whom you would not refer for CAR T-cell therapy.

 Dr Lee	Triple-class refractory patient with rapidly progressing disease with no time for apheresis, manufacture and infusion of CAR T-cell therapy
 Dr Usmani	Intermediate-fit or frail patient by IMWG criteria
 Dr Krishnan	75-year-old with rapidly progressive EM disease after DRd, KPd, CyBorD
 Dr Nooka	55-year-old patient with a PS of 1; 5 lines of therapy; EF = 30%
 Dr Raje	Patient with frailty and renal failure
 Dr Zonder	Older, frail patient with pre-existing neurocognitive issues which may make certainty about therapy-related neuro effects difficult

IMWG = International Myeloma Working Group; EM = extramedullary

A younger patient with standard-risk MM who receives initial treatment with RVd/daratumumab undergoes autologous stem cell transplant (ASCT) and experiences disease relapse after completing 2 years of maintenance lenalidomide. Regulatory and reimbursement issues aside, at what point, if any, would you like to treat this patient with a bispecific antibody? Which bispecific antibody?

	Time of therapy	Specific agent
 Dr Lee	At second relapse	Talquetamab if prior BCMA CAR T; otherwise, BCMA-targeted bispecific antibody
 Dr Usmani	At first relapse	Teclistamab
 Dr Krishnan	At second relapse	Talquetamab
 Dr Nooka	At second relapse	BCMA-targeted bispecific antibody
 Dr Raje	I would not recommend a bispecific antibody for this patient	NA
 Dr Zonder	At second relapse	Teclistamab

An older patient with standard-risk MM receives initial treatment with Rd/daratumumab and experiences disease relapse after completing 2 years of maintenance lenalidomide. Regulatory and reimbursement issues aside, at what point, if any, would you like to treat this patient with a bispecific antibody? Which bispecific antibody?

	Time of therapy	Specific agent
 Dr Lee	At first relapse	Teclistamab or another BCMA-targeted bispecific antibody
 Dr Usmani	At first relapse	Teclistamab
 Dr Krishnan	At second relapse	Teclistamab
 Dr Nooka	At first relapse	BCMA-targeted bispecific antibody
 Dr Raje	At second relapse	Elranatamab
 Dr Zonder	At first relapse	Teclistamab

Assuming you had access to both for a patient with multiregimen-relapsed MM who is eligible to receive both a bispecific antibody and CAR T-cell therapy, regulatory and reimbursement issues aside, how would you generally sequence them?

 Dr Lee	CAR T-cell therapy → bispecific antibody
 Dr Usmani	CAR T-cell therapy → bispecific antibody
 Dr Krishnan	CAR T-cell therapy → bispecific antibody
 Dr Nooka	CAR T-cell therapy → bispecific antibody
 Dr Raje	CAR T-cell therapy → bispecific antibody
 Dr Zonder	CAR T-cell therapy → bispecific antibody

RTP RESEARCH TO PRACTICE

Have you administered or would you administer BCMA-targeted CAR T-cell therapy to a patient with R/R MM who had previously received a BCMA-targeted bispecific antibody? If so, have you seen an objective response?

 Dr Lee	I have not but would for the right patient
 Dr Usmani	I have; Yes
 Dr Krishnan	I have; Yes
 Dr Nooka	I have; Pending response
 Dr Raje	I have; Yes
 Dr Zonder	I have not but would for the right patient

RTP
RESEARCH TO PRACTICE

Have you administered or would you administer a BCMA-targeted bispecific antibody to a patient with R/R MM who had previously received BCMA-targeted CAR T-cell therapy? If so, have you seen an objective response?

 Dr Lee	I have; Yes
 Dr Usmani	I have; Yes
 Dr Krishnan	I have; Yes
 Dr Nooka	I have; Yes
 Dr Raje	I have; Yes
 Dr Zonder	I have; Yes

Please describe the last patient with R/R MM to whom you administered a bispecific antibody, either on or off protocol.

	Clinical characteristics	Treatment	Outcome	CRS
 Dr Lee	78 y/o F, 11 prior treatments	Teclistamab	MR	None
 Dr Usmani	78 y/o F, 5 prior treatments	Teclistamab	sCR/MRD-neg	Grade 1 CRS
 Dr Krishnan	81 y/o F, 3 prior treatments	Cevostamab	CR	Multiple infections
 Dr Nooka	49 y/o F, RVd→SCT→IRd mtx	Teclistamab/ daratumumab on protocol	Pending	Grade 1 CRS
 Dr Raje	83 y/o F, 4 prior treatments	Teclistamab	CR	None
 Dr Zonder	48 y/o M, 5 prior treatments	Teclistamab	CR	Grade 2 CRS

MRD = minimal residual disease; mtx = maintenance

Please describe the last patient with R/R MM to whom you administered CAR T-cell therapy, either on or off protocol.

	Clinical characteristics	Treatment	Outcome	CRS
 Dr Lee	61 y/o M, 4 prior treatments	Ciltacabtagene autoleucel	Not evaluable, day 20+	Grade 1 CRS, Grade 3 ICANS
 Dr Usmani	78 y/o M, 5 prior treatments	Ciltacabtagene autoleucel	VGPR	Grade 2 CRS, Grade 2 NT
 Dr Krishnan	75 y/o M, 6 prior treatments	Idecabtagene vicleucel	CR	NT infection
 Dr Nooka	61 y/o M, 4 prior treatments	Ciltacabtagene autoleucel	PR	Grade 2 CRS
 Dr Raje	62 y/o F, 4 prior treatments	Ciltacabtagene autoleucel	CR	Grade 2 CRS
 Dr Zonder	65 y/o F, 5 prior treatments	Ciltacabtagene autoleucel	CR	Grade 1 CRS

NT = neurotoxicity

Do you expect that bispecific antibodies will ultimately be administered by general medical oncologists in an outpatient setting?

 Dr Lee	Yes
 Dr Usmani	Yes
 Dr Krishnan	Yes
 Dr Nooka	Yes
 Dr Raje	Yes
 Dr Zonder	Yes

RTP RESEARCH TO PRACTICE

If talquetamab receives FDA approval, what would be your sequencing preference for teclistamab and talquetamab?

 Dr Lee	Teclistamab → talquetamab
 Dr Usmani	Teclistamab → talquetamab
 Dr Krishnan	Talquetamab → teclistamab
 Dr Nooka	Teclistamab → talquetamab
 Dr Raje	Teclistamab → talquetamab
 Dr Zonder	Teclistamab → talquetamab

RTP RESEARCH TO PRACTICE

What would you predict to be the outcome of a Phase III randomized trial evaluating teclistamab/daratumumab/lenalidomide versus daratumumab/lenalidomide/dexamethasone for patients with newly diagnosed MM who are not eligible for ASCT?

 Dr Lee	Teclistamab/daratumumab/lenalidomide is more efficacious
 Dr Usmani	Teclistamab/daratumumab/lenalidomide is more efficacious
 Dr Krishnan	Teclistamab/daratumumab/lenalidomide is more efficacious
 Dr Nooka	Teclistamab/daratumumab/lenalidomide is more efficacious
 Dr Raje	Teclistamab/daratumumab/lenalidomide is more efficacious
 Dr Zonder	Teclistamab/daratumumab/lenalidomide is more efficacious

RTP RESEARCH TO PRACTICE

What would you predict to be the outcome of a Phase III randomized trial evaluating elranatamab versus lenalidomide for patients with newly diagnosed MM who have minimal residual disease after undergoing ASCT?

 Dr Lee	Elranatamab is more efficacious
 Dr Usmani	Elranatamab is more efficacious
 Dr Krishnan	Elranatamab is more efficacious
 Dr Nooka	Elranatamab is more efficacious
 Dr Raje	Elranatamab is more efficacious
 Dr Zonder	Elranatamab is more efficacious

Agenda

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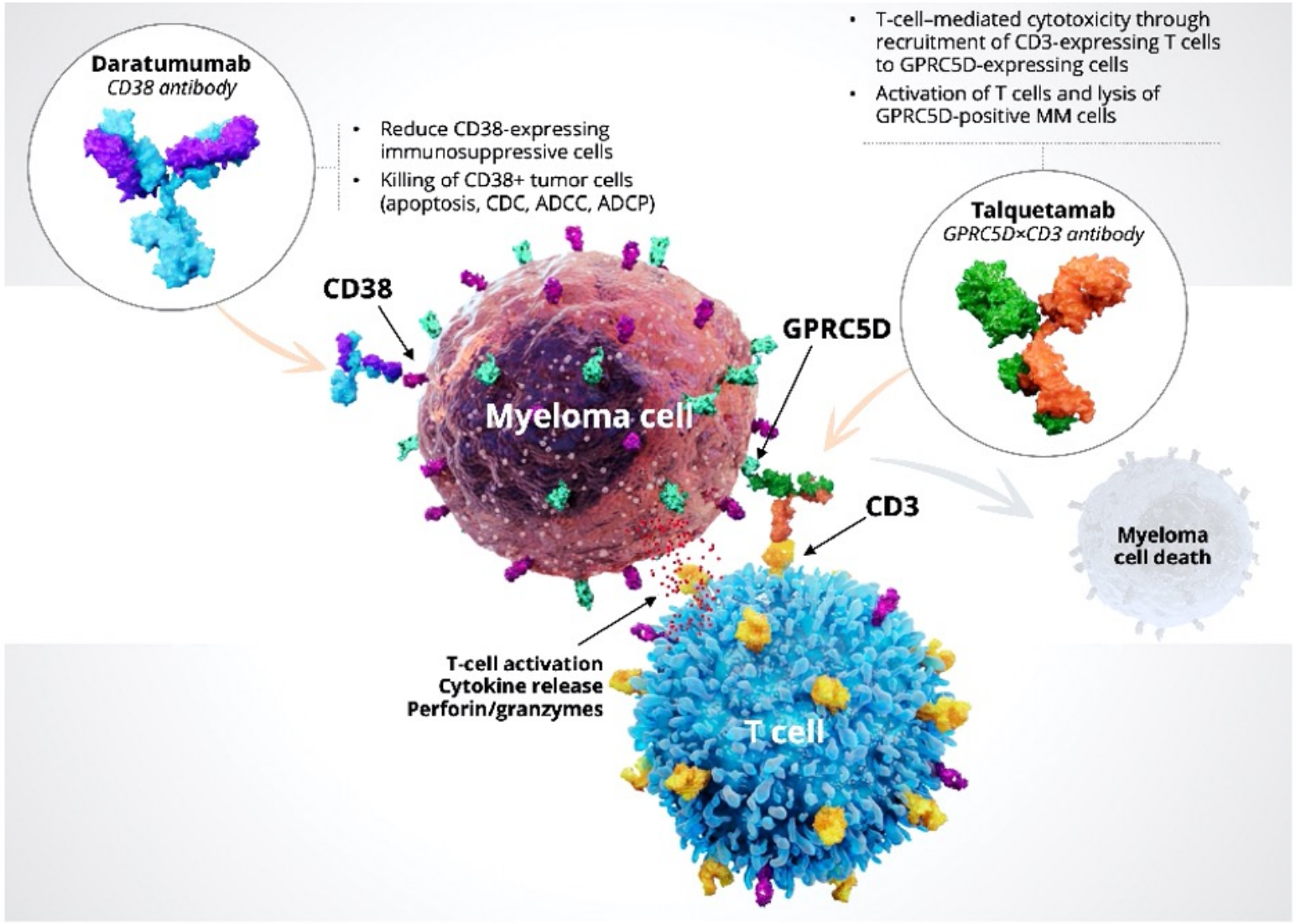
RTP
RESEARCH
TO PRACTICE

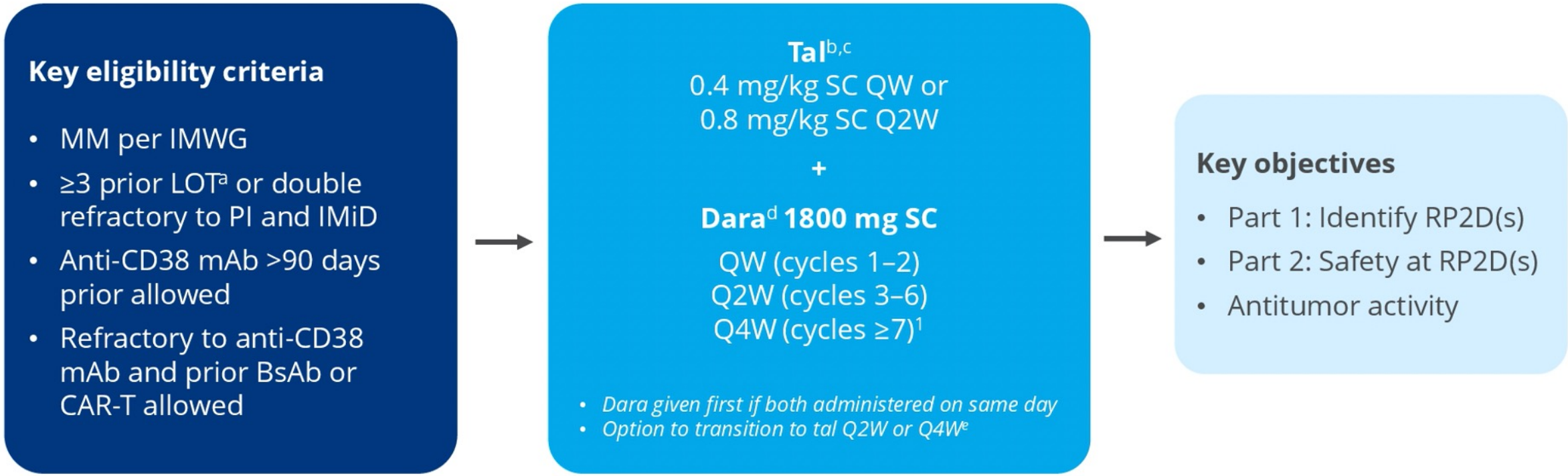
Talquetamab + Daratumumab (TRIMM-2)



Courtesy of Hans Lee, MD

Dholaria et al, *ASCO,* 2023.

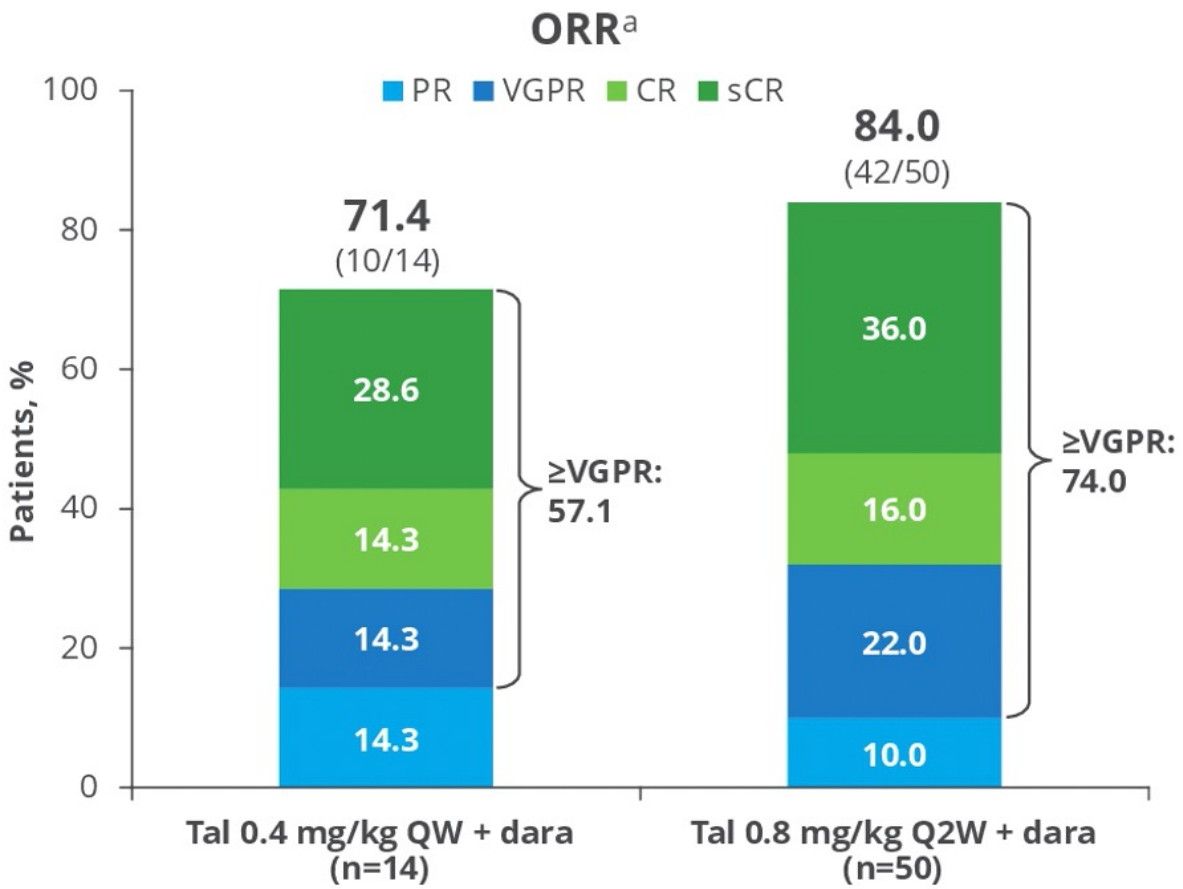
Talquetamab + Daratumumab (TRIMM-2)



Courtesy of Hans Lee, MD

Dholaria et al, *ASCO,* 2023.

Talquetamab + Daratumumab (TRIMM-2)

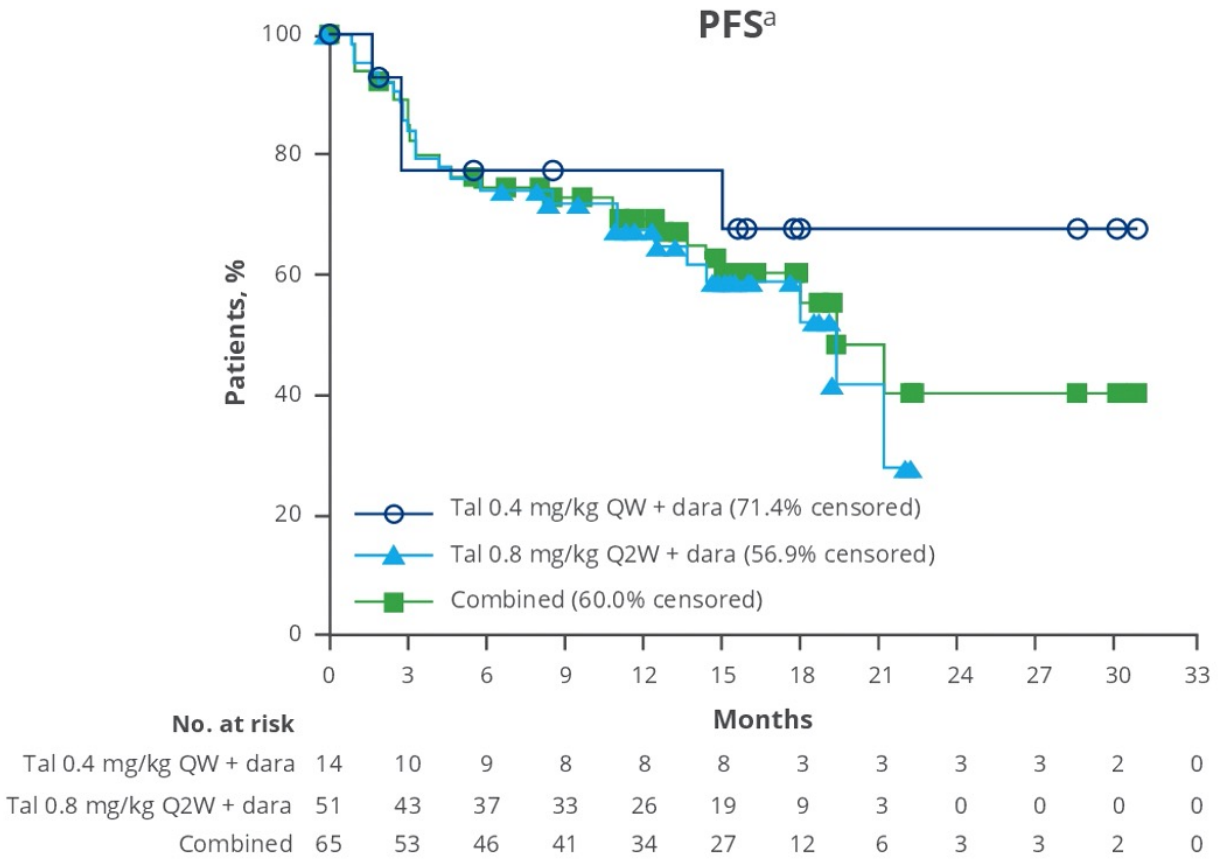


Parameter	Tal 0.4 mg/kg QW + dara (n=14)	Tal 0.8 mg/kg Q2W + dara (n=50)
Median (range) follow-up, mo	16.8 (1.9–31.0)	15.0 (1.0–23.3)
Median (range) time to first response, mo	1.0 (0.9–2.4)	1.0 (0.9–8.3)
ORR in anti-CD38, n (%) Naive Exposed Refractory	 3/3 (100.0) 7/11 (63.6) 7/11 (63.6)	 5/5 (100.0) 37/45 (82.2) 32/40 (80.0)
ORR in T-cell redirection therapy[b] exposed, n (%) CAR-T BsAb	 4/6 (66.7)[c] 1/2 (50.0) 4/5 (80.0)	 15/19 (78.9) 8/9 (88.9) 7/10 (70.0)

Courtesy of Hans Lee, MD

Dholaria et al, *ASCO,* 2023.

Talquetamab + Daratumumab (TRIMM-2)



Parameter	Tal 0.4 mg/kg QW + dara (n=14)	Tal 0.8 mg/kg Q2W + dara (n=51)
Median PFS, mo (range)	NR (2.73–NE)	19.4 (12.5–NE)
12-mo PFS, % (95% CI)	77.4 (44.9–92.1)	67.4 (52.3–78.6)
Median OS, mo (range)	NR (NE–NE)	NR (NE–NE)
12-mo OS, % (95% CI)	92.3 (56.6–98.9)	91.5 (78.8–96.7)

Courtesy of Hans Lee, MD

Dholaria et al, *ASCO,* 2023.

Teclistamab + Talquetamab (RedirecTT-1)

Primary objectives

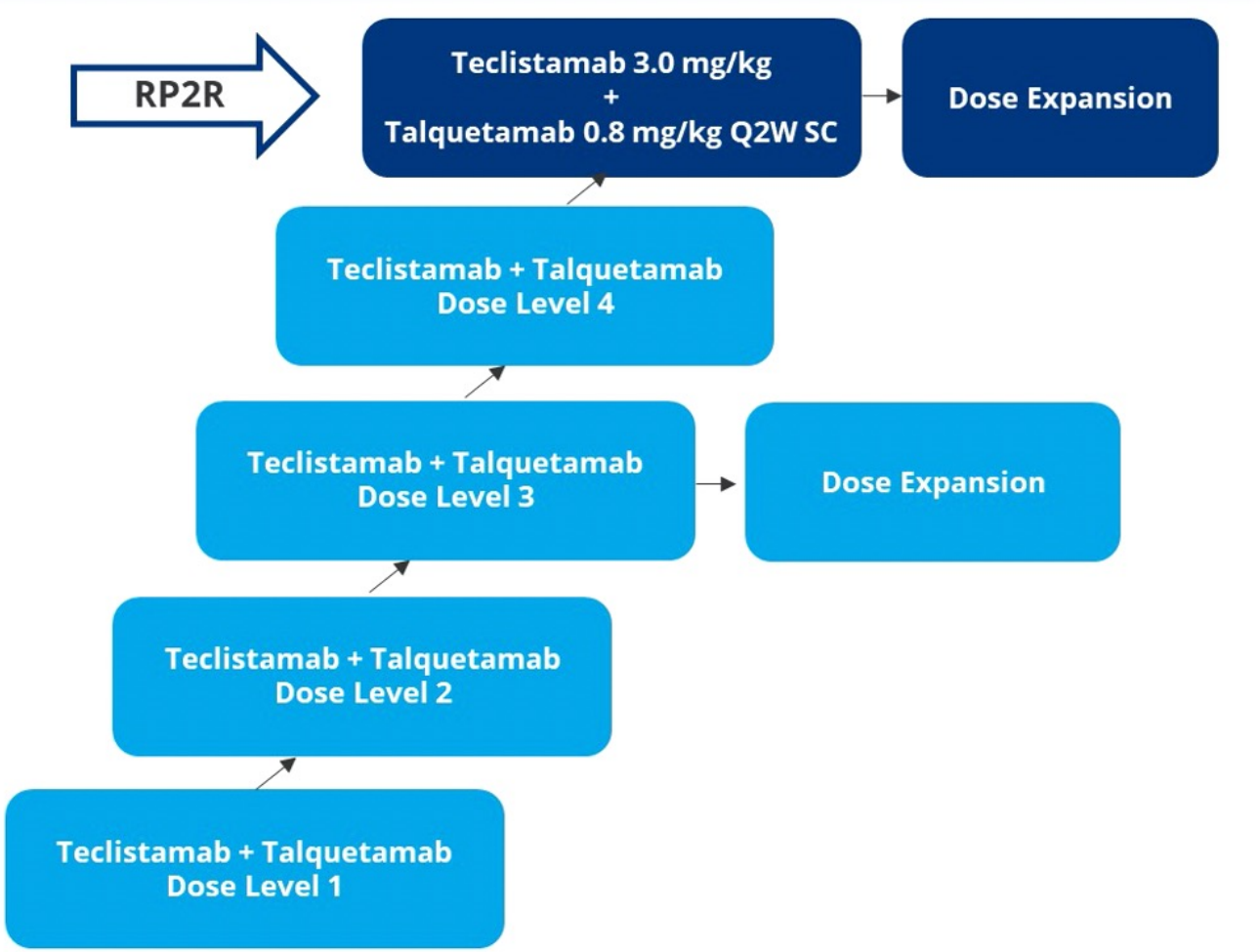
- Evaluate safety
- Identify RP2R(s) and schedule for the combination

Secondary objectives

- Preliminary anticancer activity of each study treatment at RP2R(s) in Part 2, PK, immunogenicity

Key eligibility criteria

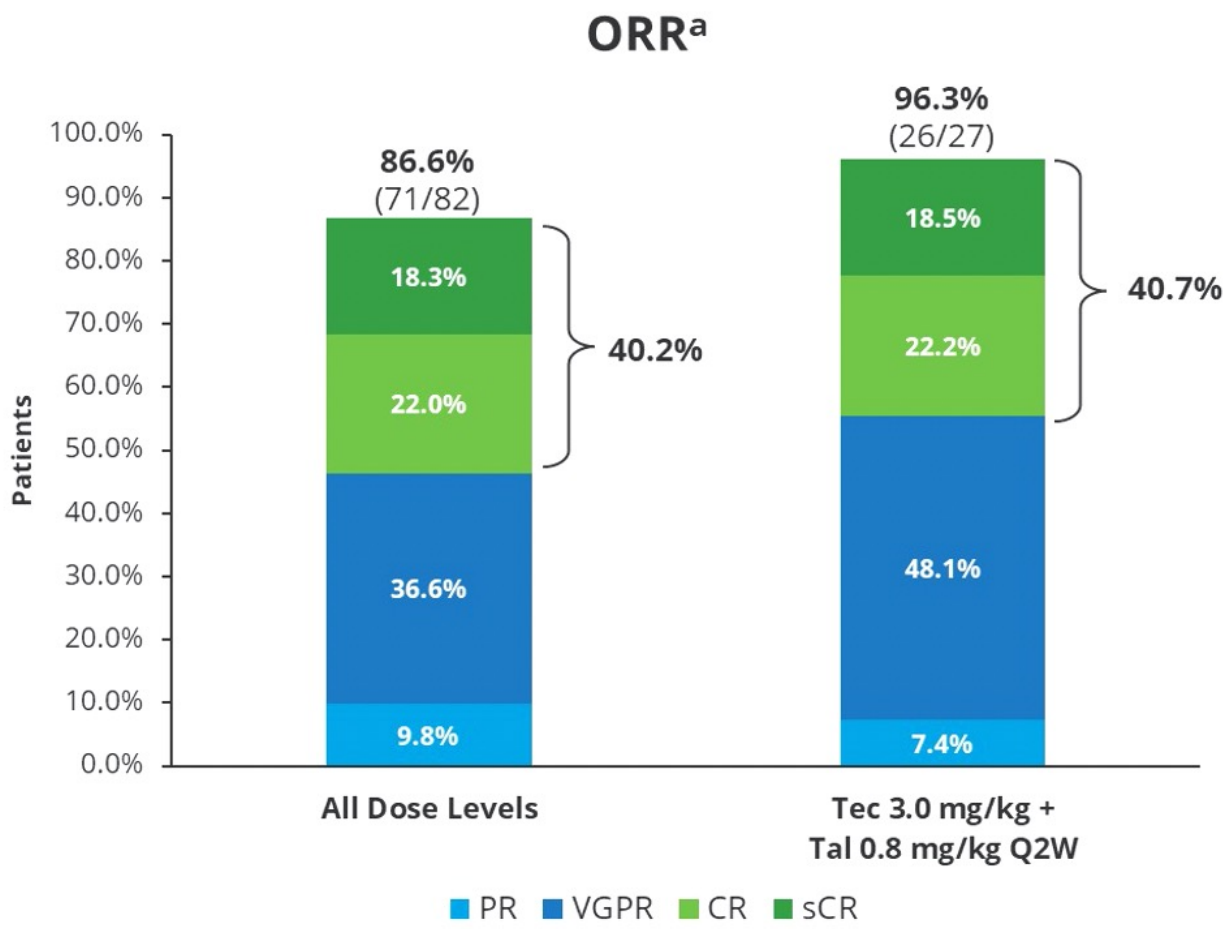
- Measurable MM
- RR or intolerant to established therapies, including last LOT
- Exposed to a PI, IMiD, and anti-CD38 mAb



Courtesy of Hans Lee, MD

Cohen et al, *ASCO,* 2023.

Teclistamab + Talquetamab (RedirecTT-1)



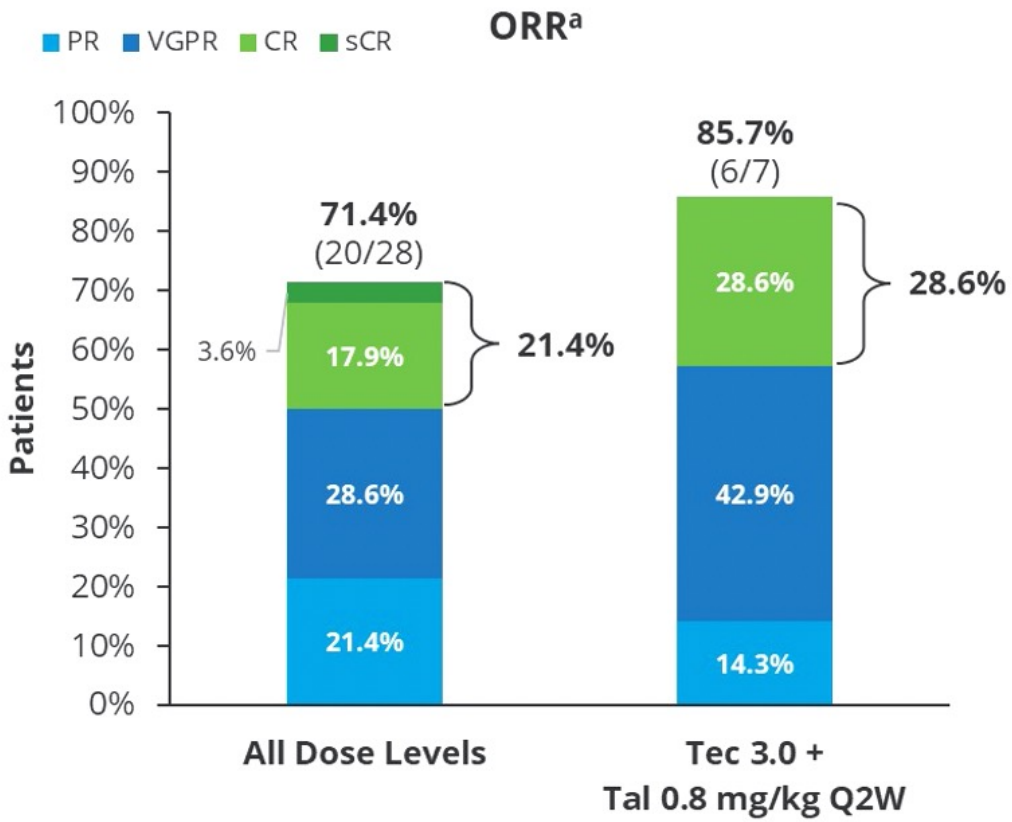
- ORR was high 86.6% across dose levels studied and 96.3% at the RP2R
- At data cutoff, 61% (57/93) of patients remained on treatment

	All Dose Levels N=93	Tec 3.0 mg/kg + Tal 0.8 mg/kg Q2W n=34
Median follow-up, months (range)	13.4 (0.3–25.6)	8.1 (0.7–15.0)
Median DOR[b], months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median time to first response[b], months (range)	1.97 (0–7.7)	1.48 (0–4.0)
Median time to best response[b], months (range)	3.98 (1.1–15.7)	3.22 (1.4–10.7)
Median PFS, months (95% CI)	20.9 (13.0–NE)	NE (9.9–NE)
9-month PFS rate (95% CI)	70.1 (58.0–79.4)	77.1 (50.8–90.5)

Courtesy of Hans Lee, MD

Cohen et al, *ASCO,* 2023.

Teclistamab + Talquetamab (RedirecTT-1)



- All were soft tissue plasmacytomas
- At the RP2R (n=11):
  - Median follow-up 7.2 mo (range 0.7–14.2)
  - 85.7% (6/7) ORR
  - 28.6% (2/7) ≥CR

	All Dose Levels N=35	Tec 3.0 mg/kg + Tal 0.8 mg/kg Q2W N=11
Median DOR[b], months (95% CI)	12.9 (4.17–NE)	NE (4.17–NE)
Median PFS, months (95% CI)	6.1 (2.5–9.9)	9.9 (2.4–NE)

Courtesy of Hans Lee, MD

Cohen et al, *ASCO,* 2023.

Planned or Ongoing Phase 3 BCMA Bispecific Studies

Study	Description
MagnetisMM-7	Elranatamab vs. lenalidomide in NDMM patients who are minimal residual disease-positive after undergoing ASCT
MagnetisMM-6	Elranatamab, daratumumab, and lenalidomide vs. daratumumab, lenalidomide, and dexamethasone in patients with NDMM who are not candidates for ASCT
MagnetisMM-5	Elranatamab monotherapy vs. elranatamab + daratumumab vs daratumumab+ pomalidomide + dexamethasone in RRMM with prior lenalidomide and proteasome inhibitor
MajesTEC-4	Teclistamab + lenalidomide vs. lenalidomide in NDMM as maintenance therapy after ASCT
MajesTEC-7	Teclistamab, daratumumab, and, lenalidomide vs. daratumumab, lenalidomide, and dexamethasone in NDMM who are either ineligible or not intended for ASCT as initial therapy
MajesTEC-3	Teclistamab + daratumumab vs daratumumab, pomalidomide, and dexamethasone OR daratumumab, bortezomib, and dexamethasone in RRMM (1-3 lines of prior therapy) with prior lenalidomide and proteasome inhibitor
MajesTEC-9	Teclistamab monotherapy vs. pomalidomide, bortezomib, dexamethasone OR carfilzomib, dexamethasone in RRMM (1-3 lines prior therapy) with anti-CD38, mAb and lenalidomide
LINKER-MM3	Linvoseltamab vs. elotuzumab, pomalidomide, and dexamethasone in RRMM

Courtesy of Hans Lee, MD

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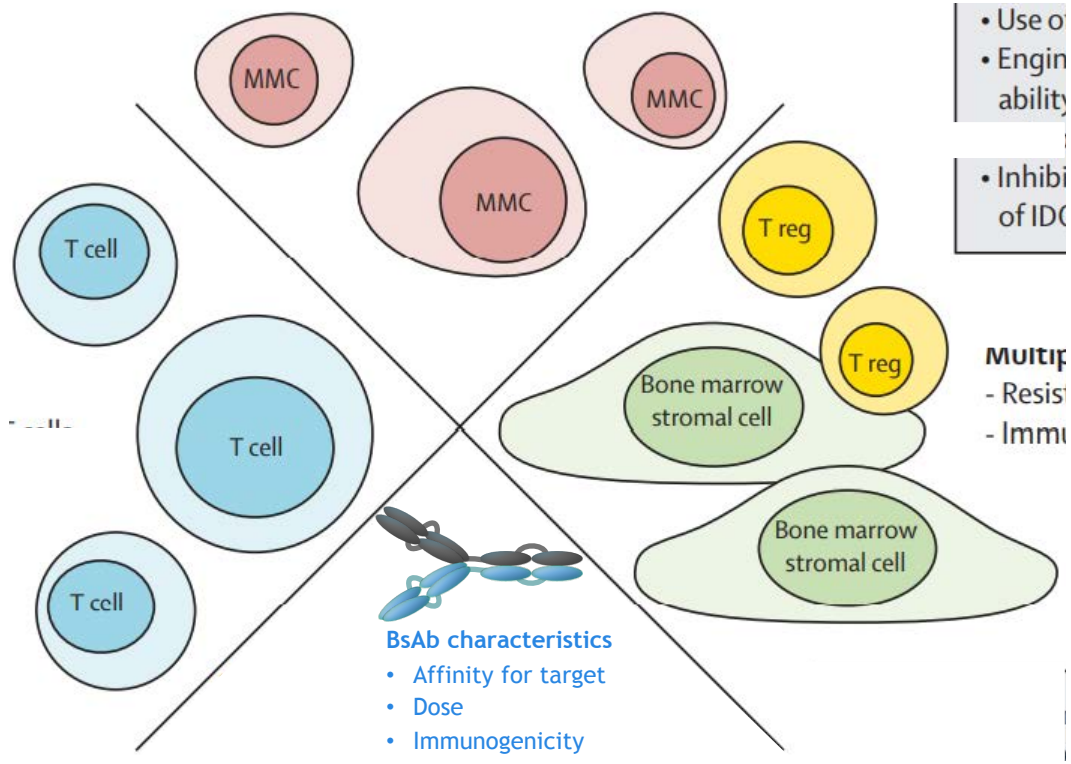
Mechanisms of resistance to BsAbs

Tumor-related features
- Antigen loss or diminished antigen expression
- Soluble BCMA (for BCMA BsAbs)
- Tumor load
- High-risk cytogenetic features
- Extramedullary disease
- Inhibitory receptors and ligands, which suppress T-cell function



T-cell characteristics
- T-cell frequency
- T-cell fitness

IMiD/CelMOD, Check point inhibitors

BsAb characteristics
- Affinity for target
- Dose
- Immunogenicity
- Dual targeting

MM microenvironment-related factors
- BM stromal cells
- Immune suppressor cells

CD38 antibody: Elimination of Tregs

BCMA, B-cell maturation antigen; BM, bone marrow; BsAb, bispecific antibody; IMiD, immunomodulatory drug; MMC, multiple myeloma cell; Tregs, regulatory T-cells

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

Adapted from: van de Donk N, Themeli M, Usmani SZ. Blood Cancer Discov 2021;2:302–18

Courtesy of Saad Zafar Usmani, MD, MBA

Agenda

MODULE 1: Biology/Immunology; Overview

MODULE 2: Current Available Data

MODULE 3: Clinical Investigator Survey

MODULE 4: Combinations/Ongoing Trials

MODULE 5: Faculty Cases

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Case Presentation – Dr Usmani

Case Description

- 49-year-old female with DS Stage IIIA IgG kappa RRMM on a BCMA-bispecific antibody.
- Diagnosed in 2/2012
- Amp 1q21, trisomy 9 and 15
- 10 prior lines of therapy including PIs, IMiDs, anti-CD38 mAb, cyclophosphamide, tandem ASCT, salvage ASCT, BCMA-directed CAR T cell therapy.
- Co-morbidities: HTN, hypothyroidism, asthma

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Case Presentation – Dr Usmani (Cont)

Patient Treatment

- Patient had BCMA-directed CAR T cell therapy with Flu/Cy conditioning on study.
  - Initially had partial response but developed progressive disease after 5 months
- Patient was then enrolled on clinical trial for BCMA-bispecific antibody.
- Tolerated step-up dosing with G1 CRS.

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Case Presentation – Dr Usmani (Cont)

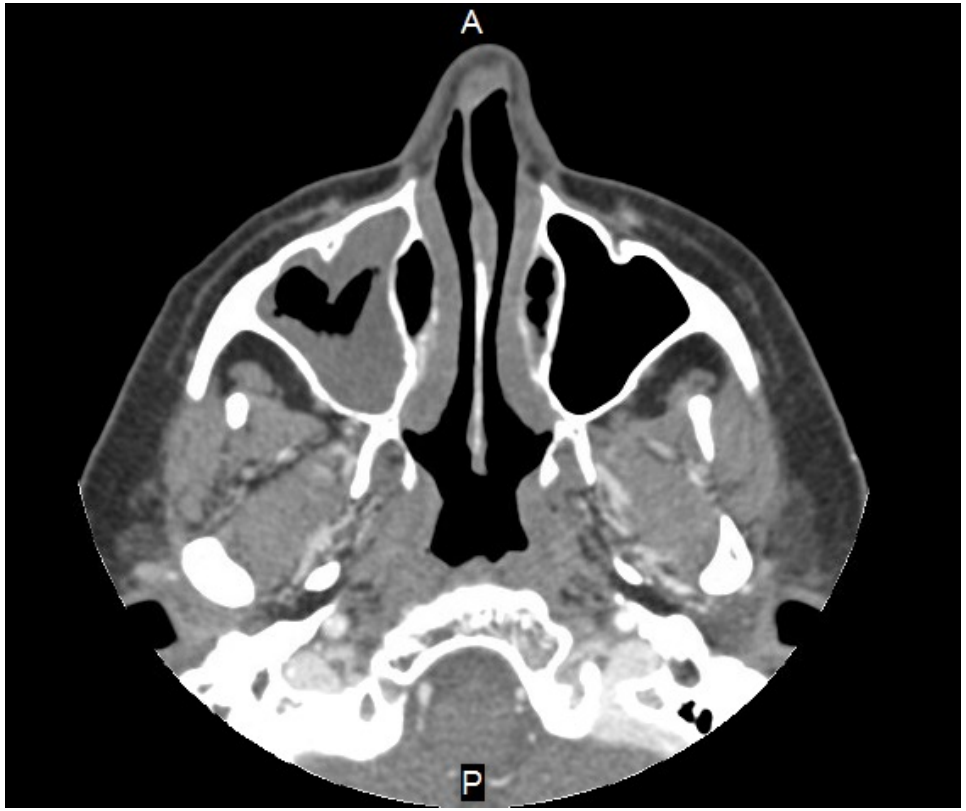
AE Development

- During C3, patient developed nasal congestion, post-nasal drip, intermittent chills, diffuse myalgias.
- Respiratory viral panel – positive for adenovirus
- CXR negative for infiltrates
- Adenovirus PCR, quantitative, blood checked with findings consistent with viremia
- Patient then developed diarrhea (~5x/day) with crampy abdominal pain→ stool positive for adenovirus
- PET/CT obtained to reassess response given history of extramedullary disease → no abnormal uptake or infiltrates in lungs
- Patient with hypogammaglobulinemia: IgG 240, IgM 12, IgA 15 mg/dL

Case Presentation – Dr Usmani (Cont)

AE Development

- Patient had persistent sinusitis symptoms with congestion, ear pressure, headaches and PND despite supportive measures.
- Patient saw ID and ENT.



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Case Presentation – Dr Usmani (Cont)

AE Management

- Respiratory symptoms initially managed with supportive measures (anti-tussive agents, decongestants) but had persistent symptoms
- Patient received antibiotics for possible superimposed bacterial sinusitis and received steroid taper due to persistent symptoms with minimal improvement.
- Patient decided to undergo endoscopic sinus surgery for chronic rhinosinusitis → after a few weeks of recovery, symptoms improved
- Patient started on IVIG 4-6 weeks due to hypogammaglobulinemia
- Adenovirus PCR was repeated with down-trending viral copies
- Imodium PRN diarrhea

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Case Presentation – Dr Usmani (Cont)

Patient Follow-Up

- Adenovirus viremia cleared
- Respiratory symptoms lasted for ~4-6 weeks
- Diarrhea symptoms resolved after 5 days
- Patient was able to restart on BCMA-bsAb.
- Patient progressed after C5 and had to come off the study

Case Presentation – Dr Lee

38 yo M with relapsed/refractory multiple myeloma

- **Initial presentation with diffuse bone disease**
- **High-risk FISH with t(4;14). Additionally had del 13q, -16q, and +15.**

Treatment History

- **Line 1:** CyBorD x 1 cycle -> VRd x 4 cycles with PR, followed by high-dose melphalan and autologous stem cell rescue with VGPR, then lenalidomide maintenance with continued VGPR, then PD (duration of response 1 year)
- **Line 2:** Daratumumab, Bortezomib, Dexamethasone x 3 cycles followed by Daratumumab, Ixazomib, Dexamethasone on protocol study with SD, then PD
- **Line 3:** Carfilzomib, Cyclophosphamide, Dexamethasone with PR, then PD (duration of response 1 month). Rapidly progressing disease with multiple new fractures, epidural disease requiring radiation therapy.

Case Presentation – Dr Lee (Cont)

38 yo M with relapsed/refractory myeloma

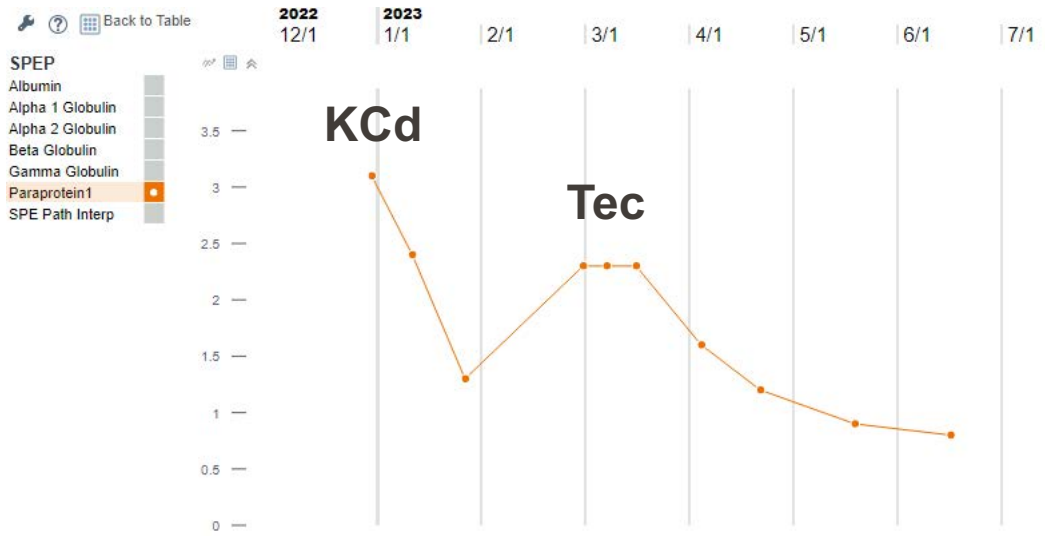
- **Refractory to Bortezomib, ixazomib, carfilzomib, lenalidomide, daratumumab, cyclophosphamide.**
- **Best option is BCMA-targeted agent – rapidly progressing disease makes BCMA CART not possible at the time**
- **Decision to proceed with standard-of-care teclistamab**

Case Presentation – Dr Lee (Cont)

38 yo M with relapsed/refractory multiple myeloma

Teclistamab treatment course:

- **Receives teclistamab step-up doses on day 1, 4, and 8 inpatient. Grade 1 CRS on day 6 and day 7 (resolved with tocilizumab x 1).**
- **Currently mid-C4 teclistamab (weekly dosing) with PR so far (ongoing duration of response of 4 months)**



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The Case for Fixed Duration Treatment with Bispecific Antibodies

75 yo RRMM s/p 16 lines, diagnosed in 2001

Line 1: VAD induction, Mel-ASCT, PR

Line 2: Thal-Dex, PR

Line 3: Bor-Dex, PR

Line 4: Len-Dex, PR

Line 5: Bor-Dex, PR

Line 6: Cyclo-Dex, SD

Line 7: CyBorD, SD

Line 8: RVd, PR

Line 9: RVd-Cy, PR

Line 10: Bendamustine-Bor-Dex, SD

Line 11: Rd, MR

Line 12: Pom-Cy-Dex, SD

Line 13: Dara, MR

Line 14: Dara-Pom-Dex, PR

Line 15: Dara-Pom-Cy-Dex. PR

Line 16: Teclistamab in summer 2019.

- Off s/p 8 cycles due to recurrent URIs, last dosed 01/2020

- Remained off therapy until late 2022, MRD-ve by NGS and flow at 10^{-5}

Courtesy of Saad Zafar Usmani, MD, MBA

Case Presentation – Dr Lee

66 yo F with relapsed/refractory multiple myeloma

- **Initial presentation with anemia**
- **High-risk FISH with +1q21 (1 extra copy) and del 17 on conventional Cg.**

Treatment History

- **Line 1: VRd** x 5 cycles with PR, followed by high-dose melphalan and autologous stem cell rescue with VGPR, then lenalidomide + elotuzumab maintenance on protocol with continued VGPR, then PD (duration of response 20 months)
- **Line 2:** Ixazomib, Lenalidomide, Dexamethasone with MR, then PD (duration of response 9 months)
- **Line 3:** Daratumumab, Pomalidomide, Dexamethasone with PR, then PD (duration of response 32 months)
- **Line 4:** Carfilzomib, Cyclophosphamide, Dexamethasone with PR, then PD (duration of response 7 months)

Case Presentation – Dr Lee (Cont)

66 yo F with relapsed/refractory myeloma

- Refractory to carfilzomib, ixazomib, lenalidomide, pomalidomide, daratumumab, elotuzumab, cyclophosphamide.
- Best option is BCMA-targeted agent – No standard-of-care BCMA CART slot available at the time
- Decision to proceed with linvoseltamab (BCMA bispecific T-cell antibody) on study

Case Presentation – Dr Lee (Cont)

66 yo F with relapsed/refractory multiple myeloma

Linvoseltamab treatment course:

- **Receives linvoseltamab step-up doses on day 1 (5 mg) and day 8 (25 mg) with inpatient monitoring, and day 15 (200 mg) outpatient. No CRS/ICANS.**
- **De-escalates dosing frequency to q2 week for Cycles 3-10**
- **De-escalates dosing frequency to q4 week starting Cycle 11 once attaining VGPR**
- **Best response MRD negative CR by Cycle 15**
- **Remains in MRD negative CR (ongoing duration of response 16 months)**

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Case Presentation – Dr Usmani

Case Description

- 69-year-old female with R-ISS Stage 2 IgG kappa RRMM with gain 1q21 on a GPRC5D-bispecific antibody.
- 5 prior lines of therapy including PIs, IMiDs, anti-CD38 mAb, SLAMF7 mAb, cyclophosphamide.
- Deferred autologous stem cell transplant.
- Co-morbidities: home O2 (2-3L) for COPD and pulmonary hypertension; hypertension; obesity
- Baseline BMI prior to start of GPRC5D-bispecific antibody was 34

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Case Presentation – Dr Usmani (Cont)

Patient Treatment

- Patient was enrolled on clinical trial for GPRC5D-bispecific antibody.
- Tolerated step-up dosing with G1 CRS.
- During C2, she started noting mild nausea and decreased appetite as well as taste alteration.
- Patient responding well to GPRC5D-bAsb with MRD negative CR.
- GI work-up negative. Symptoms gradually worsened leading to an approximately 20% decrease in body weight after ~5 months of therapy.

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Case Presentation – Dr Usmani (Cont)

AE Management

- Anti-emetic agents tried without significant relief: ondansetron, prochlorperazine, lorazepam, metoclopramide
- Patient tried dronabinol which initially helped with nausea, dysgeusia, and appetite but improvement only lasted a few weeks without significant improvement in weight
- Patient was also started on sucralfate
- GPRC5D bsAb was dose-reduced and transitioned to every other week dosing

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Case Presentation – Dr Usmani (Cont)

Patient Follow-Up

- With dose reduction and change in dosing schedule, patient's dysgeusia, nausea/vomiting, and anorexia improved.
- She started to gain back weight
- Lowest BMI was 24 → latest BMI 31
- She has remained on treatment for about 18 months and remains in an MRD negative CR.

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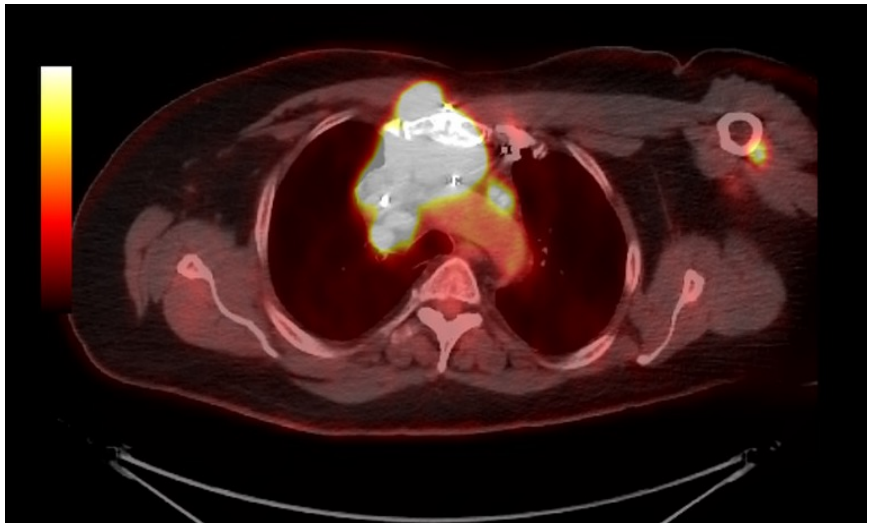
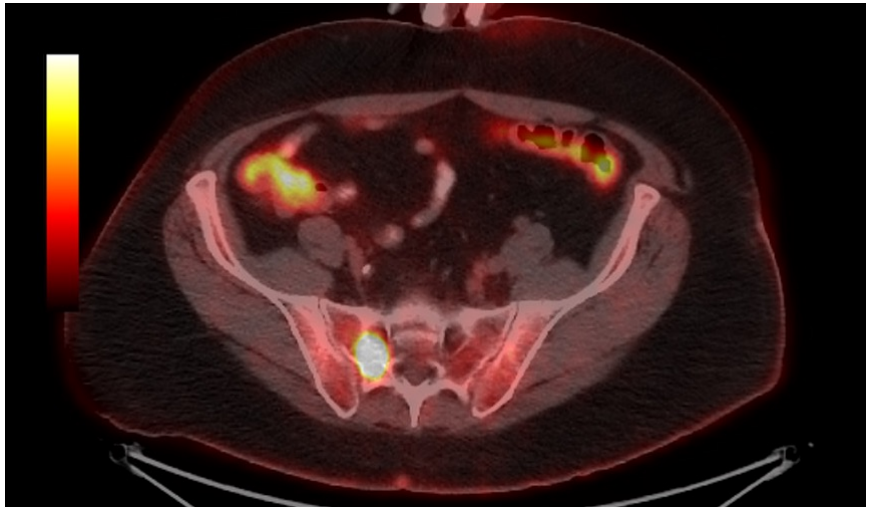
Case Presentation – Dr Usmani

Case Description

- 57-year-old male with R-ISS Stage 2 IgA kappa RRMM on an FcRH5-bispecific antibody.
- Diagnosed in 5/2017
- Standard risk cytogenetics
- 6 prior lines of therapy including PIs, IMiDs, anti-CD38 mAb, cyclophosphamide, ASCT
- Co-morbidities: HTN, CAD s/p CABG, obesity, peripheral neuropathy from prior bortezomib, HLD, NAFLD
- Significant back pain, chest wall pain, and right shoulder pain. PET/CT showed anterior mediastinal mass and multiple lytic bone lesions.





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Case Presentation – Dr Usmani (Cont)

Patient Treatment

- Patient had salvage ASCT with progressive disease based on labs and PET/CT after 4 months.
- Received palliative RT to anterior mediastinal mass and shoulder due to significant pain despite opiates*.
- Patient enrolled on clinical trial for FcRH5-bispecific antibody.
- Tolerated step-up dosing with G1 CRS.
- Patient developed bone pain involving the shoulder, chest wall, and back with each treatment dose that would resolve after 24 to 48 hours with initial cycles.

*Patient with history of narcotic abuse and wanted to minimize opiate use for pain

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Case Presentation – Dr Usmani (Cont)

AE Development

- During C2, patient noticed increased numbness and tingling in the feet, which did not affect his activities of daily living and gait.
- He has a history of bortezomib-induced peripheral sensory neuropathy which improved after bortezomib was discontinued but did not resolve completely.
- Patient developed burning sensation in his feet especially worse at night with subsequent cycles

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Case Presentation – Dr Usmani (Cont)

AE Management

- Patient was initially monitored with grade 1 peripheral sensory neuropathy
- With burning sensation, patient was started on gabapentin with some relief
- Sensory neuropathy does not affect his ADLs

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Case Presentation – Dr Usmani (Cont)

Patient Follow-Up

- Peripheral sensory neuropathy has remained stable with burning sensation controlled with gabapentin
- Patient is in a VGPR on clinical trial with FcRH5-bispecific antibody

Case Presentation – Dr Lee

78 yo M with relapsed/refractory multiple myeloma

- **Initial presentation with anemia, later developed diffuse bone disease at relapse**
- **Standard risk FISH. +Extramedullary disease at later relapse.**

Treatment History

- **10 prior lines of therapy**
- **Refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, cyclophosphamide, belantamab mafodotin, mezigdomide**

Case Presentation – Dr Lee (Cont)

78 yo M with relapsed/refractory multiple myeloma

- **Patient prefers bispecific option over CART option as lack of caregiver needed during peri-CART period**
- **Line 11 therapy: Treated with FcRH5-targeted bispecific T-cell antibody**
  - No CRS/ICANS (inpatient step-up dosing).
  - Best response: partial response (duration of response 4 months)

APPENDIX

Detailed Overview of Incidence and Management of CRS Observed with Teclistamab in the MajesTEC-1 Study for Patients with R/R MM

- CRS was observed in 72.1% of patients treated with teclistamab. Most events were Grade 1 or 2 and manageable, without treatment discontinuation.
- Most CRS events occurred during the step-up schedule, requiring vigilance during treatment initiation.
- Recommendation is to ensure fever is resolved and patients have no signs of infection before initiating the teclistamab step-up schedule or administering the next teclistamab dose, to avoid exacerbating CRS.
- Tocilizumab reduced the risk of subsequent CRS in patients receiving it for their first CRS event (20.0% vs 62.2% in those not receiving it), without affecting response to teclistamab.
- No baseline characteristics, including tumor burden or cytokine levels, appeared to clearly predict for CRS occurrence or severity.

Martin TG et al. *Cancer* 2023;129(13):2035-46.

Key Requirements of the Teclistamab Risk Evaluation and Mitigation Strategy (REMS)

- Receive training on the REMS requirements at www.TECVAYLIREMS.com using the Prescriber Training Program and the Adverse Reaction Management Guide.
- Successfully complete the Knowledge Assessment online.
- Enroll in the REMS by completing the Prescriber Enrollment Form online and submit it to the REMS.
- If teclistamab will be dispensed and administered in the same location, an Authorized Representative must complete the Pharmacy and Healthcare Setting certification.
- Counsel patients that they should be hospitalized and monitored for signs and symptoms of CRS and neurologic toxicity, including ICANS, for 48 hours after administration of all doses within the teclistamab step-up dosing schedule.

https://tecvaylirems.com/#Main

Recommendations for Management of Teclistamab-Associated CRS

Table 1: Recommendations for Management of CRS

Grade[a]	Presenting Symptoms	Actions
Grade 1	Temperature ≥100.4°F (38°C)[b]	• Withhold TECVAYLI until CRS resolves. • Administer pretreatment medications prior to next dose of TECVAYLI.[c]
Grade 2	Temperature ≥100.4°F (38°C)[b] with: Hypotension responsive to fluids and not requiring vasopressors. and/or Oxygen requirement of low-flow nasal cannula[d] or blow-by.	• Withhold TECVAYLI until CRS resolves. • Administer pretreatment medications prior to next dose of TECVAYLI.[c] • Patients should be hospitalized for 48 hours following the next dose of TECVAYLI.[c]
Grade 3	Temperature ≥100.4°F (38°C)[b] with: Hypotension requiring one vasopressor with or without vasopressin. and/or Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask.	**First Occurrence of Grade 3 CRS with Duration Less than 48 Hours:** • Withhold TECVAYLI until CRS resolves. • Provide supportive therapy, which may include intensive care. • Administer pretreatment medications prior to next dose of TECVAYLI. • Patients should be hospitalized for 48 hours following the next dose of TECVAYLI.[c] **Recurrent Grade 3 CRS or Grade 3 CRS with Duration 48 hours or Longer:** • Permanently discontinue TECVAYLI. • Provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥100.4°F (38°C)[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin). and/or Oxygen requirement of positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation).	• Permanently discontinue TECVAYLI. • Provide supportive therapy, which may include intensive care.

https://tecvaylirems.com/#Main

RTP RESEARCH TO PRACTICE

Inside the Issue: Current and Future Management of ER-Positive Metastatic Breast Cancer After Disease Progression on a CDK4/6 Inhibitor

A CME/MOC-Accredited Live Webinar

Thursday, July 20, 2023
5:00 PM – 6:00 PM ET

Faculty

Aditya Bardia, MD, MPH
Erika Hamilton, MD

Moderator

Neil Love, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

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

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