MYELOMA ROUNDS SAN FRANCISCO

Saturday, March 22, 2025
9:30am – 1:30pm

Hyatt Regency San Francisco
San Francisco, CA

This activity is provided by The Leukemia & Lymphoma Society and Medical Learning Institute Inc, in collaboration with the Association of Cancer Care Centers™ (ACCC).

Supported by educational grants from Adaptive Biotechnologies Corporation and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

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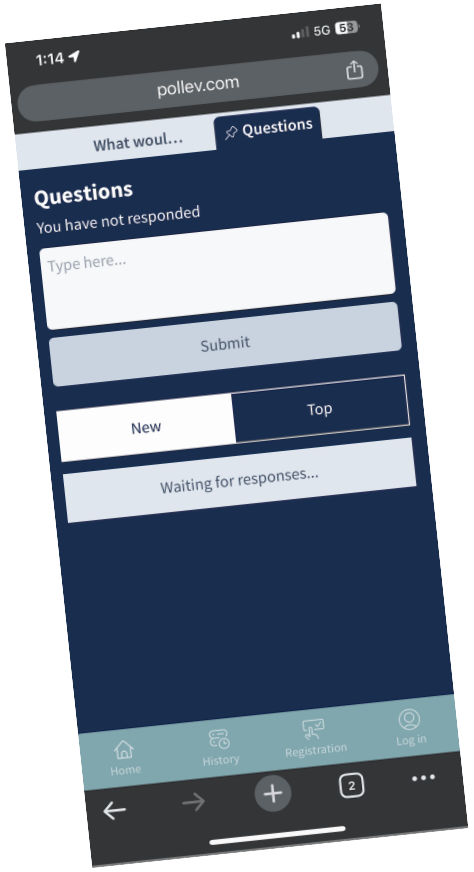
Scan the QR Code to Ask Faculty a Question!

Submit a question to the faculty at any time.



Go to the Question Tab to type and submit.

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WELCOMING REMARKS

Ajai Chari, MD (Chair)
Director of Multiple Myeloma Program
Co-Director of Clinical Research
Hematology/Oncology
Professor of Clinical Medicine
University of California, San Francisco
San Francisco, CA

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POLLING QUESTION

Have you contacted or referred a patient to The Leukemia and Lymphoma Society's Information Resource Center or Clinical Trial Support Center?

1. Within the past year
2. Within the past 2 years
3. Within the past 3 years
4. Never

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POLLING QUESTION

What is the highest amount of dollars a music concert has brought to a city?

1. $5 million
2. $15 million
3. $30 million
4. $100 million
5. $200 million

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POLLING QUESTION

Who was that Artist?

1. Madonna
2. Billy Joel
3. Pink Floyd
4. Chicago
5. Taylor Swift

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TARGET AUDIENCE

This activity is intended for hematologists-oncologists, medical oncologists, physician associates, nurse practitioners, nurses and pharmacists involved in the care of patients with myeloma.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, participants will be better able to:

- Describe the latest developments in myeloma, including current and emerging treatments
- Engage patients and caregivers in clinical trials discussions on newly approved therapies and emerging therapies for myeloma, including combination therapies, CAR T-cell therapy and bi-specific antibodies
- Explain disparities and challenges in diagnosis and treatment of myeloma
- Apply evidence-based treatment strategies for optimal patient care
- Identify patient education and support resources

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AGENDA

9:30 AM	Networking and Brunch Buffet
10:00 AM	Welcome and Overview of Program *Ajai Chari, MD*
10:10 AM	Overview of LLS Resources, including the Clinical Trial Support Center *Ashley Giacobbi, DNP, RN, ACNS-BS, AOCNS, OCN*
10:20 AM	Newly Diagnosed Multiple Myeloma: Case and Discussion *Lekha Mikkilineni, MD, MA and Yonatan Cooper MD, PhD*
11:30 AM	Treating Early Relapsed Multiple Myeloma with CAR-T: Case and Discussion *Jodi Lipof, MD and Meryl Colton, MD, MSc*
12:20 PM	Bispecifics to Treat Multiple Myeloma: Case and Discussion *Aaron Rosenberg, MD, MS and Guneet Kaleka, MD*
1:10 PM	Putting All the Pieces Together: Summarizing Best Practices and Proposed Sequencing *Michael Green, MD*
1:30 PM	Conclusion *Ajai Chari, MD*

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ADVISORY GROUP & FACULTY DISCLOSURES

*Ajai Chari, MD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Adaptive, Amgen, Antengene, Bristol Myers Squibb, FORUS, Genentech/Roche, GlaxoSmithKline, Janssen, Karyopharm, Millenium/Takeda, Sanofi/Genzyme

Richard L. Fong, PharmD, BCOP, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

*Michael Green, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Michaela Liedtke, MD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Alexion, AstraZeneca, Jazz, Prothena, Sanofi
Research Funding: AbbVie, Alexion, Allogene, AstraZeneca, Biomea, Bristol Myers Squibb, Gilead, Ichnos, Janssen

*Aaron Rosenberg, MD, MS, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Bristol Myers Squibb
Research Funding: Biomea, Kangpu, Kite, Pfizer

Meryl Colton, MD, MSc, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Yonatan Cooper, MD, PhD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Ashley Giacobbi, DNP, RN, ACNS-BS, AOCNS, OCN, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Guneet Kaleka, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Jodi Lipof, MD, has a financial interest/relationship or affiliation in the form of:
Research Funding: Karyopharm (ended Dec 2024), Kite

Lekha Mikkilineni, MD, MA, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor (both ended in 12/2023): BioLineRx, Legend Biotech

Part of the faculty and advisory board

All of the relevant financial relationships of individuals for this activity have been mitigated.

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Disclosure & Conflict of Interest Policy

Medical Learning Institute Inc and The Leukemia & Lymphoma Society, are committed to providing high quality continuing education to healthcare professionals, as individuals and teams, with a protected space to learn, teach, and engage in scientific discourse free from influence from ineligible companies that may have an incentive to insert commercial bias into education. To that end, MLI and LLS require faculty, presenters, planners, staff, and other individuals who are in a position to control the content of this CE activity to disclose all financial relationships they have had in the past 24 months with ineligible companies as defined by the ACCME, as related to the content of this CE activity, regardless of the amount or their view of the relevance to the education. All identified COI will be thoroughly vetted and mitigated according to MLI and LLS policy. These disclosures will be provided to learners prior to the start of the CE activity.

Planning Committee and Content/Peer Reviewers

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Lauren Berger, MPH, has a financial interest/relationship or affiliation in the form of:
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Disclosure of Unlabeled Use

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Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this CE activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this CE activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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CE DESIGNATION

Accreditation, Support and Credit

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute Inc and The Leukemia & Lymphoma Society. Medical Learning Institute Inc is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education

Medical Learning Institute Inc (MLI) designates this live activity for a maximum of 3.5 *AMA PRA Category 1 Credits*™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Statement

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 3.5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Participation information will be shared through the ACCME's Program and Activity Reporting System (PARS).

For Physicians requesting MOC credit, the post-test and evaluation are required in their entirety as well as your ABIM ID number, DOB (MM/DD), and a score of 70% or higher is needed to obtain MOC credit.

Physician Associate

Medical Learning Institute Inc has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 3.5 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation.

Nursing Continuing Professional Development

Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under Provider Number CEP 5832 to award 3.5 continuing education contact hours through the California Board of Registered Nursing.

Pharmacy

Medical Learning Institute Inc designates this application-based continuing education activity for 3.5 contact hours (0.35 CEUs) of the Accreditation Council for Pharmacy Education.
Universal Activity Number: JA0007322-9999-25-008-L01-P

Interprofessional Continuing Education Credit

This activity was planned by and for the healthcare team, and learners will receive 3.5 Interprofessional Continuing Education (IPCE) credits for learning and change.

Support Statement

There is no commercial support associated with this activity.

INSTRUCTIONS FOR CREDIT

There are no fees for participating in or receiving credit for this CE activity. In order to receive credit, learners must participate in the entire CE activity, complete the evaluation form. A certificate of completion will be emailed within 30 days of receipt. If you have questions regarding the receipt of your certificate, please contact us via email at ndane@mlieducation.org.

For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

For Physicians requesting MOC credit, the post-test and evaluation are required in their entirety as well as your ABIM ID number, DOB (MM/DD), and a score of 70% or higher is needed to obtain MOC credit.

For Pharmacists, Medical Learning Institute will accept your completed evaluation form for up to 30 days post-activity and will report your participation to the NABP only if you provide your NABP e-Profile number and DOB (MM/DD). Within 6 weeks, you can view your participation record at the NABP website: https://nabp.pharmacy/

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Our Mission:

Cure blood cancer and improve the quality of life of all patients and their families.

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FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

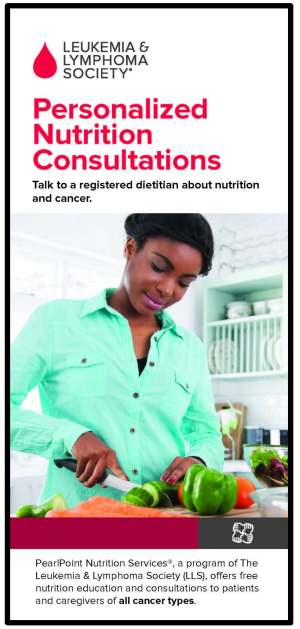
- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - www.LLS.org/IRC

- **Nutrition Education Services Center**–Free one-on-one consultations with registered dietitians for patients/caregivers of all cancer types by phone or email.
  - www.LLSnutrition.org

- **Clinical Trial Nurse Navigators** – RNs and NPs provide personalized service for patients seeking treatment in a clinical trial, reviews clinical information and provides trial information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC

- **Reach out Monday – Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat and Email: www.LLS.org/IRC
  - HCP Patient Referral Form: www.LLS.org/HCPreferral

- **Webcasts, Videos, Podcasts, Booklets**



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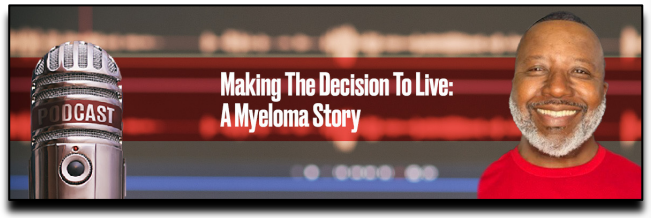
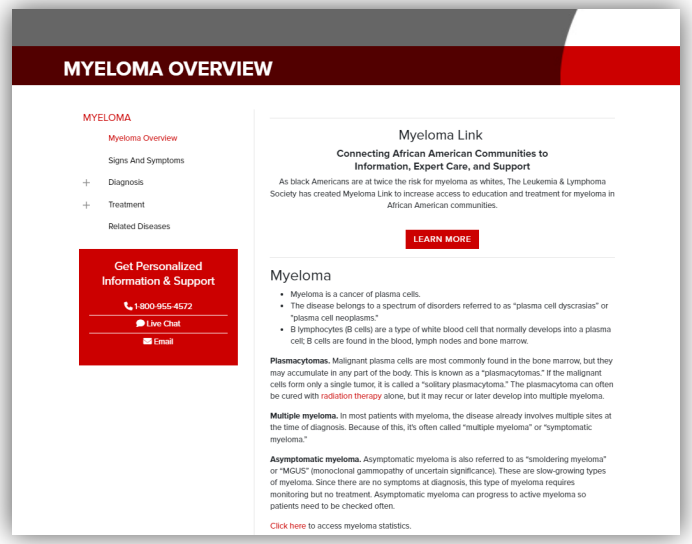
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- www.LLS.org/Myeloma
- **Webcasts, Videos, Podcasts, booklets**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets





- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
    - Medical Debt Case Management Program
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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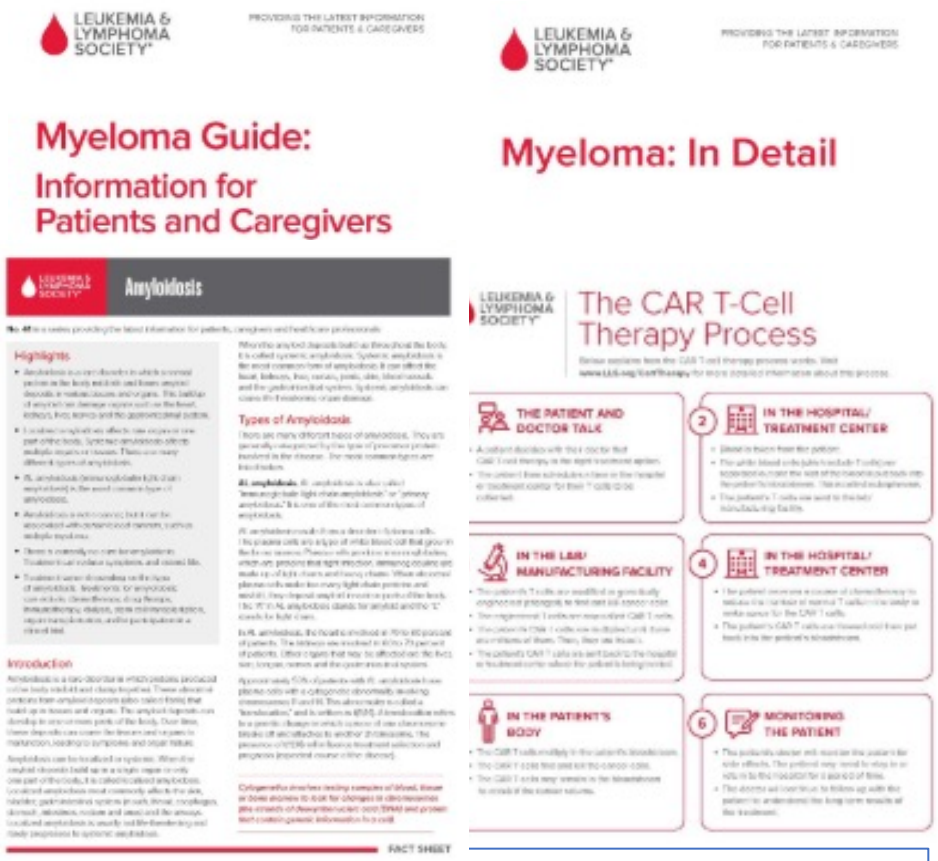
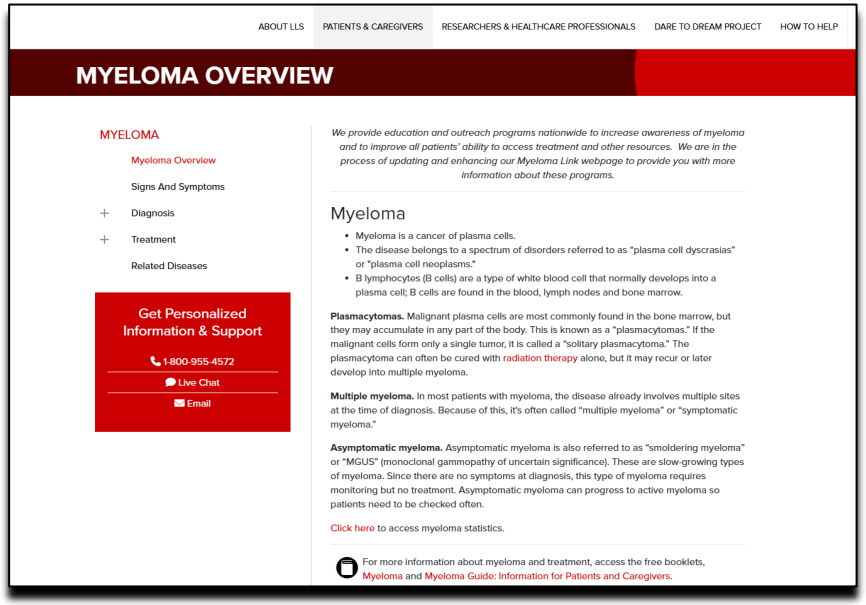
FREE LLS RESOURCES PATIENTS AND CAREGIVERS



BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales



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HERE TO HELP: LLS COMMITMENT

LLS is committed to providing education and resources to help patients access clinical trials.

CLINICAL TRIAL SUPPORT CENTER

- A team of **highly trained** nurses and nurse practitioners experienced with hematological malignancies and clinical research.
- Provide **education** to patients about clinical trials, treatment options, and other disease specific information.
- Provide patients, families, and their caregivers with a professional, detailed, **individualized** search to discuss with their HCP.
- Provide **guidance** and serve as **advocates** throughout the clinical trial process. Help make connections between the patient and the trial site to facilitate enrollment as appropriate.
- Provide a **personal connection** and develop long term relationships to help better serve our patients.
- We serve as a **bridge** between technology and patients to make accessing clinical trial information easier.

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THE CLINICAL TRIAL SUPPORT CENTER TEAM

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Director, CTSC

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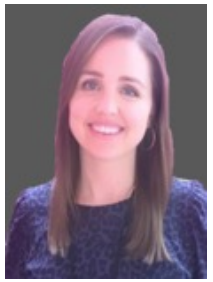

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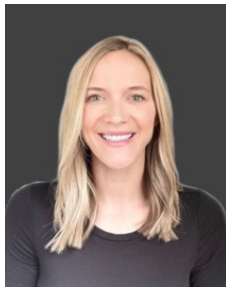
Clinical Trial Nurse Navigator



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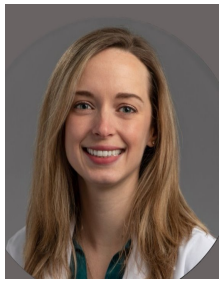

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Clinical Trial Nurse Navigator

Melanie Fyfe
MSN, APRN, AGCNS-BC, OCN, BMTCN
Clinical Trial Nurse Navigator

Michelle Bibo
CTSC Operations Specialist

ACCESSING THE CLINICAL TRIAL SUPPORT CENTER

Healthcare Professionals can complete a referral form at:
https://www.LLS.org/CTSCreferral

Email the CTSC directly with questions at: CTSC@LLS.org

Patients or caregivers can complete an online referral form at:
https://www.LLS.org/navigation

Call the Information Resource Center (IRC) 1-800-955-4572

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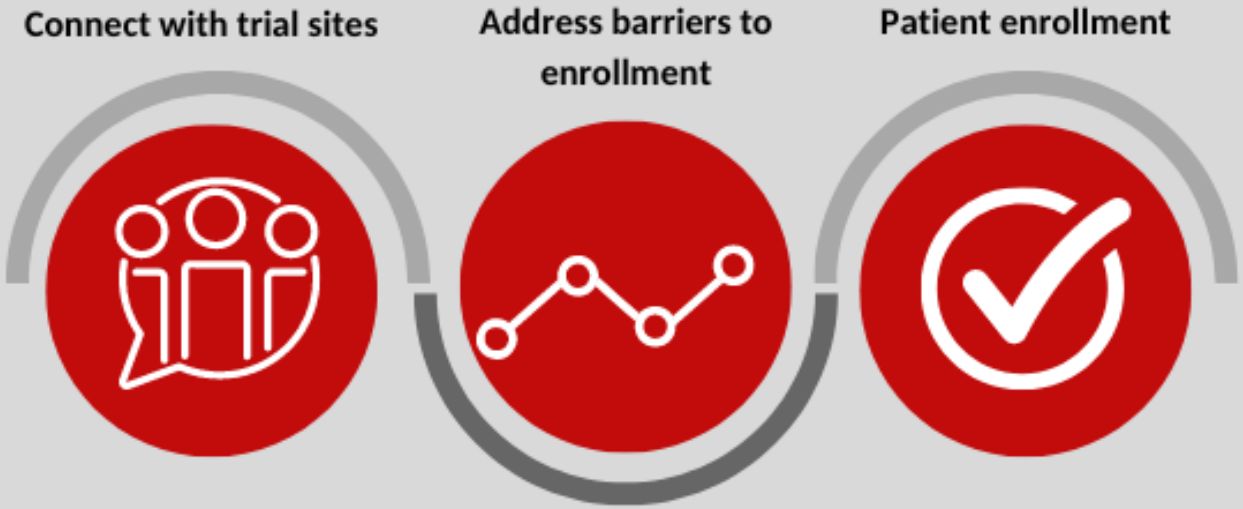
CTSC PROCESS FOR SUPPORTING PATIENTS



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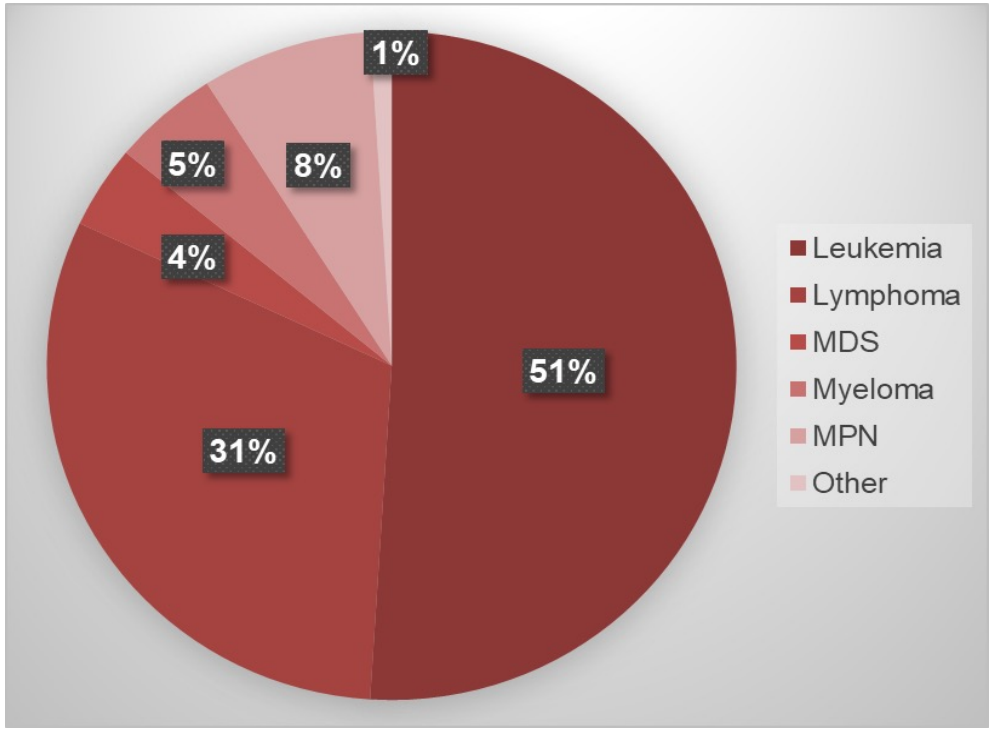
CTSC PATIENT OUTCOMES

- 12 CTSC nurse navigators assisted a total of 1,142 patients
- Nurse navigators had over 10,454 interactions with all patients, caregivers & medical professionals
- **20% of eligible patients enrolled into a clinical trial***
- **Reasons patients did not enroll:**
  - Not clinically indicated for treatment change
  - Team recommended treatment other than trial
  - Insurance constraints
  - No trial available within preferred geography
  - Financial constraints



Disease Category Breakdown of Patients That Entered Into A Clinical Trial

***8-10% of adult cancer patients enroll nationwide annually**

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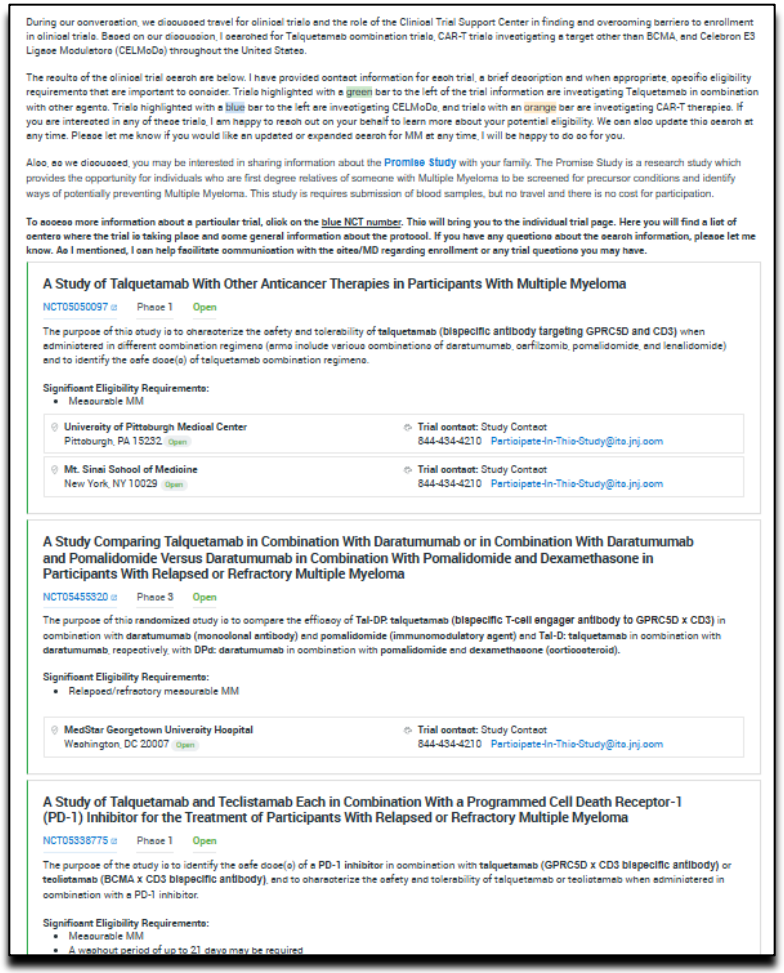
CLINICAL TRIAL SUPPORT CENTER CASE STUDY

- Heavily pre-treated MM patient referred to CTSC by physician
  - Previously treated with D-VRd, AuSCT with MRD+, Teclistamab,
  - Recommended for standard of care Talquetamab then Ide-Cel

- Seeking clinical trial with non-BCMA CAR target or Talquetamab combination regimen

- **During CTSC intake call patient shares:**
  - **Food insecurity**
  - **Significant weight loss**
  - **Insurance concerns**
    - Facility offering bispecific & Ide-Cel out-of-network
  - **Caregiver burnout**



During our conversation, we discussed travel for clinical trials and the role of the Clinical Trial Support Center in finding and overcoming barriers to enrollment in clinical trials. Based on our discussion, I searched for Talquetamab combination trials, CAR-T trials investigating a target other than BCMA, and Celebron E3 Ligase Modulators (CELMoDs) throughout the United States.

The results of the clinical trial search are below. I have provided contact information for each trial, a brief description and when appropriate, specific eligibility requirements that are important to consider. Trials highlighted with a green bar to the left of the trial information are investigating Talquetamab in combination with other agents. Trials highlighted with a blue bar to the left are investigating CELMoDs, and trials with an orange bar are investigating CAR-T therapies. If you are interested in any of these trials, I am happy to reach out on your behalf to learn more about your potential eligibility. We can also update this search at any time. Please let me know if you would like an updated or expanded search for MM at any time, I will be happy to do so for you.

Also, as we discussed, you may be interested in sharing information about the **Promise Study** with your family. The Promise Study is a research study which provides the opportunity for individuals who are first degree relatives of someone with Multiple Myeloma to be screened for precursor conditions and identify ways of potentially preventing Multiple Myeloma. This study is requires submission of blood samples, but no travel and there is no cost for participation.

To access more information about a particular trial, click on the blue NCT number. This will bring you to the individual trial page. Here you will find a list of centers where the trial is taking place and some general information about the protocol. If you have any questions about the search information, please let me know. As I mentioned, I can help facilitate communication with the sites/MD regarding enrollment or any trial questions you may have.

A Study of Talquetamab With Other Anticancer Therapies in Participants With Multiple Myeloma

NCT05050097 Phase 1 Open

The purpose of this study is to characterize the safety and tolerability of **talquetamab (bispecific antibody targeting GPRC5D and CD3)** when administered in different combination regimens (arms include various combinations of daratumumab, carfilzomib, pomalidomide, and lenalidomide) and to identify the safe dose(s) of talquetamab combination regimens.

Significant Eligibility Requirements:
- Measurable MM

University of Pittsburgh Medical Center Pittsburgh, PA 15232 Open — **Trial contact:** Study Contact 844-434-4210 Participate-In-This-Study@its.jnj.com

Mt. Sinai School of Medicine New York, NY 10029 Open — **Trial contact:** Study Contact 844-434-4210 Participate-In-This-Study@its.jnj.com

A Study Comparing Talquetamab in Combination With Daratumumab or in Combination With Daratumumab and Pomalidomide Versus Daratumumab in Combination With Pomalidomide and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma

NCT05455320 Phase 3 Open

The purpose of this **randomized** study is to compare the efficacy of **Tal-DP: talquetamab (bispecific T-cell engager antibody to GPRC5D x CD3)** in combination with **daratumumab (monoclonal antibody)** and **pomalidomide (immunomodulatory agent)** and **Tal-D: talquetamab** in combination with **daratumumab**, respectively, with **DPd: daratumumab** in combination with **pomalidomide** and **dexamethasone (corticosteroid)**.

Significant Eligibility Requirements:
- Relapsed/refractory measurable MM

MedStar Georgetown University Hospital Washington, DC 20007 Open — **Trial contact:** Study Contact 844-434-4210 Participate-In-This-Study@its.jnj.com

A Study of Talquetamab and Teclistamab Each in Combination With a Programmed Cell Death Receptor-1 (PD-1) Inhibitor for the Treatment of Participants With Relapsed or Refractory Multiple Myeloma

NCT05338775 Phase 1 Open

The purpose of the study is to identify the **safe dose(s) of a PD-1 inhibitor** in combination with **talquetamab (GPRC5D x CD3 bispecific antibody)** or **teclistamab (BCMA x CD3 bispecific antibody)**, and to characterize the safety and tolerability of talquetamab or teclistamab when administered in combination with a PD-1 inhibitor.

Significant Eligibility Requirements:
- Measurable MM
- A washout period of up to 21 days may be required

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CLINICAL TRIAL SUPPORT CENTER CASE STUDY

- Heavily pre-treated MM patient referred to CTSC by physician
  - Previously treated with D-VRd, AuSCT with MRD+, Teclistamab,
  - Recommended for standard of care Talquetamab then Ide-Cel

- Seeking clinical trial with non-BCMA CAR target or Talquetamab combination regimen

- **During CTSC intake call patient shares:**
  - **Food insecurity** → **LLS Financial Aid Programs**
  - **Significant weight loss** → **Nutrition Education and 1:1 Consult with Dietitian**
  - **Insurance concerns** → **Medical Debt Case Management Program**
    - Facility offering bispecific & Ide-Cel out-of-network
  - **Caregiver burnout** → **Information Resource Center**

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Thanks again so much for your help- it is truly so helpful to have this overview of available trials to make most informed recommendations for our patients.

Very best wishes,

Dr. W

Hello Ashley,

I just wanted to take some time to thank you for helping me with the information about available clinical trials in my general area. I really appreciate your time and effort given to my cause, and I am sure the cause of many like me in this fight against such a scourge. The information you sent is currently being reviewed by my care team and I am fortunate that some of my doctors happen to know many of those doctors involved in the trials. Without carrying on to long, I just wanted to thank you with all my heart. It is a tremendous gift unto itself that people such as yourself and establishments like LLS exist and are there with the support and heart felt commitment to war on cancer.

Thank you so much,

LEUKEMIA & LYMPHOMA SOCIETY®

FREE LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

- ❑ CME & CE courses: www.LLS.org/CE
- ❑ Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- ❑ Videos for HCPs: www.LLS.org/HCPvideos
- ❑ Podcast series for HCPs: www.LLS.org/HCPpodcast

Myeloma Fact Sheet Coming Soon!

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EQUITY IN ACCESS RESEARCH PROGRAM

The Leukemia & Lymphoma Society's (LLS) Equity in Access Research Program was created in 2021 to generate **actionable solutions** to the barriers that prevent all patients from accessing the care they need and deserve. www.LLS.org/EquityinAccess

Program Goals

1) Advance understanding of modifiable, underlying causes of inequitable access to care for blood cancer patients and survivors within the current healthcare system.

2) Generate actionable evidence to assist LLS in advocating for policies and developing programs that tangibly improve the lives of blood cancer patients and survivors.

3) Identify healthcare policies and practices that have the potential to increase equitable access to cancer care and improve the quality of life and outcomes for blood cancer patients and survivors.

4) Cultivate health services researchers in the blood cancer space and contribute to LLS being recognized as a funding and thought leader in this area.

Program Activities

- The program has awarded over $12 million in funding for seminal health services research addressing critical issues such as the cost of oral anticancer medications, the role of health insurance in financial toxicity, and access to clinical trials.
- In 2024 alone, the program awarded $4.8 million to studies testing multi-level interventions to improve clinical trial access and enrollment, with the aim of disseminating those that are effective.

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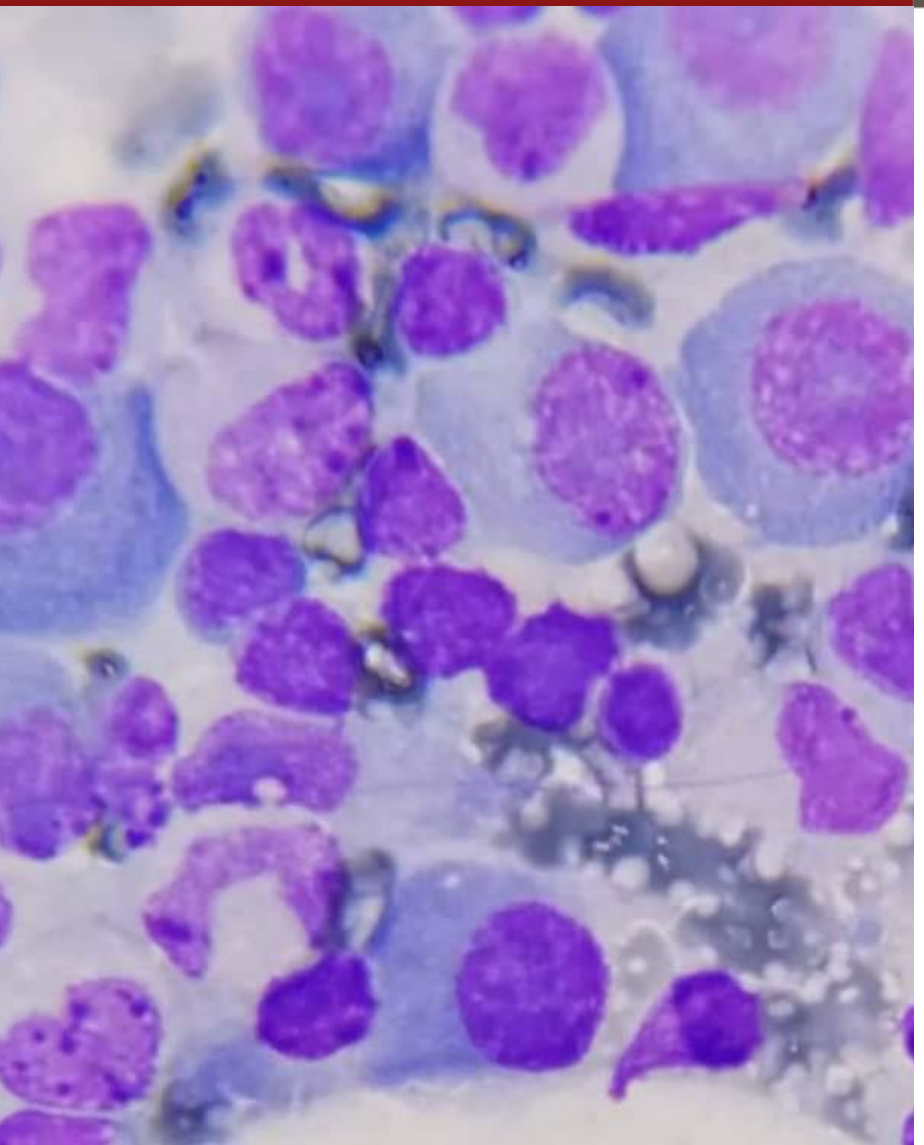


Newly Diagnosed Multiple Myeloma – Treatment Paradigms

Yonatan Ariel Cooper, MD PhD
PGY2, Fast-Track Residency-Hematology-Oncology Fellowship Program
Stanford School of Medicine
Palo Alto, CA

Lekha Mikkilineni, MD MA
Assistant Professor – Division of BMT
Stanford School of Medicine
Palo Alto, CA

Outline

- Case highlights & overview of MM
- Newly Diagnosed MM Treatment Paradigms
- Future directions & conclusions

Case Presentation

History:

Mr. M is a 71-year-old, relatively active male, who has a past medical history of benign prostatic hyperplasia and L-inguinal hernia.

- He is active for his age, golfing regularly. He can perform all activities of daily living independently
- Six months prior to presentation, he started experiencing lower back and right hip pain that progressively worsened until presentation
- Experienced a unintentional, 20-pound weight loss

Initial Presentation Workup:

- To further work up his progressive backpain, Mr. M undergoes an MRI of his lumbar spine and pelvis
- His MRI demonstrates compression deformities in T11, T12, and L1, and a laminar L3 mass overall concerning for malignancy
- Full malignancy workup is pursued at this point

Bone Lesions & L3 Soft Tissue Mass Work Up:

Physical Exam:

- ECOG 1 – still active but limited by pain, walking slower than normal. Notices some shortness of breath when exerting himself.
- Pain in ribs, lower back.
- Denies chest pain, orthopnea, edema, abdominal pain, diarrhea, neuropathy.

Medications: Ibuprofen as needed for pain control.

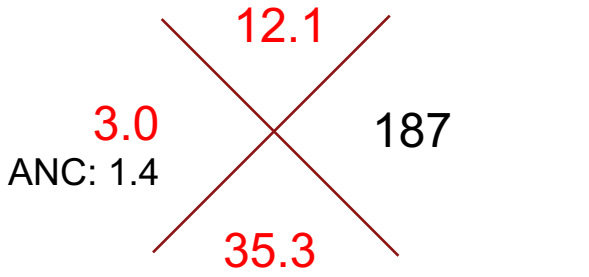
Medical History: Benign prostatic hyperplasia with episode of cystitis, inguinal hernia.

Surgical History: Transurethral Resection of the Prostate (TURP) (07/2024).

Family History: Mother had cholangiocarcinoma, father had prostate cancer, sister with breast cancer.

Social History: 10 pack-year smoker (quit 29 years ago), one alcoholic drink per month. Lives with his partner. Formerly worked in a café and in construction.

Laboratory Assessment



135	105	0.75	87
4.3	26	27	

Kappa: 26.5 mg/dL
Lambda: 0.6 mg/dL
K/L ratio: 29.84
SPEP M-spike: 3.6 g/dL
Serum protein: 9.4 g/dL

Ca: 9.5 mg/dL
Alb: 4.5 g/dL
LDH: 120 u/L
IgG: 5178 mg/dL
IgA: 23 mg/dL
IgM :14 mg/dL
B2M: 3.73 mg/L

Bone marrow biopsy

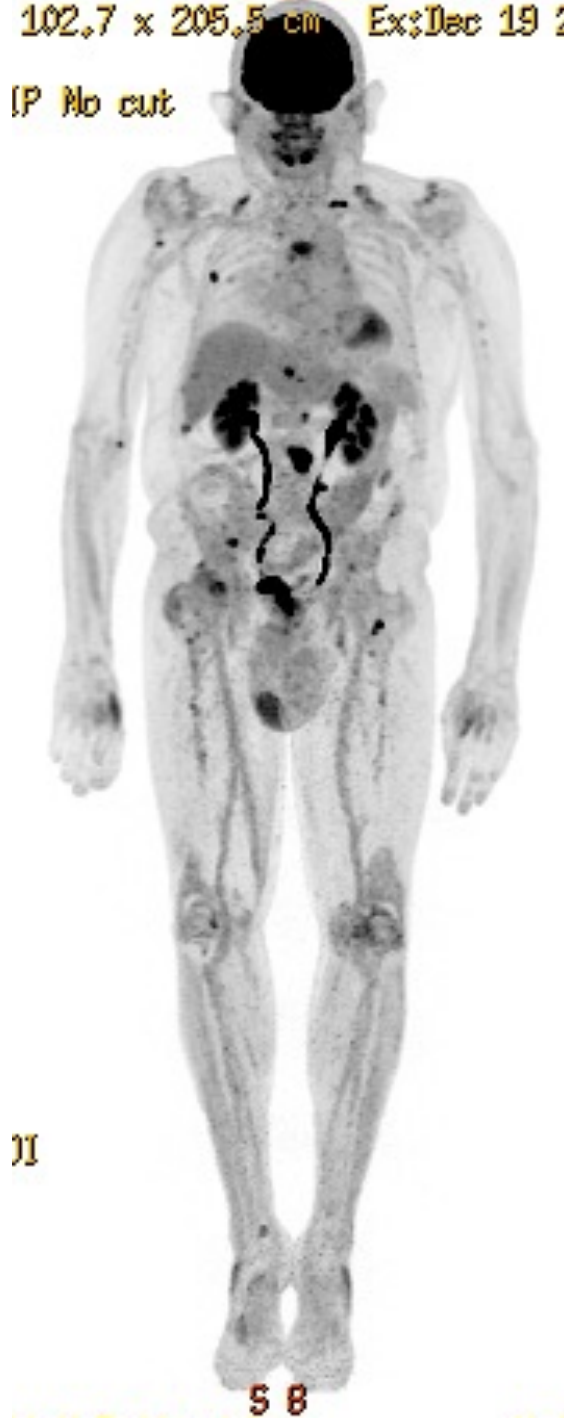
- Plasma cell neoplasm, **60-70% of marrow cellularity**
- Normocellular marrow (30%), <1% blasts by morphology
- Negative for ringed sideroblasts
- **Abnormal kappa-restricted plasma cell pop.** (92% CD38+)
- Congo red stain performed on core biopsy : Negative

Fluorescence In-Situ Hybridization (FISH):

Probe	Chrom. Target	Result	Comment
CCND1/IGH	t(11;14)(q13;q32)	Negative	8.5% nuclei with three CCND1 signals
D13S319/LAMP1	del(13q)/monosomy 13	**Positive**	13.0% nuclei with del(13q)
TP53/D17Z1	TP53 deletion at 17p13	Negative	
D3Z1/D7Z1	polysomy: 3 and/or 7	**Positive**	12.5% nuclei with gain of 3 & 7
CEP9/D15Z1	polysomy: 9 and/or 15	**Positive**	8.5% nuclei with gain of 9

Baseline Imaging: PET/CT

- Multiple osteolytic lesions (bone lesions) with focal FDG uptake.
- An osteolytic lesion and **soft tissue mass associated with L3**. Left **L5 transverse process lesion with soft tissue component**.
- Increased focal FDG uptake involving nearly the entire **T5 vertebral body with moderate pathological fracture deformity**.
- Mild pathological **fracture deformity of T11, T12 and multiple ribs**.
- Increased focal FDG uptake with **nondisplaced pathological fracture of right femoral neck**.



SLiM CRAB – Diagnostic Criteria

S	Li	M	C	R	A	B
>60% plasma cells on BMBx	Free light chain ratio > 100	MRI: >1 lesion >5 mm in size	Hypercalcemia: Calcium > 1 mg/dL above ULN or >11 mg/dL	Renal Insufficiency: CrCl < 40 mL/min or Cr > 2 mg/dL	Anemia: Hgb > 2 g/dL below LLN or <10 g/dL	Bone lesions: 1+ osteolytic lesions on CT or PET/CT

Risk Stratification

ISS	Criteria
I	• Albumin > 3.5 g/dl • B2M < 3.5 mg/L
II	• Not stage I or III
III	• B2M > 5.5 mg/L

R-ISS	Criteria
I	• Albumin > 3.5 g/dl • B2M < 3.5 mg/L • No high-risk cytogenetics • Normal LDH
II	• Not stage I or III
III	• B2M > 5.5 mg/L • High-risk cytogenetics: t(4; 14), t(4;16), del(17p) or elevated LDH

R2-ISS	Risk	Points
I	Low	0
II	Low-Intermediate	0.5 - 1
III	High-Intermediate	1.5 - 2.5
IV	High	3+

Points

- ISS III = 1.5
- ISS II or elevated LDH = 1
- del(17) or t(4;14) = 1
- 1q+ = 0.5

Diagnosis: IgG Kappa Multiple Myeloma

- **IgG Kappa Multiple Myeloma**
- FISH: 13q-. Polysomy 3, 7, 9, 11. No high-risk genetic lesions.
- R-ISS stage II: Intermediate risk
- ECOG1 due to symptoms
- No major comorbidities, organ dysfunction, psychosocial barriers

Pre-treatment Supportive Care

Myeloma patients typically present with end organ dysfunction, pathologic fractures, and pain requiring multidisciplinary care prior to or concurrent with induction therapy:

- Nephrology referral as needed for patients with kidney complications
- Radiation oncology for palliative XRT for cord compression, bone lesions, pain
- Orthopedic/neurosurgical referral for fracture stabilization or kyphoplasty
- Cardiology consultation if concern for cardiac amyloid
- Dental clearance prior to initiation of Zoledronic acid infusion

Transplant Eligibility Criteria

- Holistic patient specific evaluation based on performance status, comorbidities, psychosocial factors.

Sample of eligibility criteria:

- Karnofsky performance score ≥ 70
- Age generally < 74 years of age but at Stanford no firm age cutoff
- EF ≥ 45%
- DLCO ≥ 50% predicted
- **Strong psychosocial support with caregiver support!**

Treating Mr. M: Induction Followed by Autologous Transplant vs Clinical Trial

Key Considerations:

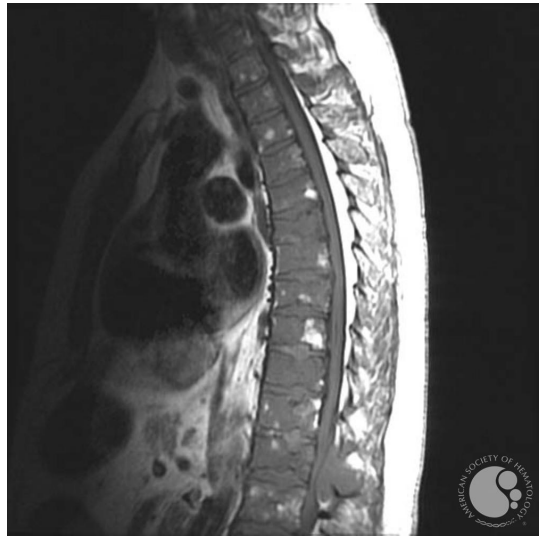
- Healthy, maintained good physical activity & relatively fit despite boney disease
- Transplant-eligible by all standard transplant parameters
- Discussed CARTITUDE-6 Trial
  - Upfront induction quadruplet therapy followed by autologous transplant + maintenance vs
  - Upfront induction quadruplet therapy followed by CAR T-cell therapy + maintenance

Patient opted to sign on to trial (discussed at the end)

Multiple Myeloma

- Multiple myeloma (MM) is a plasma cell neoplasm – malignant plasma cells infiltrate bone marrow and/or tissues/organs.

- Malignant clones produce monoclonal proteins including immunoglobulin, free light chains, cytokines that disrupt bone metabolism, kidney function, immune mechanisms and with extramedullary MM, other organ functions.



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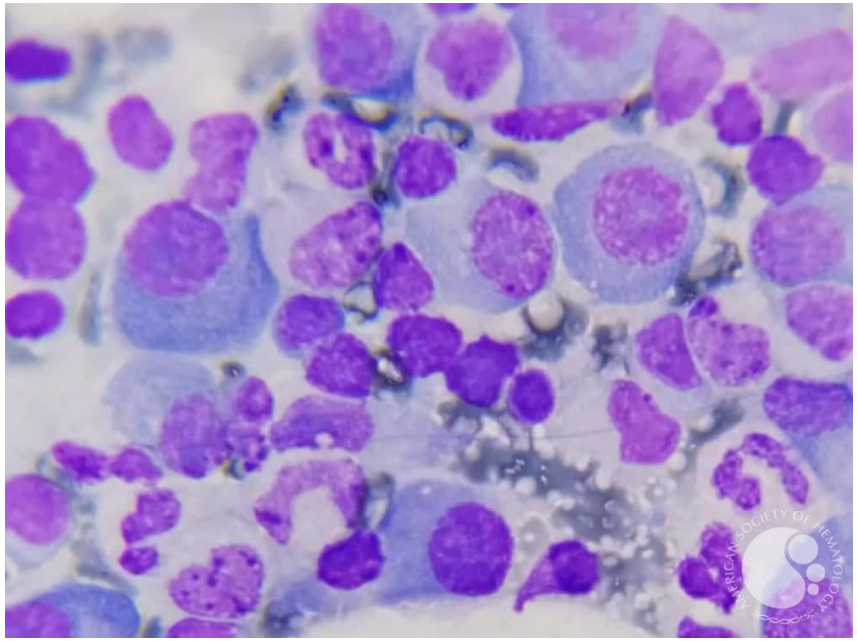

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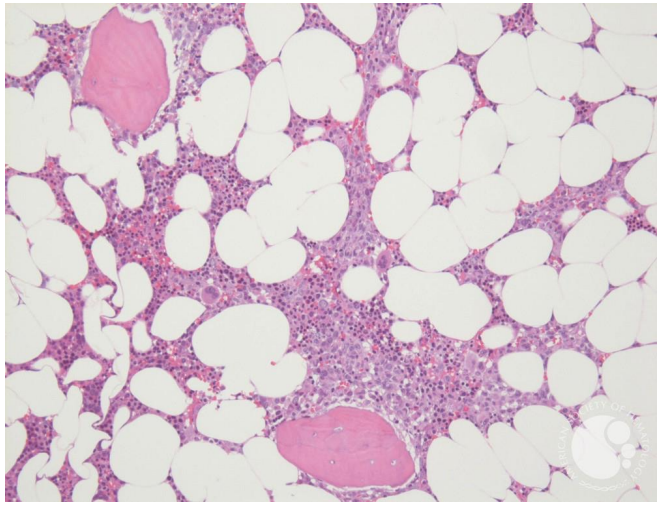

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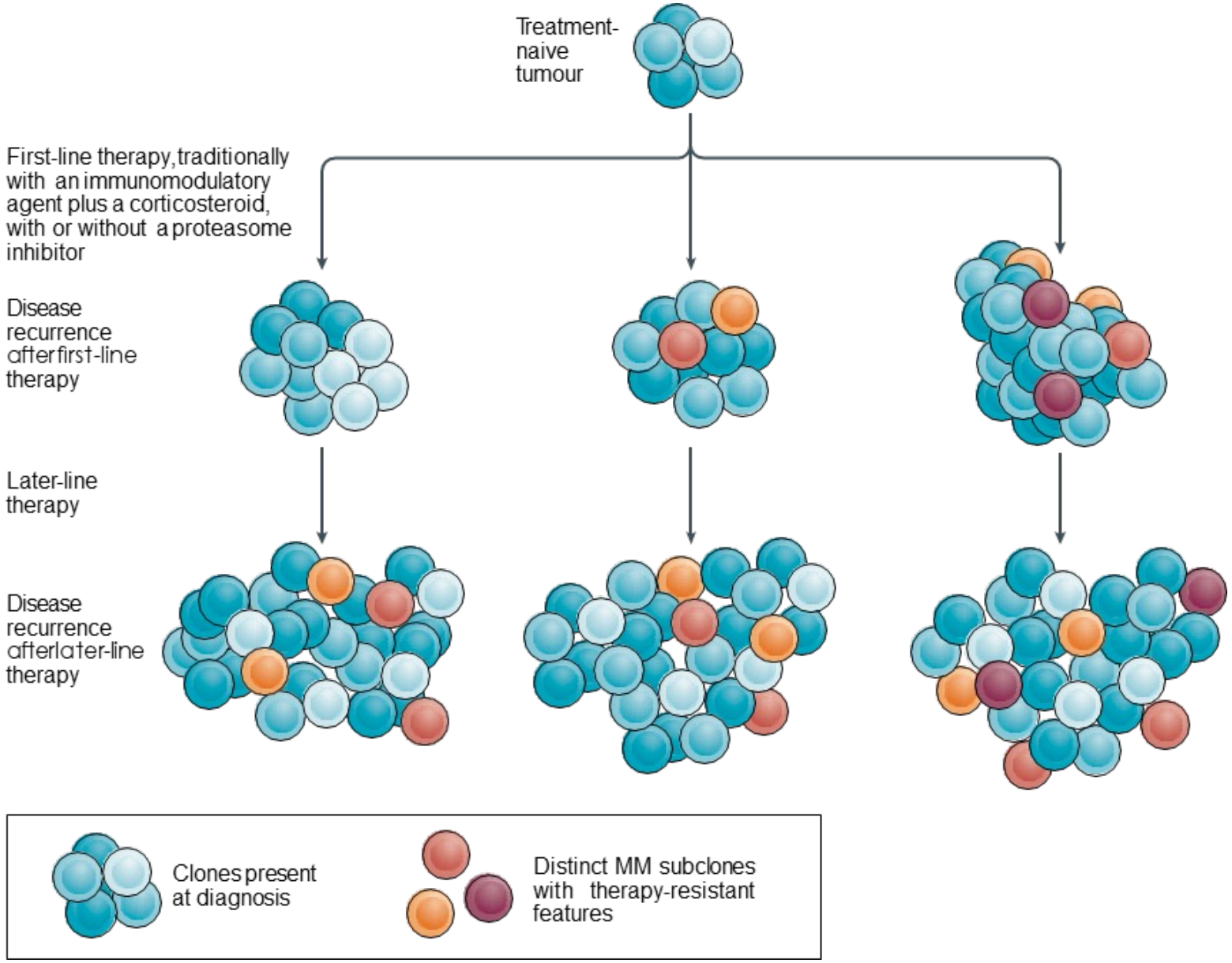
Over Time…

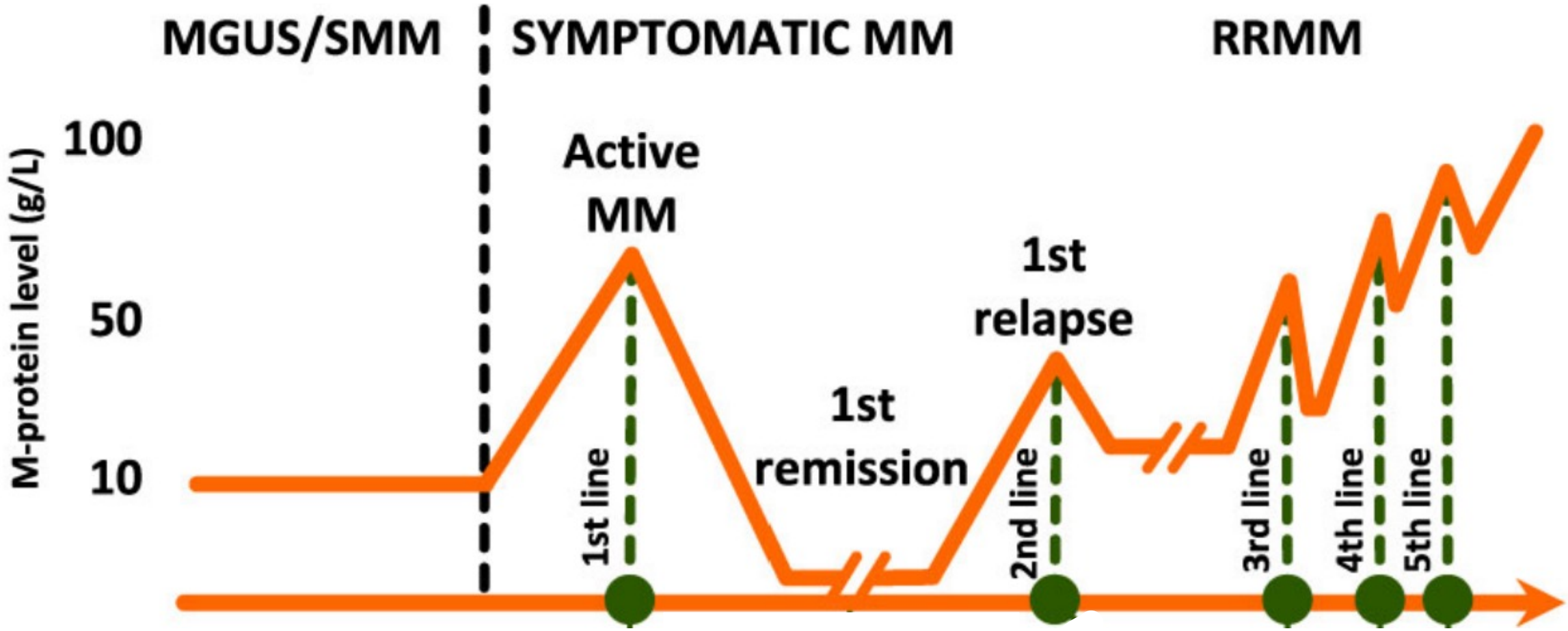


Clonal evolution

Resistance to standard therapies

Mikkilineni et al 2020 Nature Reviews Clinical Oncology

MM is a Marathon – Using Right Tools in the Toolbox at the Right Time is Key



Bonello et al 2022, Frontiers Oncology

Overview of Treatment of NDMM Patients

Transplant Eligible

Induction Therapy

- Dara-RVd (Griffin, Perseus)
- Dara-Krd (Master)
- Isa-RVd (GMMG-HD7)
- Isa-KRd (Iskia)

→ **Autologous Transplant** → **Maintenance Therapy**

Transplant Ineligible (due to performance status, co-morbidities)

Induction Therapy

- Cepheus
- Imroz
- Benefit

→ **Maintenance Therapy**

Induction Therapy

Goals:

- Rapid disease control to avoid further end-organ damage and for pain mitigation
- Achieve deep response prior to transplant, ideally with minimal residual disease negativity (MRD neg at 10-5 detection level)
- Collect stem cells
- Quadruplet vs triplet induction

Quad Therapy vs Triplet therapy

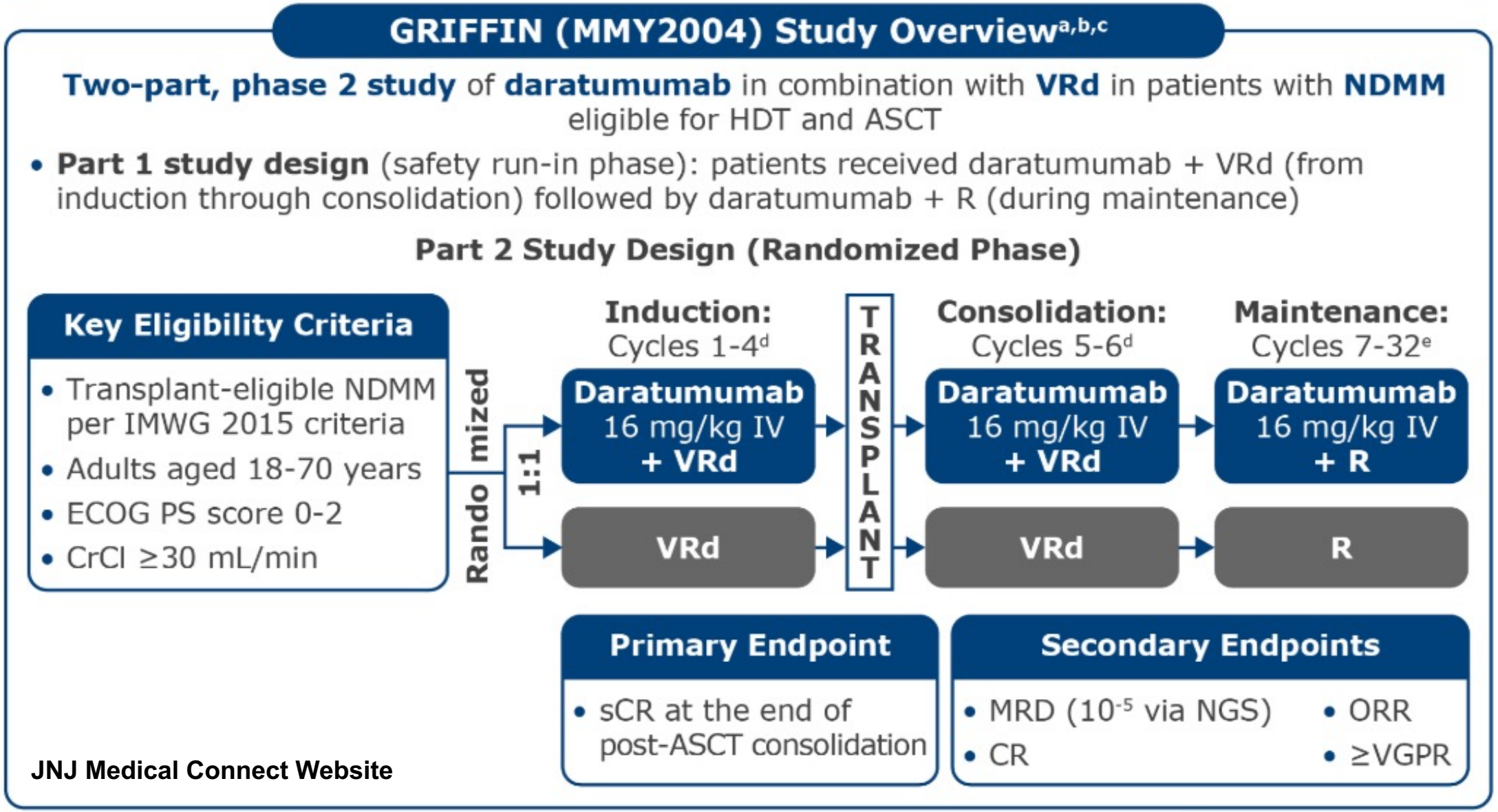
Triplet Therapy:

- Immunomodulatory agent (ex: lenalidomide, pomalidomide)
- Proteosome Inhibitor (ex: bortezomib, carfilzomib)
- Corticosteroid

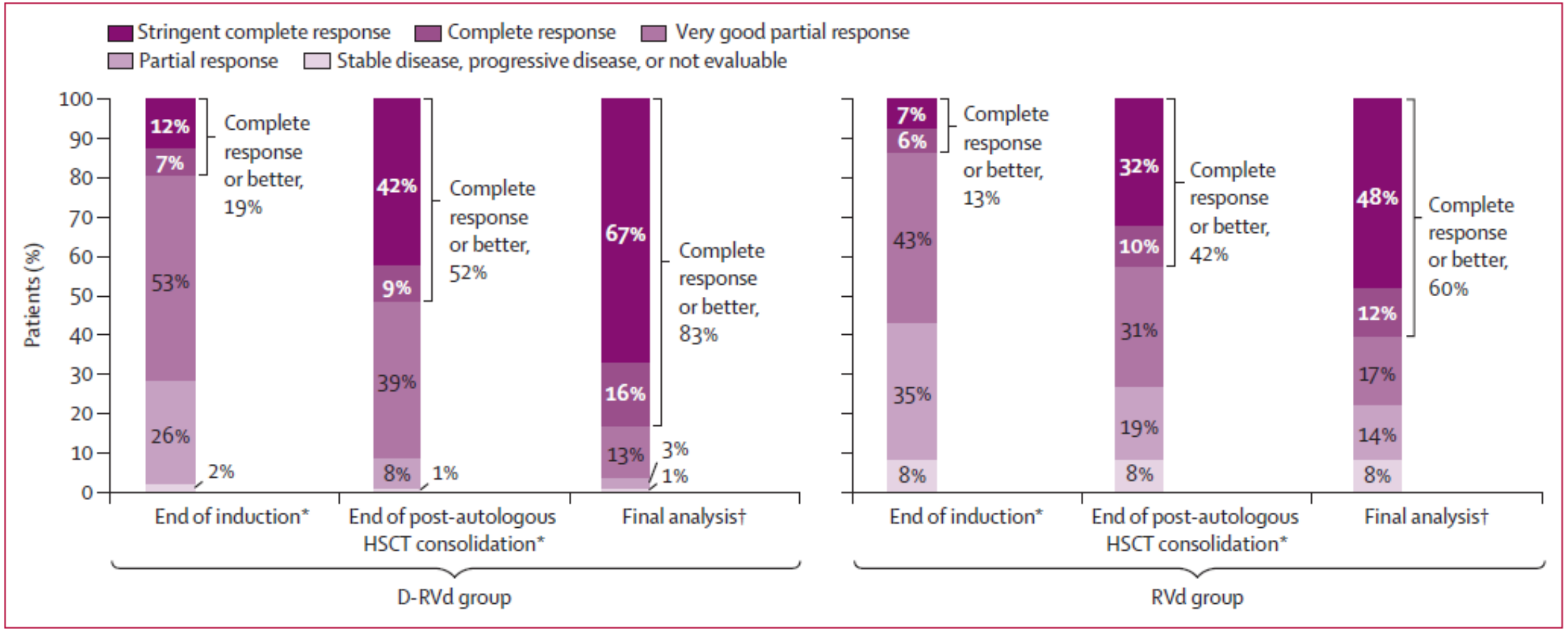
Quadruplet Therapy:

- Immunomodulatory agent (ex: lenalidomide, pomalidomide)
- Proteosome Inhibitor (ex: bortezomib, carfilzomib)
- Corticosteroid
- *Anti-CD38 monoclonal antibody (ex: daratumumab, isatuximab)*

Transplant Eligible - Griffin

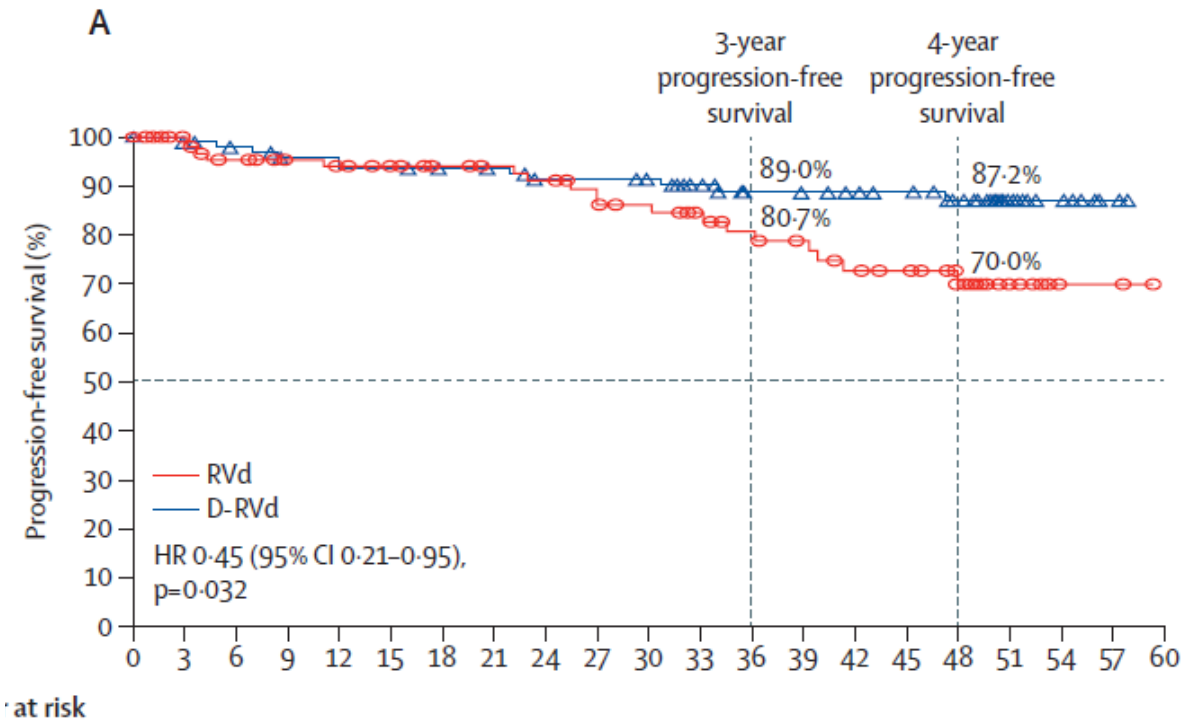


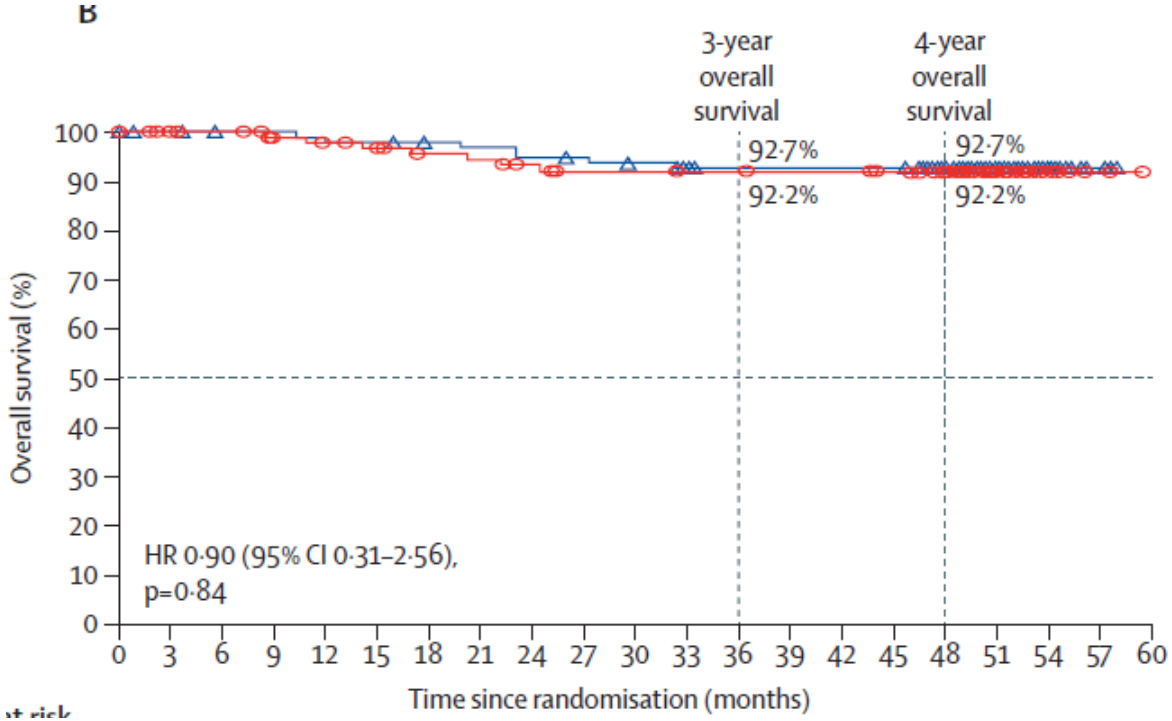
Transplant Eligible – Griffin



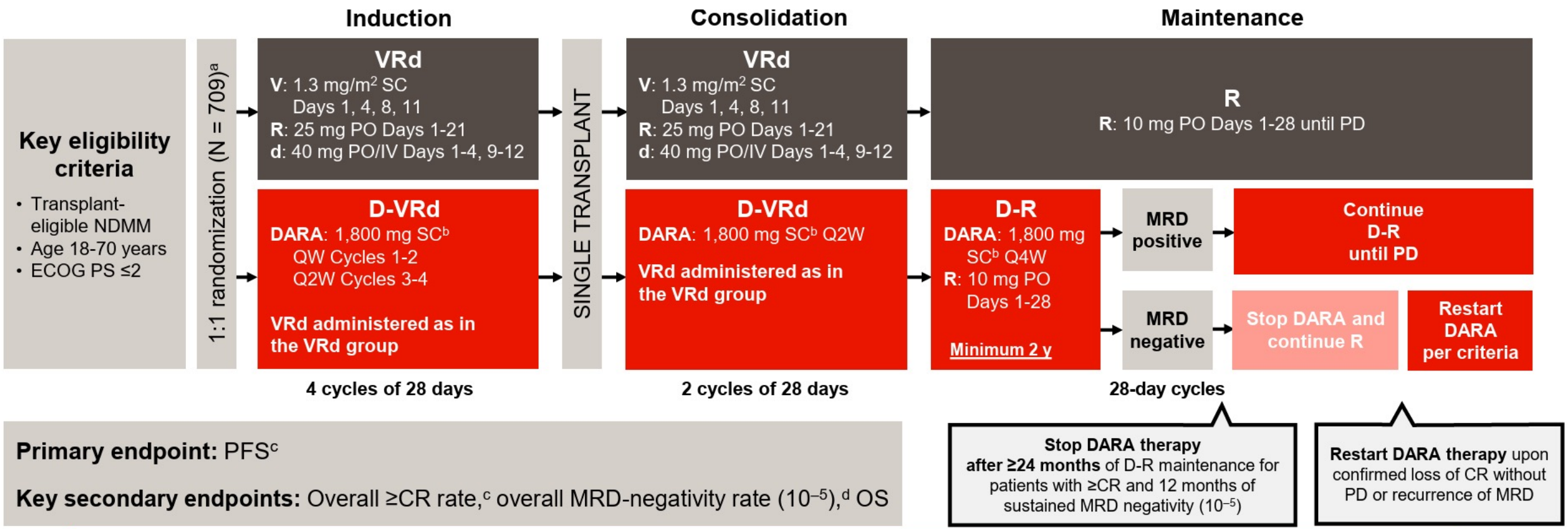
Voorhees et al *Lancet 2023*

Transplant Eligible - Griffin





Transplant Eligible - Perseus



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate (10^{-5}),[d] OS

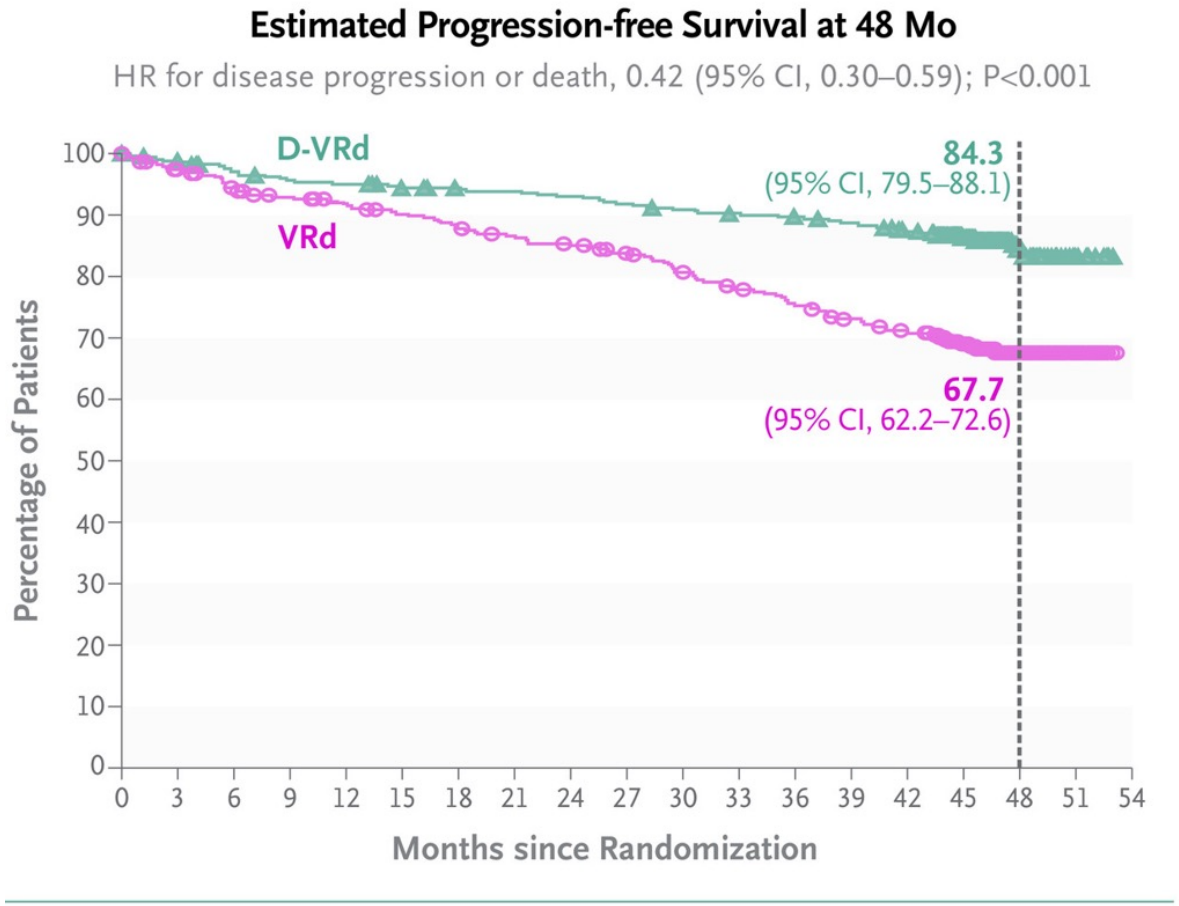
Stop DARA therapy after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity (10^{-5})

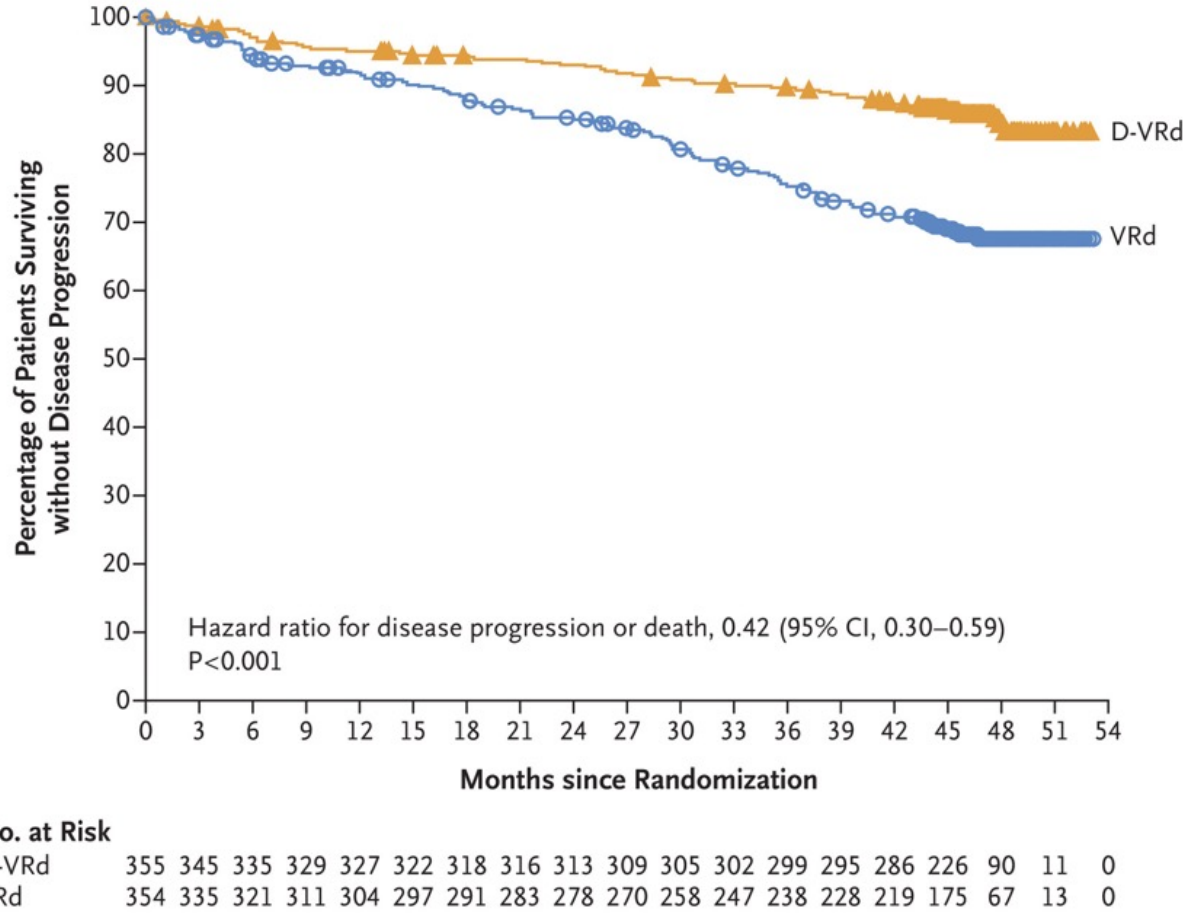
Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive.

Sonneveld et al *NEJM 2024*

Transplant Eligible - Perseus



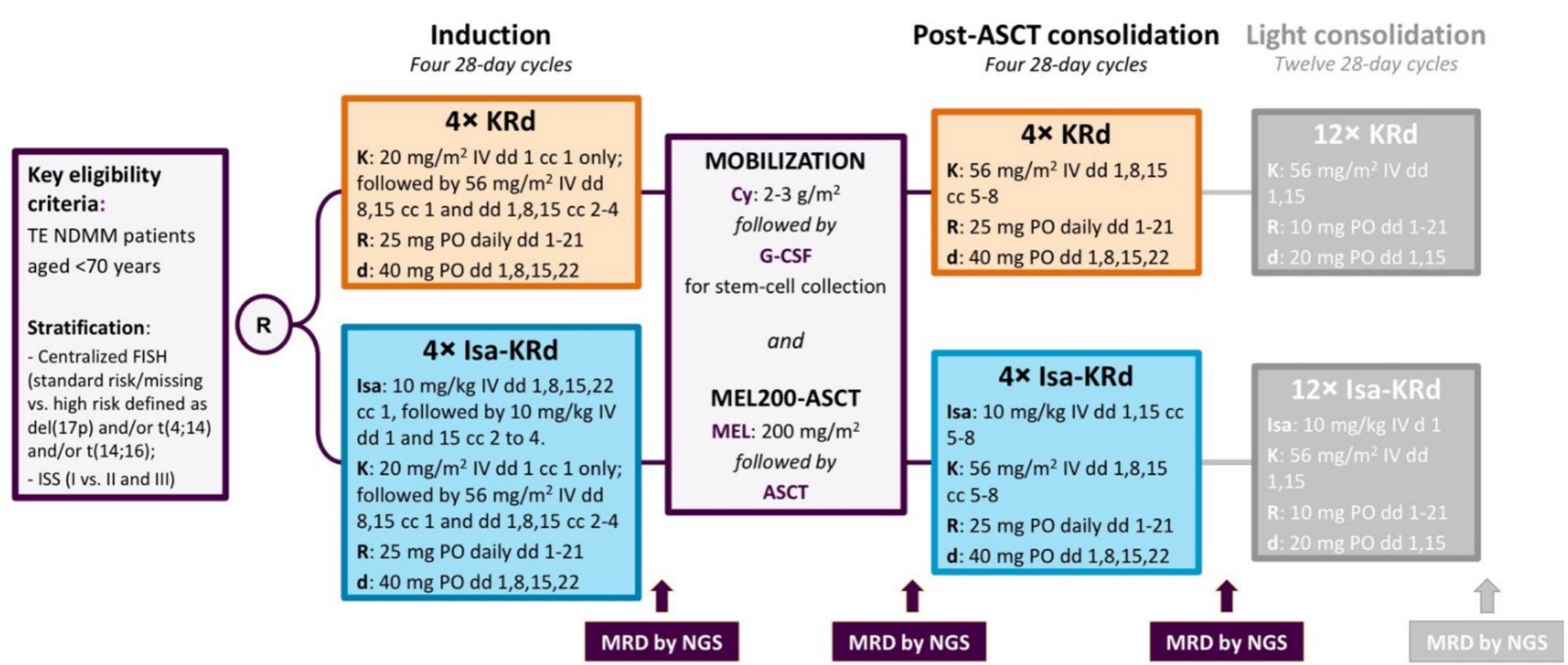


No. at Risk

D-VRd	355	345	335	329	327	322	318	316	313	309	305	302	299	295	286	226	90	11	0
VRd	354	335	321	311	304	297	291	283	278	270	258	247	238	228	219	175	67	13	0

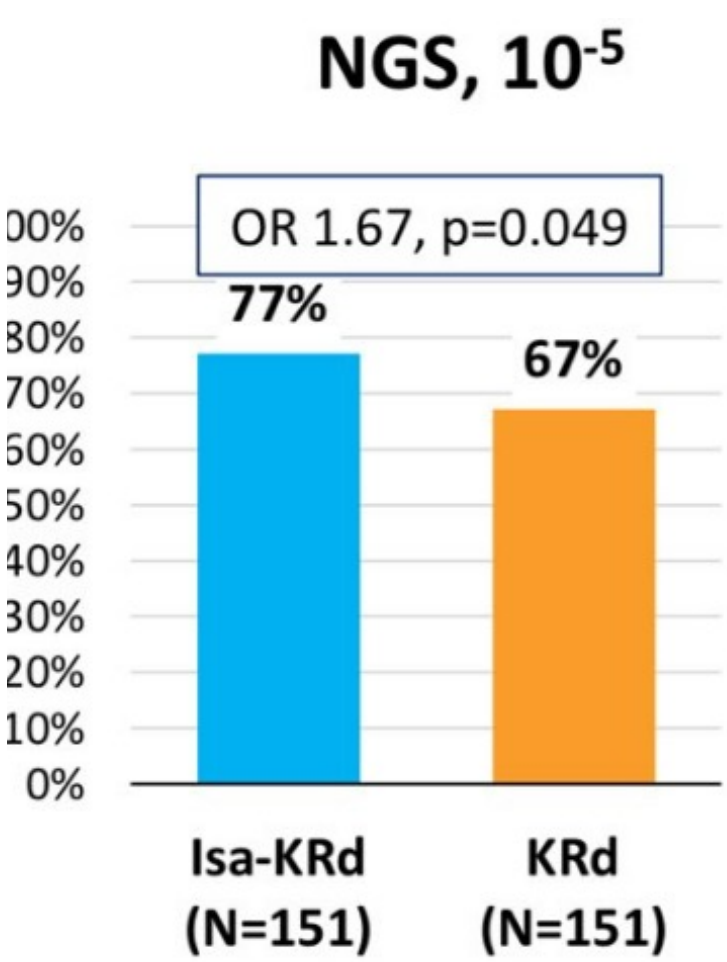
Sonneveld et al *NEJM 2024*

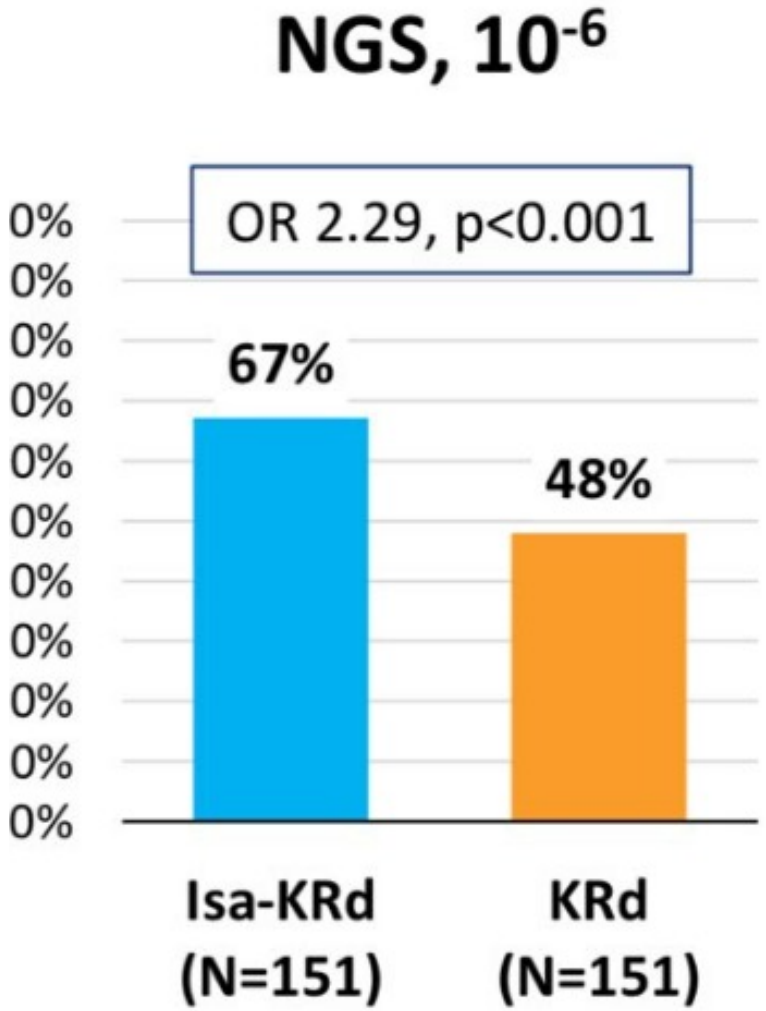
Transplant Eligible - IsKia

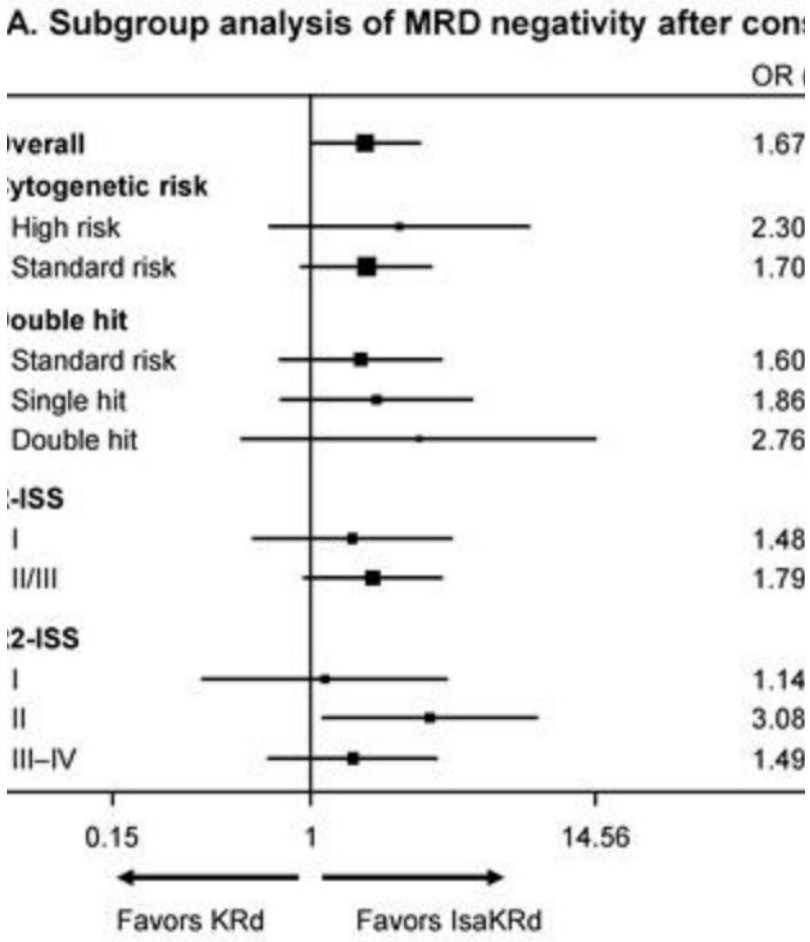


Slide c/o ASH 2023 Presentation – Gay et al

IsKia Results







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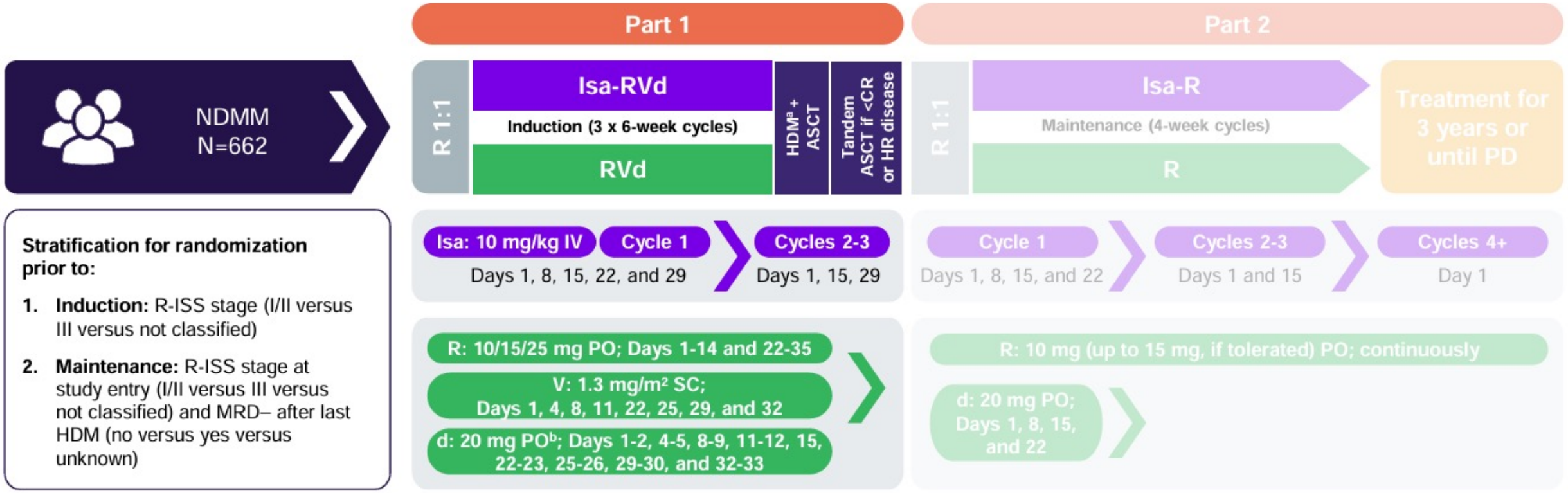
Slide c/o ASH 2023 Presentation – Gay et al

Transplant Eligible - GMMG HD7



Primary end points[c]: Post-induction MRD– (NGF, 10^{-5}); PFS after second randomization

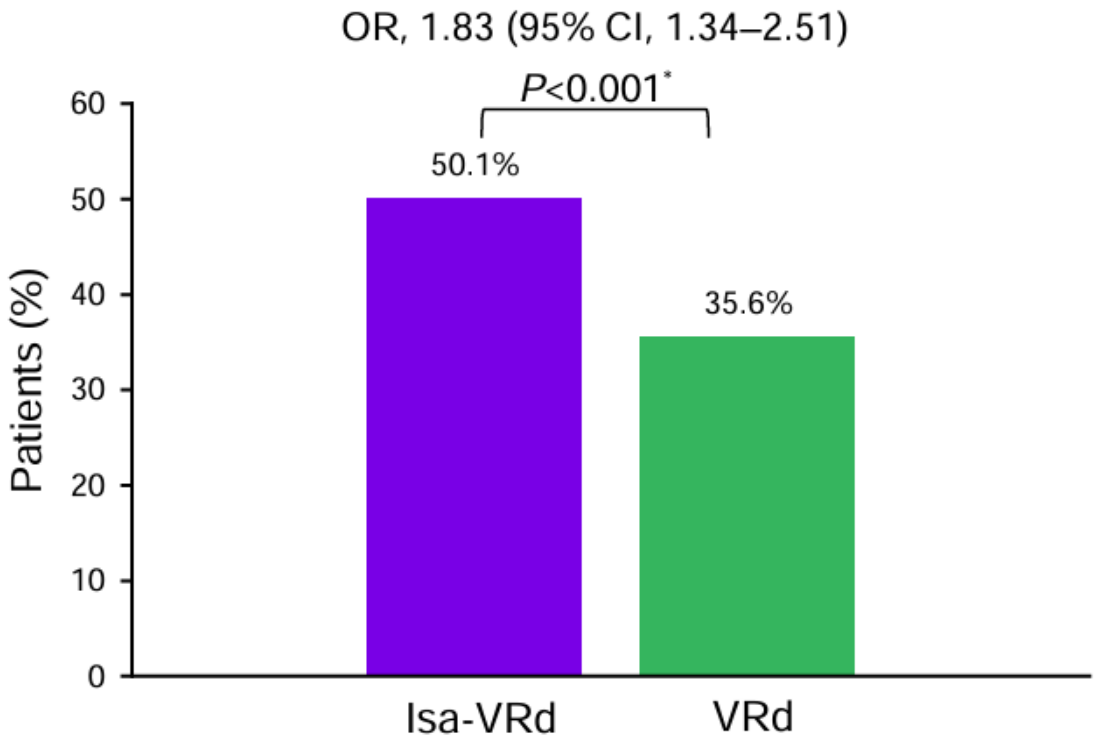
Key secondary end points: PFS (whole study); OS (whole study and from second randomization); post-induction CR; CR and MRD– after HDM and during and after maintenance therapy

Selected secondary end point: PFS after first randomization

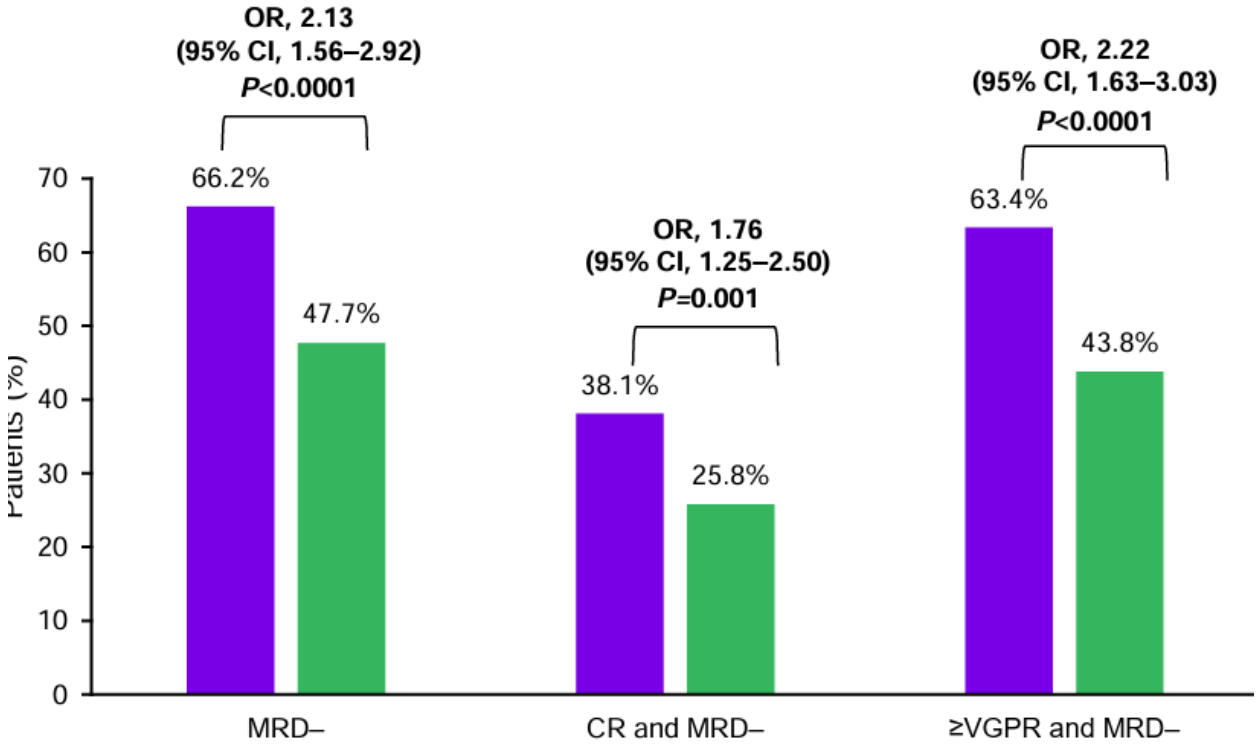
Goldschmidt et al ASH Meeting 2024

GMMG HD7

MRD Rates After Induction



MRD Rates After Transplant ITT Population



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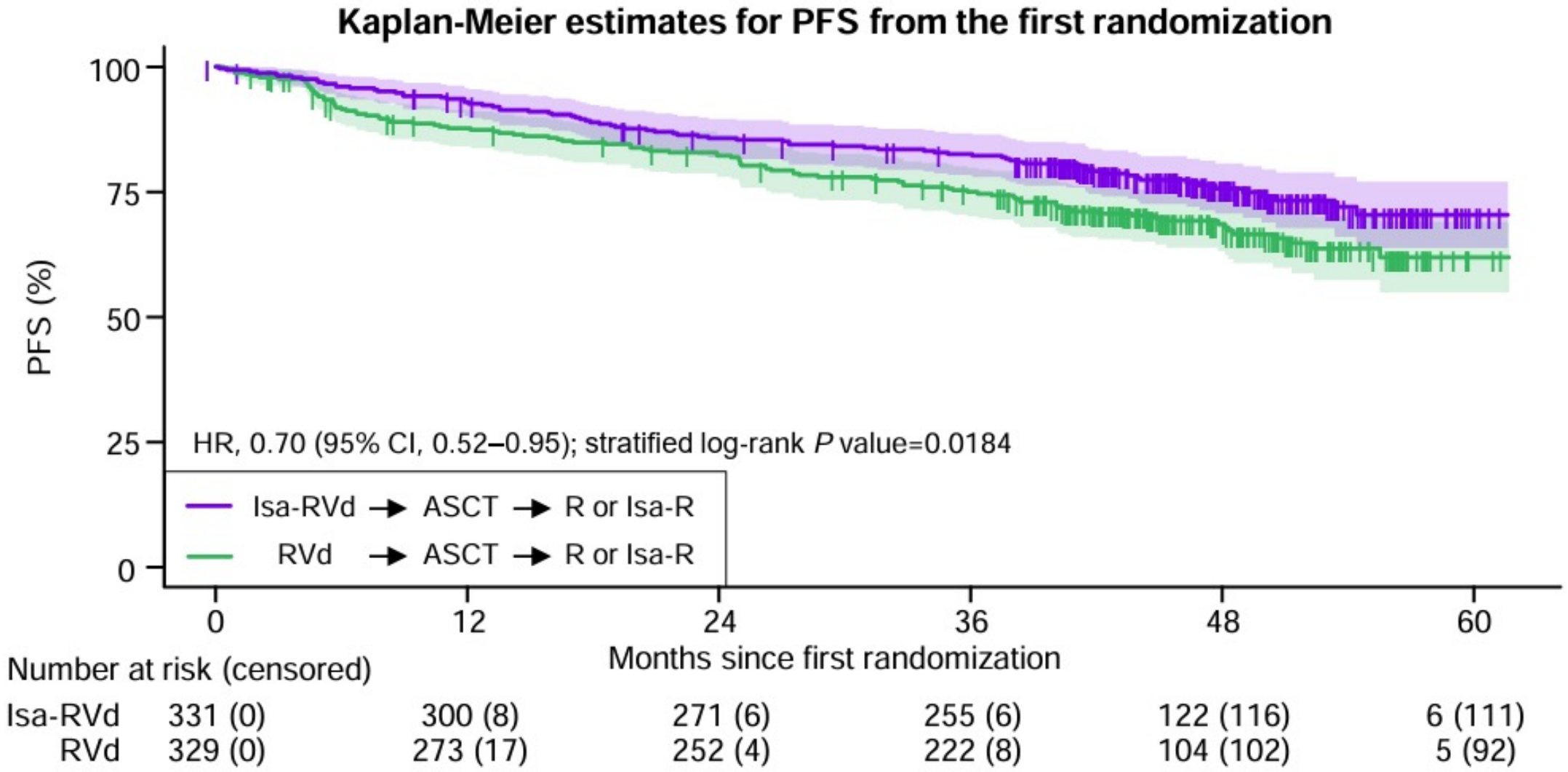
GMMG HD7



Goldschmidt et al ASH Meeting 2024

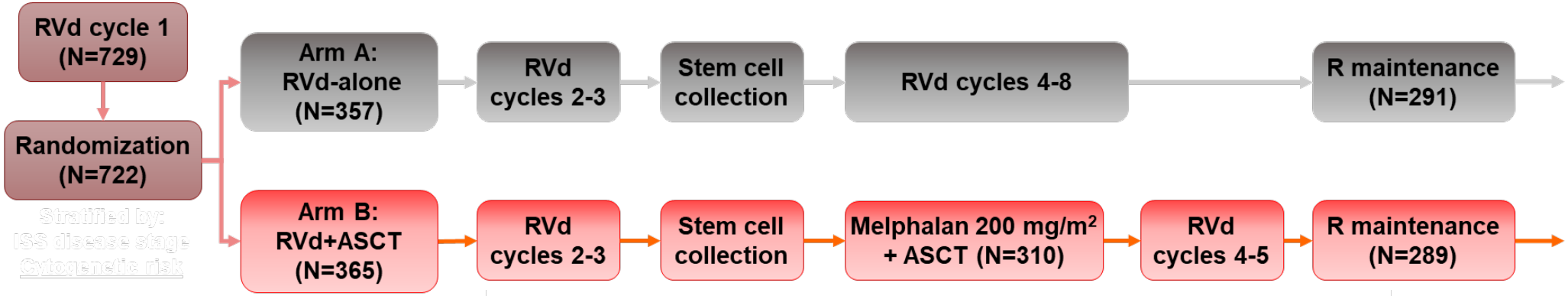
Quadruplet Tolerability (Adverse Events)

Table 3. GRADE summary of findings for toxicity outcomes

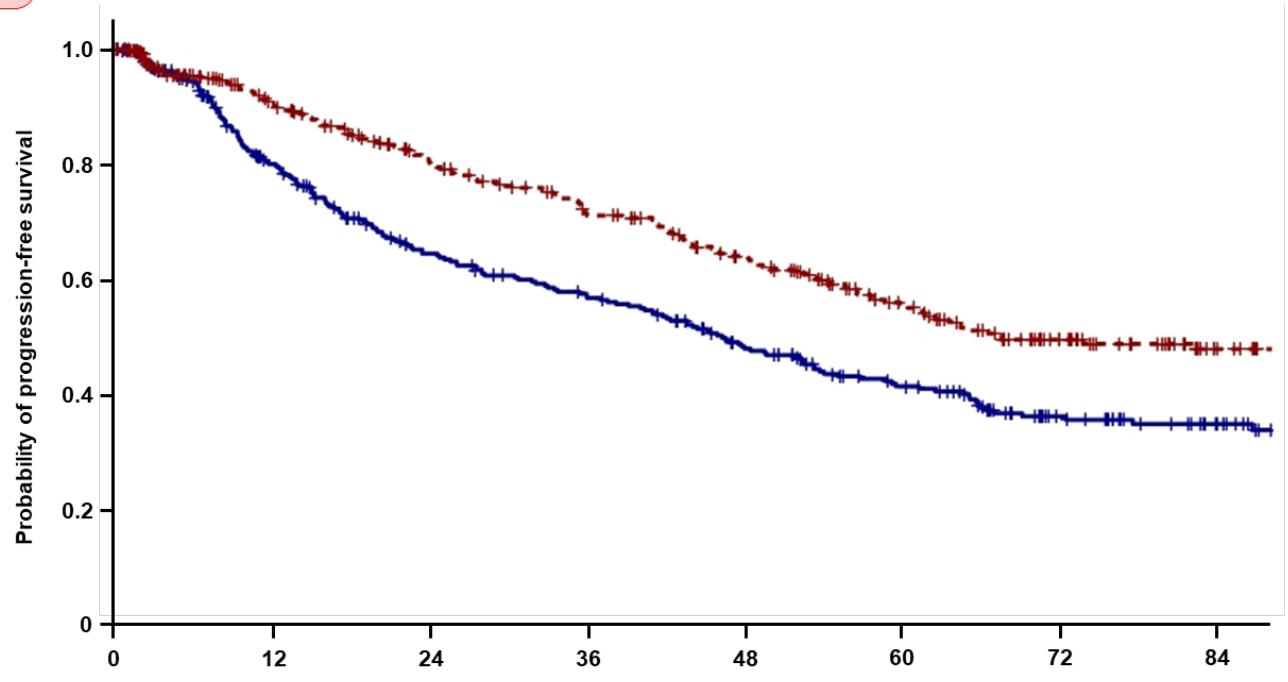
Quadruplet vs triplet therapy for patients with NDMM					
	Anticipated absolute effects* (95% CI)				
Outcomes	Risk with triplets	Risk with quadruplets	Relative effect (95% CI)	No. of participants (studies)	Comments
SAEs	464/1000	482/1000 (450-520)	**RR, 1.04** (0.97-1.12)	3077 (5 studies)	Quadruplet therapy likely results in little to no difference in serious adverse effects.
Grade 3-4 neutropenia	244/1000	441/1000 (346-563)	**RR, 1.81** (1.42-2.31)	3686 (7 studies)	Quadruplet therapy increases grade 3-4 neutropenia.
Grade 3-4 thrombocytopenia	124/1000	162/1000 (133-197)	**RR, 1.30** (1.07-1.58)	3686 (7 studies)	Quadruplet therapy increases grade 3-4 thrombocytopenia slightly.
Grade 3-4 infections	188/1000	229/1000 (201-261)	**RR, 1.22** (1.07-1.39)	3384 (6 studies)	Quadruplet therapy increases grade 3-4 infections slightly.
Secondary malignancy	53/1000	73/1000 (52-101)	**RR, 1.37** (0.98-1.90)	2229 (4 studies)	Quadruplet therapy likely results in little to no difference in rate of secondary malignancy.
Rescue stem cell mobilization	132/1000	240/1000 (149-386)	**RR, 1.82** (1.13-2.93)	1810 (3 RCTs)	Quadruplet therapy likely increases the need for rescue stem cell mobilization.
Median stem cell yield	The mean median stem cell yield was 7.01×10^6.	MD 2.22×10^6 lower (2.98 lower to 1.47 lower)	NA	1745 (2 RCTs)	Quadruplet therapy likely reduces median stem cell yield.

Ebraheem et al, *Blood Advances* 2024

DETERMINATION: Role of autologous transplant



Primary Endpoint: PFS Benefit



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

Richardson et al 2022

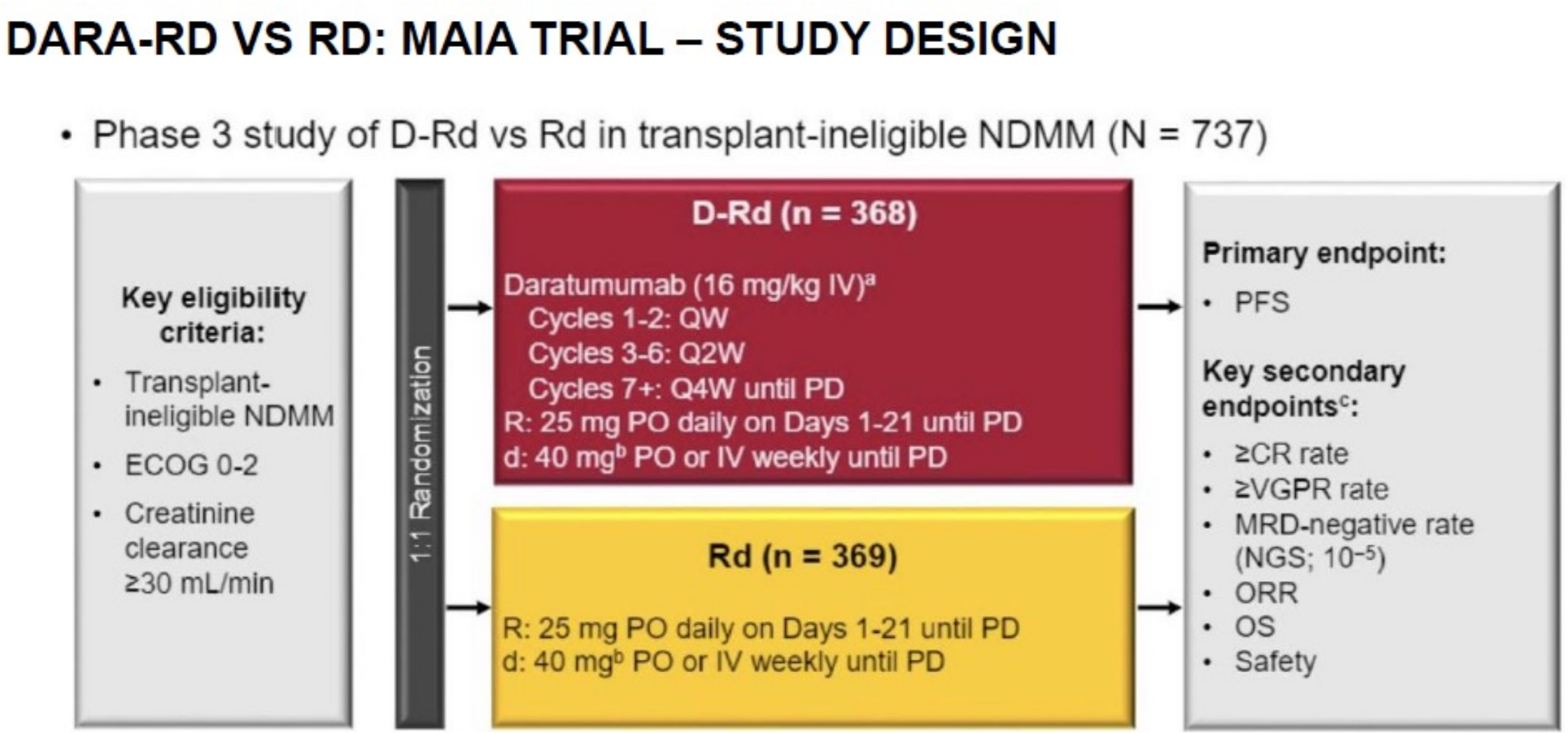
Consolidation & Maintenance Therapy

- Lenalidomide maintenance until relapse is still the standard-of-care, however duration of maintenance is still debated
- Dual maintenance for high risk – Len + PI vs Len + dara
- Future directions: tailoring maintenance based on MRD detection, use of novel agents (CELMoD agents, bispecifics)

Transplant Ineligible

- Patients ineligible for autologous stem cell transplant are often older or have comorbidities.
- Optimizing frontline therapy is crucial to improve their outcomes, as historically their survival lagged behind transplant-eligible patients.
- Recently reported results from large phase III studies in newly diagnosed multiple myeloma (NDMM) patients not undergoing transplant setting have resulted.
- These studies evaluate adding CD38 monoclonal antibodies (daratumumab or isatuximab) to standard regimens to deepen response.

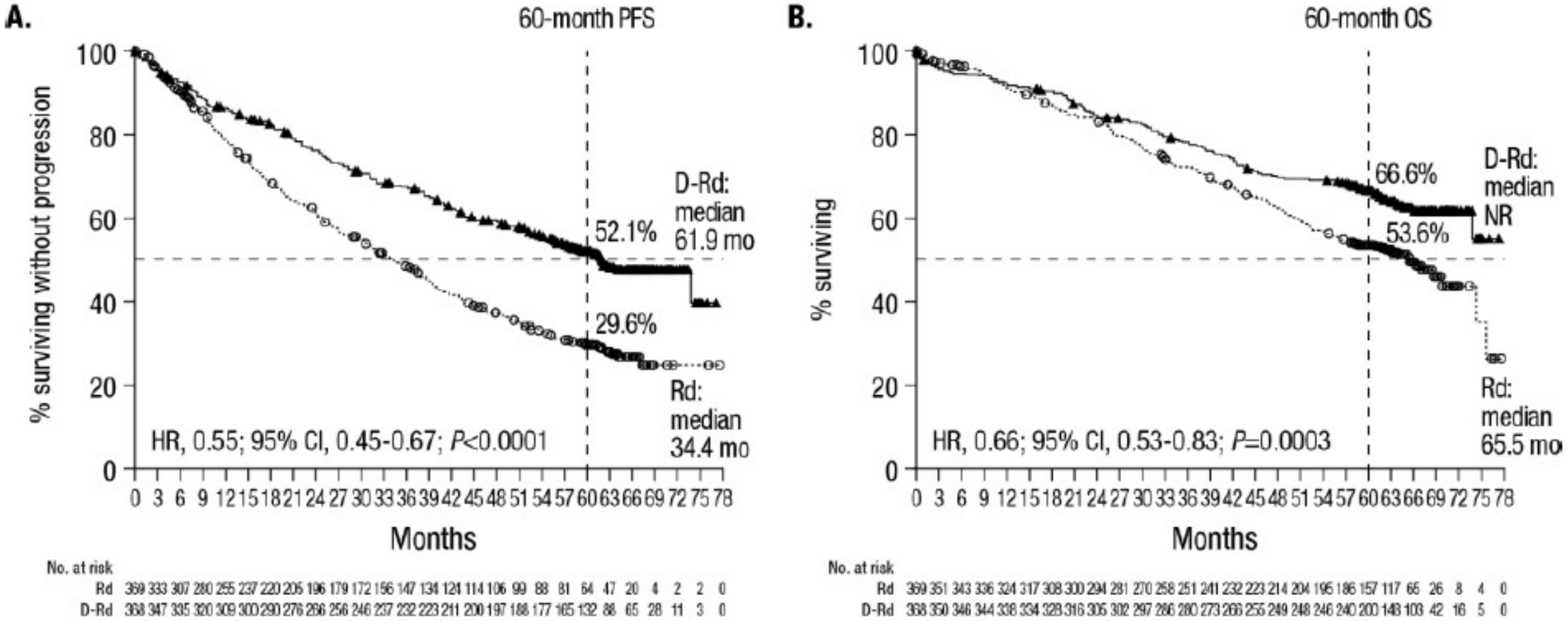
Transplant Ineligible - MAIA



Facon et al NEJM 2022

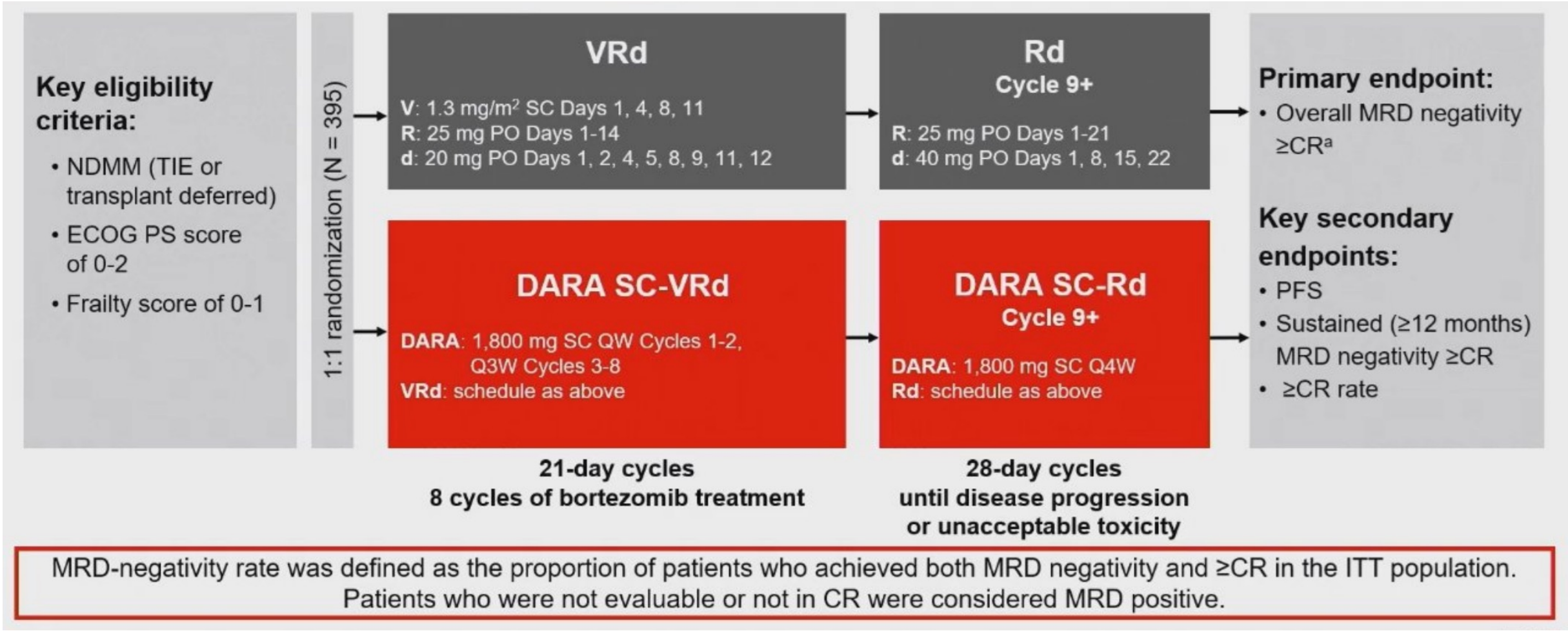
MAIA

Figure: Progression-free survival (A) and overall survival (B) with D-Rd and Rd in the intent-to-treat population.



Facon et al NEJM 2022

Cepheus Trial Design

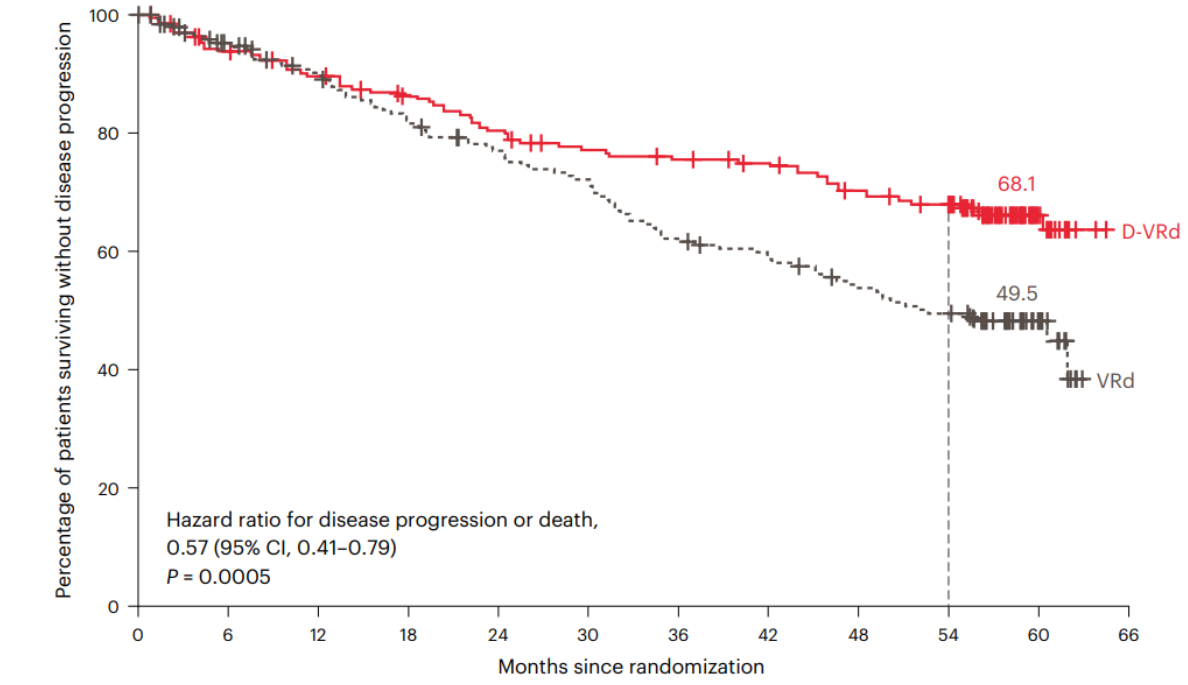


MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or not in CR were considered MRD positive.

Usmani et al Nature Medicine 2025

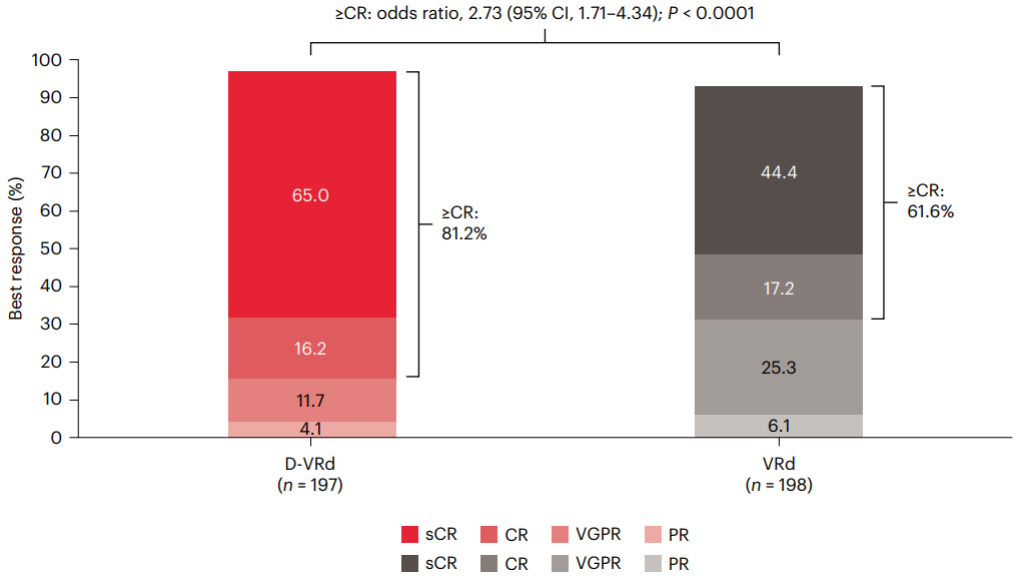
Cepheus

PFS



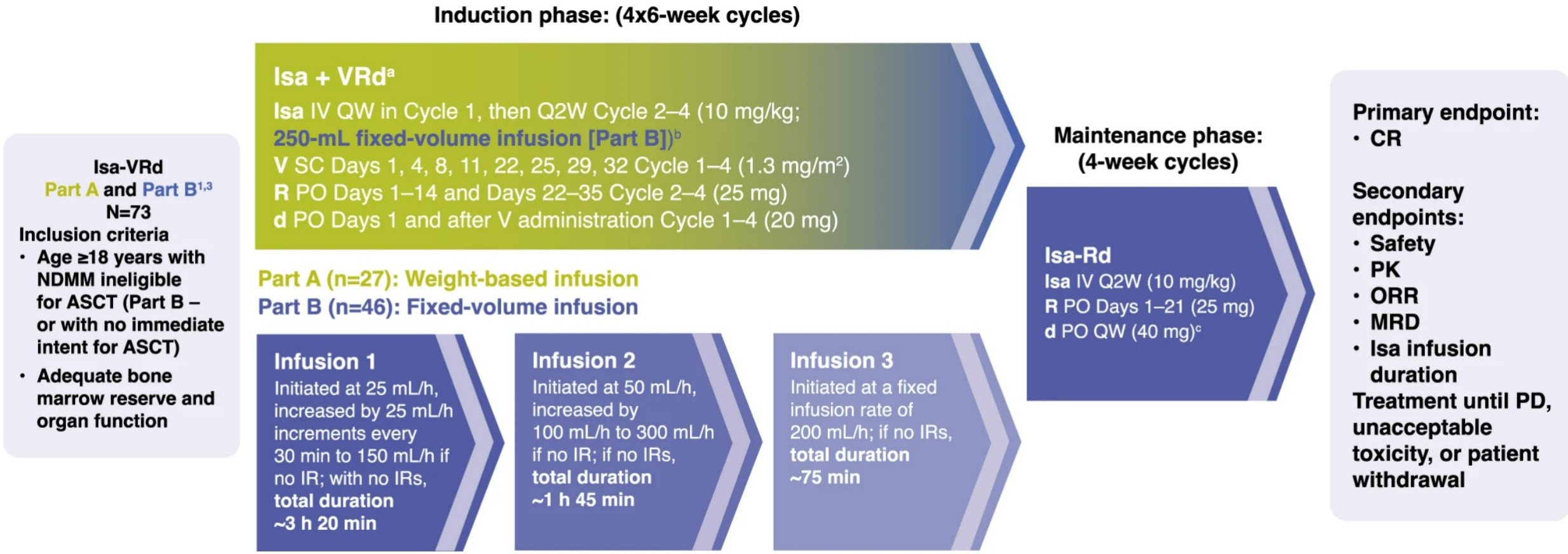
No. at risk

D-VRd	197	180	170	160	149	140	136	132	122	115	33	0
VRd	198	174	157	143	131	123	105	98	88	81	21	0



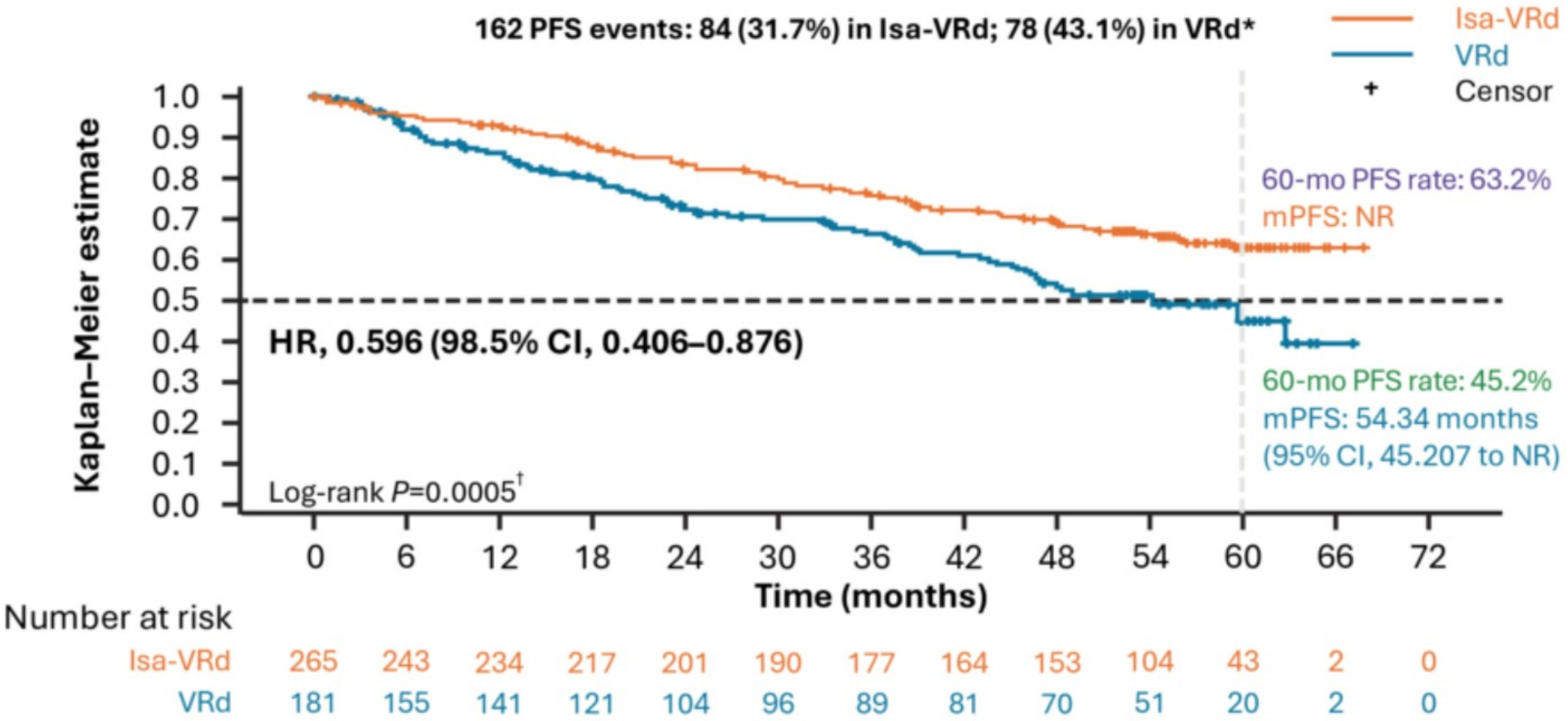
Usmani et al Nature Medicine 2025

Imroz



Facon et al 2024 NEJM

Imroz



At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

Facon et al 2024 NEJM

Back to Patient Case: Front Line Autologous Transplant vs Clinical Trial?

- Mr. M was relatively healthy and fit for his age and wanted to understand what his options on clinical trial would be.

- We discussed the CARTITUDE-6 Trial that aims to interrogate the role of upfront CAR T-cell therapy compared to current standard, upfront autologous transplant.

Cell-Surface Protein Expression on MM Cells

CAR-T takes advantage of unique cell-surface expression of MM proteins that are not on epithelial or hematopoietic stem cells

B-cell maturation antigen (BCMA)

- Expressed by plasma cells and a subset of memory B cells
- Absent on epithelial tissue and hematopoietic stem cells

G-coupled protein receptor 5 D (GPRC5D)

- Expressed on hair follicles and hard keratinizing tissue
- Pattern independent of BCMA

Targets under investigation:

- FcRH5, SLAMF7, CD44, CD70 & putative MM stem-cell targets

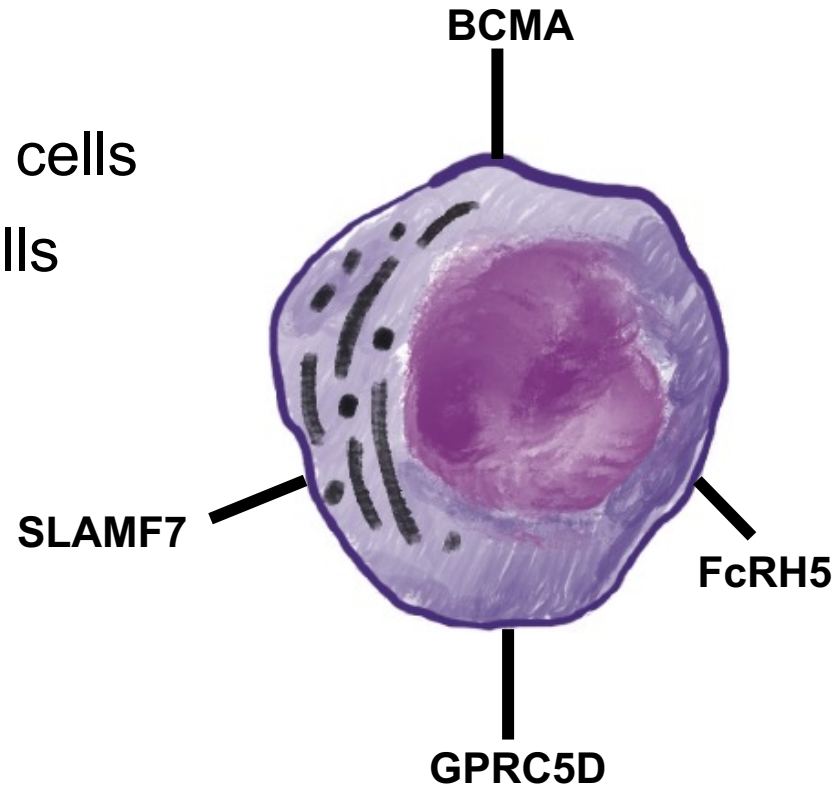


Image created with ProCreate

CAR T-cell Therapy for MM

CAR T cells are engineered with genes encoding a receptor that recognizes a MM cell

CARs are made of extracellular and intracellular domains

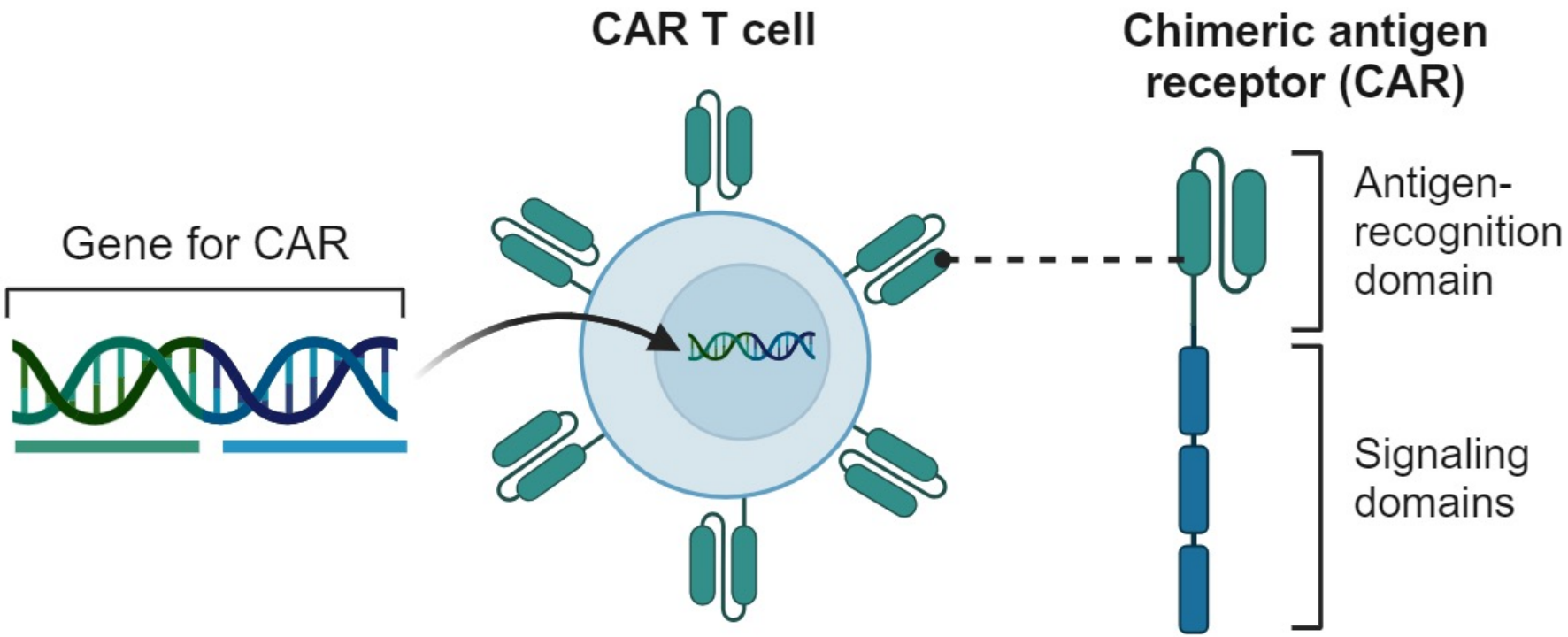


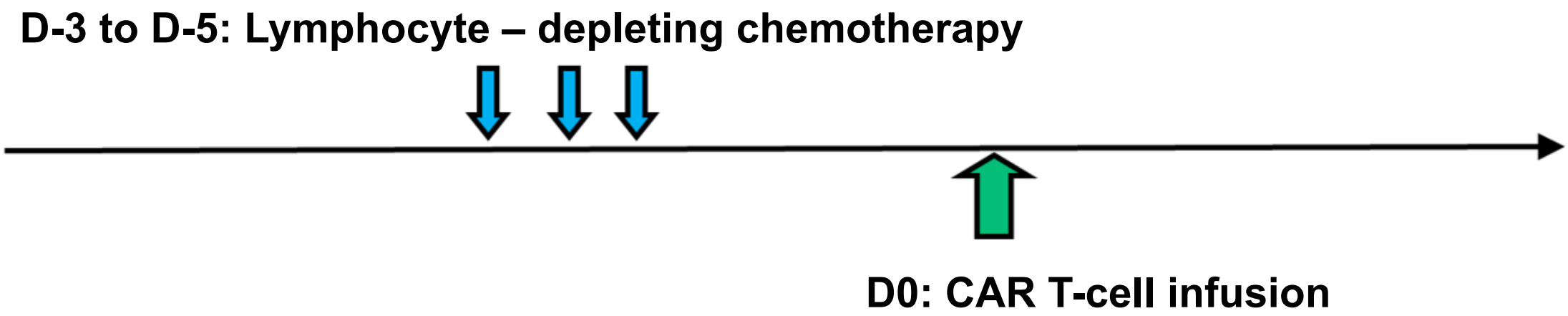
Image by BioRender

CAR-T Treatment Paradigm

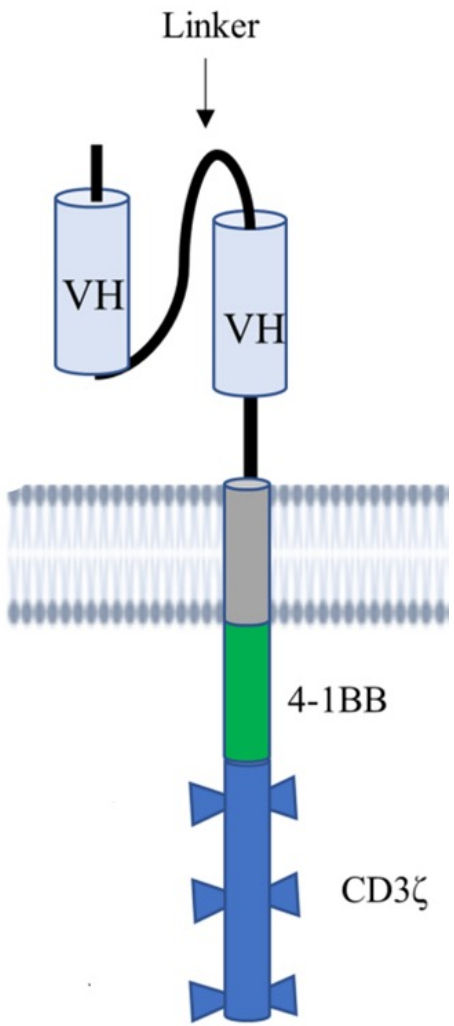
Both standard of care products follow the same overall treatment timeline

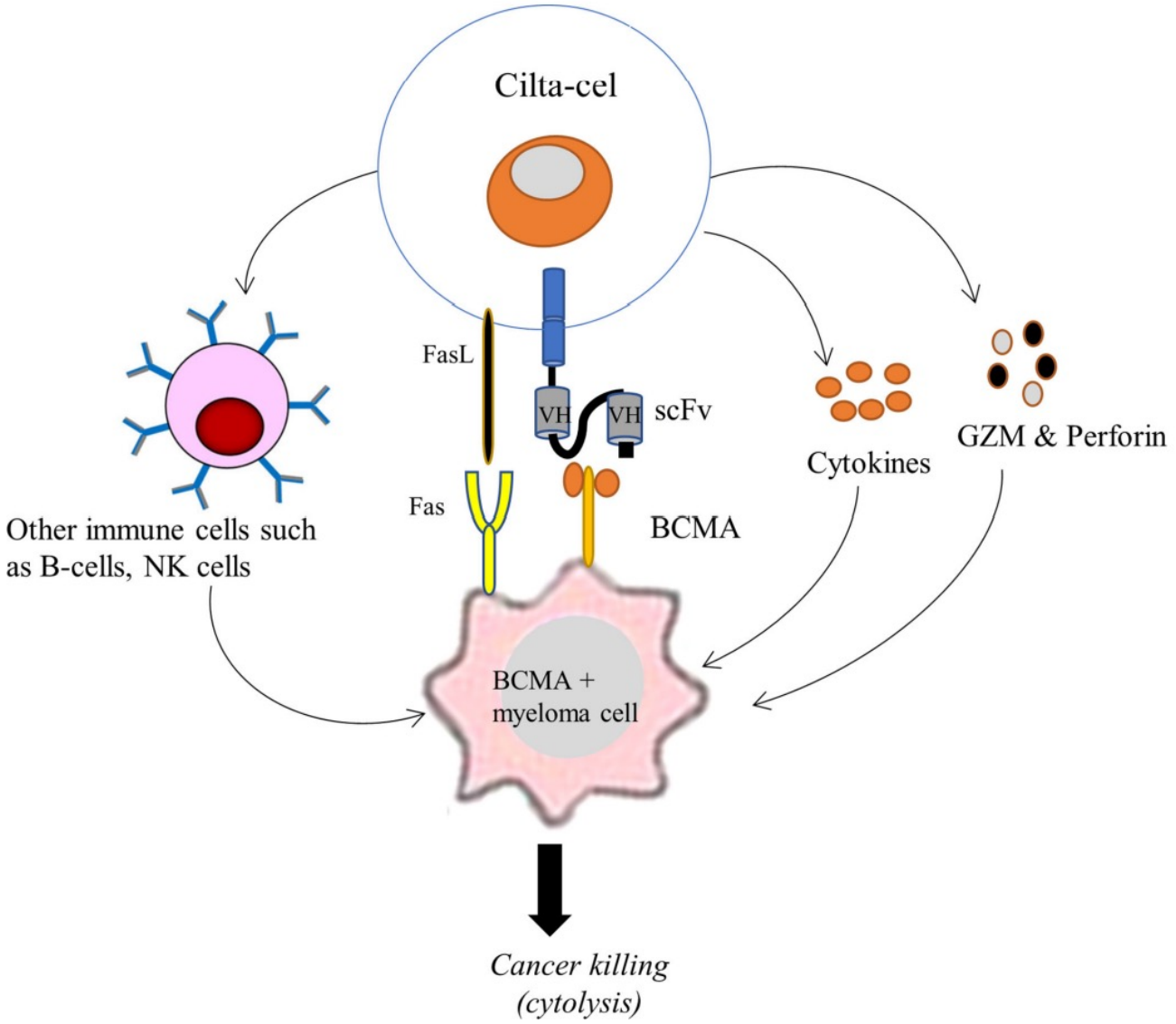
Lymphocyte-depleting chemotherapy:

- fludarabine/cyclophosphamide
- deplete endogenous T cells and create optimal cytokine mileu



CARTITUDE-1: Ciltacabtagene Autoleucel





Abebe et al 2022 Frontiers in Immunology

Toxicities Associated with CAR-T Therapy

Acute toxicities (within 30-60 days)

- Cytokine release syndrome (CRS)
- Immune-effector cell-associated neurotoxicity syndrome (ICANS)
- Immune-effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)

Mitigation strategies (acute & delayed toxicities)

- Treat when MM burden is low
- Effective bridging therapies is key!
- Patient age & co-morbidities

Acute & delayed toxicities

- Cytopenias
- Infections
  - Viral and bacterial predominate
- Movement and neurocognitive adverse events (MNTs)
- On-target, off-tumor toxicities
  - GPRC5D: dysgeusia, skin/nail toxicity, cerebellar toxicity
- Secondary cancers
- Unknown/evolving

Movement and Neurological Adverse Events (MNTs)

Cognitive Impairment
- Amnesia
- Confusion
- Depressed level of consciousness
- Inattentiveness
- Apraxia

Cranial nerve palsy
- CNVII most common
- CNV and III

Personality Changes
- Flat affect
- Reduced facial expression
- Personality shift

Movement Disorders
- Ataxia
- Bradykinesia
- Parkinsonism
- Postural instability
- Motor dysfunction
- Increased muscle tone
- Tremor
- Dysmetria
- Gait disturbance

Potential mechanism: On-target, off-tumor BCMA-recognition in basal ganglia

Associated with:
- High-circulating CD3+ T cells
- High baseline tumor burden
- CRS/ICANS

Therapy: Corticosteroids? Chemotherapy?

Cohen et al. 2022 Blood Cancer Journal ; Van Oekelen et al. 2021 Nature Medicine; Van de Donk, Sidana 2023 ASH Abstract

Induction therapy = effective bridging?

When to Treat with CAR-T:

Patient & Disease Factors

- Age, performance status, comorbidities
- Quality of life (treatment-free interval vs long-term tox surveillance)
- In late-line setting – treat as close to 5L as possible before MM is refractory to possible bridging tx. Planning at 2-3L for 5L treatment.
- If approved in front-line setting, must weigh safety profile vs benefit. Clinical trial results will help answer questions.

System Factors

- Apheresis slots
- Timing of therapy/timing of bridging therapy
- Close coordination between teams essential –
- Care delivery to rural and underrepresented populations

Thank You!

Stanford Multiple Myeloma Team

Ask A Question!

Return to your smartphone and submit your questions on the Question Tab

MLI.LINK/join

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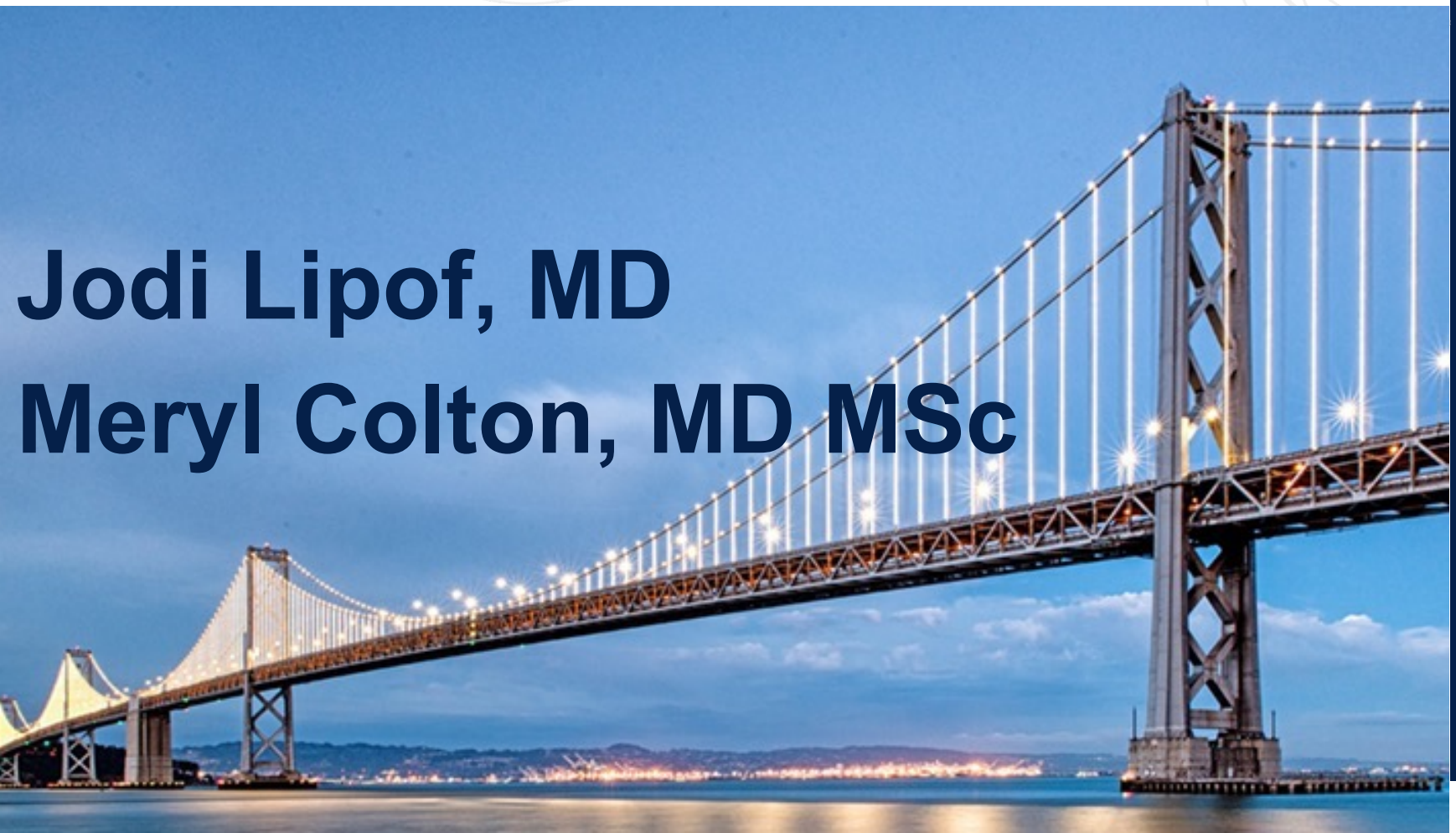
CAR T-cell Therapy in Early Relapsed Multiple Myeloma



Jodi Lipof, MD

Meryl Colton, MD MSc

UCSF Helen Diller Family Comprehensive Cancer Center

March 22, 2025
San Francisco, CA

Clinical Case

- Mr. H is a previously healthy 66 year old male with well-controlled hypertension who presented with rib pain and lower back pain that started while he was playing pickleball.
- X-Ray revealed 3 pathological fractures in the right anterior 6^{th}-8^{th} ribs. Spine XR showed pathological compression fractures in the T8, T12, and L1 vertebral bodies
- PET/CT revealed numerous osseous lytic lesions throughout the axial and appendicular skeleton, along with the aforementioned compression fractures. Findings were concerning for multiple myeloma vs metastatic disease.

Clinical Case

Labs:

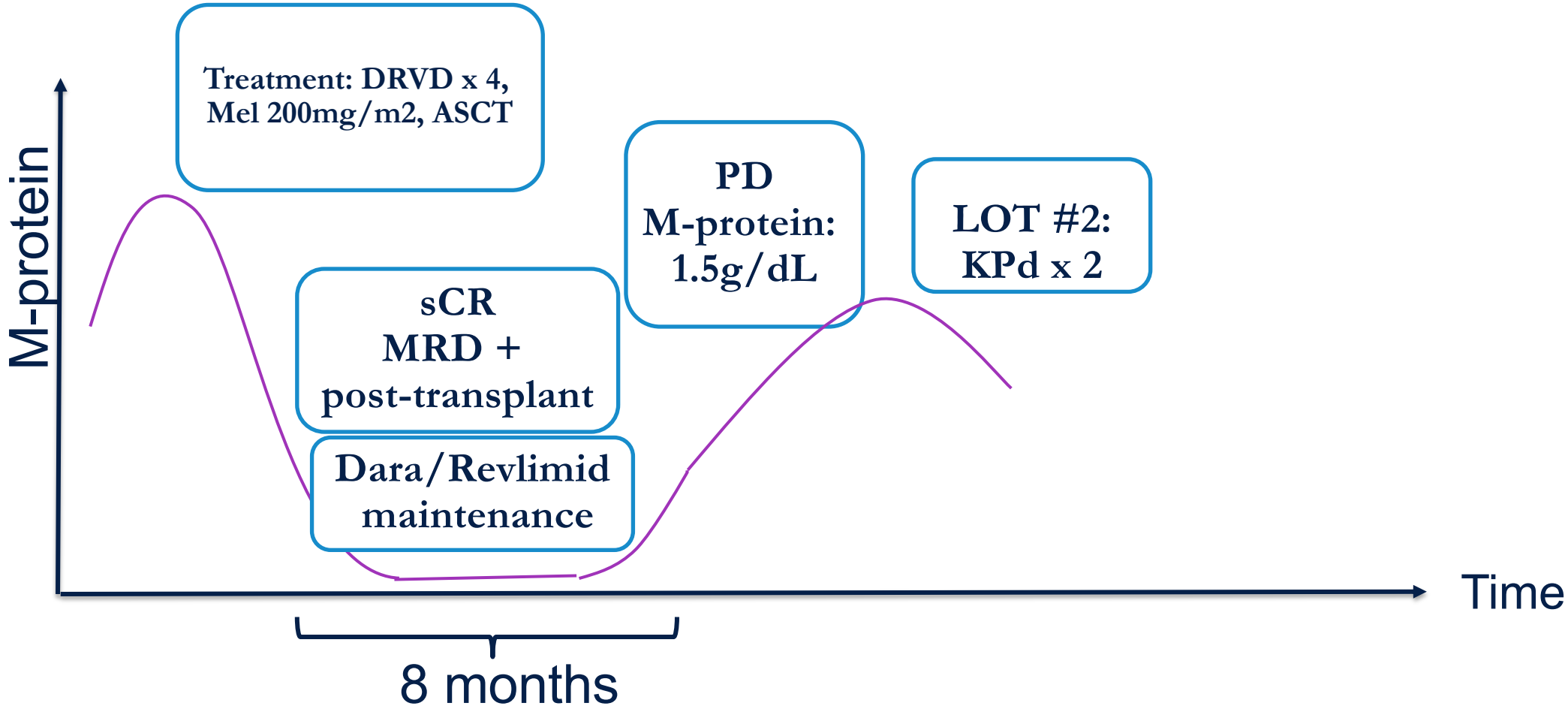
- M-spike 4.0g/dL
- IFE IgA Kappa
- KLC 2390 mg/L, LLC 8.32. K/L 287
- Calcium: 10.6mg/dL
- Creatinine 1.07
- Hemoglobin 9.8g/dL
- LDH: 236
- Beta-2 microglobulin 4.6
- Albumin 2.9

Bone marrow biopsy:

- 90% cellularity
- Kappa-restricted plasma cell neoplasm comprising 80-90% of the marrow cellularity
- Congo red stain negative
- FISH: +1q

Clinical Case

66 yo with newly diagnosed IgA Kappa MM with +1q



Please Scan the QR Code to Participate in Polling!

Return to your smartphone for polling questions

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What is the Next Best Course of Action?

1. Continue KPd
2. Daratumumab, pomalidomide, and dexamethasone (DPd)
3. Anti-BCMA CAR T-cell therapy
4. Anti-BCMA bispecific antibody
5. Clinical Trial

Current Multiple Myeloma Armamentarium

IMiDs	Proteasome Inhibitors	Anti-CD38	Bispecific T-cell Engagers	CAR T-cell Therapy	Others
Lenalidomide	Bortezomib	Daratumumab	Teclistamab (BCMA)	Ciltacabtagene Autoleucel (cilta-cel)	Steroids
Pomalidomide	Carfilzomib	Isatuximab	Elranatamab (BCMA)	Idecabtagene vicleucel (Ide-cel)	Melphalan
Thalidomide	Ixazomib		Talquetamab (GPRC5D)		Cyclophosphamide
					Belantamab mafadotin
					Selinexor
					Bendamustine

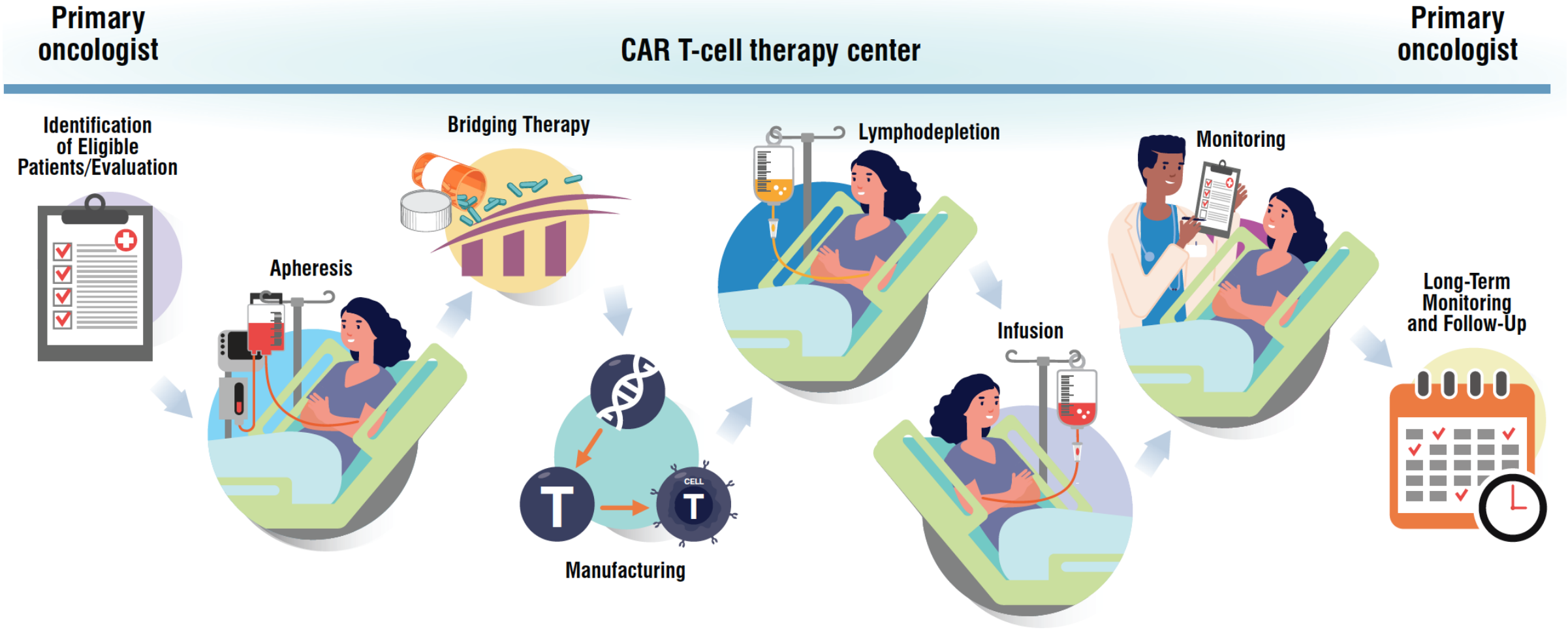
Challenges in RRMM

- All patients eventually relapse
- Duration of remission is typically shorter with each successive therapy
- Alterations in the immune microenvironment with each treatment can affect the efficacy of the next treatment
- Mechanisms of resistance are incompletely understood
- Toxicity from prior treatments can affect eligibility and appropriateness of future treatments
- In the era of novel agents, optimal sequencing is unknown

Questions Driving Current and Future Investigations in RRMM

- As most patients are receiving quadruplet regimens up front, how do we sequence therapies in relapse to prolong survival?
- Which patients benefit from CAR T-cell therapy or other T-cell redirecting therapies earlier in the course of treatment?
- Can targets for T-cell redirection be combined to improve efficacy without adding prohibitive toxicity?

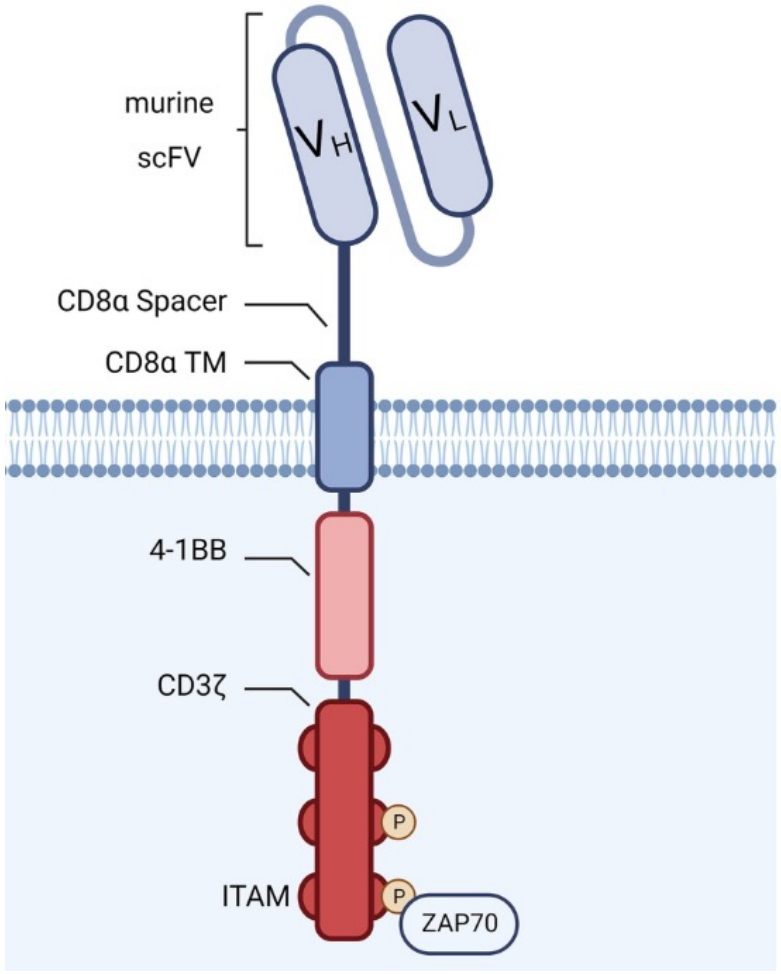
CAR-T Process



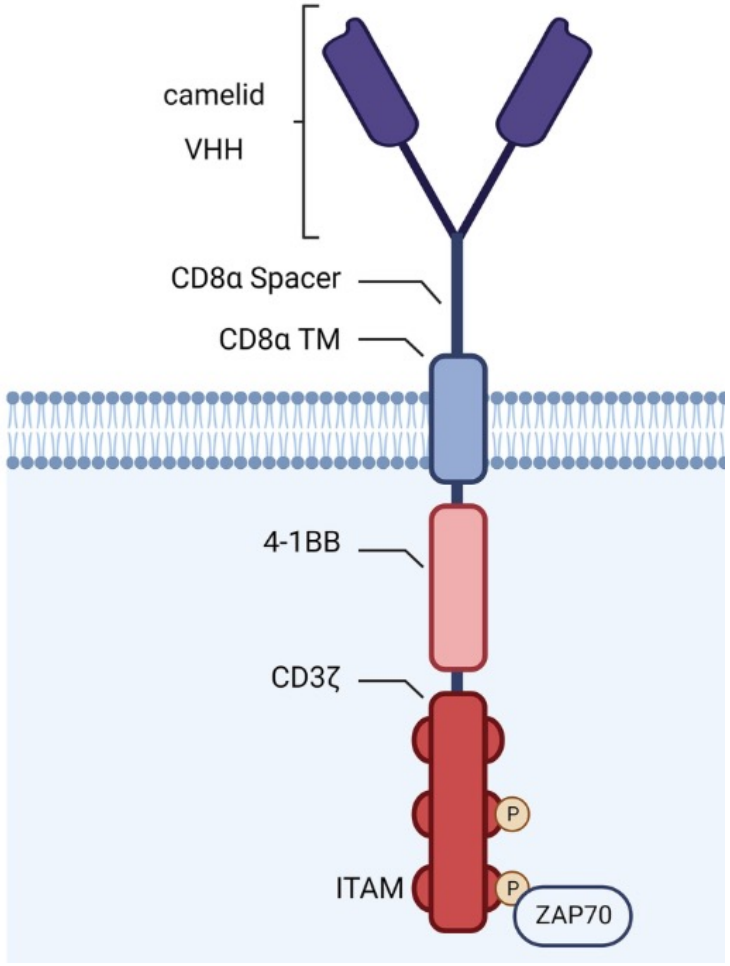
*The median time from apheresis to cilta-cel infusion is 70 days (range, 36-275)

Sidana et al, IMS Annual Meeting, 2024

CAR T-cell Constructs



Idecabtagene vicleucel



Ciltacabtagene Autoleucel

Scheller et al. *Leuk & Lymph*, 2023.

CARTITUDE 1

Overview of the trial

- Phase 1b/2 study investigating ciltacabtagene autoleucel (cilta-cel) in heavily relapsed/refractory multiple myeloma (RRMM)
- ≥3 lines of prior therapy
- **Primary endpoint**: overall response rate (ORR)
- **Secondary endpoints**: PFS, OS, MRD to 10^{-5}

CARTITUDE 1

PFS by response ORR 97%

Subgroup	N	mPFS (95% CI), mo	36-mo PFS rate
All patients	97	34.9 (25.2-NE)	47.5%
≥CR	76	38.2 (34.9-NE)	59.8%
6-mo sustained MRD negativity	34	32.2 (25.1-NE)	45.7%
12-mo sustained MRD negativity	26	NR (NE-NE)	NE
12-mo sustained MRD negative CR	20	NR (NE-NE)	NE

Abbreviations. NE, not estimable; CR, complete response; MRD, minimal residual disease; NR, not reached
MRD rates were measured at 10^{-5}

CARTITUDE 4: Cilta-cel vs SOC

Overview of the study

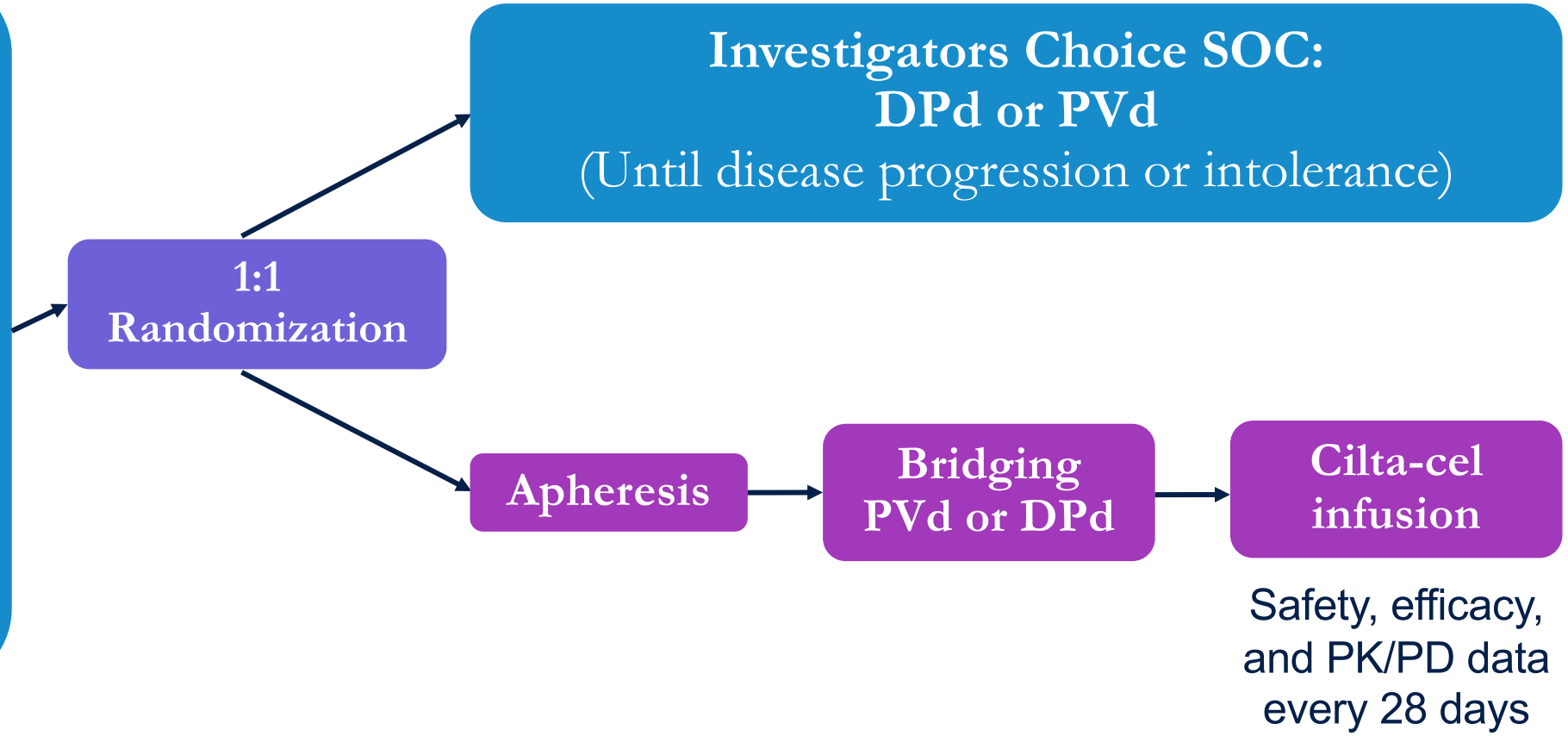
- Phase 3 randomized trial of ciltacel vs SOC
- 1-3 prior lines of therapy
- Excluded patients with prior BCMA directed therapy or prior CAR T-cell therapy
- **Primary endpoint**: progression free survival (PFS)
- **Key secondary endpoints**: sCR/CR, ORR, MRD negativity, and overall survival (OS)
- Assessments by computerized algorithm and independent review committee

CARTITUDE 4

Trial Design

Patients:
Age ≥18, MM
1-3 prior LOT (including PI and IMiD)
Len-refractory
ECOG 0-1

Exclusion:
Prior CAR-T (any target) and ANY prior BCMA-targeted therapy



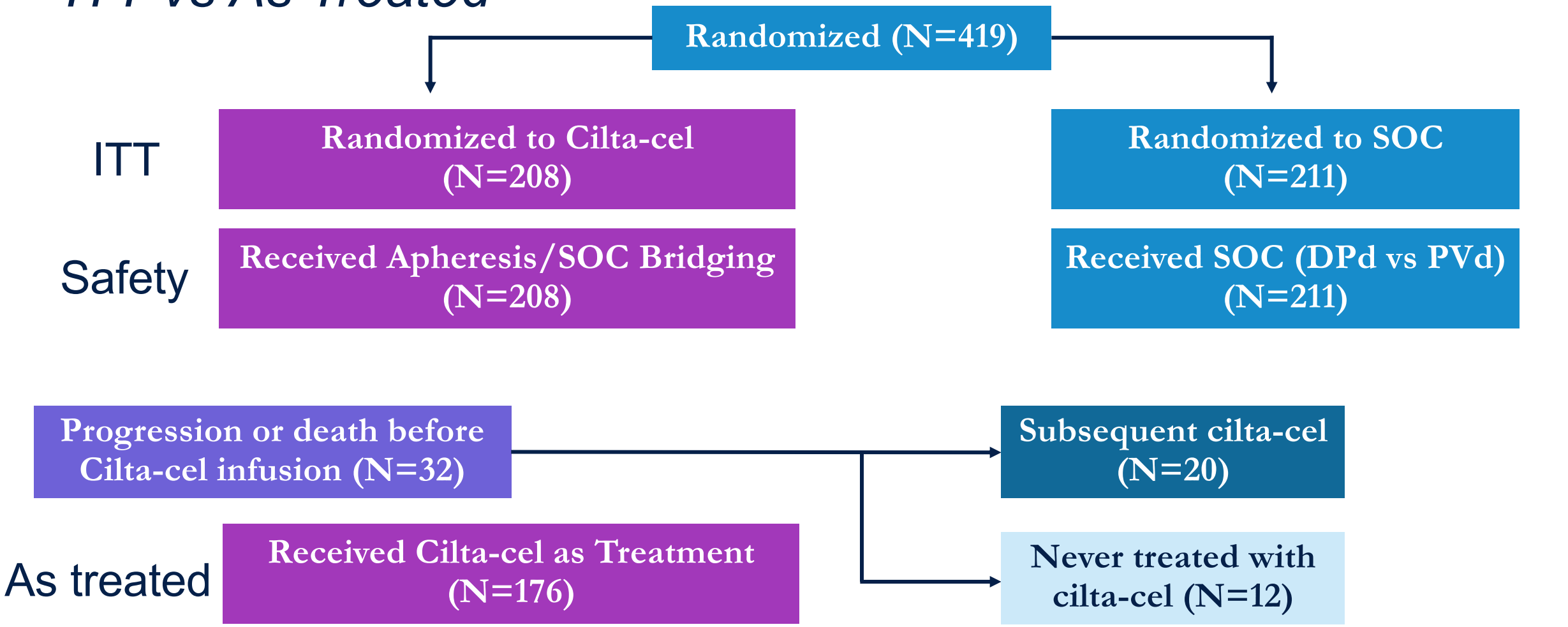
CARTITUDE 4

Baseline Characteristics

Characteristic	Cilta-cel (N=208)	SOC (N=211)
Median Age (range)—yr	61.5 (27-78)	61.0 (35-80)
Caucasian (%)	75.5	74.4
R-ISS no. (%)		
I	136 (65.4)	132 (62.6)
II	60 (28.8)	65 (30.8)
III	12 (5.8)	14 (6.6)
Soft tissue plasmacytomas	44 (21.2)	35 (16.6)
Bone marrow plasma cells ≥60%	42/206 (20.4)	43/208 (20.7)
Cytogenetic risk		
Standard	69/207 (33.3)	70/210 (33.3)
High (+1q, del 17p, t(4;14), t(14;16))	123/207 (59.4)	132/210 (62.9)
>1 high risk abnormality	43/207 (20.8)	49/210 (23.3)

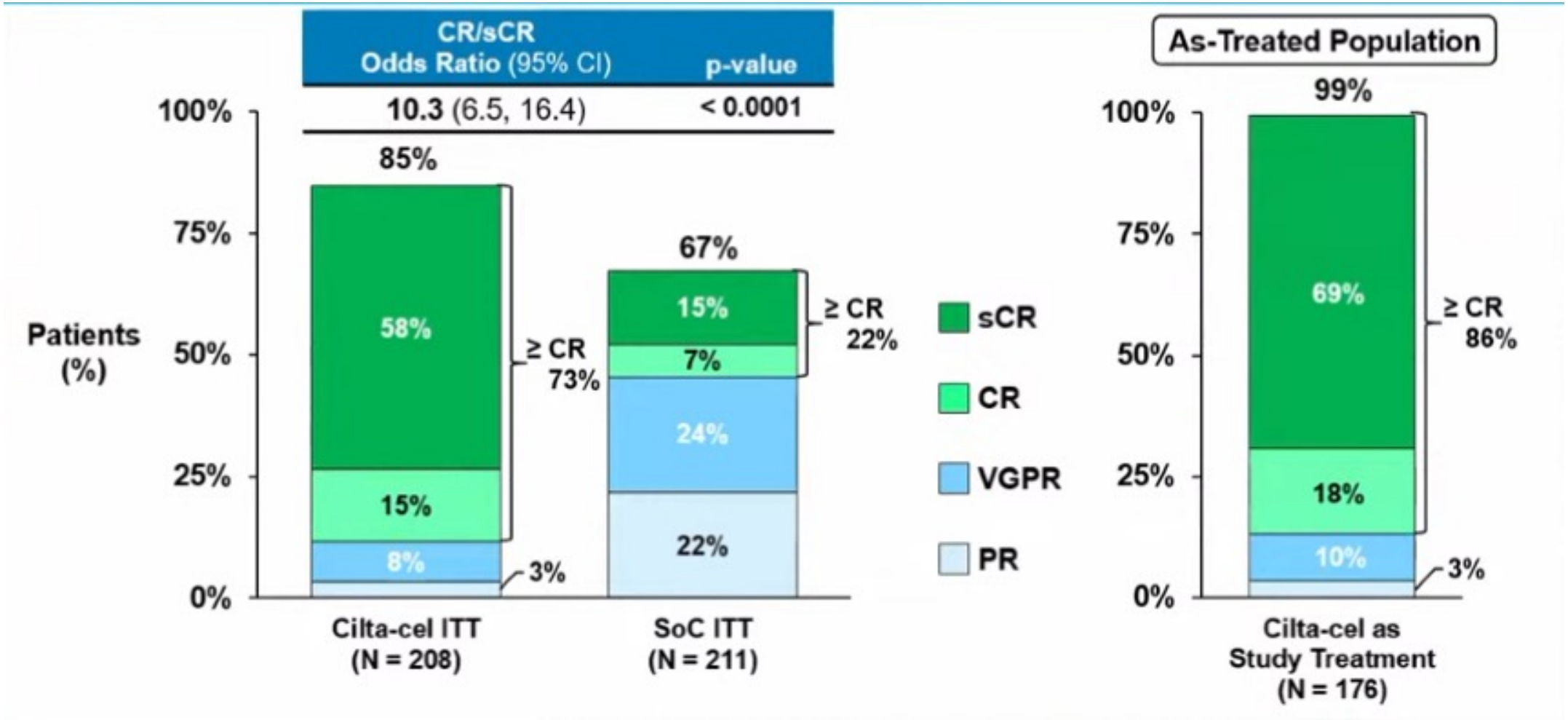
CARTITUDE 4:

ITT vs As Treated



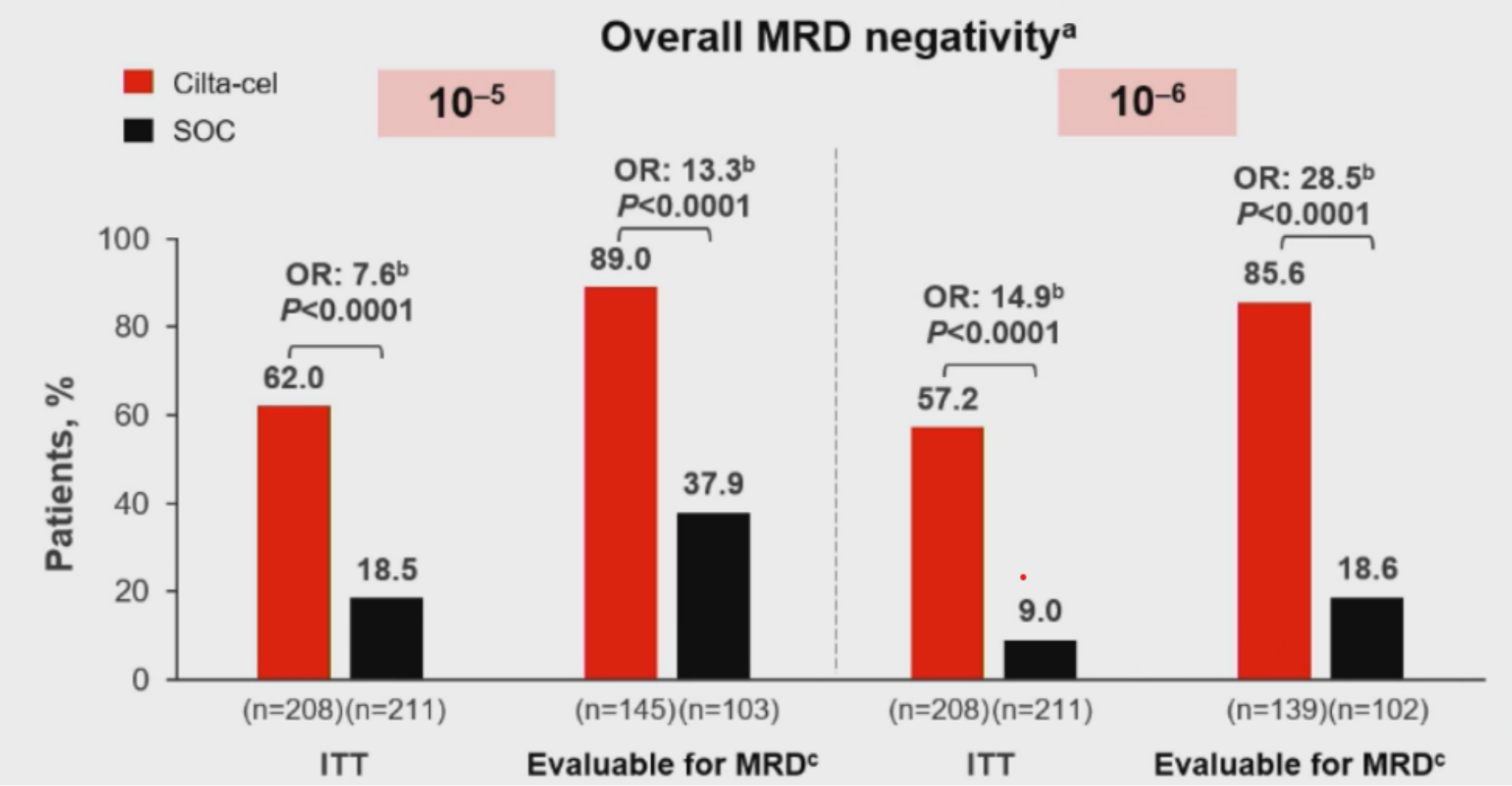
CARTITUDE 4

Response Rates



CARTITUDE 4

Rates of MRD negativity

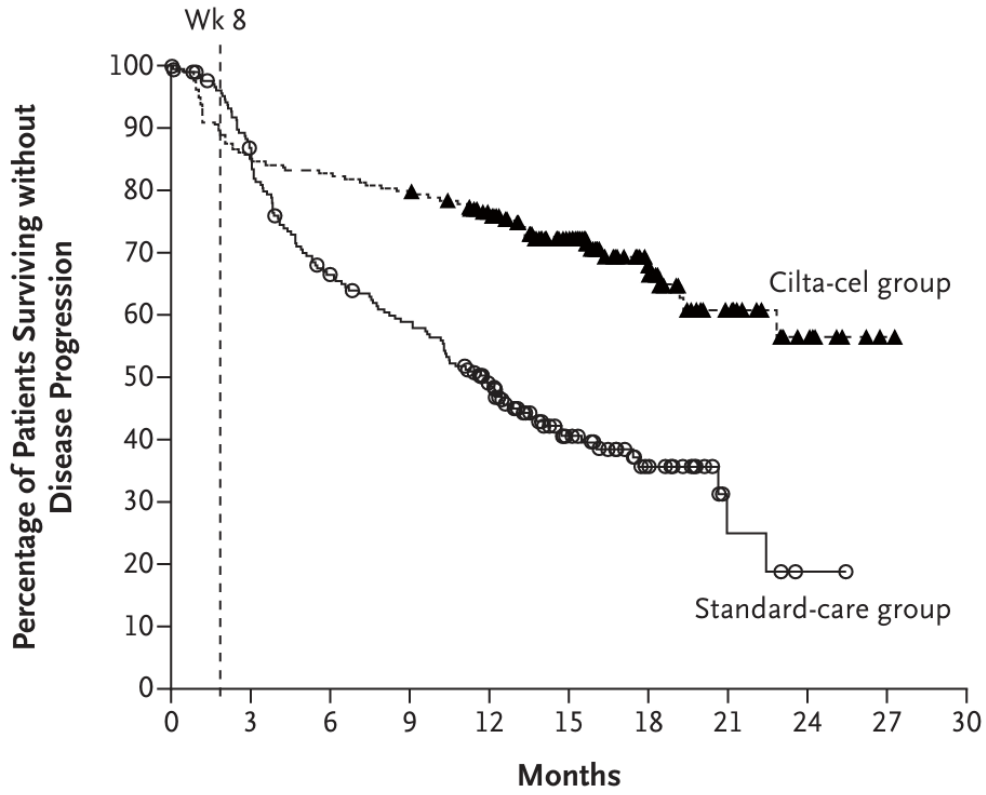


Popat et al. *ASH* Dec 2024

UCSF Helen Diller Family Comprehensive Cancer Center

CARTITUDE 4

Phase 3 RCT of Cilta-cel vs SOC



No. at Risk

Cilta-cel group	208	177	172	166	146	94	45	22	9	1	0
Standard-care group	211	176	133	116	88	46	20	4	1	0	0

	Ciltacel	SOC
ORR	85%	67%
≥CR	73%	22%
12 m PFS	75.9%	45%
mPFS	NR	11.8m

Median follow-up 33.6 months.

Prespecified HR (weighted): 0.26 (0.18, 0.38), p<0.0001

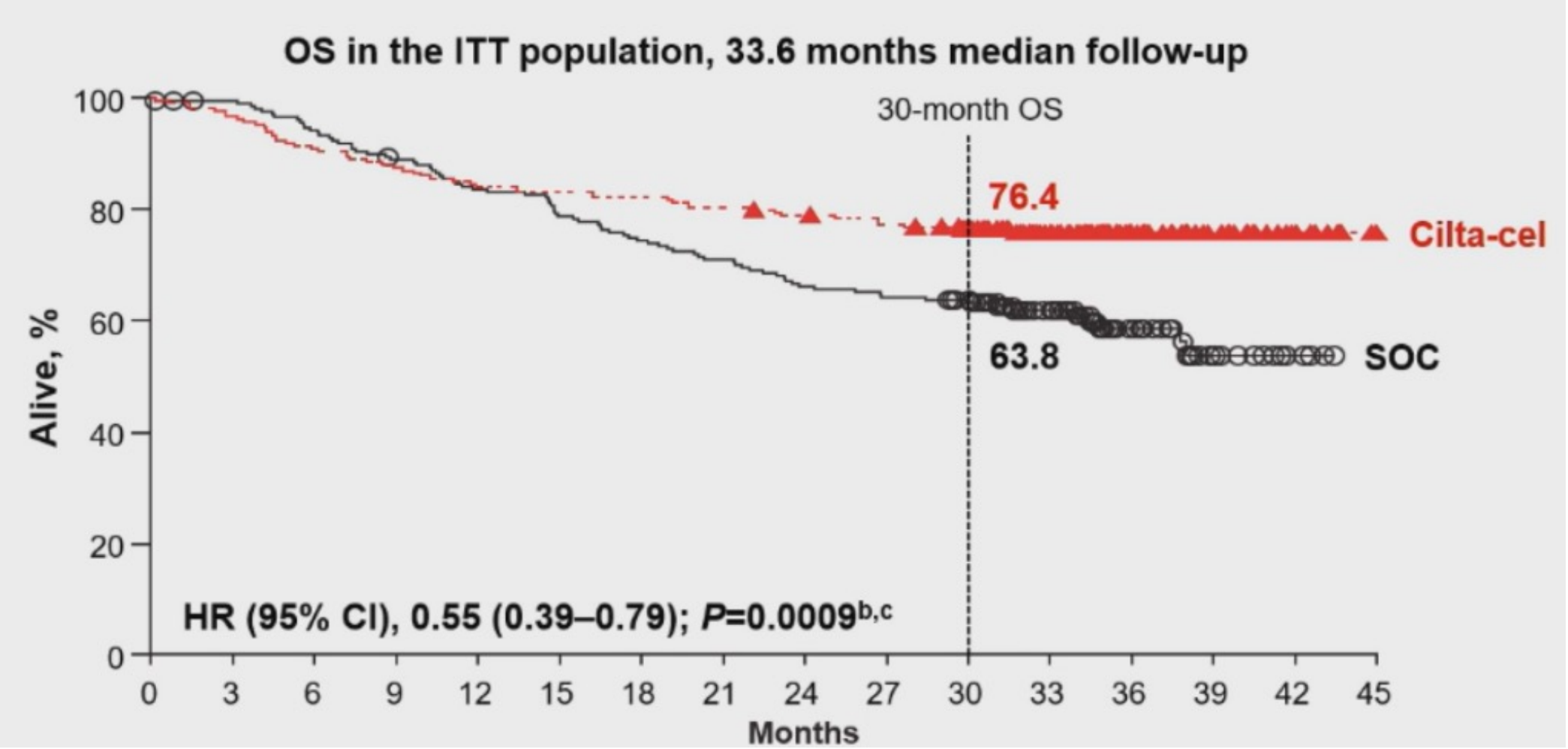
*weighted includes events that occurred 8 weeks post randomization and afterwards

ITT HR (unweighted): 0.40 (0.29, 0.55) p<0.0001

Popat et al. *ASH* Dec 2024

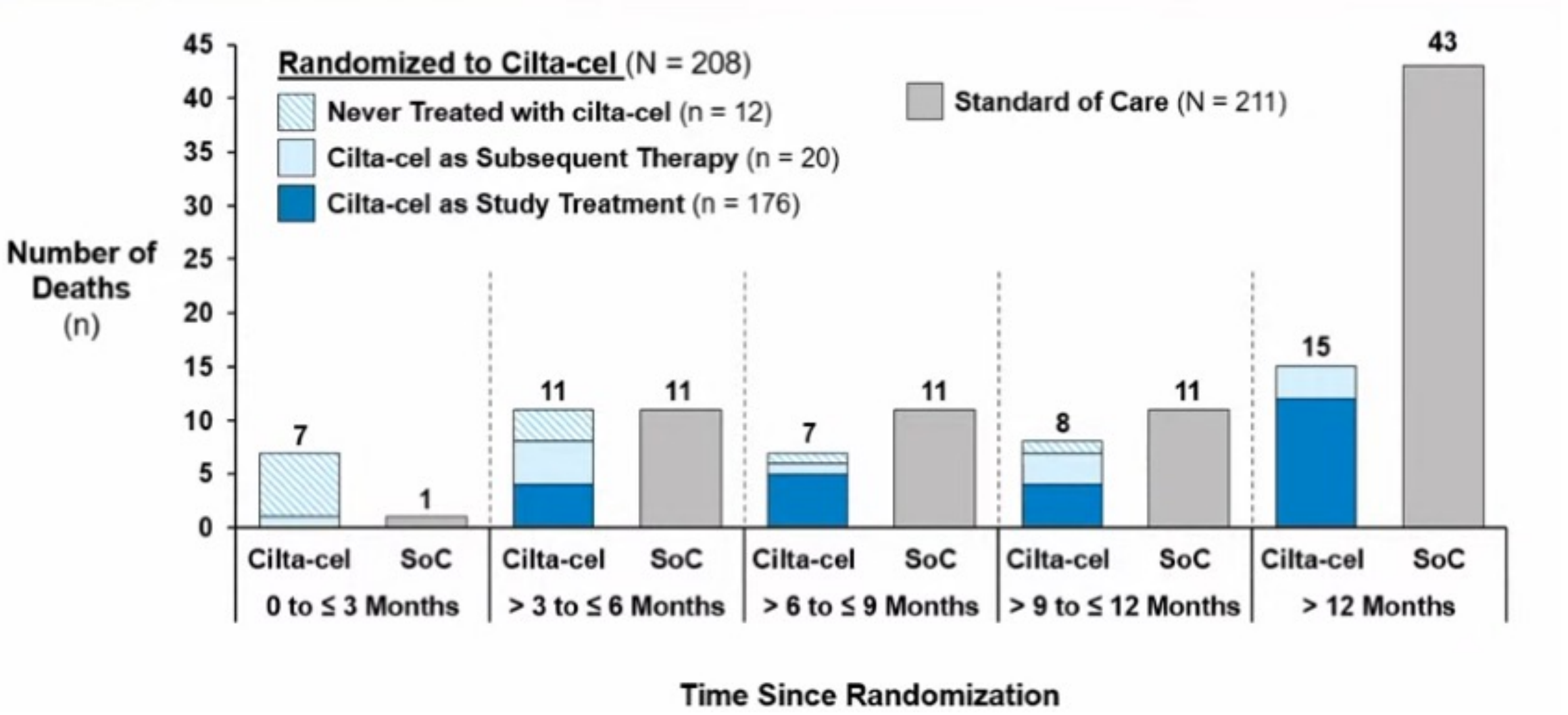
CARTITUDE 4

Overall survival



Popat et al. *ASH* 2024

CARTITUDE 4
Analysis of Deaths



CARTITUDE 4

Toxicities of Interest

CAR T specific AEs	Cilta-cel study treatment CARTITUDE 4		Cilta-cel study treatment CARTITUDE 1	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
CRS	78	3	95	5
ICANS	7	0.5	23	3
Cranial nerve palsies	9	1	3	1
Peripheral neuropathy	7	0.5	7	2
MNT (parkinsonism)	1	0	6	4

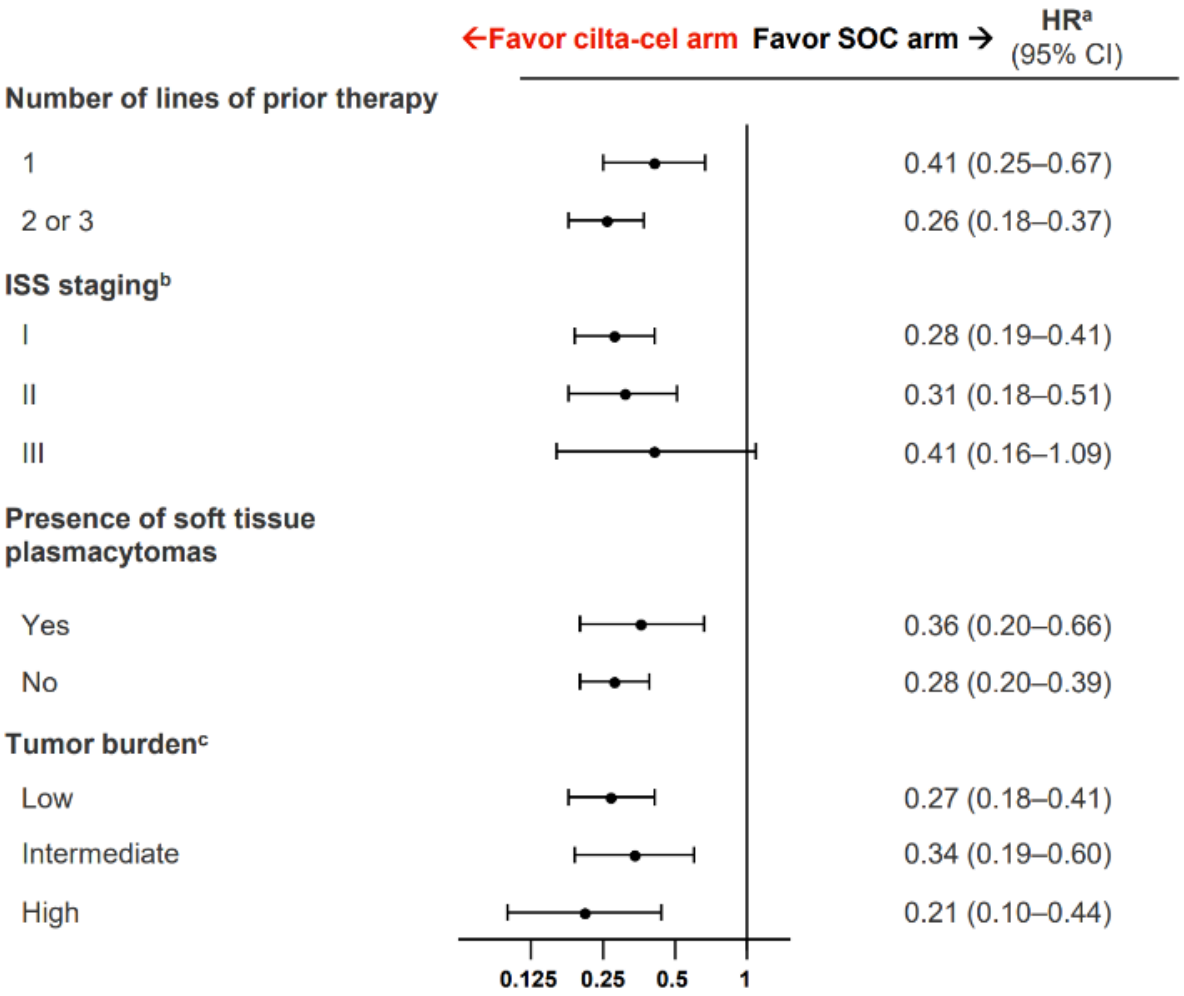
CARTITUDE 4

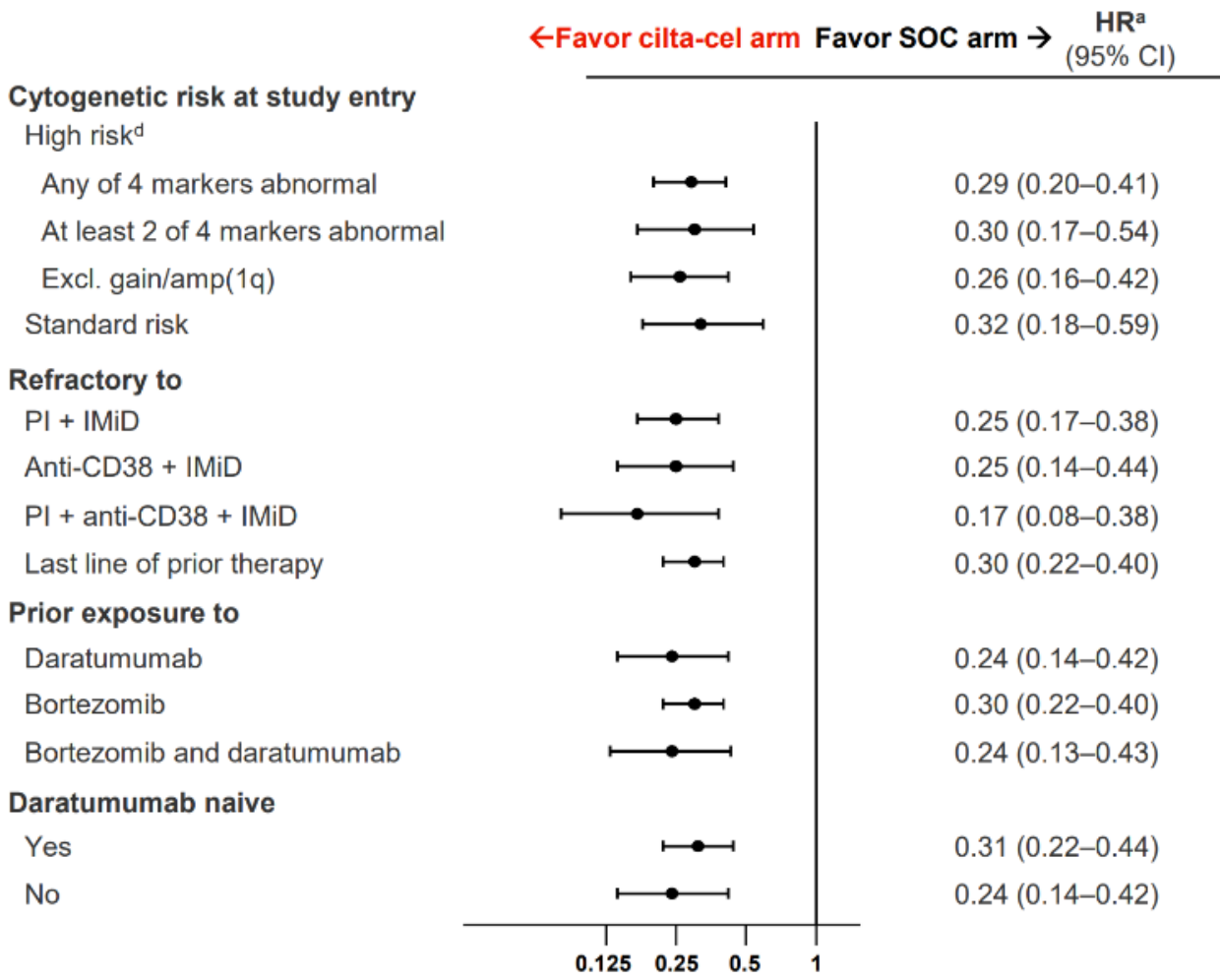
Secondary malignancies

Secondary malignancy	Cilta-cel (N=188)	SOC (N=208)
Patients with secondary malignancies	13%	11.5%
Cutaneous/non-invasive	7.2%	7.2%
Hematologic malignancies AML/MDS T-cell lymphoma EBV-associated lymphoma	3.4% 2.4% 1.0% 0%	0.5% 0% 0% 0.5%
Non-cutaneous/invasive	2.9%	3.8%

CARTITUDE 4

Subgroup analyses





Popat et al. *ASH* Dec 2024

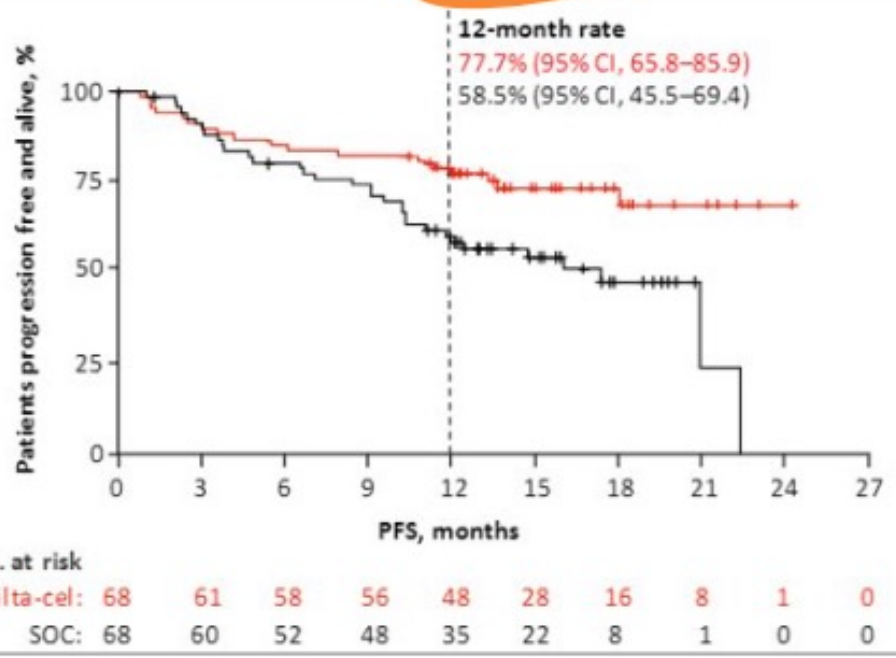
UCSF Helen Diller Family Comprehensive Cancer Center

Functionally High-Risk

Additional PFS benefit from ciltacel vs SOC

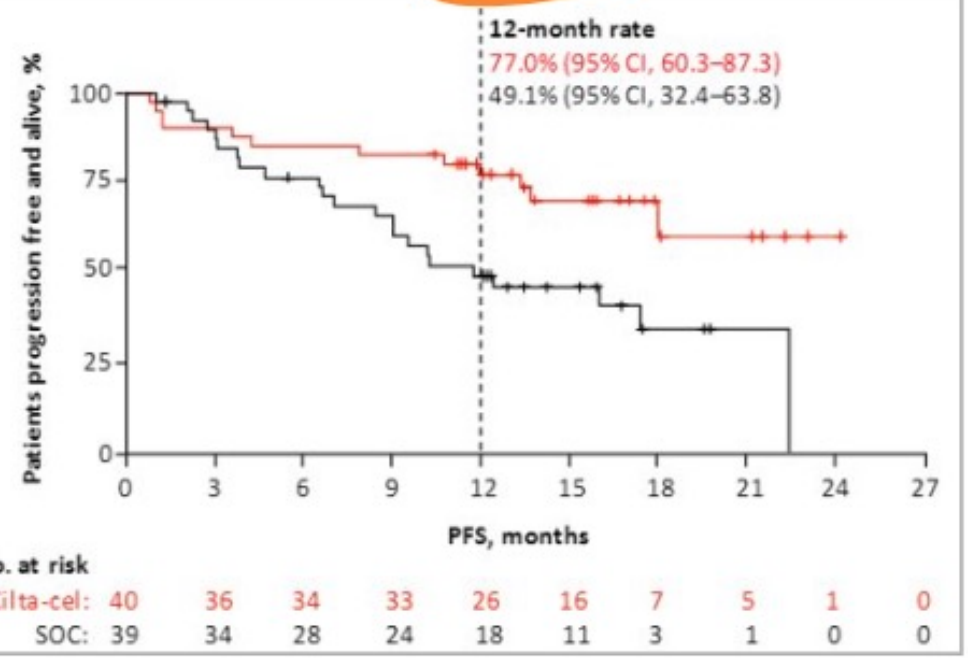
1 Prior LOT, All

	Cilta-cel (n=68)	SOC (n=68)
Median PFS (95% CI), months	NR (NE–NE)	17.41 (11.10–NE)
HR (95% CI); *P* value	0.35 (0.19–0.66); 0.0007	



1 Prior LOT With Functional High Risk

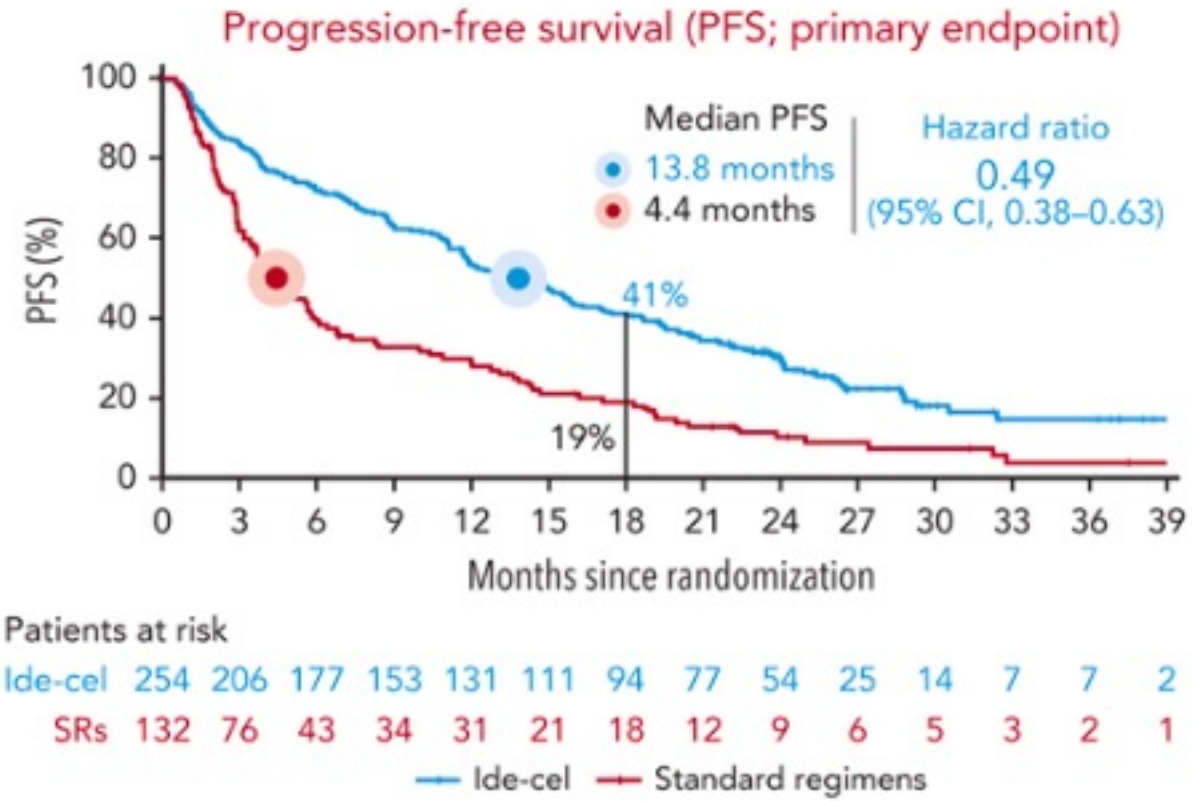
	Cilta-cel (n=40)	SOC (n=39)
Median PFS (95% CI), months	NR (18.00–NE)	11.79 (8.44–NE)
HR (95% CI); *P* value	0.27 (0.12–0.60); 0.0006	

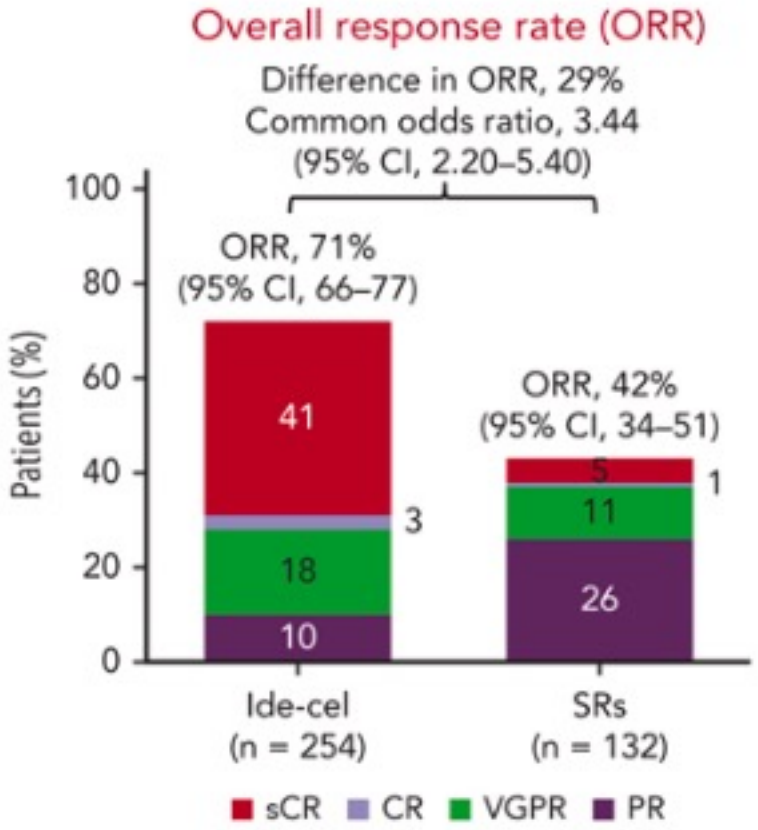


Costa et al. *ASCO* 2024.

KarMMa-3

Idecabtagene vicleucel (Ide-cel) vs SOC



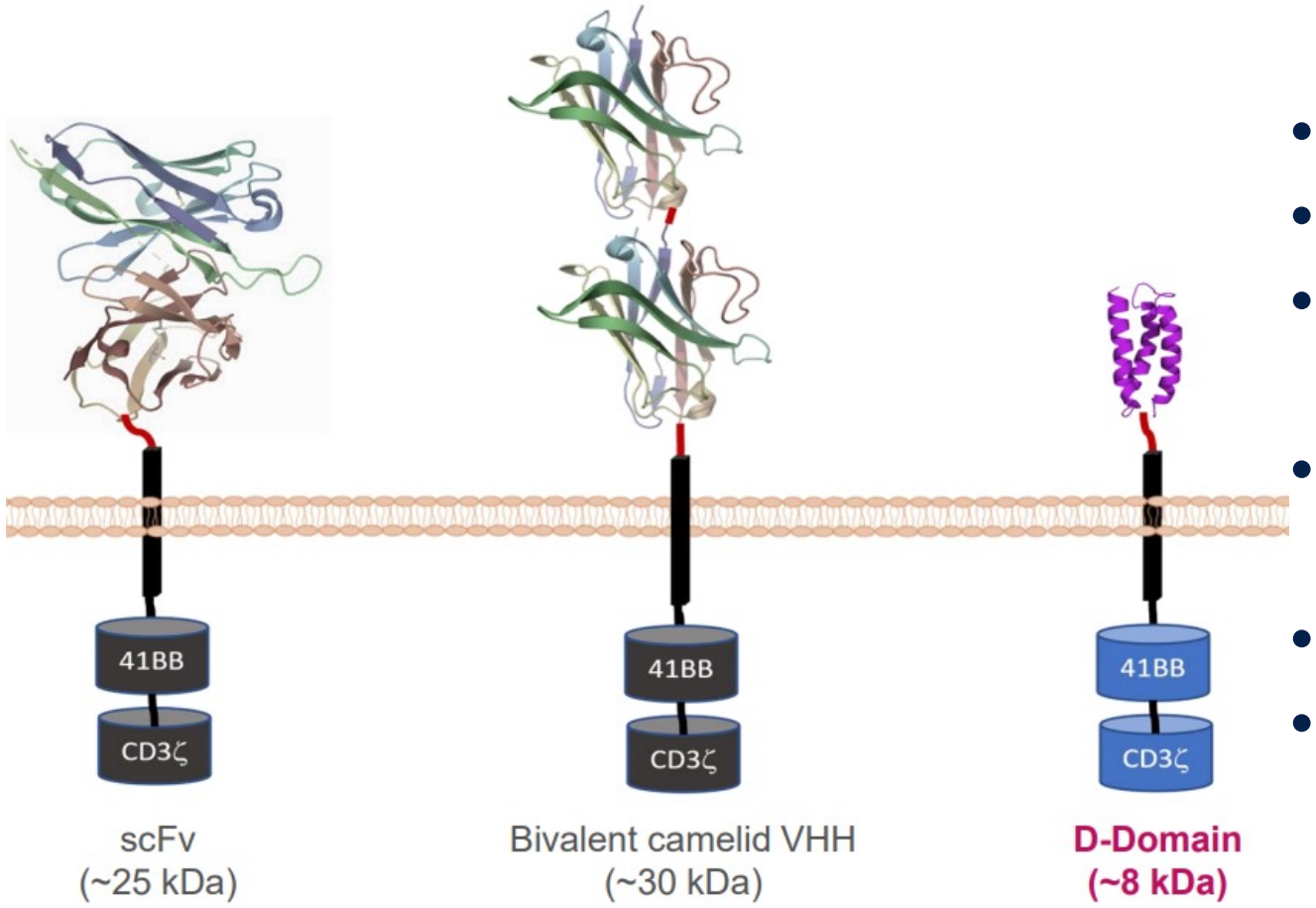


mOS: Ide-cel 41.4 mo vs SOC 37.9 mo

Ailawadhi et al. *ASH*, 2024

UCSF Helen Diller Family Comprehensive Cancer Center

Anitocabtagene Autoleucel (Anito-cel)



- BCMA-directed CAR T-cell
- Small, novel D-domain binder
- High transduction efficiency and CAR positivity
- Fast off-rate due to lack of disulfide bonds and rapid folding
- Allows for lower cell dose
- Leads to lower risk of tonic signaling

Freeman et al. ASH 2024

iMMagine-1

Phase 1

- 40 patients enrolled, 38 received anito-cel (32 DL1, 6 DL2)

Baseline Characteristic	
Median Age (range)	66 (44-76)
Median LOT (range)	4 (3-16)
Median time since diagnosis, years (range)	6.5 (1.5-14.9)
Extramedullary disease, n(%)	13(34%)
High risk cytogenetics, n(%)	11(29%)

iMMagine-1

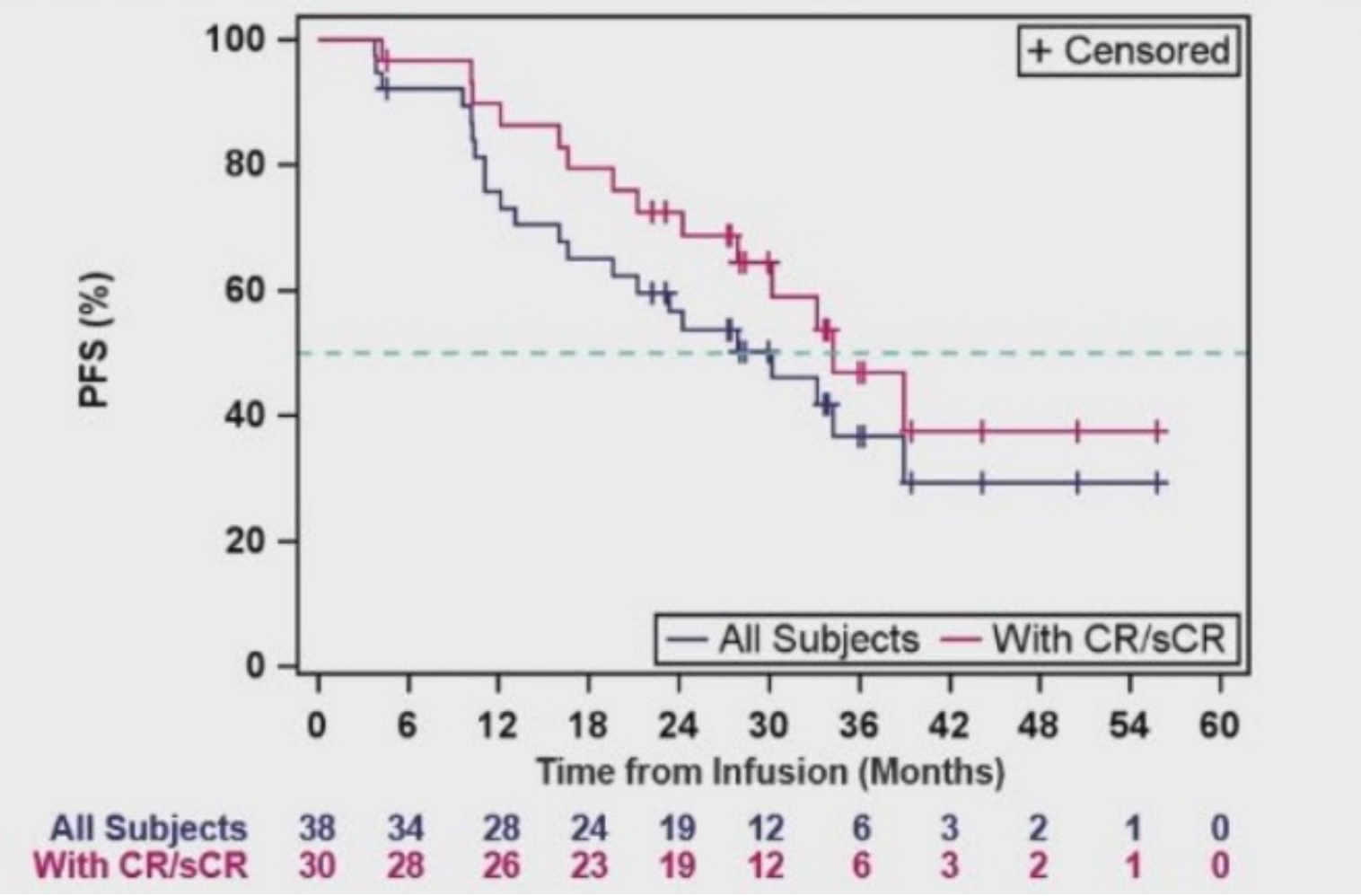
Results

Median follow-up of 34 months

Outcome	%
ORR	100%
≥CR	79%
≥VGPR	92%
MRD negative at 10^{-5} (28 evaluable patients)	89%
27-month PFS	52%
27-month OS	78%

iMMagine-1

Phase 1

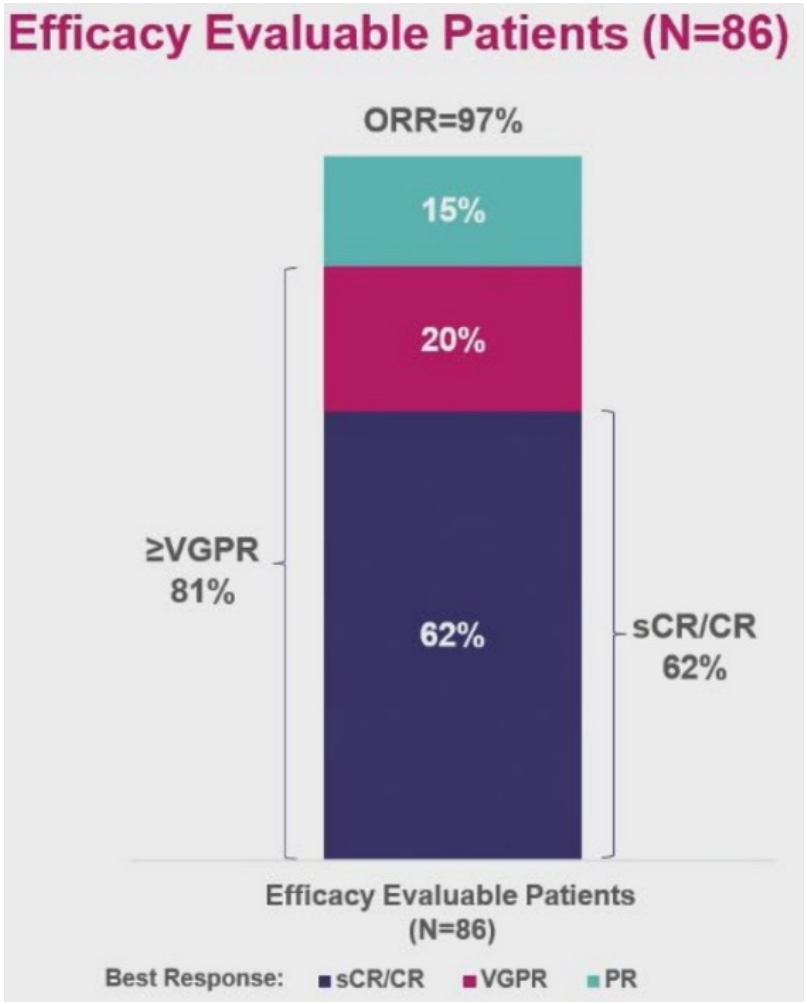


Median f/u 38.1 mo:
mPFS 30.2 months
mOS: NR

Freeman et al. ASH 2024

iMMagine-1

Phase 2 ORR and MRD-negativity

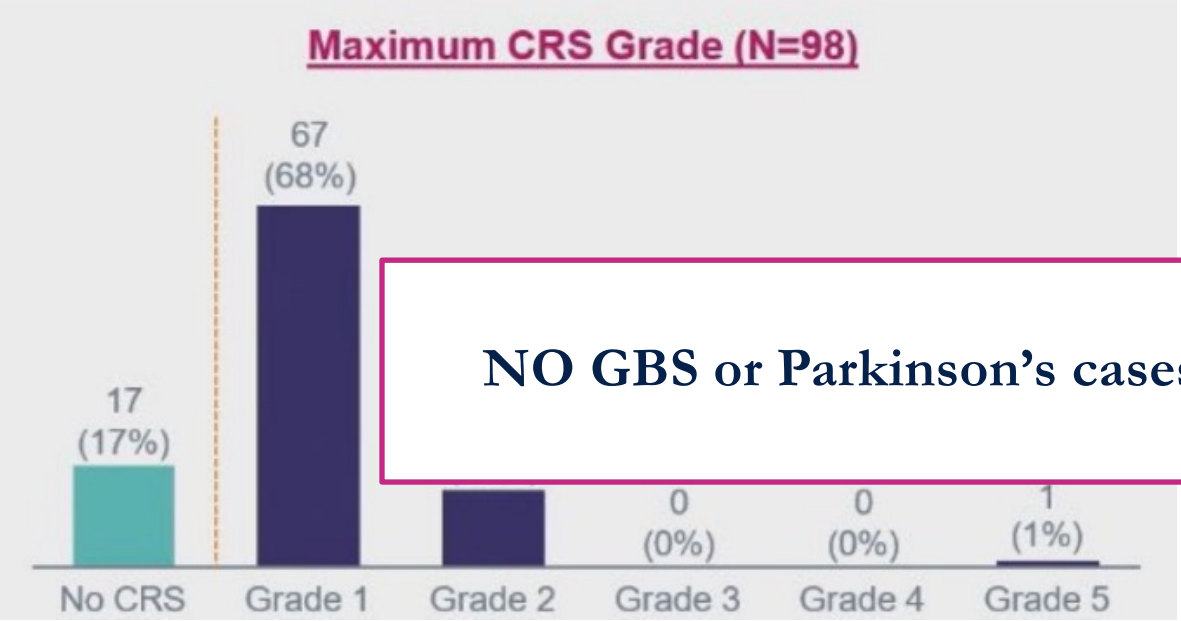


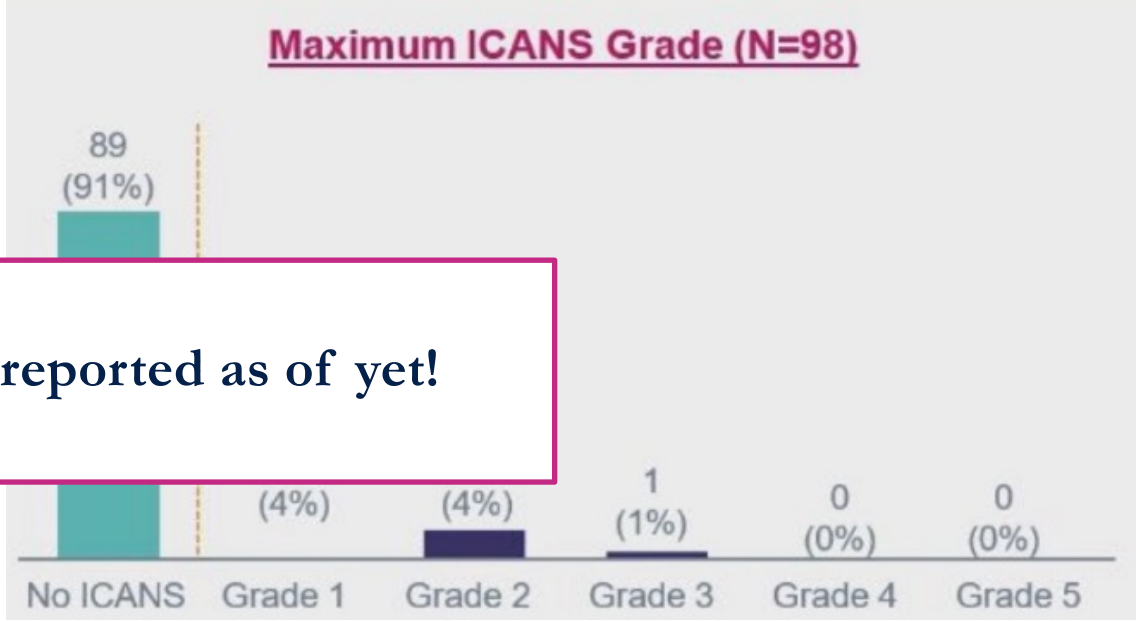
Median follow-up 9.5 months
ORR 97%
sCR/CR 62%

MRD negative (10^{-5}): 93.1%

iMMagine-1

Phase 2 CRS and ICANS





NO GBS or Parkinson's cases reported as of yet!

CRS	Safety evaluable patients (N=98)
Median onset (range)	4 days (1-17 days)
Median duration (range)	3 days (1-9 days)

ICANS	Safety evaluable patients (N=98)
Median onset (range)	7 days (2-10 days)
Median duration (range)	4 days (1-10 days)

Freeman et al. ASH 2024

iMMagine-3

Phase 3 Trial Design

Patients:
Age ≥18, MM
1-3 prior LOT
(including PI,
IMiD, and anti-
CD38)

Exclusion:
Prior CAR-T
(any target) and
ANY prior
BCMA-targeted
therapy

1:1
Randomization

Investigators Choice SOC:
DKd, DPd, PVd, Kd
(Until disease progression or intolerance)

Apheresis → Bridging (SOC above) → Anito-cel infusion

Please Scan the QR Code to Participate in Polling!

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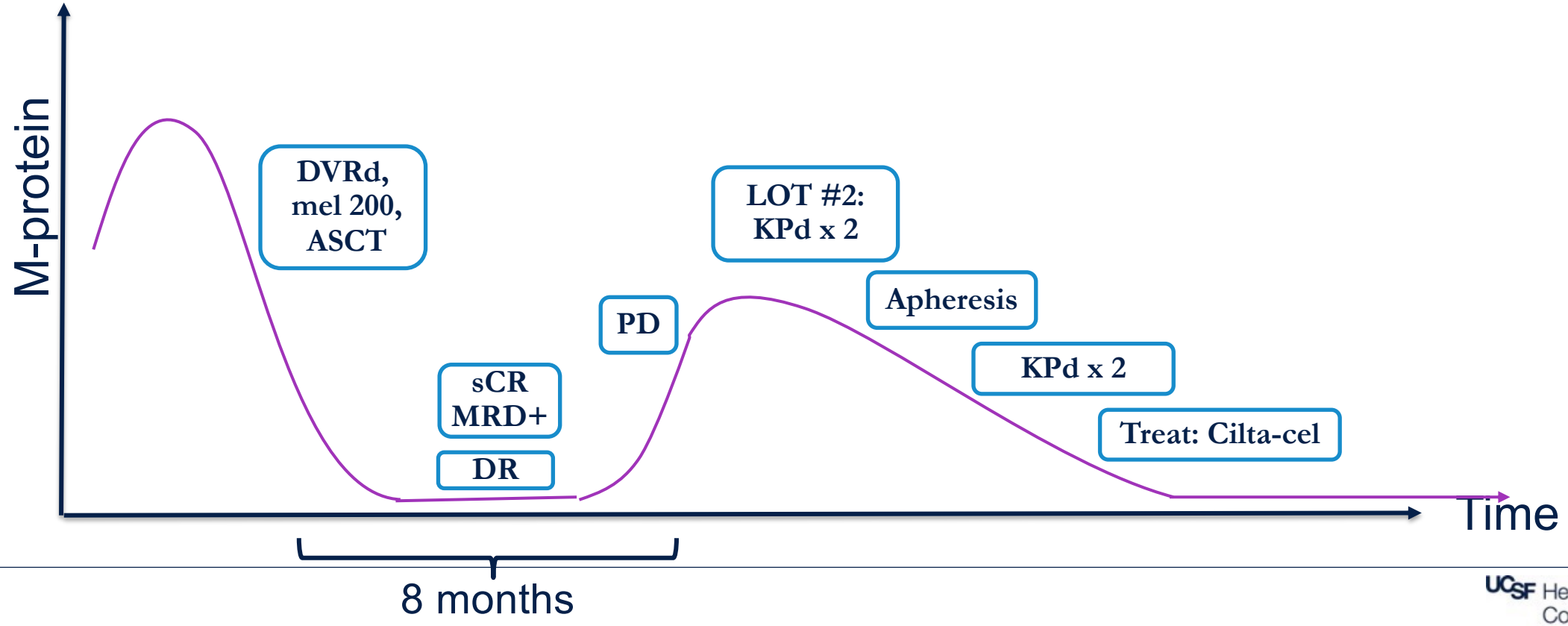
What is the Next Best Course of Action?

1. Continue KPd
2. Daratumumab, pomalidomide, and dexamethasone (DPd)
3. Anti-BCMA CAR T-cell therapy
4. Anti-BCMA bispecific antibody
5. Clinical Trial

Clinical Case

Mr. H is a 66 yo male with IgA kappa MM +1q s/p DRVd x 4 followed by mel 200mg/m2 and ASCT, dara/rev maintenance 8 months with biochemical relapse and KPd x 2 cycles with PR. He had apheresis for ciltacel followed by an additional 2 cycles of KPd bridging without dose reductions prior to ciltacel infusion.

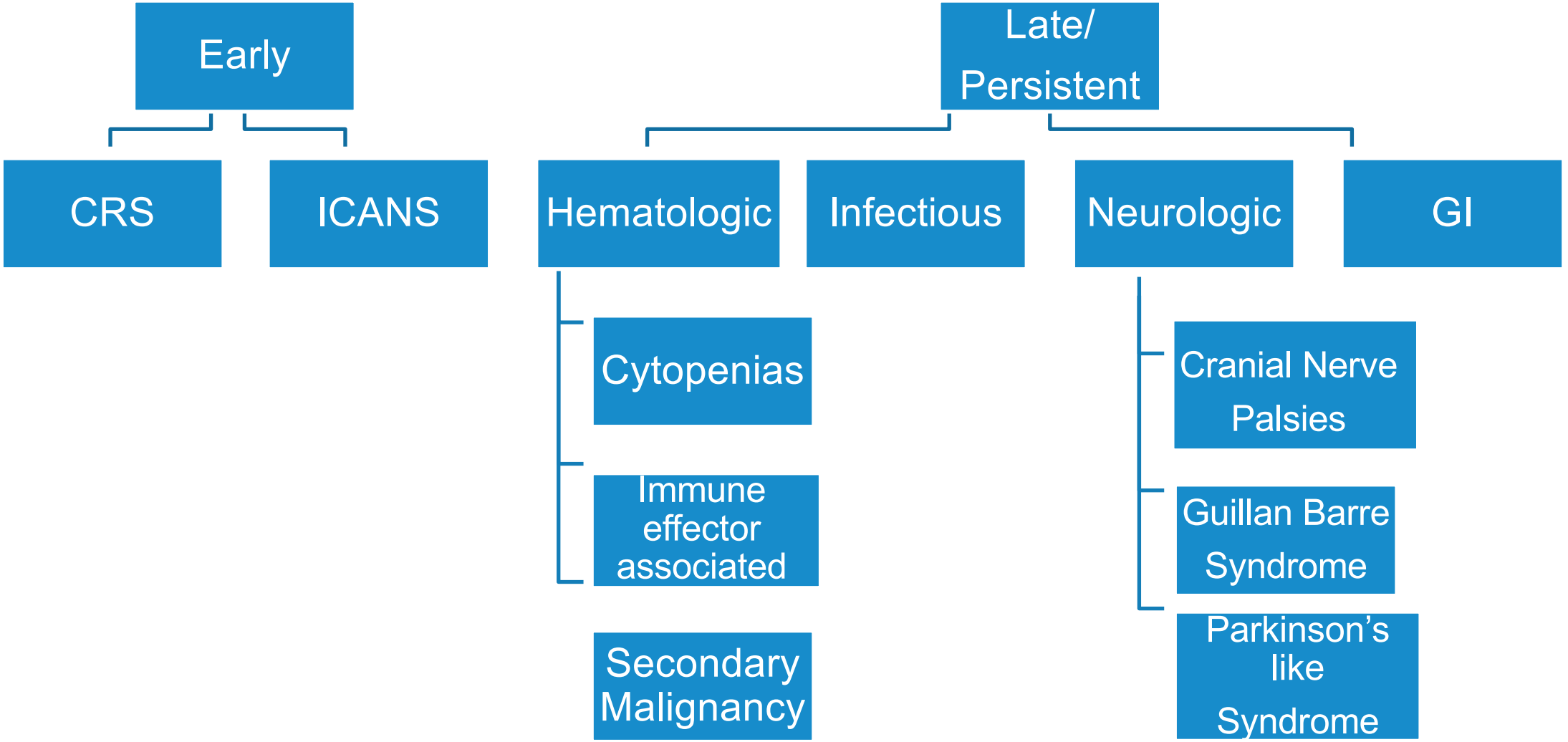


Back to the Case…

CAR T-cell therapy course

- Mr. H was admitted after outpatient lymphodepletion therapy with fludarabine and cyclophosphamide and outpatient ciltacel infusion.
- On day +7 he had onset of grade 1 CRS with fevers and tachycardia. He required tocilizumab x 1 and acetaminophen. The rest of his inpatient course was uncomplicated with no ICANS and he went home on day +11 with recovery in his WBC to 3.2 after his nadir, ANC 1.2.
- He followed up on day +28 and had recurrence of neutropenia with ANC 0.4 and platelets 25. He received GCSF and was started on prophylactic levofloxacin/antifungal with plan to follow-up with repeat labs the following week. He required GCSF for 3 weeks and had spontaneous recovery of his counts on his day +60 evaluation
- On day +43 Mr. H called in with complaints of right facial droop. He had CT head and MRI head performed which showed enhancement of cranial nerve 7. He was given a course of dexamethasone and symptoms resolved in about 21 days.
- Mr. H has been treatment-free and progression-free for 34 months, last bone marrow biopsy MRD negative 10^{-6}

Anti-BCMA CAR-T Toxicities



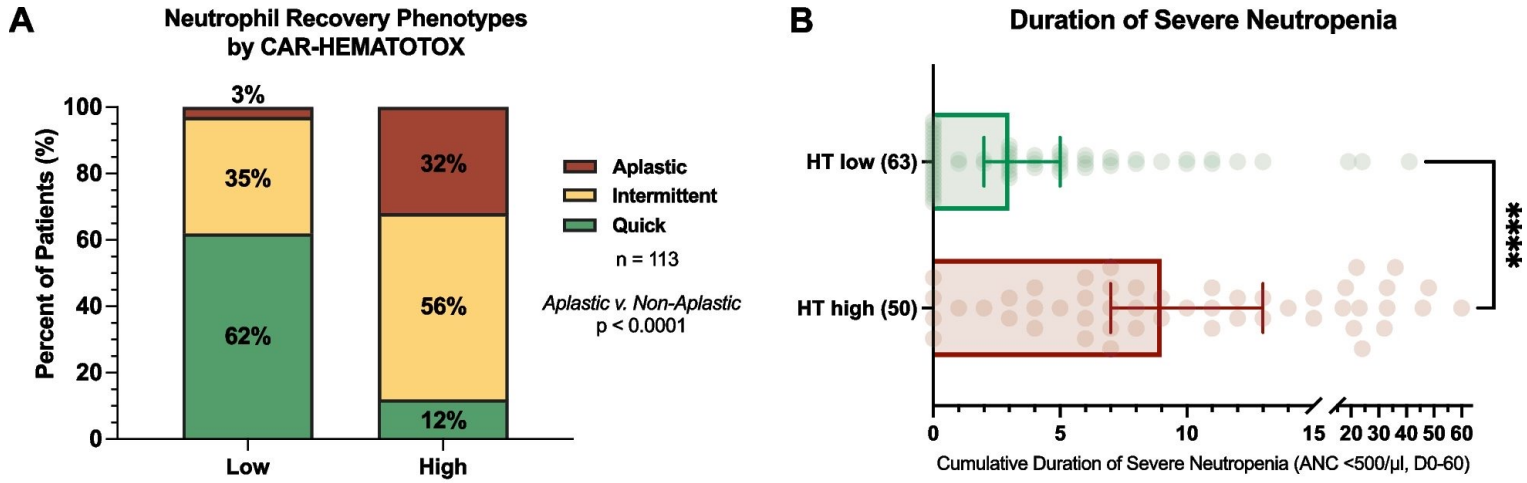
Cytopenias

CAR-HEMATOTOX predicts cytopenias and other toxicities

CAR-hematotox score: ≥2 high risk (HT high), 0-1 low risk (HT low)

1 point: ANC ≤1200, Hgb ≤ 9.0 g/dL, plt 76-175k, CRP≥3.0 mg/dL, and ferritin 650-2000ng/mL

2 points: plt count ≤ 75k and ferritin ≥2000ng/mL



High CAR-HEMATOTOX correlated with:

Toxicity: severe infections (40 vs 5%, p<0.001); 1 yr NRM (13 vs 2%, p=0.019);
severe ICANS (Gr≥3: 16 vs 0%, p<0.001)

Efficacy: ORR (44 vs 70%, p=0.001, mPFS (5 vs 15 months, p<0.001), mOS (10.5 mo vs NR, p<0.001)

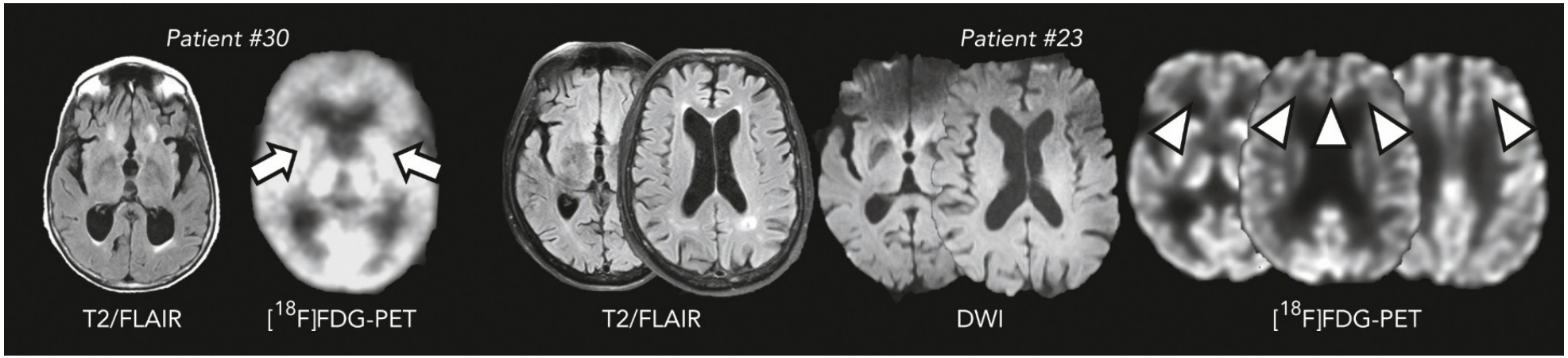
Rajeski et al, 2023

Slide adapted from Ajai Chari

UCSF Helen Diller Family Comprehensive Cancer Center

Parkinson-like Movement Disorders

- Hypothesized mechanism: on-target-off-tumor toxicity
- Risk factors: High CAR expansion, high tumor burden, any grade ICANS, and grade ≥3 CRS.
- Approaches to treatment have primarily included T-cell lowering therapy (steroids and/or cyclophosphamide) with limited success



Karschnia et al Blood, 2023
Cohen et al, Blood cancer 2022

Currently Open CAR T-cell Trials at UCSF

- **CARTITUDE 6:** Phase 3 RCT DVRd followed by ciltacel vs ASCT
- **aMMbition**: different sequences of early ciltacel with tec/talq in NDMM standard risk
- **iMMagine-3:** Phase 3 RCT anitocel vs SOC (DKd, DPd, PVd, Kd) with 1-3 prior LOT (IMiD, PI, anti-CD38)
- **BMS-986453** (BCMA x GPRC5D dual target CAR)
- **Arlocabtagene Autoleucel (BMS-986393) –** GPRC5D targeted

Summary

Use of CAR T-cell Therapy in Early Relapsed Multiple Myeloma

- Consider early referral for patients that are primary refractory or considered functionally high-risk (relapse within 18 months of first line treatment initiation OR within 12 months of frontline ASCT)
- Optimizing bridging therapy is crucial to getting patients to CAR T-cell dosing, minimize toxicity and maximize clinical benefit.
- Numerous CAR T-cell products are under investigation including additional BCMA-targeted, GPRC5D-targeted, dual-targeted, and allogeneic products
- When possible and appropriate, clinical trial participation should be prioritized for these patients

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MULTIPLE MYELOMA ROUNDS: USE OF BISPECIFIC MONOCLONAL ANTIBODIES IN CLINICAL PRACTICE

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Case Presentation

- HPI: 65yo female with hx of IgA lambda multiple myeloma who is s/p Melphalan preparative regimen followed by an autologous stem cell transplant (Day 0 = 8/26/2016), s/p 5th line Ix/Cy/Dex now presenting with biochemical relapse.
  - Subtype: IgA lambda Light Chain
  - ISS Stage: Stage II; rISS Stage: Stage II
  - Bone marrow biopsy: 3/11/16: 85% involved with lambda restricted PC
  - Cytogenetics/Karyotype: FISH 3/11/16: +1q, t(4;14), del(13), +15
- PMH: benign meningioma s/p resection in 02/2021
- SH: Denies any alcohol, tobacco or recreational drug usage
- Physical Exam: ECOG: 0
  - Well appearing female in on acute distress
  - RRR, 2/6 systolic murmur at RUSB.
  - No spinal tenderness, cyanosis, joint swelling or edema.

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Treatment History

Treatment 1:

- Induction: 4/5/16: RVd (boretzomib on days 1,4, 8, 11 at 1.3mg/m2, lenalidomide 25 mg PO days 1-14; dexamethasone 40 mg d 1, 2, 4, 5, 8, 9, 11, 12)
- Transplant: 8/26/16: Day 0 melphalan 200 mg/m2, complicated by neutropenic fever, discharged D+12
- Maintenance: lenalidomide 10 mg, complicated by neutropenia

Treatment 2: 5/10/2019 - 5/2021 daratumumab + bortezomib + dexamethasone

Treatment 3: 6/4/2021 - 6/2022 : carfilzomib + lenalidomide + cexamethasone weekly

Treatment 4: 7/2022 - 11/2022: elotuzumab + pomalidomide + dexamethasone

Treatment 5: 11/2022 - present: Ixazomib + cyclophosphamide + dexamethasone

Treatment 6:

- late Aug- 9/25/23 Bridge to CAR-T : selinexor + velcade+ dexamethasone
- 10/16/23 CAR-T Cell therapy: Cilta-cel

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Labs

Date	M-Spike	Immunofix	Kappa	Lambda	Kappa:Lambda	IgA	
3/1/16		IgA Lambda	5.5	750.2	0.07	4493	
7/2022							EPd
12/8/22	0.1					328	ICd
1/11/23	0.25		3.65	100.16	0.04	212	
2/14/23			4.6	75.04	0.06	202	
3/29/23			3.69	129.6	0.03	329	
4/19/23			3.1	98.1	0.03	217	
6/20/23	0.1		10	217		241	
8/22/23			20	330	<0.1	239	Sel/vel/dex bridge
1/08/24			.1	.1	1	<10	Post Cilta-cel
4/9/24	ND		<0.1	<0.1	UTC	<10	Post Cilta-Cel
11/18/24			< 0.6	66.69	0.01	65	At visit

Bone Marrow Biopsy (12/05):

- **Plasma cell neoplasm, 15% kappa-restricted plasma cells by CD138 immunohistochemistry**
- **Normocellular marrow with trilineage hematopoiesis**

ESTIMATED MRD VALUE:

36,339 residual clonal cells per million nucleated cells
(Range: 24,009 - 53,749)

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Next Line of Treatment?

A. BCMA Bispecific

B. GPRC5D Bispecific

C. Bendamustine-based triple therapy

D. Selinexor/dexamethasone

E. Belantamab Mafodotin combination therapy

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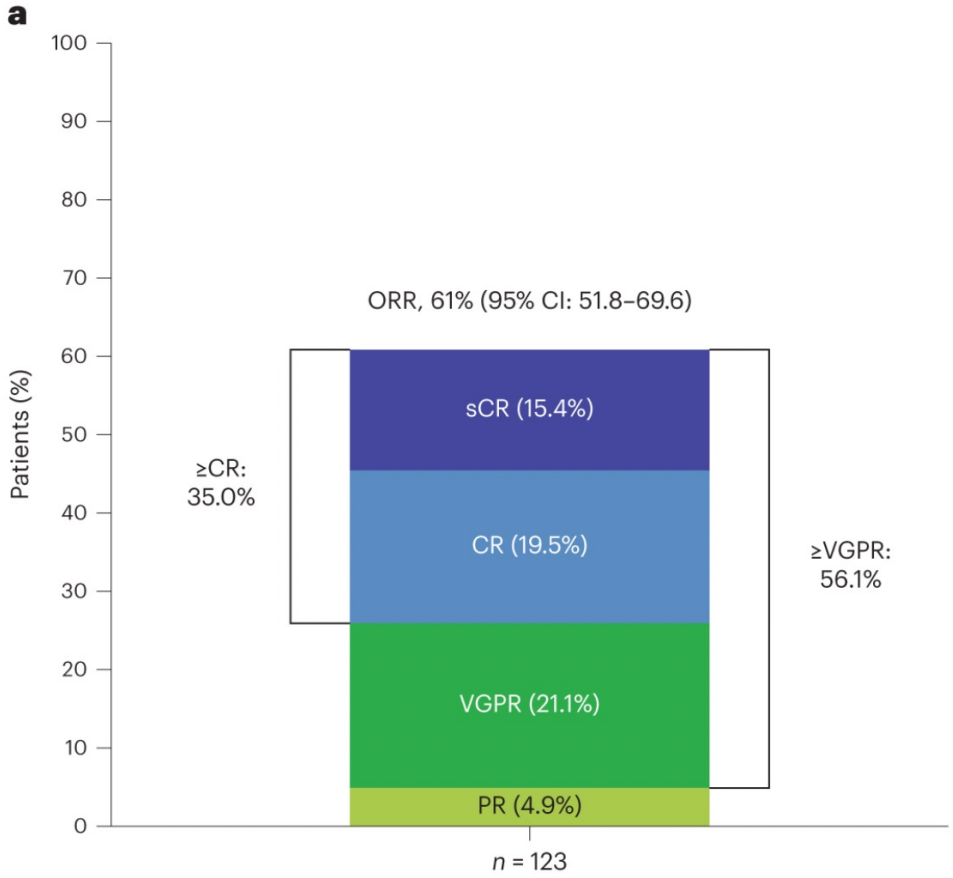
MagnetisMM-3 Trial

- Elranatamab: BCMA-CD3 bispecific antibody
- Relapsed MM, refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody
- Did not receive prior BCMA directed therapy.
- ORR: 61%; CR: 35%
- 15 month DOR, PFS and OS: 71.5% 50.9% and 56.7%, respectively



Lesokhin et al; *Nat Med,* 2023

Characteristics	Total (*n*=123)
Median age (range), years	68.0 (36–89)
Male, *n* (%)	68 (55.3)
Race, *n* (%)	
White	72 (58.5)
Asian	16 (13.0)
Black or African American	9 (7.3)
Not reported or unknown[a]	26 (21.1)
Geographical region, *n* (%)	
North America	58 (47.2)
Europe	45 (36.6)
Asia	12 (9.8)
Other	8 (6.5)
ECOG performance status, *n* (%)	
0	45 (36.6)
1	71 (57.7)
2	7 (5.7)
Type of myeloma, *n* (%)	
IgG	65 (52.8)
Non-IgG	21 (17.1)
IgA	20 (16.3)
IgD	1 (0.8)
Light chain	24 (19.5)
Unknown	13 (10.6)
R-ISS disease stage, *n* (%)	
I	28 (22.8)
II	68 (55.3)
III	19 (15.4)
Unknown	8 (6.5)
Cytogenetic risk, *n* (%)	
Standard	83 (67.5)
High[b]	31 (25.2)
Missing	9 (7.3)
Extramedullary disease by BICR, *n* (%)[c]	39 (31.7)
Bone marrow plasma cells, *n* (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
≥1 poor prognosis feature[d]	94 (76.4)
Median no. of prior antimyeloma lines of therapy (range)	5 (2–22)
Prior stem cell transplant, *n* (%)	87 (70.7)
Exposure status, n (%)	
Triple-class[e]	123 (100)
Penta-drug[f]	87 (70.7)
Refractory status, *n* (%)	
Triple-class[e]	119 (96.7)
Penta-drug[f]	52 (42.3)
Refractory to last line of therapy, *n* (%)	118 (95.9)

Lesokhin et al; *Nat Med,* 2023

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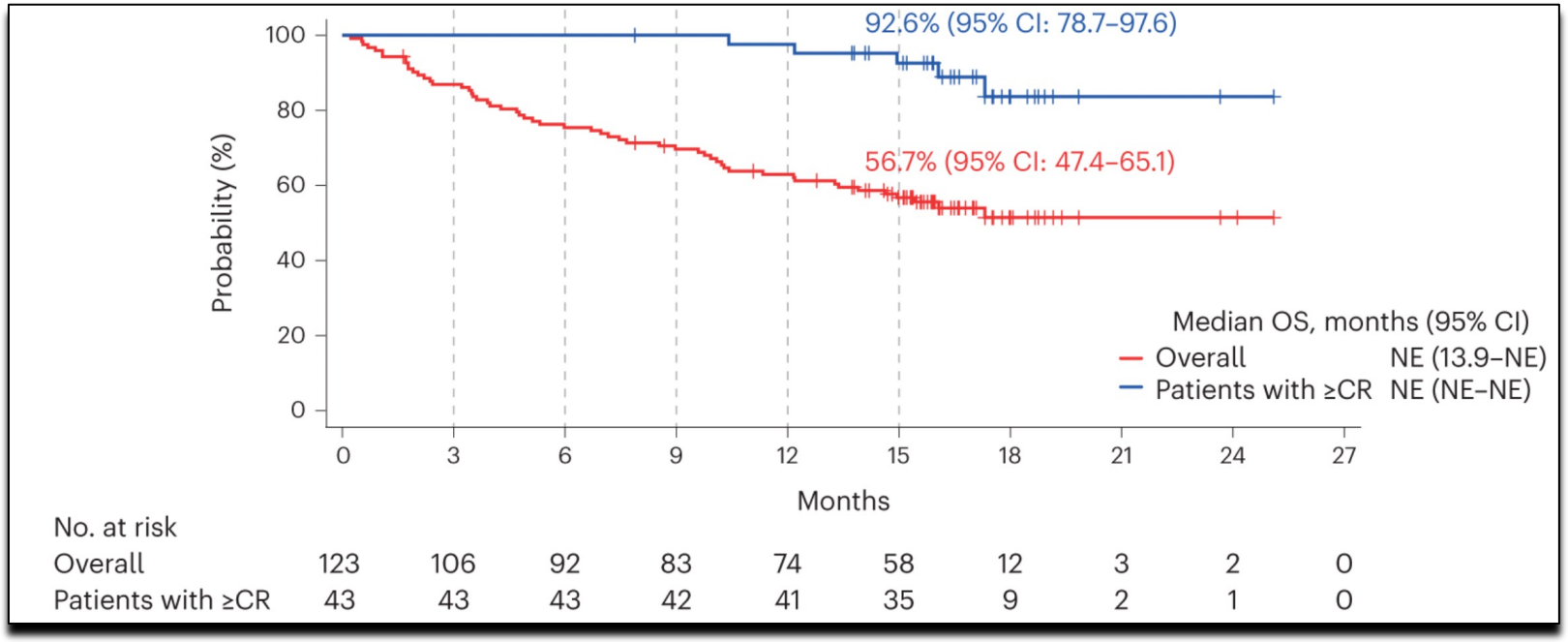

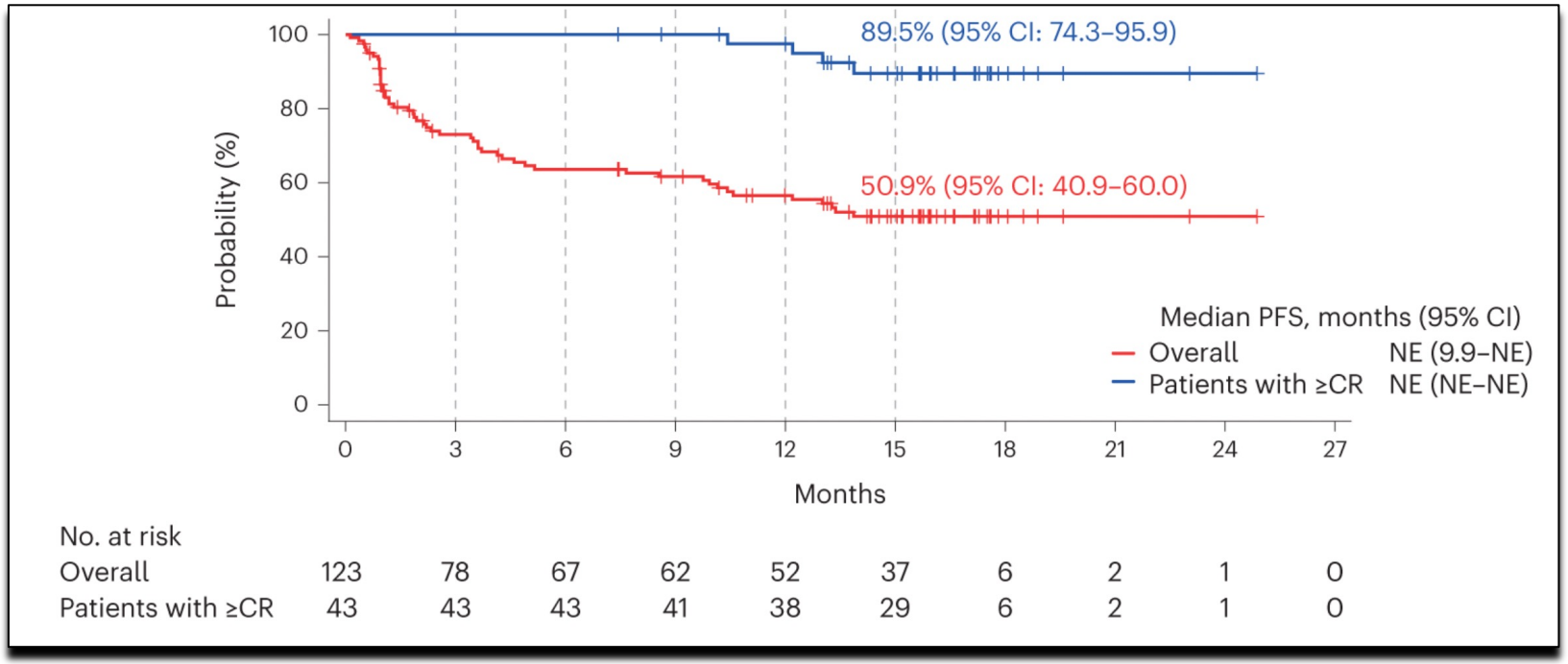

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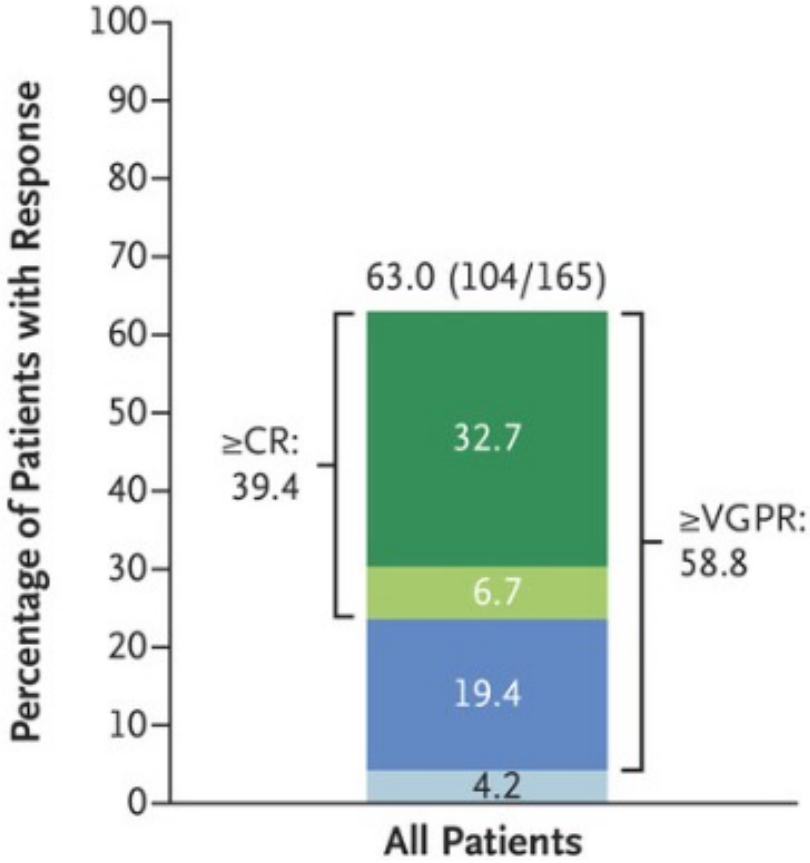
Lesokhin et al; *Nat Med,* 2023

MajesTEC-1

- Teclistamab: BCMA-CD3 bispecific antibody
- ≥ 3 lines w/exposure to:
  - imid
  - PI
  - anti-CD38 antibody
- No prior BCMA directed therapy
- At 14.1 months, ORR: 63.0% and CR: 39.4% 26.7% MRD negative.
- mDOR: 18.4 mos; mPFS: 11.3mos



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Moreau et al, *NEJM* 2022

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Phase 1 (N=40)	Phase 2 (N=125)	Total (N=165)
Age			
Median (range) — yr	62.5 (39.0–84.0)	64.0 (33.0–83.0)	64.0 (33.0–84.0)
≥75 yr — no. (%)	5 (12.5)	19 (15.2)	24 (14.5)
Sex — no. (%)			
Male	26 (65.0)	70 (56.0)	96 (58.2)
Female	14 (35.0)	55 (44.0)	69 (41.8)
Race — no. (%)*			
White	34 (85.0)	100 (80.0)	134 (81.2)
Black	1 (2.5)	20 (16.0)	21 (12.7)
Asian	0	3 (2.4)	3 (1.8)
Other	5 (12.5)	2 (1.6)	7 (4.2)
Median time since diagnosis (range) — yr	5.6 (0.8–17.4)	6.2 (0.9–22.7)	6.0 (0.8–22.7)
≥1 Extramedullary plasmacytoma — no. (%)†	8 (20.0)	20 (16.0)	28 (17.0)
≥60% Plasma cells in bone marrow — no./total no. (%)	3/38 (7.9)	15/122 (12.3)	18/160 (11.2)
ECOG performance-status score — no. (%)‡			
0	17 (42.5)	38 (30.4)	55 (33.3)
≥1	23 (57.5)	87 (69.6)	110 (66.7)
International Staging System class — no./total no. (%)			
I	24/39 (61.5)	61/123 (49.6)	85/162 (52.5)
II	11/39 (28.2)	46/123 (37.4)	57/162 (35.2)
III	4/39 (10.3)	16/123 (13.0)	20/162 (12.3)
High-risk cytogenetic profile — no./total no. (%)	12/37 (32.4)	26/111 (23.4)	38/148 (25.7)
del(17p)	9/37 (24.3)	14/111 (12.6)	23/148 (15.5)
t(4:14)	4/37 (10.8)	12/111 (10.8)	16/148 (10.8)
t(14:16)	1/37 (2.7)	3/111 (2.7)	4/148 (2.7)
Median no. of lines of previous therapy (range)	5 (2–11)	5 (2–14)	5 (2–14)
Previous stem-cell transplantation — no. (%)	34 (85.0)	101 (80.8)	135 (81.8)
Previous therapy exposure — no. (%)			
Triple-class§	40 (100.0)	125 (100.0)	165 (100.0)
Penta-drug¶	26 (65.0)	90 (72.0)	116 (70.3)
Refractory status — no. (%)			
Immunomodulatory agent‖	38 (95.0)	114 (91.2)	152 (92.1)
Proteasome inhibitor**	34 (85.0)	108 (86.4)	142 (86.1)
Anti-CD38 monoclonal antibody††	39 (97.5)	109 (87.2)	148 (89.7)
Triple-class§	32 (80.0)	96 (76.8)	128 (77.6)
Penta-drug¶	16 (40.0)	34 (27.2)	50 (30.3)
Refractory to last line of therapy	33 (82.5)	115 (92.0)	148 (89.7)

Moreau et al, *NEJM* 2022

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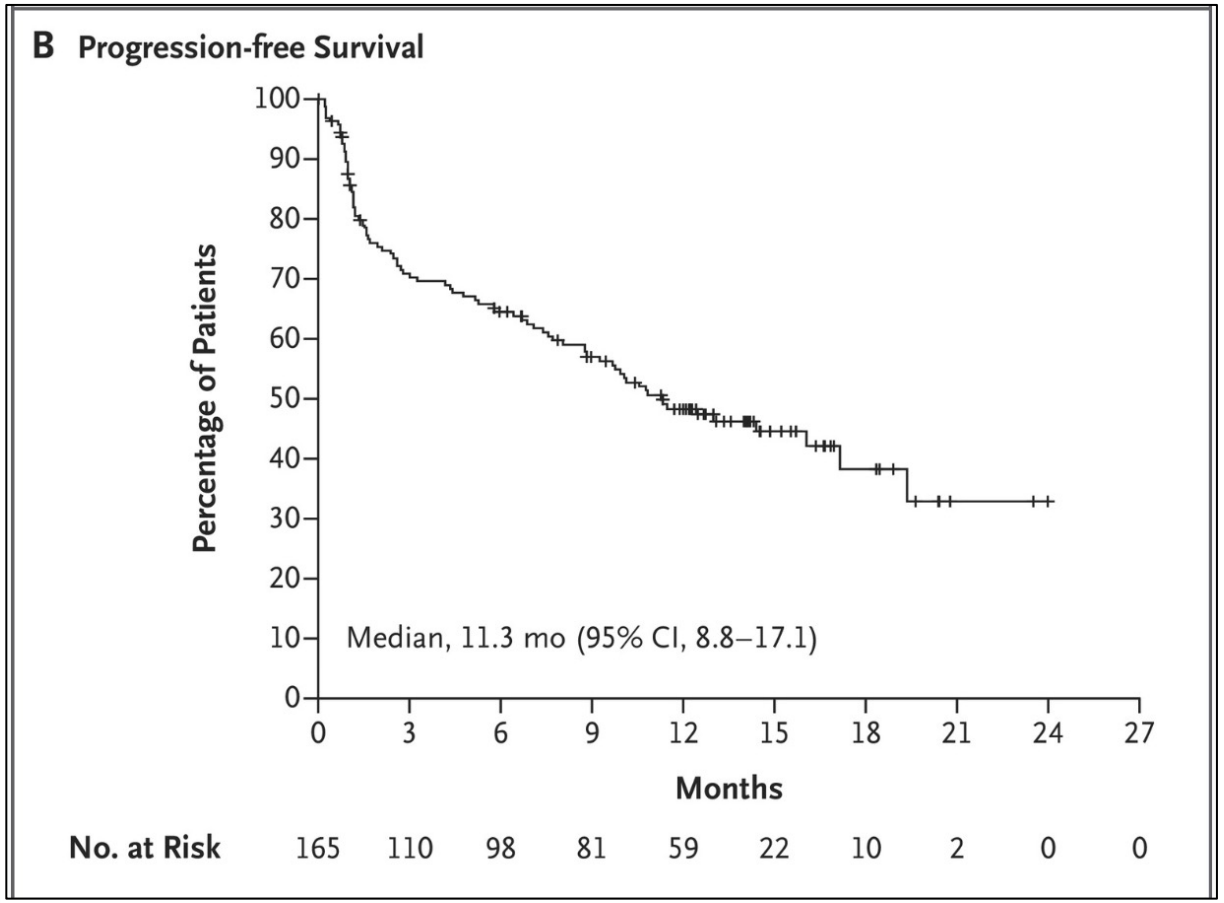

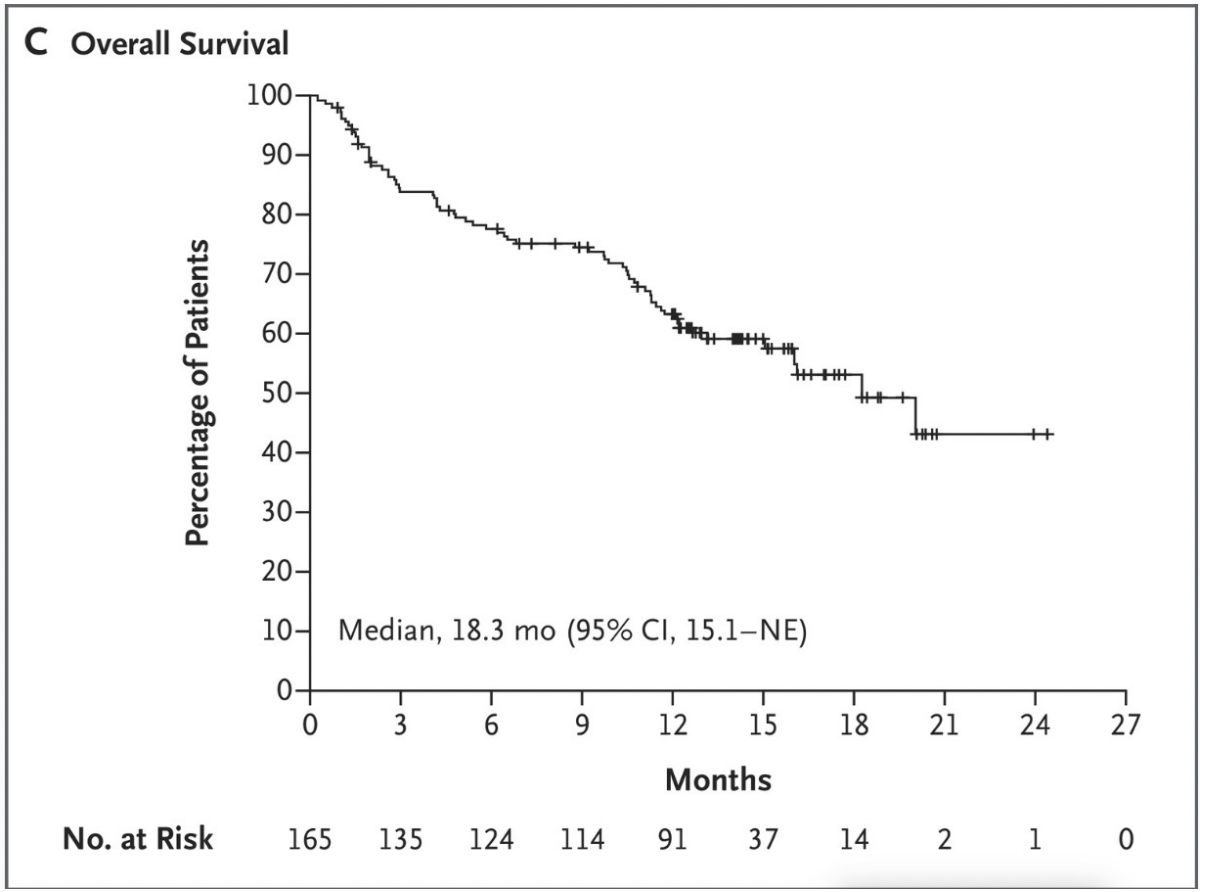

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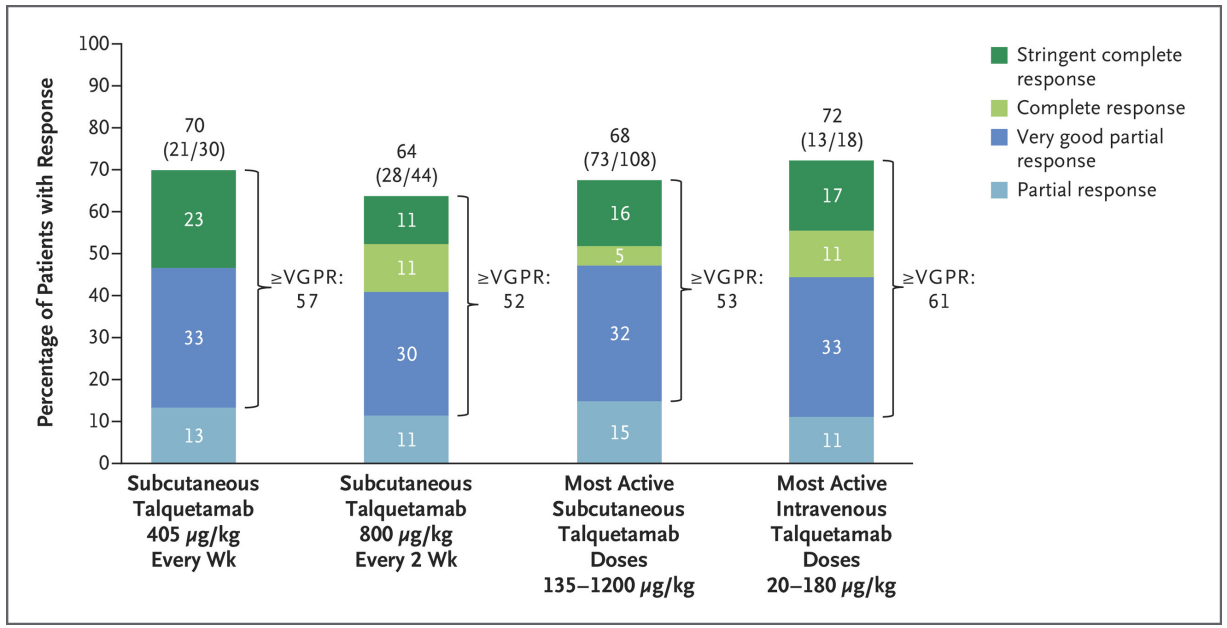
Moreau et al, *NEJM* 2022

MonumenTAL-1

- Talquetamab: GPRC5D-CD3 bispecific antibody
- Phase-1 dose finding: explored IV, Sub-q, weekly and Q2 week dosing
- RRMM ineligible for other standard treatment due to intolerance or refractoriness
- ORR at 11.7 months (405μg): 70%
- ORR at 4.2 months (800 μg): 64%
- mDOR: 10.2 mos and 7.8 mos



Chari et al; *NEJM,* 2022

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Table 1. Characteristics of the Patients at Baseline.

Characteristic	Subcutaneous Talquetamab, 405 μg Weekly (N=30)	Subcutaneous Talquetamab, 800 μg Every 2 Wk (N=44)	Subcutaneous Talquetamab, All Doses* (N=130)	Intravenous Talquetamab, All Doses* (N=102)
Age				
Median (range) — yr	62 (46–80)	64 (47–84)	64 (39–84)	65 (33–79)
≥70 yr — no. (%)	7 (23)	15 (34)	37 (28)	32 (31)
Sex — no. (%)				
Male	19 (63)	21 (48)	75 (58)	57 (56)
Female	11 (37)	23 (52)	55 (42)	45 (44)
Race or ethnic group — no. (%)†				
White	25 (83)	35 (80)	107 (82)	82 (80)
Black	4 (13)	4 (9)	13 (10)	14 (14)
Asian	0	3 (7)	4 (3)	2 (2)
Other or not reported	1 (3)	2 (5)	6 (5)	4 (4)
Median time since diagnosis (range) — yr	5.6 (1.7–19.6)	6.4 (0.8–21.3)	6.1 (0.8–21.3)	6.6 (0.9–27.0)
≥1 Extramedullary plasmacytoma — no. (%)	11 (37)	15 (34)	42 (32)	15 (15)
≥60% Plasma cells in bone marrow — no./total no. (%)	6/29 (21)	5/41 (12)	21/121 (17)	22/100 (22)
International Staging System class — no./total no. (%)				
I	12/29 (41)	16/43 (37)	44/124 (35)	33/100 (33)
II	13/29 (45)	18/43 (42)	56/124 (45)	43/100 (43)
III	4/29 (14)	9/43 (21)	24/124 (19)	24/100 (24)
High-risk cytogenetic abnormalities — no./total no. (%)‡	3/27 (11)	9/40 (22)	18/112 (16)	14/88 (16)
del(17p)	1/27 (4)	7/40 (18)	12/112 (11)	7/88 (8)
t(4;14)	2/27 (7)	3/40 (8)	9/112 (8)	7/88 (8)
t(14;16)	0	0	0	1/88 (1)
Median no. of lines of previous therapy (range)	6 (2–14)	5 (2–17)	6 (2–17)	6 (3–20)
Previous stem-cell transplantation — no. (%)	27 (90)	33 (75)	111 (85)	87 (85)
Previous therapy exposure — no. (%)				
Triple-class exposure§	30 (100)	43 (98)	129 (99)	101 (99)
Penta-drug exposure¶	24 (80)	30 (68)	100 (77)	79 (77)
Refractory status — no. (%)				
Immunomodulatory drug‖	28 (93)	42 (95)	121 (93)	98 (96)
Proteasome inhibitor**	25 (83)	36 (82)	106 (82)	92 (90)
Anti-CD38 monoclonal antibody††	30 (100)	39 (89)	119 (92)	97 (95)
Triple-class refractory‡‡	23 (77)	33 (75)	97 (75)	87 (85)
Penta-drug refractory§§	6 (20)	9 (20)	33 (25)	36 (35)
Refractory to last line of therapy	26 (87)	39 (89)	111 (85)	91 (89)

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Chari et al; *NEJM,* 2022

MonumenTAL-1: Prior BCMA Exposure

- 16 patients at recommended phase-2 dose had prior BCMA directed Bispecific or CAR-T cell
- ORR 50%

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Chari et al; *NEJM,*

Our Patient

- **12/15/2024 Admitted for Talquetamab step up dosing**
  - Day 1: 0.01 mg/kg subQ
    - Tolerated without adverse effects
  - Day 4: 0.6mg/kg subQ
    - Overnight, pt febrile to 101.2 with associated hypoxia. SpO2 on room air 88%. Started on 3L NC
  - Treated for CRS grade 2 with tocilizumab

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BCMA- Bispecifics: Adverse Effects

Treatment-emergent adverse events, *n* (%)	*n*=123	
	Any grade	Grade 3 or 4
Any treatment-emergent adverse event	123 (100)	87 (70.7)
Hematologic[a]		
Anemia	60 (48.8)	46 (37.4)
Neutropenia	60 (48.8)	60 (48.8)
Thrombocytopenia	38 (30.9)	29 (23.6)
Lymphopenia	33 (26.8)	31 (25.2)
Nonhematologic		
Cytokine release syndrome	71 (57.7)	0
Diarrhea	52 (42.3)	2 (1.6)
Fatigue	45 (36.6)	4 (3.3)
Decreased appetite	41 (33.3)	1 (0.8)
Pyrexia	37 (30.1)	5 (4.1)
COVID-19 related[b]	36 (29.3)[c]	19 (15.4)
Injection site reaction	33 (26.8)	0
Nausea	33 (26.8)	0
Hypokalemia	32 (26.0)	13 (10.6)
Cough	31 (25.2)	0
Headache	29 (23.6)	0

Table 2. Adverse Events in 165 Patients (Safety Population).*

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

Lesokhin et al, *Nat Med,* 2023;
Moreau et al, *NEJM* 2022

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GPRC5D Bispecific Toxicity (talquetamab)

Table 2. Adverse Events.*

Event	Subcutaneous Talquetamab, 405 μg Weekly (N=30)		Subcutaneous Talquetamab, 800 μg Every 2 Wk (N=44)		Intravenous Talquetamab, All Doses (N=102)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)					
Any adverse event	30 (100)	26 (87)	44 (100)	38 (86)	102 (100)	92 (90)
Hematologic event						
Anemia	18 (60)	9 (30)	19 (43)	10 (23)	59 (58)	34 (33)
Neutropenia	20 (67)	18 (60)	16 (36)	14 (32)	48 (47)	27 (26)
Lymphopenia	12 (40)	12 (40)	17 (39)	17 (39)	53 (52)	48 (47)
Thrombocytopenia	11 (37)	7 (23)	10 (23)	5 (11)	36 (35)	13 (13)
Leukopenia	12 (40)	9 (30)	8 (18)	6 (14)	38 (37)	16 (16)
Nonhematologic event						
Cytokine release syndrome	23 (77)	1 (3)	35 (80)	0	50 (49)	5 (5)
Skin-related event†	20 (67)	0	31 (70)	1 (2)	24 (24)	0
Dysgeusia	19 (63)	NA	25 (57)	NA	38 (37)	NA
Fatigue	10 (33)	1 (3)	12 (27)	0	37 (36)	1 (1)
Nail-related event‡	17 (57)	0	12 (27)	1 (2)	20 (20)	0
Pyrexia	10 (33)	0	8 (18)	0	32 (31)	0
Headache	6 (20)	0	11 (25)	0	35 (34)	2 (2)
Rash-related event§	14 (47)	0	13 (30)	7 (16)	15 (15)	1 (1)
Diarrhea	9 (30)	0	7 (16)	0	29 (28)	4 (4)
Cough	6 (20)	0	5 (11)	0	36 (35)	0
Dry mouth	9 (30)	0	25 (57)	0	7 (7)	0
Nausea	9 (30)	0	7 (16)	0	23 (23)	0
Arthralgia	7 (23)	0	4 (9)	0	33 (32)	3 (3)
Decreased weight	9 (30)	0	14 (32)	1 (2)	12 (12)	0
Increased alanine aminotransferase	6 (20)	1 (3)	13 (30)	3 (7)	13 (13)	2 (2)
Increased aspartate aminotransferase	3 (10)	0	15 (34)	3 (7)	14 (14)	2 (2)
Back pain	3 (10)	0	9 (20)	0	22 (22)	1 (1)
Hypophosphatemia	8 (27)	5 (17)	8 (18)	3 (7)	19 (19)	14 (14)
Dysphagia	11 (37)	0	12 (27)	0	5 (5)	0
Decreased appetite	6 (20)	1 (3)	9 (20)	0	15 (15)	1 (1)
Constipation	2 (7)	0	6 (14)	0	18 (18)	2 (2)
Increased γ-glutamyltransferase	6 (20)	1 (3)	10 (23)	3 (7)	14 (14)	3 (3)

Chari et al; *NEJM,* 2022

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Grading CRS

Table2. ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Lee et al. *Biol Blood Marrow Transplant*. 2019

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Management of CRS "By the Book"

Grade	Supportive Care + Intervention
1	Withhold until CRS resolution and administer pretreatment medications prior to next dose
2	Grade 1 interventions + 48-hr hospitalization following next dose according to institutional and manufacturer guidelines
3	*First grade 3 occurrence with duration ≤48 hr:* grade 2 interventions + ICU/critical care as needed *Recurrent grade 3 or grade 3 with duration >48 hr:* grade 4 interventions
4	Permanently discontinue; provide ICU/critical care as needed

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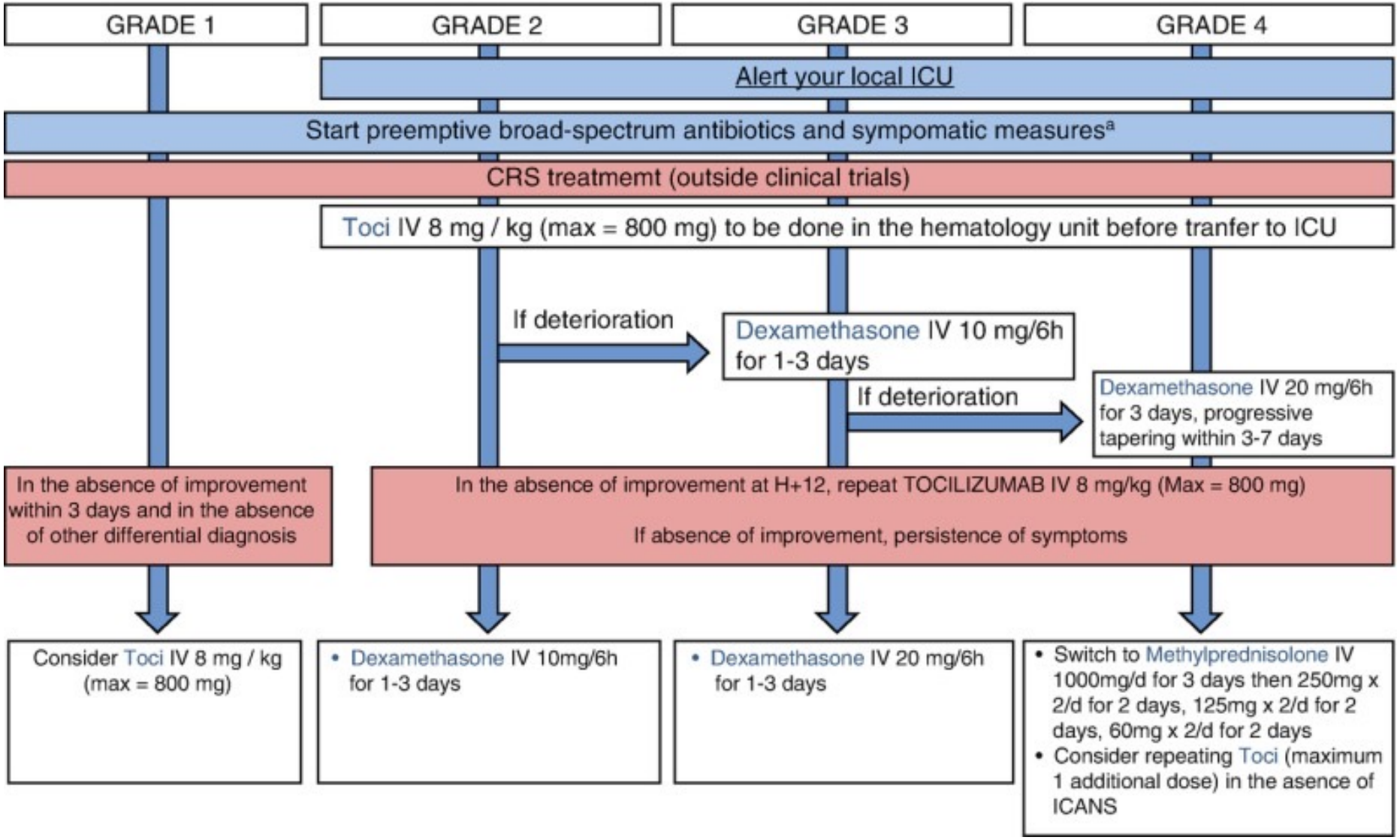
Elranatamab PI. Teclistamab PI.

Managing CRS: Lessons from CAR-T Cell Therapy



Ayuketang et al, 2022

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Our Patient

- Resolution of grade 2 CRS following Tocilizumab.
- Tolerated therapeutic dose on day 7: 0.4mg/kg
- Continued step up on day 9: 0.8 mg/kg
- Developed Dysgeusia after 4th step-up dose
- Discharged following 48 hours of monitoring. No further vital sign aberrations

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Management of Oral and Skin Toxicity on Talquetamab: Dose Modification on MonumenTAL-1

- 24 decreased dose prospectively after achieving a >/= PR
  - 89% of patients maintained a response 6 months after de-escalation
  - Side effects diminished in a minority of patients
    - 25% of oral tox improved
    - 29% of nail bed tox improved
    - 38% of skin tox improved

Management of Oral and Skin Toxicity on Talquetamab: Supportive Care

- **Taste Alteration**
  - Baking soda / salt rinses pre- / post- meals
  - Maintain good oral hygiene
  - If food is bitter or metallic: adding lemon, sweeteners, oil may help
  - If food is bland: salt, sweeteners and lemon may help
- **Oral Pain**
  - Dexamethasone and nystatin rinses
- **Dry mouth**
  - Avoid caffeine and EtOH
  - Push hydration
  - Lemon drops
  - Pilocarpine
- **Meeting with dietician to support with calorie and nutrient dense supplements, and focus on smaller, frequent meals**
- **Skin toxicity:**
  - Heavy moisturizers on hands and feet wearing gloves and socks at night
  - Topical steroids for rash
  - Sarna for itching
  - Amlactin for skin peeling
- **Nail toxicity:**
  - Frequent moisturizing
  - File to smooth nail edges and keep them short
  - Biotin

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Infections While on Bispecifics

Infection	Teclistamab (MajesTEC-1)	Elranatamab (MagnetisMM-3)	Talquetamab (MonumenTAL-1)
Infections (bacterial, viral, fungal)	76.4%	69.9%	47% (405 g dose Q week) 34% (800 g dose Q 2 week)
Hypogammaglobulinemia (IgG < 500 mg/dL)	74.5%	75.5% (IgG < 400 mg/dL)	87% (405 g dose Q week) 71% (800 g dose Q 2 week)
Grade >3 Neutropenia	64.2%	48.8%	60% (405 g dose Q week) 32% (800 g dose Q 2 week)

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Infection Prophylaxis on Bispecifics

- IVIG: consider supplementation for duration of bispecific administration (we give when IgG <400)
- Levofloxacin: can be considered during first cycle
- Pneumococcal vaccination PRIOR to bispecific
- PJP prophylaxis: Consider during entire duration of treatment (we follow CD4 count, and stop if rises > 200)
- Acyclovir for duration of treatment

Noopur, R., Anderson, K., et al. Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel, Blood Cancer Journal (2023) 13:116 ; https://doi.org/10.1038/s41408-023-00879-7

Neurologic Toxicity

Toxicity	Teclistamab (MajesTEC-1)	Elranatamab (MagnetisMM-3)	Talquetamab (MonumenTAL-1)
ICANS	3%	6%	10%
ICANS Grade 3-4	1%	0%	2%
Neurotoxicity	57%	59%	55%
Sensory Neuropathy	15%	13%	14%
Motor Dysfunction	16%	13%	10%

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Package Insert: Teclistamab, Elranatamab, Talquetamab

Our Patient

02/28/2025: Presented for follow up visit

Date	M-Spike	Immunofix	Kappa	Lambda	Kappa:Lambda	IgA	
1/08/24			.1	.1	1	<10	Post Cilta-cel
4/9/24	ND		<0.1	<0.1	UTC	<10	Post Cilta-Cel
11/18/24			< 0.6	66.69	0.01	65	
2/28/25	0.2g/dL	IgA Lambda	< 0.65	697.37	UTC		At visit

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What Next?

Has now progressed following Cilta-Cel and Talquetamab, next line?

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Elranatamab Post-BCMA

- Pooled analysis of MAGNETISMM-1, 3 and 9
- 86 patients with previous imid, PI, anti-CD38, anti-BCMA
  - 67% ADC
  - 42% CAR-T
  - 9% both
- Short median follow up (10.3 mo)
- Median duration of treatment only 3.3 mo

Nooka et al, ASCO 2023
Nooka et al, IMW 2023

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Elranatamab Post-BCMA

Response	Any Prior BCMA Tx (n = 87)	Prior ADC (n = 59)	Prior CAR T-Cell (n = 36)
ORR, %	46.0	42.4	52.8
Median DoR, mo (95% CI)*	17.1 (9.8-NE)	13.6 (6.8-NE)	NE (9.8-NE)
Median PFS, mo (95% CI)	5.5 (2.2-10.0)	3.9 (1.9-6.6)	10.0 (1.9-NE)
Median OS, mo (95%CI)	12.1 (7.5-NE)	12.1 (6.4-NE)	12.1 (6.5-NE)

Nooka et al, ASCO 2023
Nooka et al, IMW 2023

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Salvage Therapies – Retreatment with BCMA Directed Approaches After CAR-T Relapse

- **Retrospective review of 68 pts with R/R disease after BCMA directed CAR-T**
  - Median 7 prior lines of therapy (1-14)
  - Tripple class refractory 66%
  - Penta-drug refractory 26%
- **34 pts received ≥ 1 line of salvage BCMA directed treatment**
- **Response rates in subsequent LOTs:**
  - BCMA directed CAR-T: 89%
  - BCMA directed BsAbs: 60%

Reyes et al. *Blood Adv*. 2024

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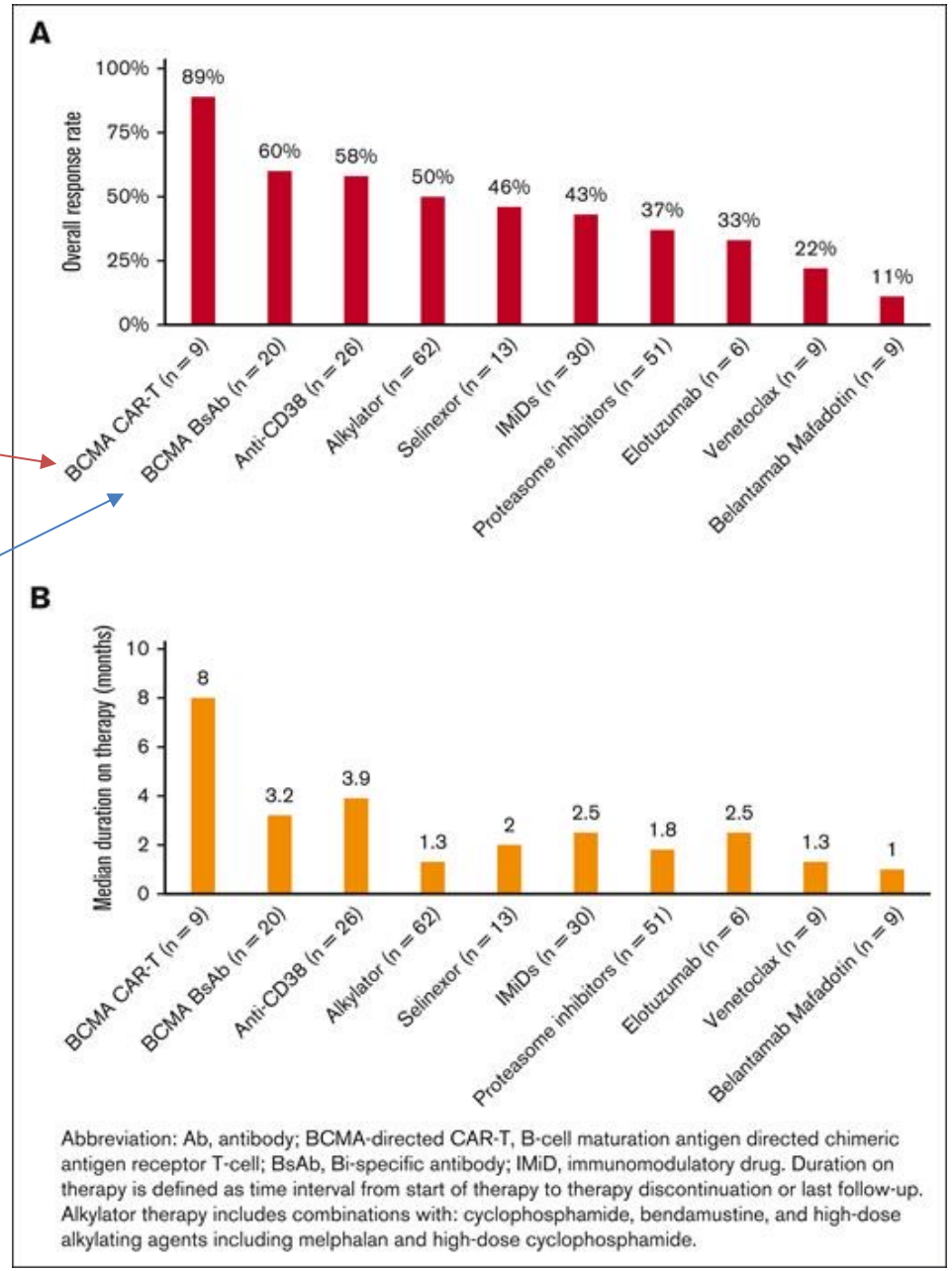
Median time from BCMA CAR-T:
23.8 mo

Median time from BCMA CAR-T:
13.7 mo



Abbreviation: Ab, antibody; BCMA-directed CAR-T, B-cell maturation antigen directed chimeric antigen receptor T-cell; BsAb, Bi-specific antibody; IMiD, immunomodulatory drug. Duration on therapy is defined as time interval from start of therapy to therapy discontinuation or last follow-up. Alkylator therapy includes combinations with: cyclophosphamide, bendamustine, and high-dose alkylating agents including melphalan and high-dose cyclophosphamide.

Reyes et al. *Blood Adv*. 2024

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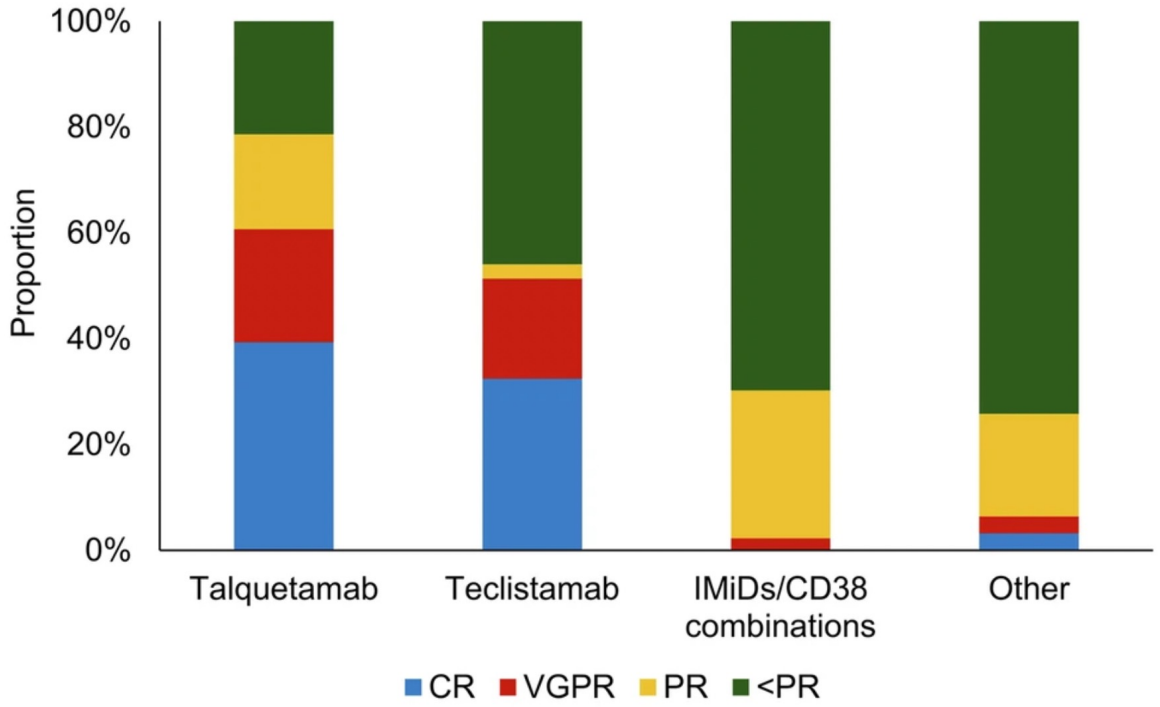
Efficacy of Bispecific Antibodies Targeting BCMA or GPRC5D in Relapsed Myeloma after CAR-T Therapy

- **Analyzed outcomes of post-CAR T-cell therapy relapse in 139 patients**
  - 28 pts received talquetamab
  - 37 received teclistamab
- **ORR and CR:**
  - Talquetamab: 79%; 39%
  - Teclistamab: 64%; 32%



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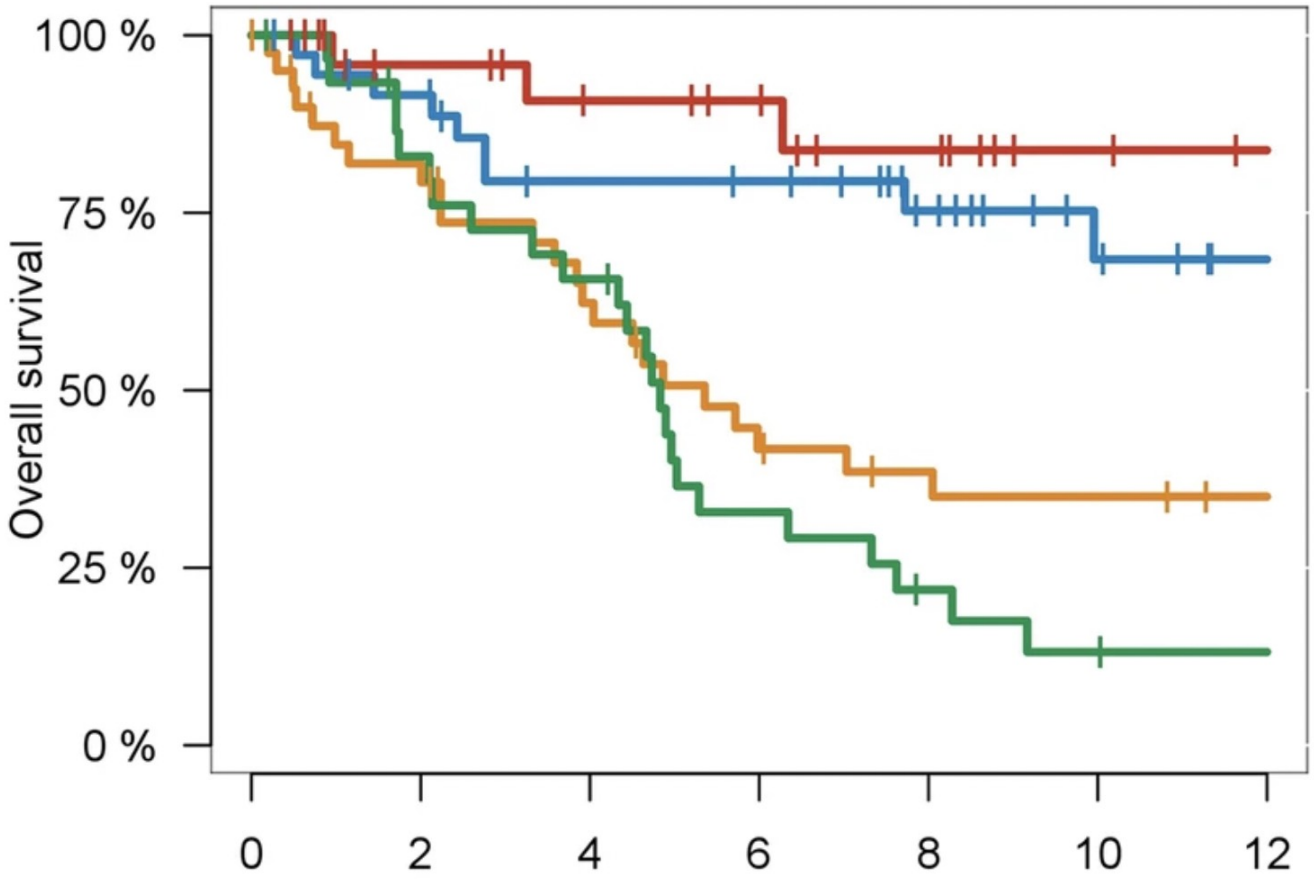
Merz et al. *Blood Cancer J*. 2024



No. at risk							
Talquetamab	28	21	16	14	9	4	2
Teclistamab	37	32	25	24	17	10	6
IMiDs/CD38	43	31	22	14	11	10	8
Other	31	24	19	9	5	3	2

Merz et al. *Blood Cancer J*. 2024

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Our Patient

- **Admitted for step up dosing of teclistamab**
  - Day 1: 0.06mg/kg
  - Day 4: 0.3 mg/kg
  - Day 7: 1.5mg/kg
- **Tolerated without occurrence of CRS**
- **Discharged after 48 hours of monitoring following day 7 therapeutic dose**
- **Continuing teclistamab presently**

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The Future of Bispecifics: Combinations in RR MM

Trial	# of Patients	Treatment Regimen	Response
MajesTEC-2	32	Teclistamab + Daratumumab + Lenalidomide	- In the 0.72mg/kg cohort ORR: 13/13 VGPR: 12/13
MonumenTAL-2	35	Talquetamab + Pomalidomide	ORR: 80%
TRIMM-2	65	Talquetamab + Daratumumab	ORR: 75% CR: 45%; VGPR: 66%
RedireTT-1	63	Teclistamab + Talquetamab	ORR: 84%; CR: 34%

- Ongoing trials: MajesTEC-9, MajesTEC-3, MonumenTAL-6, MagnetisMM-4, MagnetisMM-5, MagnetisMM-20

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Devasia et al., *Blood Cancer J.* 2024

The Future of Bispecifics: In ND MM

Trial	Patient Population	Treatment
MajesTEC-7	ND MM not eligible/intended for upfront ASCT	• Teclistamab + Daratumumab + Lenalidomide vs • Talquetamab + Daratumumab + Lenalidomide vs • Daratumumab-Lenalidomide-Dexamethasone
MagnetisMM-6	ND MM not eligible for ASCT	• Elranatamab + Daratumumab + Lenalidomide vs • Daratumumab + Lenalidomide + Dexamethasone
MajesTEC-2	ND MM based on treatment arm. (Arms A to F)	Arm A – Teclistamab + Daratumumab + Pomalidomide Arm B – Teclistamab + Daratumumab + Lenalidomide + Bortezomib (q21d) Arm C – Teclistamab + Nirogacestat Arm D – Teclistamab + Lenalidomide Arm E – Teclistamab + Daratumumab + Lenalidomide Arm F – Teclistamab + Daratumumab + Lenalidomide + Bortezomib (q28d)
MASTER-2	ND MM post Dara-VRD induction if MRD+	Daratumumab + Teclistamab vs Daratumumab + Lenalidomide consolidation and maintenance
MajesTEC-4	ND MM post ASCT	Teclistamab-Lenalidomide vs Lenalidomide as maintenance post ASCT
MagnetisMM-7	ND MM post ASCT	Elranatamab vs Lenalidomide as maintenance post ASCT

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Devasia et al., *Blood Cancer J.* 2024

MajesTEC-5: Phase 2 Study of Teclistamab-based Induction Regimens in Patients with Transplant Eligible, Newly Diagnosed MM

- **Multi-arm, phase 2 study**
  - A: Weekly teclistamab, daratumumab/ lenalidomide / Dex (Tec-DRd)
  - A1: Monthly teclistamab, daratumumab/ lenalidomide / Dex (Tec-DRd)
  - B: Monthly teclistamab, daratumumab/ bortezomib / lenalidomide / dex (Tec DVRd)
- **Enrolled sequentially (A-> A1+B)**
- **49 enrolled**
  - Of the 36 who had completed 3 cycles, 100% MRD negative at 10e-5
  - 23 patients mobilized stem cells, median yield 8.7 x10e6
- **Toxicity:**
  - Grade 3-4 infections: 26.5%

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Raab et al, ASH 2024, Abs 493

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PUTTING ALL THE PIECES TOGETHER: SUMMARIZING BEST PRACTICES AND PROPOSED SEQUENCING

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