MYELOMA ROUNDS SEATTLE

Thursday, March 20, 2025
6:30pm – 9:00pm

Hyatt Regency Lake Washington
Renton, WA

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 an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

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WELCOMING REMARKS

Andrew J. Cowan, MD
Associate Professor, Clinical Research Division
Clinical Director, Myeloma Service
Fred Hutchinson Cancer Center
Associate Professor of Medicine
Division of Hematology and Oncology
University of Washington School of Medicine
Seattle, WA

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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

After completing this activity, participants will be better able to:

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

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AGENDA

6:30 PM	Dinner and Networking
7:00 PM	Overview of Program and Updates in Treatment *Andrew J. Cowan, MD*
7:10 PM	Overview of LLS Resources, including the Clinical Trial Support Center *Ashley Giacobbi, DNP, RN, ACNS-BS, AOCNS, OCN*
7:20 PM	Smoldering Myeloma: Now Even More Complicated than Before *Rahul Banerjee, MD, FACP and August Chen, MD*
7:50 PM	Extramedullary Disease in Multiple Myeloma *Henry Li, MD and Swathi Namburi, MD*
8:20 PM	Optimizing Unique Toxicities Related to Targeted Therapy *Grace Baek, PharmD, BCOP and Miryoung Kim, PharmD, BCOP*
8:50 PM	Discussion and Wrap-up *All Faculty*
9:00 PM	Conclusion *Andrew J. Cowan, MD*

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ADVISORY GROUP/FACULTY

Andrew J. Cowan, MD (Chair)*
Associate Professor, Clinical Research Division
Clinical Director, Myeloma Service
Fred Hutchinson Cancer Center
Associate Professor of Medicine
Division of Hematology and Oncology
University of Washington School of Medicine
Seattle, WA

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Clinical Hematology Pharmacist
Fred Hutchinson Cancer Center
Seattle, WA

Rahul Banerjee, MD, FACP
Assistant Professor, Clinical Research Division
Fred Hutchinson Cancer Center
Seattle, WA

August Chen, MD
Internal Medicine PGY2
University of Washington School of Medicine
Seattle, WA

Ivan Huang, PharmD, BCOP
Lead Clinical Pharmacist, Hematology
Fred Hutchinson Cancer Center
University of Washington School of Medicine
Seattle, WA

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Senior Clinical Trial Nurse Navigator
The Leukemia & Lymphoma Society
Washington, D.C.

Mohammed Kanaan, MD
Medical Oncologist/ Hematologist
Northwest Medical Specialties
Tacoma, WA

Miryoung Kim, PharmD, BCOP
Clinical Hematology Pharmacist
Fred Hutchinson Cancer Center
Seattle, WA

Henry Li, MD
Medical Oncologist
Optum Washington
Seattle, WA

Swathi Namburi, MD*
Hematologist
Swedish Cancer Institute
Seattle, WA

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**** Advisory Group and Faculty***

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ADVISORY GROUP & FACULTY DISCLOSURES

*Andrew J. Cowan, MD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Adaptive, Bristol Myers Squibb, HopeAI, Janssen, Pfizer, Sanofi, Sebia
Research Funding: AbbVie, Adaptive, Bristol Myers Squibb, Caelum, Celgene, Harpoon, IGM, Johnson & Johnson, Karyopharm, Nektar, Opna Bio, Regeneron, Sanofi
Other: Stocks: HopeAI

Ivan Huang, PharmD, BCOP, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Mohammad Kanaan, MD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Tempus (part-time consultant for clinical trial review)

*Swathi Namburi, MD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor (all have ended in 2024): GlaxoSmithKline, Janssen, Sanofi

Grace Baek, PharmD, BCOP, has a financial interest/relationship or affiliation in the form of:
Other: CE speaker for Postgraduate Healthcare Education LLC (talk was supported by grant from Bristol Myers Squibb). Postgrad Healthcare Edu (ended June 2024).

Rahul Banerjee, MD, FACP, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Adaptive Biotech, Bristol Myers Squibb, Caribou Biosciences, Genentech/Roche, Gilead/Kite, GlaxoSmithKline, Johnson & Johnson, Karyopharm, Legend Biotech, Pfizer, Poseida Therapeutics, Sanofi, SparkCures
Research Funding: AbbVie, Bristol Myers Squibb, Johnson & Johnson, Novartis, Pack Health, Prothena, Sanofi

August Chen, MD, 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.

Miryoung Kim, PharmD, BCOP, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

** Part of the faculty and advisory board.*
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Disclosure & Conflict of Interest Policy
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Planning Committee and Content/Peer Reviewers
The planners and content/peer reviewers from Medical Learning Institute Inc and The Leukemia & Lymphoma Society do not have any relevant financial relationships to disclose with ineligible companies unless listed below.

Lauren Berger, MPH, has a financial interest/relationship or affiliation in the form of:
Stock Ownership with Bristol Myers Squibb, Gilead Sciences, Inc., Merck & Co., Inc., Organon & Co., Pfizer Inc., and Viatris Inc.

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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 2.0 *AMA PRA Category 1 Credits*™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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 2.0 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 2.0 continuing education contact hours through the California Board of Registered Nursing.

Pharmacy
Medical Learning Institute Inc designates this application-based continuing education activity for 2.0 contact hours (0.2 CEUs) of the Accreditation Council for Pharmacy Education.
Universal Activity Number: JA0007322-9999-25-010-L01-P

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/

Interprofessional Continuing Education Credit
This activity was planned by and for the healthcare team, and learners will receive 2.0 Interprofessional Continuing Education (IPCE) credits for learning and change.

IPCE CREDIT™

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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 and 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 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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Clinical Research Updates at FHCC and SCI

Andrew Cowan, MD

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Providence SWEDISH Cancer Institute

Multiple Myeloma and AL Amyloidosis Clinical Trials

First Hill, Seattle (all phase 1, CAR-T)

Issaquah, WA

Edmonds, WA

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MM Trials Currently Open at Providence Swedish

iMMagine-3 Phase 3 Cellular Therapy RRMM 1 to 3 prior lines NCT06413498	Phase 3, randomized, open-label: anitocabtagene autoleucel versus investigator's choice from 4 SOCT options in participants with RRMM who have received 1 to 3 prior lines of therapy including an IMiD and an anti-CD38 mAb.
MonumenTAL-6 Phase 3 Bi-specific RRMM 1 to 4 prior lines NCT06208150	A Phase 3 Randomized Study Comparing Talquetamab in Combination with Pomalidomide (Tal-P), Talquetamab in Combination with Teclistamab (Tal-Tec), and Investigator's Choice of Either Elotuzumab, Pomalidomide, and Dexamethasone (EPd) or Pomalidomide, Bortezomib, and Dexamethasone (PVd) in Participants with Relapsed or Refractory Myeloma who Have Received 1 to 4 Prior Lines of Therapy Including an Anti-CD38 Antibody and Lenalidomide
BMS-986453 Phase 1 Cellular Therapy RRMM 3+ prior lines NCT06153251	Phase 1, Open-Label, Dose-Finding Study of BMS-986453, Dual Targeting BCMA x GPRC5D Chimeric Antigen Receptor T Cells, in Participants with Relapsed and/or Refractory Multiple Myeloma
NXC-201 CAR-T Phase 1b/2 Cellular Therapy R/R Amyloidosis NCT06097832	Open-label phase 1b dose expansion study exploring the safety and efficacy of NXC-201 in a population of relapsed or refractory AL amyloidosis (AL).

Providence SWEDISH Cancer Institute

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MM Trials Currently Open at Providence Swedish

A062102 Phase 2 Alliance Trial Post Ide-cel Iberomide maintenance NCT06179888	Randomized Phase 2 Study of Iberdomide Maintenance Therapy Following Idecabtagene Vicleucel CAR-T in Multiple Myeloma Patients
S2209 Phase 3 SWOG NDMM NCT05561387	This phase III trial compares three-drug induction regimens followed by double-or single-drug maintenance therapy for the treatment of newly diagnosed multiple myeloma in patients who are not receiving a stem cell transplant and are considered frail or intermediate-fit based on age, comorbidities, and functional status.
AZD0120 Phase 1b/2 Cellular Therapy RRMM 3+ prior lines NCT05850234 Opening Soon	A Phase 1b/2 Study of GC012F (AZD0120), a Chimeric Antigen Receptor T-cell (CAR T) Therapy Targeting CD19 and B-cell Maturation Antigen (BCMA) in Subjects With Relapsed/Refractory Multiple Myeloma

Providence SWEDISH Cancer Institute

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FHCC Myeloma Faculty

Core faculty

- Rahul Banerjee (CS)
- Andrew Cowan (CS)
- Kara Cicero (CC)
- Mary Kwok (CC)
- Danai Dima (CS)
- Andrew Portuguese (CS)
- Soon… Madhav Dhodapkar (PS)

Affiliated faculty

- Leona Holmberg
- Kate Markey
- Chris Su

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Opened Recently

- CARTITUDE-6
- ABBV383b Amyloidosis trial
- MRD-Guided Sequential Therapy for Deep Response in Newly Diagnosed Multiple Myeloma (RG1124347)
- Monumental-6
- GPRC5D CAR T Phase 2 (Arlo-Cel)
- IMMAGINE-3 trial – Anito-cel vs SOC

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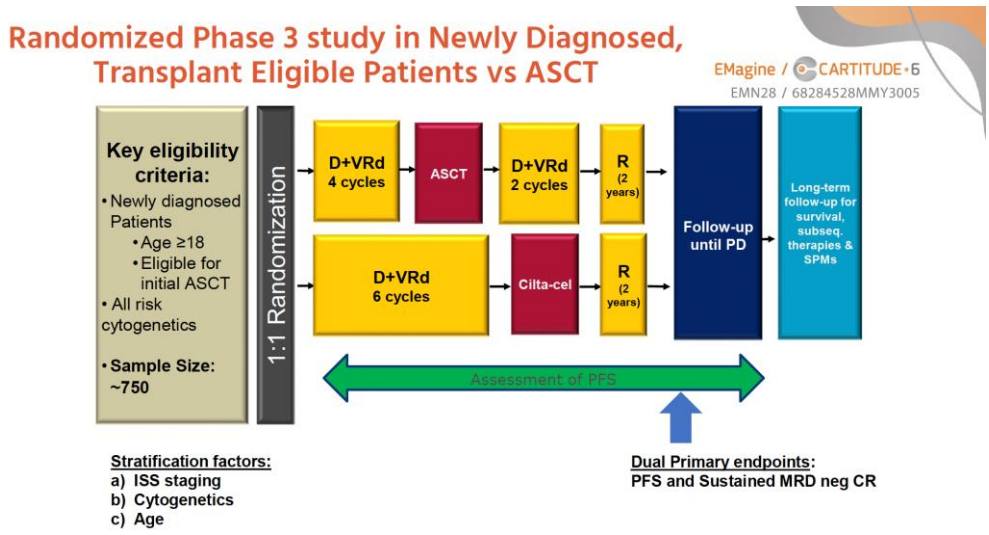
CARTITUDE-6 – LPI 10/31/2025



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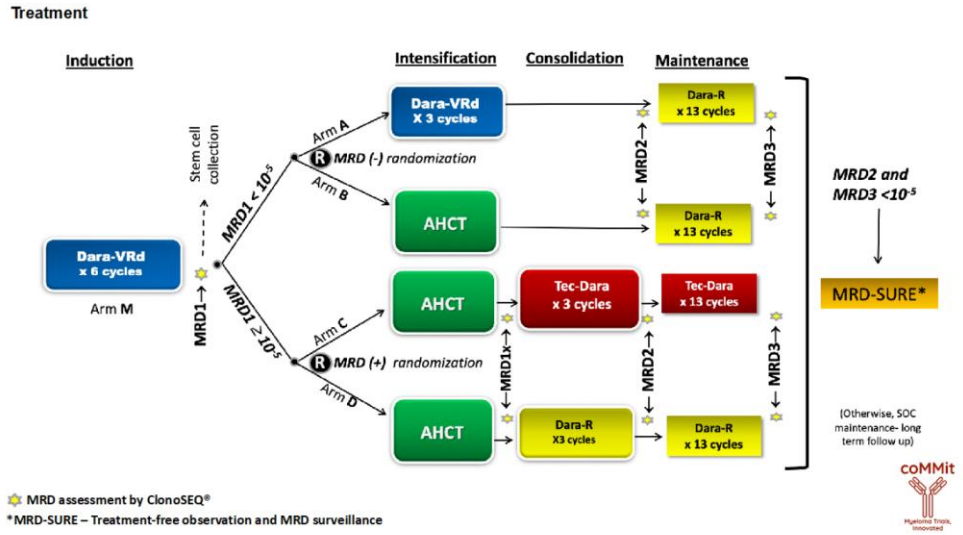
MASTER-2 Schema



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MASTER 2: Eligibility

- Inclusion
  - Newly diagnosed MM
  - ECOG 0 – 2
  - No prior MM-directed therapy except for dexamethasone (up to 160 mg) and/or bortezomib (up to 5.2 mg/m2) and/or cyclophosphamide up to 1000 mg/m2 and/or lenalidomide (up to 21 days of therapy) and/or daratumumab (no more than 4 doses) administered for a duration of time not longer than 4 weeks (pre induction). If subject received any prior therapy, pretreatment parameters necessary for disease characterization and response assessment must be available.
  - Measurable disease

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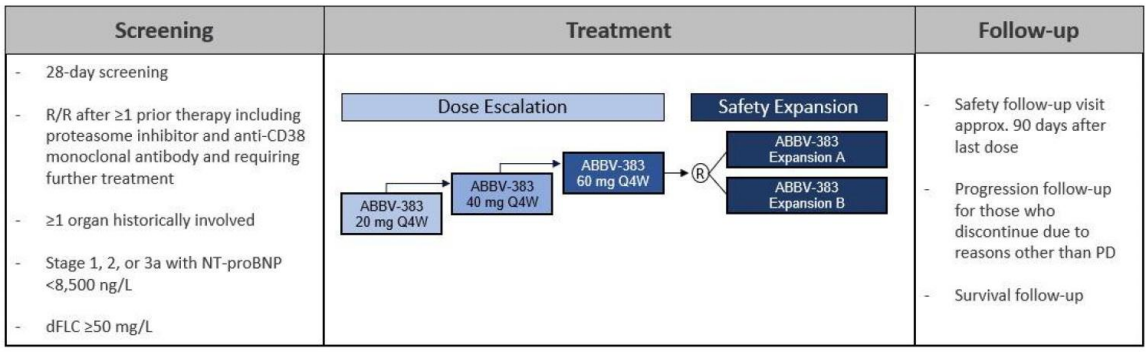
ABB383b in AL Amyloidosis: M24-209

Figure 1. Study Schematic



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Non-Cellular Therapy Trials for R/R MM

- OpnaBio EP300 inhibitor – phase 1 trial
- Selinexor: Selinexor, Mezigdomide, and Dexamethasone phase 1 of STOMP study

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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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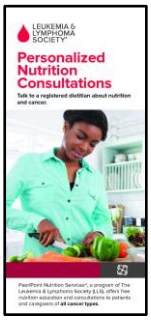
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **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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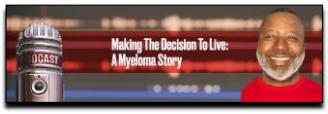
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- ❑ 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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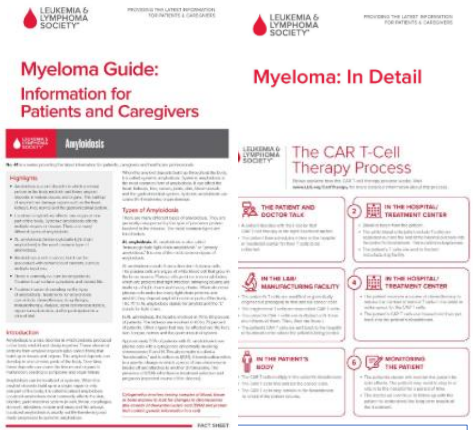
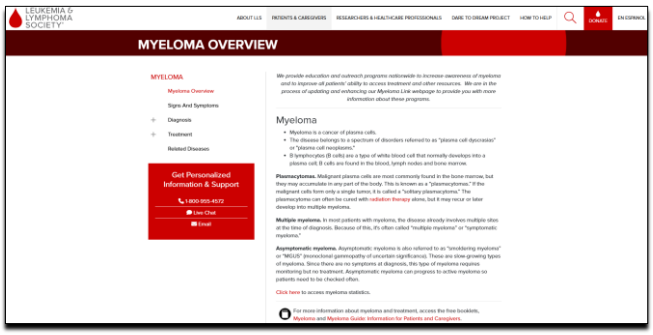
FREE LLS RESOURCES PATIENTS AND CAREGIVERS



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

Leah Szumita
MS, RN, ACNS-BC
Director, CTSC

Kelly Laschinger
CPNP, MSN, RN, CPHON
Manager, CTSC

Melissa Komlosi Melendez
MSN, RN, CPNP
Senior Clinical Trial Nurse Navigator

Ashley Giacobbi
DNP, RN, ACNS-BC, AOCNS, OCN
Senior Clinical Trial Nurse Navigator

Beth Davison
MSN, APRN, CNM, FAACM
Clinical Trial Nurse Navigator

Christen Hawthorne
RN, BSN, BMT-CN
Clinical Trial Nurse Navigator

Kelly Stackhouse
BSN, RN
Clinical Trial Nurse Navigator

Whitney Meeks
MSN, RN, CHPN, CNL
Clinical Trial Nurse Navigator

Sloane Cammock
MSN, RN, CPNP
Clinical Trial Nurse Navigator

Elise Curry
BA, BSN, RN, OCN
Clinical Trial Nurse Navigator

Meghan McGrath
MSN, RN, AGACNP-BC
Clinical Trial Nurse Navigator

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

Michelle Bibo
CTSC Operations Specialist

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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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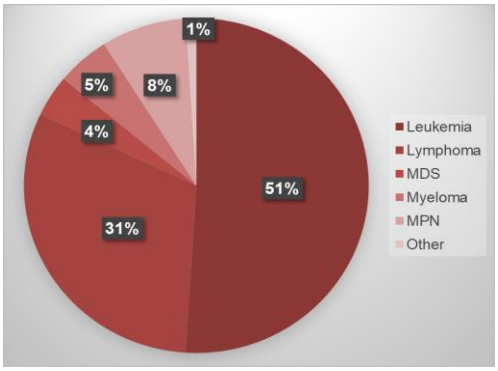
CTSC PATIENT OUTCOMES

- 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

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



Disease Category Breakdown of Patients That Entered Into A Clinical Trial

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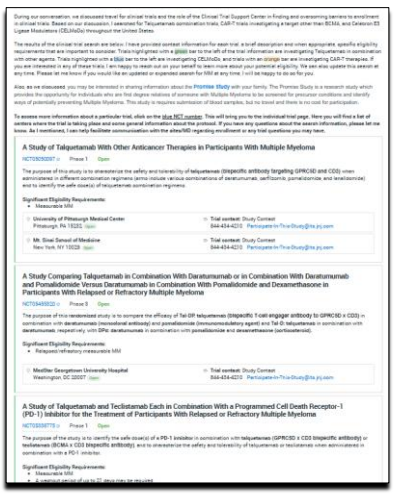
CLINICAL TRIAL SUPPORT CENTER CASE STUDY

- 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**



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CLINICAL TRIAL SUPPORT CENTER CASE STUDY

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  - 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,

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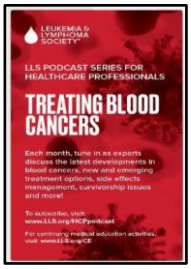
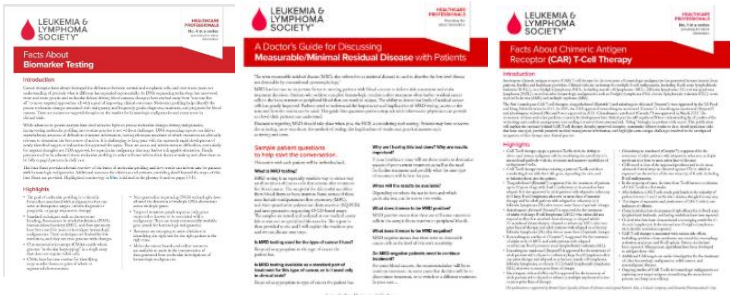
FREE LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

- ❑ 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.

LEUKEMIA & LYMPHOMA SOCIETY®

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Fred Hutch Cancer Center

Smoldering Myeloma: Case Presentation

August Chen, MD
Internal Medicine PGY2
University of Washington

LLS Myeloma Rounds
March 20, 2025

UW Medicine

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Case Presentation

June - July 2023

- 64 year-old female who presented after found to have elevated total protein on routine labs

- Workup:
  - CBC: Hgb 12.2, WBC 6.2, platelets 294
  - Creatinine 1.18 with EGFR 52
  - Calcium 10.4
  - Total Protein 9.9
  - SPEP with M protein 3.2 g/dL (IgG lambda)
  - Lambda free light chains 523.6 mg/L with K/L ratio of 0.02
  - wbMRI: negative
  - BM biopsy: 40% lambda-restricted PCs
  - FISH: standard risk

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Case Presentation

- Family History: Mother diagnosed with multiple myeloma at age 66 and passed away with myeloma
  - Many lytic lesions at baseline

September 2023
- Established at FHCC SLU

No myeloma defining events
- Imaging was negative, no fractures
- Intermittent mild hypercalcemia, always < 11. Most recent iCal normal at 1.37.
- Determined to have high-risk sMM based on BM biopsy, K/L ratio and M spike

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Case Presentation

- Options discussed:
  - Observation (q3mo labs, annual BMBx, annual wbMRI)
  - SOC lenalidomide
  - DETER-SMM trial of Dara-Rd vs Rd.

- Patient chose DETER-SMM trial

- Complications with insurance
  - Patient is self-pay
  - Waiting until age 65 in December 2023 to go on Medicare
  - Decision made to monitor until then and then start treatment

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Case Presentation

October 2023

- Presented to ED with back pain worse with activity
- MRI L spine: new T12, L2, and L3 cortical bone abnormalities consistent with early acute pathologic fractures
- M spike 6.2 (from 3.2)
- Diagnosed with active MM
- Started on pulse dose steroids
- Emergency Medicaid and started on Dara-VRd

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Case Presentation

Summary

WORKUP	DIAGNOSIS	ESTABLISHED	PATHOLOGIC FRACTURES	PLANNED TREATMENT START
Elevated total proteins found SPEP, Free light chains, wbMRI	BM biopsy and FISH Diagnosed with high-risk sMM	Established at FHCC SLU Discussed treatment options	New T and L spine fractures since June Diagnosed with active MM	Initial plan to go on Medicare and starting DETER-SMM trial
2023 June	2023 July	2023 September	2023 October	2023 December

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Fred Hutch Cancer Center

What Could Have Been Done Differently?

UW Medicine

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Fred Hutch Cancer Center

Smoldering Myeloma: Now Even More Complicated than Before…

Rahul Banerjee, MD, FACP
Assistant Professor, Division of Hematology & Oncology
University of Washington / Fred Hutchinson Cancer Center

LLS Myeloma Rounds
March 20, 2025

UW Medicine

@rahulbanerjeemd

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Agenda

- 5 min SMM: what we can agree on
- 5 min SMM: The ‘destroy’ strategy
- 5 min SMM: The ‘deflect’ strategy

Agenda

- **5 min** **SMM: what we can agree on**
- 5 min SMM: The ‘destroy’ strategy
- 5 min SMM: The ‘deflect’ strategy

Smoldering Myeloma (SMM): The Basics

	MGUS	Smoldering MM	MM
Circulating paraprotein	Serum M-spike < 3.0	Doesn't meet criteria for MGUS (left) or for MM (bottom right)	Irrelevant
Bone marrow findings	<10% clonal PCs in bone marrow		Irrelevant
Symptoms	NONE	NONE	**CRAB-SLiM**

- SMM is, by its very existence, a "wastebasket" diagnosis
- MGUS is easy to manage, MM is easy-ish to manage (frontline, at least)… but smoldering, not so much

CRAB-SLiM, hypercalcemia / renal issues / anemia / bone lesions / ≥60% BMPCs / light chain ratio ≥100:1 / MRI focal lesions. PC, plasma cells.

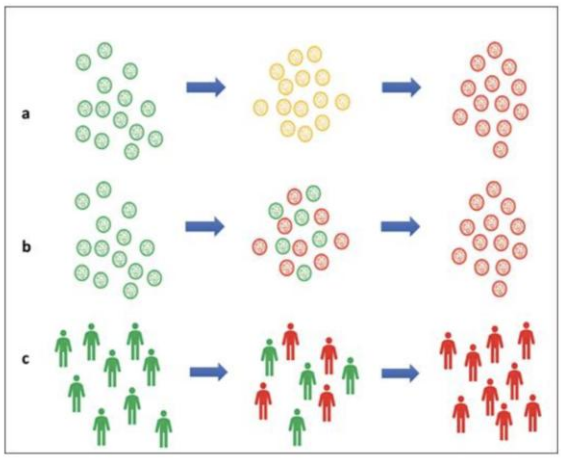
Why is SMM so Difficult to Manage?

Because we don't yet have a handle on what it is genomically... Is it?

a) An 'intermediate' cellular state in terms of disease biology

b) A mixture of true MM cells lurking amongst MGUS cells

c) A mixture of patients, some of whom have 'stage 0' myeloma already and the rest will forever be MGUS



Kumar SK, Rajkumar SV. The Hematologist. 2023. doi: 10.1182/hem.V20.2.202325.

Audience Response Question #1

If you were told that you had an **20%** chance of developing active myeloma in 2 years, would you pursue:

A. Daratumumab (**63**% ORR, **5**% hospitalization risk) now

B. Teclistamab (**100**% ORR, **58**% hospitalization risk) now

C. Observe for now, treat prn as active MM

D. Treat as active MM now

Audience Response Question #2

If you were told that you had an **80%** chance of developing active myeloma in 2 years, would you pursue:

A. Daratumumab (**63**% ORR, **5**% hospitalization risk) now

B. Teclistamab (**100**% ORR, **58**% hospitalization risk) now

C. Observe for now, treat prn as active MM

D. Treat as active MM now

What I Think We Can All Agree On

I made these slides before discussing with all of you, so I hope what I write below is still true…

1. Low-risk SMM does not need to be treated (in the absence of syndromes like AL amyloidosis, of course)
2. High-risk SMM is challenging because there are many factors, including patient preferences & values, to consider
3. SMM treatment paradigms, if pursued, can range widely between the "deflect" and the "destroy" strategies

What Do I Mean By Deflect vs Destroy?

- The more traditional terminology is "control versus curative" in terms of how one might approach SMM therapies


The New York Times

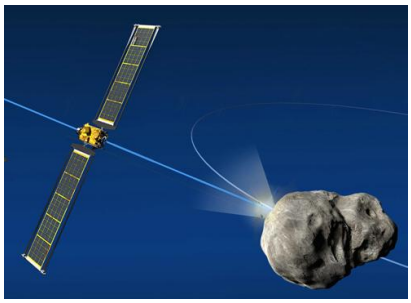
GIVE THE TIMES

Will That Asteroid Strike Earth? Risk Level Rises to Highest Ever Recorded.

The threat from space rock 2024 YR4 has surpassed that of Apophis, an asteroid feared by scientists 20 years ago. The danger remains low, but experts are estimating the damage that could be done.

By Robin George Andrews

Feb. 18, 2025



Agenda

- 5 min SMM: what we can agree on
- **5 min** **SMM: The 'destroy' strategy**
- 10 min SMM: The 'deflect' strategy

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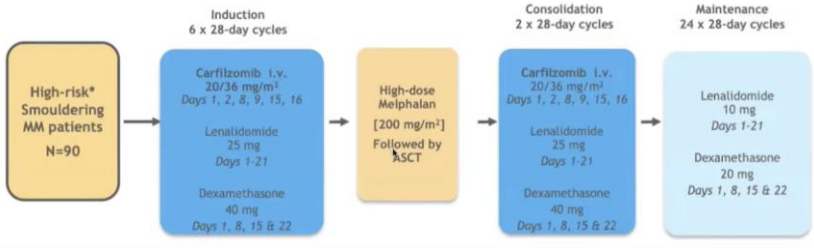
The Goal of the 'Destroy' Strategy

- Completely eliminate all smoldering myeloma cells, i.e. with planned curative intent if done correctly
- Example #1 of a 'destroy' strategy: **GEM-CESAR**



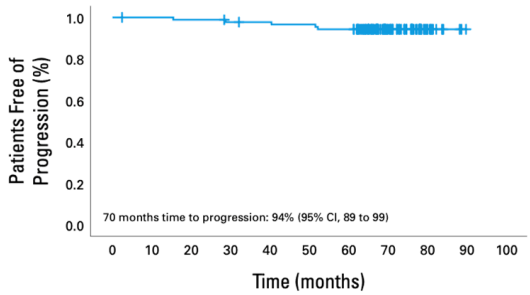
- In brief, what if we treated HR-SMM like active MM?

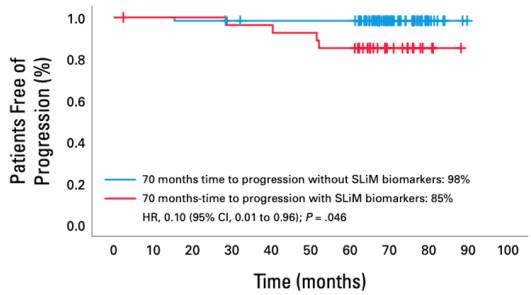
Mateos MV et al. JCO. 2024;42(27):3247-3256. Slides also used from the ASH 2022 presentation for the same study.

@rahulbanerjeemd

GEM-CESAR: The Good News (Efficacy)

- Primary endpoint: MRD negativity (10^{-5} by flow) after ASCT
  - 62% at 3 months after ASCT, 31% at 4 years after ASCT
- Time to CRAB criteria shown below:





Mateos MV et al. JCO. 2024;42(27):3247-3256. Slides also used from the ASH 2022 presentation for the same study.
MRD, measurable residual disease; SLiM, sixty percent plasma cells or light chain ratio > 100:1 (for this study).

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GEM-CESAR: The Bad News (safety)

TABLE 3. Safety Profile Through the Different Phases of the Protocol

Adverse Event (N = 90)	Induction Overall/G3-4, No. (%)	Consolidation Overall/G3-4, No. (%)	Maintenance Overall/G3-4, No. (%)
Hematologic			
Neutropenia	9 (10)/3 (3)	14 (16)/8 (9)	28 (31)/21 (23)
Thrombocytopenia	11 (12)/4 (4)	14 (16)/7 (8)	13 (14)/3 (3)
Anemia	11 (12)/—	8 (9)/—	8 (9)/—
Nonhematologic			
General symptomatology	20 (22)/2 (2)	4 (5)/—	23 (25)/1 (1)
G-I toxicity	19 (21)/2 (2)	5 (6)/—	23 (25)/6 (7)
Skin rash	20 (22)/8 (9)	1 (1)/—	1 (1)/—
Infections	22 (24)/9 (10)[a]	11 (12)/5 (6)	32 (36)/8 (9)
Cardiac events	1 (1)/1 (1)	—/—	1 (1)/—
SPM			3 (4)[b]

Including four deaths that, in my mind, were treatment related: two from SPMs (lung CA and MDS), one from cardiac arrest, and one from an ischemic stroke.

Mateos MV et al. JCO. 2024;42(27):3247-3256. Slides also used from the ASH 2022 presentation for the same study
SPM, second primary malignancy.

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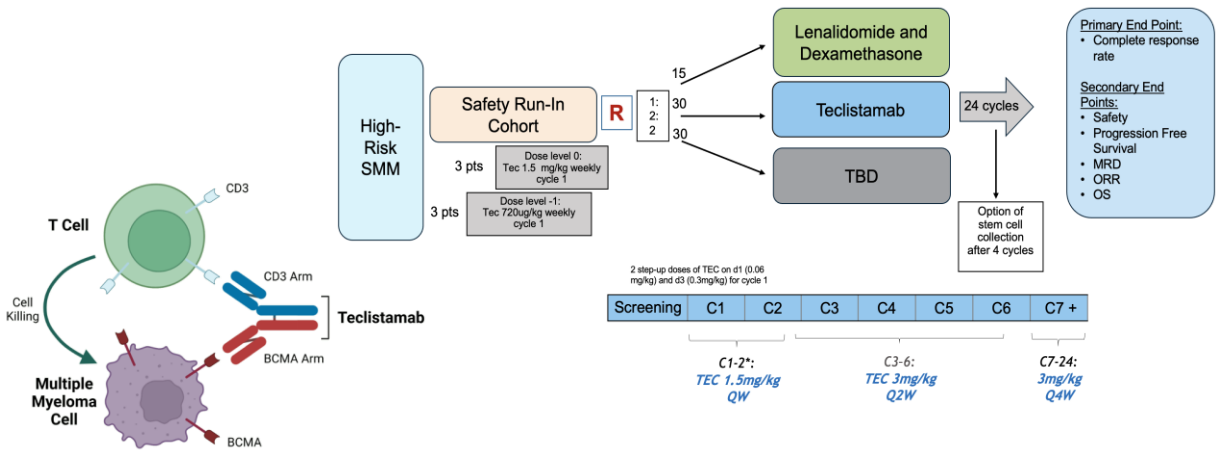
How I Think About GEM-CESAR

- **If you treat SMM like active MM:**
  - Some patients do quite well (e.g., no SLiM criteria)
  - Some patients still have progression to active MM (e.g., those with SLiM criteria despite similar response rates).
  - Some patients do very poorly ☹
- **What if we had more modern tools than KRd and ASCT?**

The ImmunoPRISM Study of Teclistamab



Nadeem et al, ASH 2023.
BMPC, bone marrow plasma cells; FISH, fluorescent *n situ* hybridization; FLC, free light chains; tec, teclistamab.

The ImmunoPRISM Study of Teclistamab

- ***n* = 19 patients for safety run-in**
  - Median BMPC percentage 20% (range: 10-55%)
- **Safety profile (no DLTs noted)**
  - 58% CRS (max Grade 2); tocilizumab in 2 patients
  - No ICANS or other neurotoxicity
  - 58% infections, including 2 Grade 3. IVIG used consistently

	Immuno-PRISM	Majes TEC-1	Tec RWE
Setting	HR-SMM	MM, 3+ LOT	MM, 4+ LOT
ORR	100%	63%	66%
CR rate	83%	39%	29%
MRD-neg 10^{-5} (ITT)	**100%**	27%	N/A

Nadeem O et al, ASH 2023. Moreau P et al, NEJM 2022;387(6):495-505. Dima D et al. 2024;30(3):308.e1-308.e13.
CRS, cytokine release syndrome; DLT, dose-limiting toxicity; LOT, line of therapy.

How I Think About ImmunoPRISM

- If a curative (or Armageddon-style asteroid destruction) approach exists to smoldering MM, this would be it
- Teclistamab works much better in smoldering MM than it does in relapsed/refractory MM:
  - Likely due to better T-cell fitness and less clonal heterogeneity
- However, 58% incidence of any-grade CRS and several Grade 3 infections. This approach comes with real risks.

Can a Milder Strategy Still Do the Trick?

- Several studies are investigating lenalidomide as treatments for high-risk smoldering myeloma
  - QuiRedex study of lenalidomide (2 years) + dexamethasone (6 months), albeit CT/MRI scans to rule out active MM not used
  - ECOG E3A06 study of lenalidomide 25mg 21/28 day cycles (continued until progression) versus observation
  - Ongoing DETER-SMM trial (enrolling at Fred Hutch) comparing Dara-Rd versus Rd for up to 2 years

Mateos MV et al, Lancet Oncol. 2016;17(8):P112-1136.
Lonial S et al. JCO. 2019;38(11):1126-1137.

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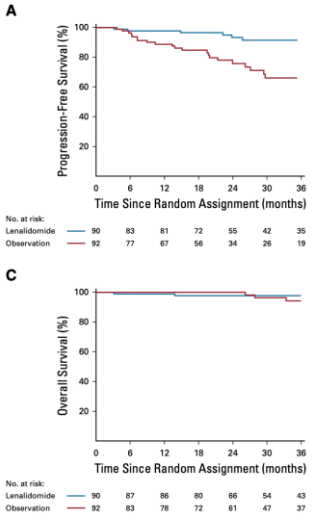
ECOG Trial of Lenalidomide in SMM

- **50% ORR, including 4.5% VGPR rate**
  - Median time to response 5 months (range 1-23)
  - No patients achieved CR. MRD not mentioned
- **Significantly better PFS**
  - 3-year PFS: 91% len versus 66% observation
  - PFS benefit in many subgroups, including Mayo high-risk (HR 0.09, 95% CI 0.02-0.44)



Lonial S et al. JCO. 2019;38(11):1126-1137.

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Agenda

- 5 min SMM: what we can agree on
- 5 min SMM: The ‘destroy’ strategy
- **5 min** **SMM: The ‘deflect’ strategy**

So Why is Len Rarely Used for SMM?

- **Safety data from ECOG trial:**
  - 25% of Ph3 treated patients (18/73) discontinued treatment for AEs
  - In single-arm Ph2 run-in, 5% (2/44) fatal AEs including PE
- **Real-life considerations about lenalidomide:**
  - Many Grade 1 toxicities: rash, fatigue, arthralgias, and more
  - Difficulties with financial toxicity and stem cell collection
  - SPM risk (5.2% vs 3.5% in trial, but underpowered)

Lonial S et al. JCO. 2019;38(11):1126-1137.
AE, adverse event; PE, pulmonary embolism; Ph2, Phase 2; Ph3, Phase 3; SPM, second primary malignancy.

Is There a Better 'Deflect' Strategy?

The NEW ENGLAND JOURNAL of MEDICINE

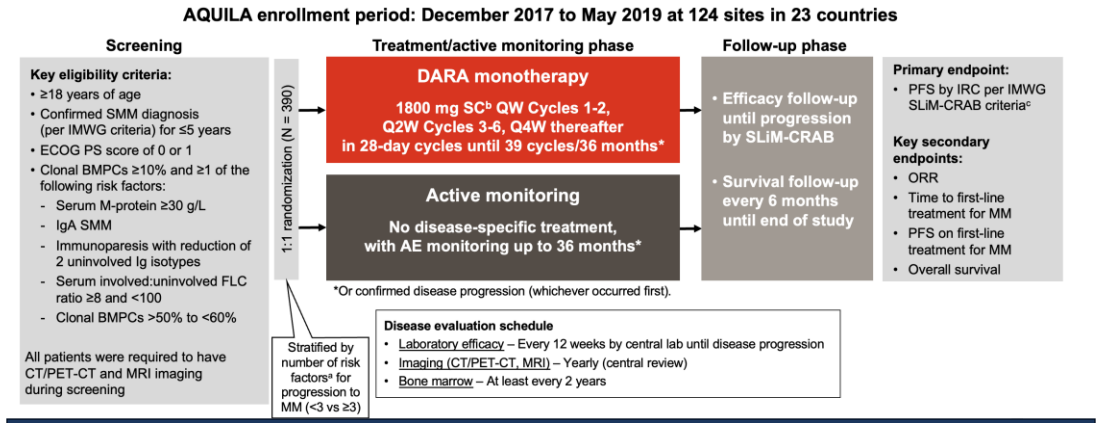
ORIGINAL ARTICLE

Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma

M.A. Dimopoulos, P.M. Voorhees, F. Schjesvold, Y.C. Cohen, V. Hungria, I. Sandhu, J. Lindsay, R.I. Baker, K. Suzuki, H. Kosugi, M.-D. Levin, M. Beksac, K. Stockerl-Goldstein, A. Oriol, G. Mikala, G. Garate, K. Theunissen, I. Spicka, A.K. Mylin, S. Bringhen, K. Uttervall, B. Pula, E. Medvedova, A.J. Cowan, P. Moreau, M.-V. Mateos, H. Goldschmidt, T. Ahmadi, L. Sha, A. Cortoos, E.G. Katz, E. Rousseau, L. Li, R.M. Dennis, R. Carson, and S.V. Rajkumar, for the AQUILA Investigators*

Dimopoulos MA et al, NEJM. 2024. doi: 10.1056/NEJMoa2409029. Online ahead of print.

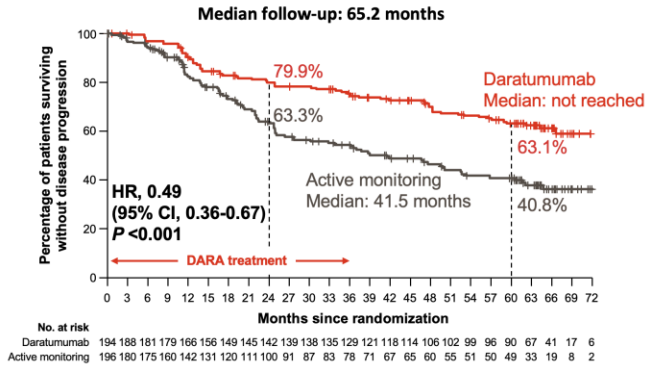
AQUILA Trial Study Design



Note: Only 37% of dara pts and 44% of obs pts were Mayo high-risk.

Dimopoulos MA et al, NEJM. 2024. doi: 10.1056/NEJMoa2409029. Online ahead of print.

AQUILA Trial: Efficacy



	DARA (n = 194)	Active monitoring (n = 196)
PFS event, n (%)	67 (34.5)	99 (50.5)
Death without disease progression	5 (2.6)	5 (2.6)
Disease progression[a]	62 (32.0)	94 (48.0)
CRAB criteria	12 (6.2)	34 (17.3)
Calcium elevation	0	2 (1.0)
Renal insufficiency[b]	0	0
Anemia	2 (1.0)	14 (7.1)
Bone disease	10 (5.2)	18 (9.2)
SLiM criteria	50 (25.8)	65 (33.2)
Clonal BMPCs	5 (2.6)	16 (8.2)
Serum FLC	33 (17.0)	33 (16.8)
Focal lesion by MRI	12 (6.2)	16 (8.2)

ORR 63.4% (9% ≥CR rate) in all-comers. PFS graph above for all-comers.

Dimopoulos MA et al, NEJM. 2024. doi: 10.1056/NEJMoa2409029. Online ahead of print.

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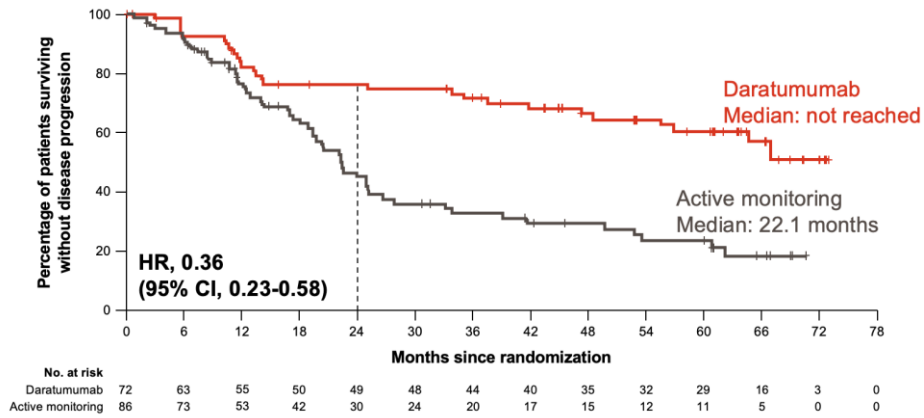
AQUILA Trial: Modernly Defined HR SMM



The trial wasn't powered for this patient population, but a difference emerged.

Dimopoulos MA et al, NEJM. 2024. doi: 10.1056/NEJMoa2409029. Online ahead of print.

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AQUILA Trial: Safety

- Compared to ECOG trial of lenalidomide:
  - ECOG: Most common Grade 3+ AEs were fatigue, neutropenia, and infections
  - ECOG: SPM risk 5.2% in len arm versus 3.5% in trial arm
    - However, median follow-up 35 months in ECOG trial (versus 65 months in AQUILA)

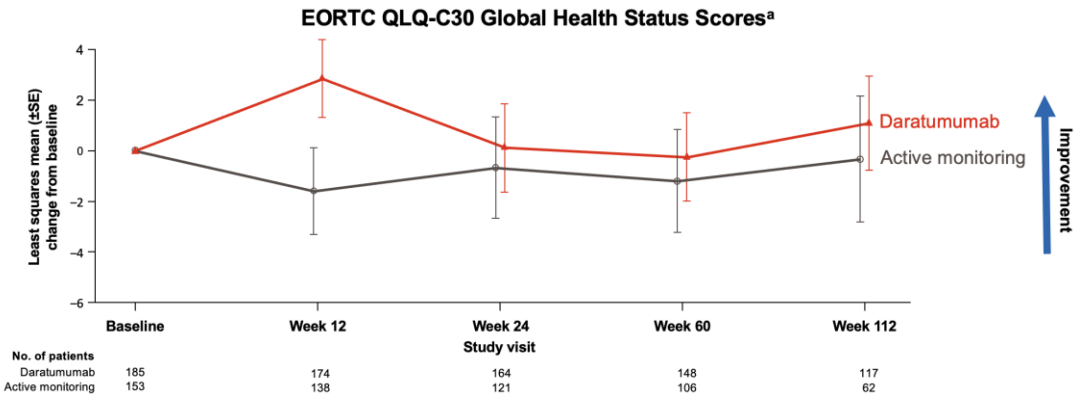
Table 3. Summary of Adverse Events (Safety Population).

Event	Daratumumab (N=193)	Active Monitoring (N=196)
	number of patients (percent)	
Any adverse event	187 (96.9)	162 (82.7)
Most common adverse events*		
Fatigue	66 (34.2)	26 (13.3)
Upper respiratory tract infection	58 (30.1)	15 (7.7)
Diarrhea	53 (27.5)	10 (5.1)
Arthralgia	52 (26.9)	35 (17.9)
Nasopharyngitis	49 (25.4)	23 (11.7)
Back pain	46 (23.8)	38 (19.4)
Insomnia	43 (22.3)	5 (2.6)
Grade 3 or 4 adverse event	78 (40.4)	59 (30.1)
Most common grade 3 or 4 adverse event: hypertension	11 (5.7)	9 (4.6)
Serious adverse event	56 (29.0)	38 (19.4)
Most common serious adverse event: pneumonia	7 (3.6)	1 (0.5)
Adverse event that led to death†	2 (1.0)	4 (2.0)
Second primary cancer	18 (9.3)	20 (10.2)

* Adverse events of any grade that were reported in ≥20% of the patients in either group are listed.
† Adverse events that led to death were coronavirus disease 2019 (Covid-19) and Covid-19 pneumonia in the daratumumab group and pulmonary edema, cardiac arrest, pulmonary embolism, and cardiac failure in the active-monitoring group.

Dimopoulos MA et al, NEJM. 2024. doi: 10.1056/NEJMoa2409029. Online ahead of print.

AQUILA Trial: Patient-Reported Outcomes



Trial not powered for PROs, but this certainly didn't happen with lenalidomide…

Dimopoulos MA et al, NEJM. 2024. doi: 10.1056/NEJMoa2409029. Online ahead of print.

AQUILA Critiques and Rebuttals

Theme	Critique	Rebuttal

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AQUILA Critiques and Rebuttals

Theme	Critique	Rebuttal
PFS events aren't "real" enough	Even the bony lesions detected on imaging were all asymptomatic without fractures.	Good! We should not be waiting for fractures anyways. A new cancer diagnosis is still concerning.

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AQUILA Critiques and Rebuttals

Theme	Critique	Rebuttal
PFS events aren't "real" enough	Even the bony lesions detected on imaging were all asymptomatic without fractures.	Good! We should not be waiting for fractures anyways. A new cancer diagnosis is still concerning.
No crossover in the control arm	Only ~25% patients in the control arm received dara-containing induction for MM.	This isn't standard crossover. It's monthly dara now versus intensive MM induction ± ASCT later.

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AQUILA Critiques and Rebuttals

Theme	Critique	Rebuttal
PFS events aren't "real" enough	Even the bony lesions detected on imaging were all asymptomatic without fractures.	Good! We should not be waiting for fractures anyways. A new cancer diagnosis is still concerning.
No crossover in the control arm	Only ~25% patients in the control arm received dara-containing induction for MM.	This isn't standard crossover. It's monthly dara now versus intensive MM induction ± ASCT later.
Patients are getting "robbed" of dara by giving it early	A third of patients receiving dara still had PD, and we rely on CD38 mAbs in induction so now they'll do poorly.	Many PD events happened >4 years out, meaning ≥12 months since last dara dose. Plus, induction in the year 2030 will look quite different.

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AQUILA Critiques and Rebuttals

Theme	Critique	Rebuttal
PFS events aren't "real" enough	Even the bony lesions detected on imaging were all asymptomatic without fractures.	Good! We should not be waiting for fractures anyways. A new cancer diagnosis is still concerning.
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Patients are getting "robbed" of dara by giving it early	A third of patients receiving dara still had PD, and we rely on CD38 mAbs in induction so now they'll do poorly.	Many PD events happened >4 years out, meaning ≥12 months since last dara dose. Plus, induction in the year 2030 will look quite different.
Insurance	This isn't an FDA-approved indication yet.	… I agree as of March 2025.

@rahulbanerjeemd

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So How Will I Approach SMM in Near Future?

1. **Risk-stratification:**
   - 20/2/20/HR but also "functional HR SMM" with rising biomarkers
2. **Shared decision-making:**
   - Personal values, family history, co-morbidities
3. **Treatment for some patients:**
   - Daratumumab for 3 years as studied in AQUILA
   - BUT only after full MM rule-out, including whole-body MRI!

@rahulbanerjeemd

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Audience Response Question #3 – *Same as Before*

If you were told that you had an **80%** chance of developing active myeloma in 2 years, would you pursue:

A. Daratumumab (**63**% ORR, **5**% hospitalization risk) now

B. Teclistamab (**100**% ORR, **58**% hospitalization risk) now

C. Observe for now, treat prn as active MM

D. Treat as active MM now

@rahulbanerjeemd

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Fred Hutch Cancer Center

Thank You!

"In 2005, a man diagnosed with multiple myeloma asked me if he would be alive to watch his daughter graduate from high school in a few months. In 2009, bound to a wheelchair, he watched his daughter graduate from college. The wheelchair had nothing to do with his cancer. The man had fallen down while coaching his youngest son's baseball team."

– Siddhartha Mukherjee, The Emperor of All Maladies: A Biography of Cancer

UW Medicine

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Extramedullary Multiple Myeloma

Presented by:

Henry Li, MD (Optum Washington)
Swathi Namburi, MD (Swedish Cancer Institute)

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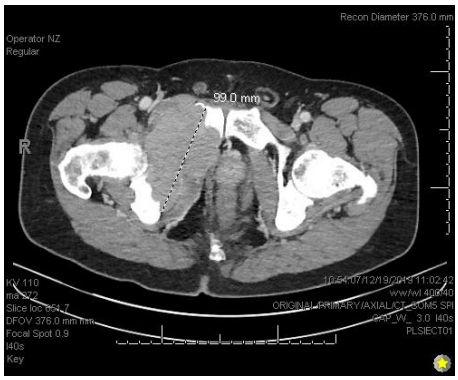
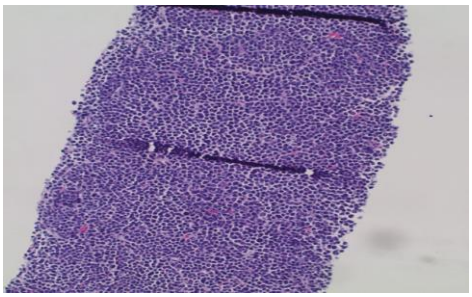
42-year-old Fish Processing Plant Worker Presents with Worsening Right Groin Pain in Fall 2019





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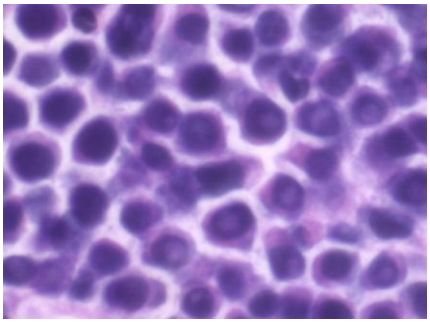
Pubic Ramus Mass 12/2019



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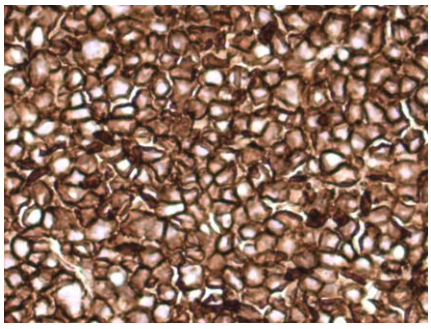

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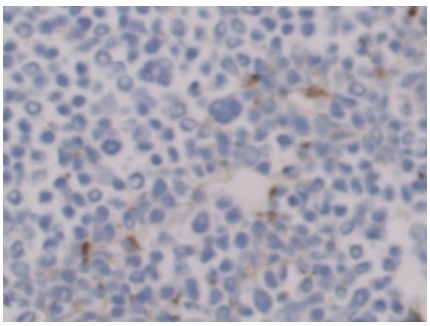
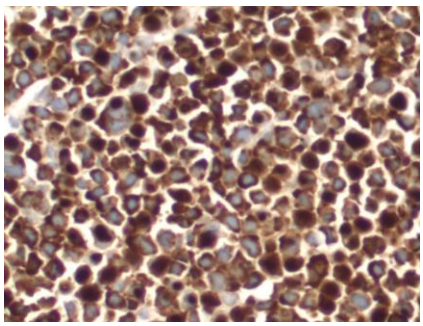
Pubic Ramus Mass 12/2019



Kappa light chain



Lambda light chain

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Pubic Ramus Mass 12/2019

- Multiple myeloma FISH analysis:
  - CDKN2/CKS1B 1p32/1q21 Trisomy/Tetrasomy of 1p and 1q
  - FGFR3/IGH t(4;14)(p16;q32) Gains (Tetrasomy) of 4p and 14q
  - CCND1(BCL1)/IGH t(11;14)(q13;q32) ABNORMAL
  - TP53/D17Z1 17p13/17p11.1-17q11.1 Trisomy/Tetrasomy of 17

- Interpretation: consistent with abnormal cell clone(s) characterized by CCND1/IGH t(11;14) gene rearrangements and gains (or hyperdiploidy) of chromosomes 1, 4p, and 17.

- Serum markers:
  - Serum/Urine protein electrophoresis: no M-spike
  - Serum/Urine free kappa / lambda light chains: normal
  - CBC, metabolic panel: normal

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Bone Marrow Biopsy 01/2020

- Cellularity: 50%
- Plasma cell fraction: 60-70% of cellularity
- Congo red: negative
- Cytogenetics: 46,XY

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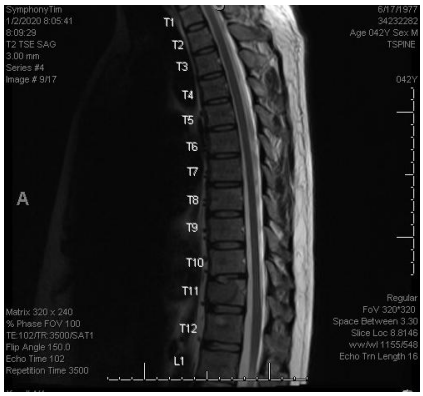
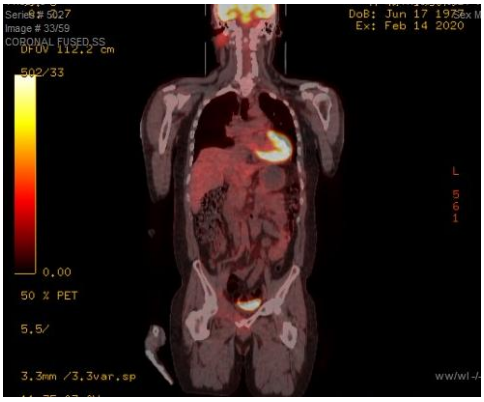
Other Imaging – Jan/Feb 2020

- MRI: Enhancing lesion in the T11 vertebral body at the anterior/mid aspect measuring 3.0 x 2.3 x 1.9 cm
- Note that PET scan was done after 1 cycle of chemotherapy (delay due to insurance)





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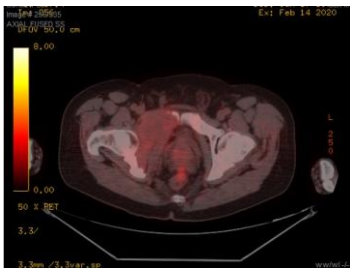
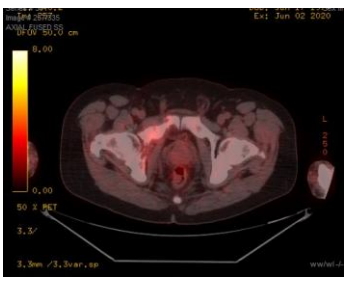
Initial Treatment Course

- First line therapy:
  - 01/2020: Started carfilzomib + dexamethasone + lenalidomide x 5 cycles (KRD) with complete response per bone marrow biopsy and PET.
  - 10/22/2020: Underwent autologous hematopoietic stem cell transplantation.
  - 03/2021: Started maintenance chemotherapy with lenalidomide.
  - 03/2023: Completion of 2-year maintenance course of lenalidomide (10 mg).



February 2020



June 2020

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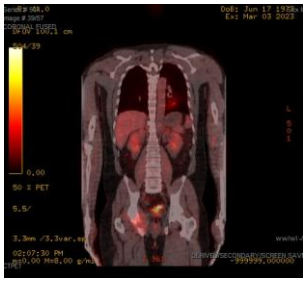
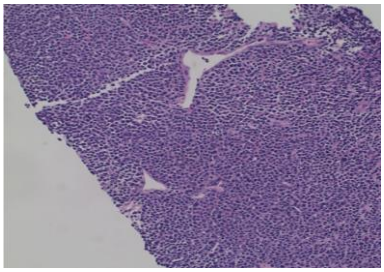
First Relapse - Spring 2023

- Spring 2023: waxing and waning right groin pain
- March 2023: PET scan showed hypermetabolic mass adjacent to the right ischial tuberosity with pathologic fracture through the ischial tuberosity
- May 2023: biopsy of right pelvic bone lesion showed recurrent multiple myeloma





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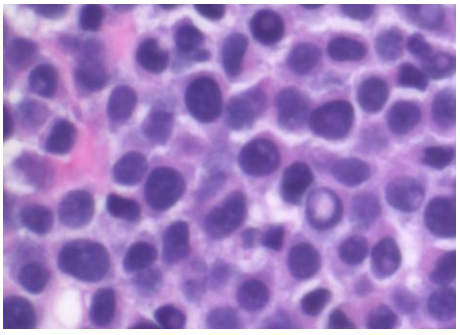
First Relapse - Spring 2023



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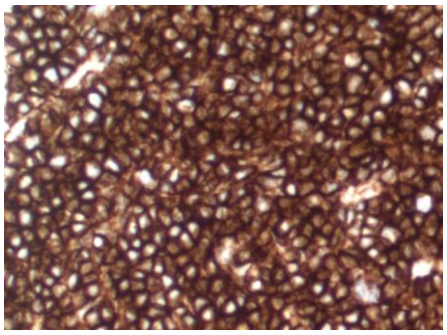

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Second Treatment Course

- Bone marrow biopsy: negative
- SPEP and serum light chains: negative
- June-July 2023: underwent external beam radiation therapy to right pubic ramus
- August 2023: began systemic therapy with daratumumab-hyaluronidase along with zolendrate

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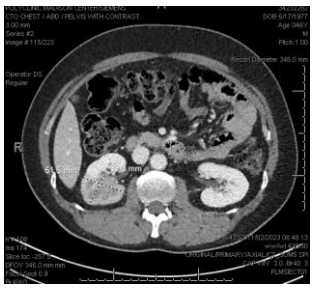
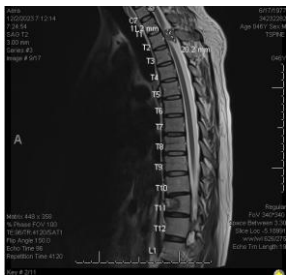
Second Relapse - Autumn 2023

- Late October: pain and numbness in right scapular / axillary region
- Mid-November: numbness in torso and lower extremity along with gait instability. High-dose dexamethasone initiated pending imaging
- 11/02/23: CT notable for right renal mass reported to likely represent infectious etiology.
- 11/30/23: PET negative
- 12/02/23: MRI notable for intradural extramedullary masses in spinal canal at T1,T2, T5-6; largest (20 mm) at T2 with resultant spinal cord compression





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Third Treatment Course

- 12/4/23: started radiation therapy to C7-T7 – 2000 cGy
- 01/2024: started cyclophosphamide and carfilzomib in addition to ongoing dexamethasone
- Initial clinical improvement overall: resolution of radiculopathy, marked improvement in weakness and gait, resolution of anemia

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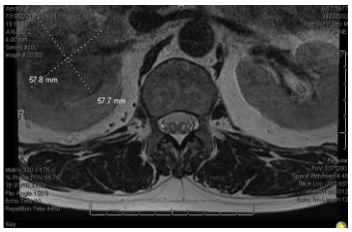
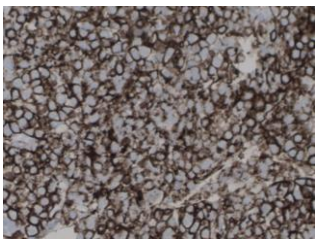
Third Relapse - Summer 2024

- July 2024: restaging spine MRI showed resolution of spinal cord lesions but progression of right renal mass
- August 2024: biopsy of renal mass showed sheets of plasma cells





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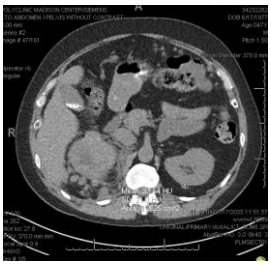
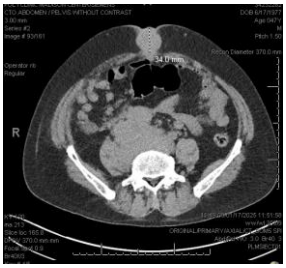
Fourth Treatment Course

- 9/14/24: started venetoclax given presence of t(11;14) translocation at time of initial diagnosis; continued carfilzomib and dexamethasone
- Initial clinical improvement was noted
- January 2025: developed abdominal distention. CT showed marked disease progression





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Extramedullary Disease

Swathi Namburi, MD

Multiple Myeloma and Plasma Cell Dyscrasias

Swedish Cancer Institute, Seattle, WA

LLS Myeloma Rounds, March 20, 2025

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Next Choice: Single Agent Bispecific Antibody Therapy

Teclistamab for R/R Multiple myeloma

- Day 1, 4, 7 step-up, then weekly administration
- CRS occurred in 72% of patients with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%.
- Neurologic toxicity occurred in 57% of patients with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients.
- Infection risk quite high
- ~36% ORR with mDOR 14 mo with EMD

Talquetamab for R/R Multiple myeloma

- Day 1, 4, 7 step-up, then weekly administration
- CRS occurred in 76% of patients, with Grade 1 CRS occurring in 57% of patients, Grade 2 in 17%, and Grade 3 in 1.5%
- Neurologic toxicity, including ICANS, occurred in 55% of patients
- Skin reactions occurred in 62% of patients (Gr 1-2)
- Dysgeusia (70%)
- Nail disorder (50%)
- ~43% ORR with mDOR 8.1 months with EMD

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Points to Review

1. Why is EMD so challenging?
2. Bispecific antibodies: RedirectTT-1
3. CAR-T efficacy in EMD

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EMD: When Blood Cancers Act Like Solid Tumors

- What is EMD vs paramedullary/paraskeletal disease?
- Primary EMD (rare and worse) 7% at diagnosis, young, high-risk translocations, poor OS.
- Secondary EMD - 6-20% at relapse, will become more common.

Clinical entities of EMM reported in the myeloma literature

EMM entities	Definition	Clinical presentation
Bone-related plasmacytomas	Plasmacytomas developed from the bone, arising in continuity with the bone marrow.	Tumor masses affecting the axial skeleton: ribs, vertebrae, skull, sternum, pelvis.
Extramedullary disease	Soft-tissue plasmacytoma or PC infiltration of an anatomical site distant from the bone marrow. Secondary to a hematogenous spread.	Mainly affect the liver, skin, CNS, pleural effusion, kidneys, lymph nodes, pancreas. May be triggered by invasive procedures (ie, catheter insertion, surgical scars).
PCL	Aggressive variant of myeloma characterized by the presence of circulating plasma cells (>20% and/or absolute count >2 × 10^9/L).	Could be considered as EMM because of blood involvement. Extramedullary disease is also very common in PCL patients.
SP	Localized bone or extramedullary infiltration by clonal plasma cells without systemic tumor dissemination.	Bone marrow and skeletal survey are both normal. CRAB symptoms are absent. Focal radiotherapy is the treatment of choice.

Touzeau, C, Moreau, P. *Blood* (2016) 127 (8): 971–976.

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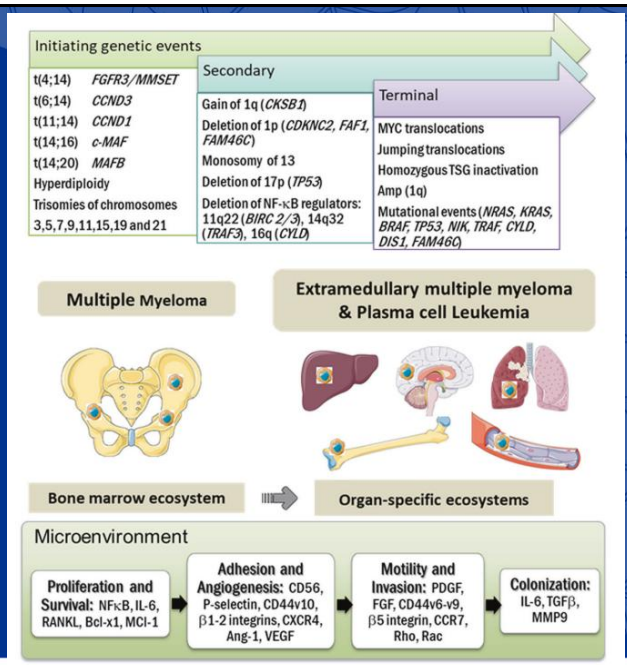
Gradual accumulation of genetic events as the disease transitions to a more aggressive phenotype

Reduced expression of targets: CD38, SLAMF7, GPRC5D, FCRH5



Bhutani, M, etal.Leukemia (2020) 34:1–20

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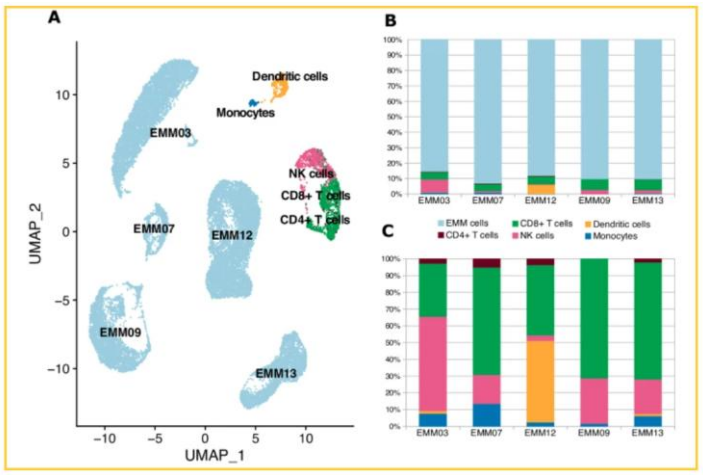
What is in the Tumor Microenvironment?



A UMAP combining cells from five EMM samples. **B** Stacked bar plot describing the composition in whole samples. **C** Bar plot focusing only on immune cells, excluding EMM cells.

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Jelinek, T., Zihala, D., Sevcikova, T. *et al. Leukemia* 38, 1323–1333 (2024).

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Outcomes

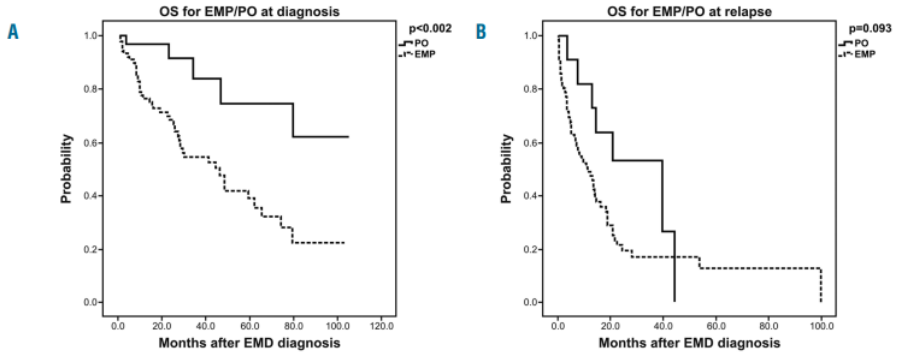

Figure 1. Overall survival (OS) estimates comparing patients with extramedullary plasmacytomas (EMP) to those with paraosseous (PO) lesions (A) at diagnosis and (B) at relapse. EMD: extramedullary disease.

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Beksak, M. et al. Haematologica 2020 Volume 105(1):201-208

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RedirecTT-1 : Teclistamab + Talquetamab

- Phase 1b/2 study, 94 patients treated
- Talquetamab at a dose of 0.8 mg per kilogram of body weight plus teclistamab at a dose of 3.0 mg per kilogram every other week was selected as the recommended phase 2 regimen.
- With the recommended phase 2 regimen, a response occurred in 80% of the patients (including in 61% of those with extramedullary disease)
- 82% chance of continued response at 18 months in responders with EMD
- Grade 3 or 4 AEs 96%
- Grade 3 or 4 Infections 64%

Exposure status — no. (%)		
Triple-class exposure	94 (100)	44 (100)
Penta-drug exposure	61 (65)	28 (64)
Belantamab mafodotin	18 (19)	5 (11)
Bispecific antibody††	7 (7)	2 (5)
CAR T-cell therapy	4 (4)	2 (5)

- Median age 64.5 and 4 prior LOT
- Grade 3 CRS and ICANS <5% of patients

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Cohen, Y.C et al. N Engl J Med 2025;392:138-49.

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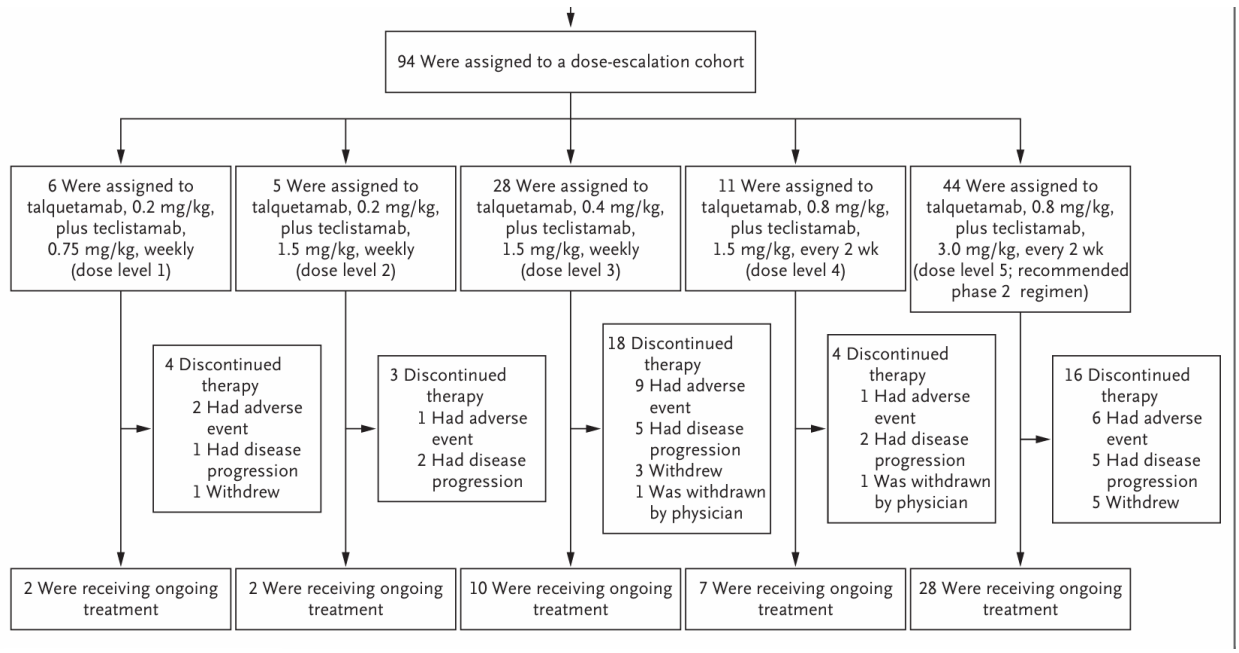

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Cohen, Y.C et al. N Engl J Med 2025;392:138-49.

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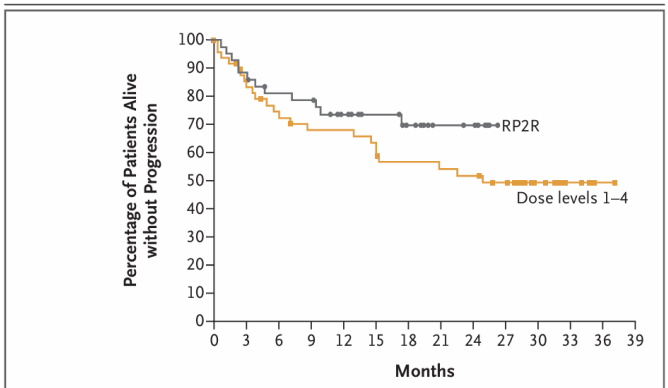

No. at Risk													
RP2R	44	38	33	32	26	20	16	8	7	0	0	0	0	0
Dose levels 1–4	50	39	34	30	30	28	24	23	22	19	10	4	1	0
No. of Events														
RP2R	0	5	8	9	11	11	12	12	12	12	12	12	12	12
Dose levels 1–4	0	8	12	15	15	17	20	21	22	23	23	23	23	23
No. with Censored Data														
RP2R	0	1	3	3	7	13	16	24	25	32	32	32	32	32
Dose levels 1–4	0	3	4	5	5	5	6	6	6	8	17	23	26	27

Figure 3. Kaplan–Meier Analysis of Progression-free Survival.

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Cohen, Y.C et al. N Engl J Med 2025;392:138-49.

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MonumenTAL-2: Talquetamab + Pomalidomide

- Phase 1b
- 35 patients who received pomalidomide 2 mg daily alongside talquetamab at either 0.4 mg/kg once weekly (QW; n=16) or 0.8 mg/kg once every two weeks
- Overall response rates were 93.8% and 84.2% and median times to first response were 1.7 months and 1.2 months, respectively. (Q2W; n=19).
- We may find that iMIDs or CELMoDs be a better partner than additional tumor antigen targets when it comes to immunotherapy.
  - Stimulate T and NK cell activity
  - Enchance Th1 type cytokine production
- Toxicity, especially hematologic toxicity, remains a concern

Providence SWEDISH

Searle E et al. Abstract #MM-349. Presented at the Society of Hematologic Oncology Annual Meeting; September 4-7, 2024; Houston, Texas.

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Future Combination BCMA+GPRC5D Bispecifics

- MonumenTAL-6 – a 3 arm randomized trial in earlier lines.
  - 1 arm including Teclistamab + Talquetamab
  - 1 arm including Talquetamab + Pomalidomide, with monthly dosing long-term and defined duration of therapy
- Trispecific antibody trials: JNJ-79635322.
  - Single arm
  - Randomized against bispecifics

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What About CAR-T Compared with Bispecifics?

- Can CAR-T infiltrate into an unforgiving tumor microenvironment?
- Will the newer CAR-Ts overcome some of these challenges?
- Phase 1 Anito-cel had 36% patients with EMD but specific report out just for this population is not available.
- There are indeed several new CAR-T products that will enter the myeloma space in the future.

Supplementary Table 4. Immune effector therapies in Extramedullary Multiple Myeloma

Parameter	CAR-T	Bispecific antibodies
N	20 (%)	12 (%)
Median Prior Lines of therapy (range)	5 (4-8)	5 (4-8)
Type	idecabtagene vicleucel: 11 ciltacabtagene autoleucel: 4 CC-98633: 3 CT053: 1 ALLO715: 1	TNB383B: 7 REGN5459: 3 GPRC5DxCD3:1 FcRH5xCD3: 1
Response (PR or better)	15/20 (75%)	4/12 (33%)
MRD negative CR CR with MRD positivity VGPR PR SD PD	8 (53%) 2 (13%) 2 (13%) 3 (20%) 1 (7%) 4 (27%)	1 (8%) 0 0 3 (25%) 2 (17%) 6 (50%)
Median PFS (95%CI)	4.9 months (3.1- NR)	2.9 months (2.2-NR)
Site of Progression	Progressed=15	Progressed=10
Systemic + Extramedullary Extramedullary alone Systemic Alone	7 (46%) 4 (27%) 4 (27%)	8 (80%) 1 (10%) 1 (10%)

CAR-T: chimeric antigen receptor-t cell therapy; CR: complete response; MRD: minimal residual disease; PD: progressive disease; PFS: progression free survival; PR: partial response; SD stable disease; VGPR: very good partial response
*two patients received both a CAR-T and Bispecific antibody

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Zanwar S, et al. Am J Hematol. 2023;98(10):1540-1549

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What Can We Do? Are There Any Trials?

- No specific prospective trials for EMD available
- Increasing population of patients with EMD
- Use PET-CT with relapsed disease esp with high risk patients

Other orphaned related conditions:

- Non-secretory disease
- Plasma cell leukemia
- MGRS

- Restrictive clinical trials result in limited data for us to treat patients with challenging subtypes

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Questions / Discussion

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Fred Hutch Cancer Center

Unique Toxicities of Targeted Therapy in Multiple Myeloma

Miryoung Kim, PharmD, BCOP
Grace Baek, PharmD, BCOP

March 20, 2025

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Selinexor

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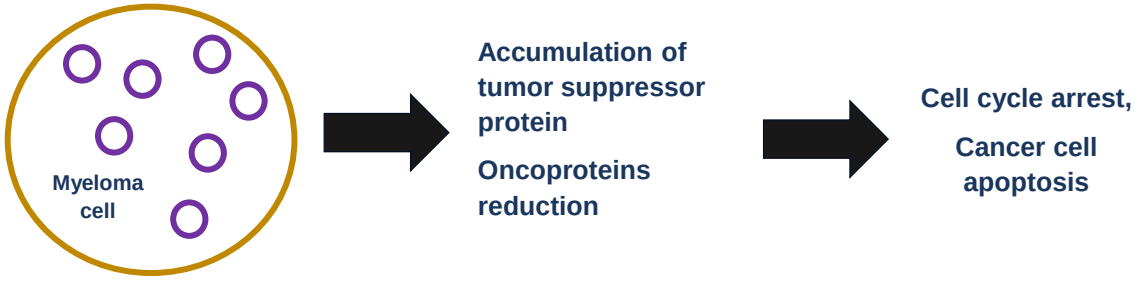
Selinexor Background

- **Indication:** Relapsed or refractory multiple myeloma after 4 prior lines of therapy
  - refractory to 2 proteasome inhibitor, 2 immunomodulatory agent, and anti-CD38 monoclonal antibody – penta-refractory myeloma
- **Mechanism of action:** Oral selective inhibitor of exportin 1 (XPO1)
  - Reversibly inhibits nuclear export of tumor suppressor proteins, growth regulators, and mRNAs of oncogenic proteins by blockage of exportin 1 (XPO1).



XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020—US FDA; Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7
Schiller GJ, et al. Clin Lymphoma Myeloma Leuk. 2023 Sep;23(9):e286-e296; Podar K, et al. Expert Opin Pharmacother. 2020 Mar;21(4):399-408; Gavriatopoulou M, et al. Leukemia. 2020;34(9):2430-2440

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Selinexor Dosing

Trial	STORM	BOSTON	STOMP		
Regimen	Sd 28-day cycle	SVd 35-day cycle	SPd 28-day cycle	SKd 28-day cycle	SDd 28-day cycle
Dosing	**Selinexor** 80mg **twice weekly** Dexamethasone 20mg twice weekly	**Selinexor** 100mg **weekly** Bortezomib 1.3mg/m2 SQ weekly Dexamethasone 20mg twice weekly	Dose escalation phase **Selinexor** 60 or 80mg **twice weekly** OR 60, 80, 100mg **weekly** Pomalidomide 2,3,4mg D1-21 Dexamethasone 20mg twice-weekly or 40mg weekly	Dose eval phase **Selinexor** 100mg **weekly** Carfilzomib 56mg/m2 D1,8,15 Dexamethasone 40mg weekly	Dose escalation phase **Selinexor** 60mg **twice-weekly** or 100mg **weekly** Daratumumab IV 16mg/kg Dex 20mg twice-weekly or 40mg weekly
			Phase 2 (RP2D) dose **Selinexor** 60mg **weekly** Pomalidomide 4mg D1-21 Dexamethasone 40mg weekly	**MTD, RP2D** **Selinexor** 80mg **weekly** Carfilzomib 56 mg/m2 D1,8,15 Dexamethasone 40mg weekly	**MTD, RP2D** **Selinexor** 100mg **weekly** Daratumumab IV 16mg/kg Dexamethasone 20mg twice-weekly or 40mg weekly

STORM - Sd (Selinexor, dexamethasone)
BOSTON - SVd (Selinexor, bortezomib, dexamethasone)

STOMP -
- SPd (selinexor, pomalidomide, dexamethasone)
- SKd (selinexor, carfilzomib, dexamethasone)
- SDd (selinexor, daratumumab, dexamethasone)

Chari et al, N Engl J Med 2019;381(8):727-738 – STORM; Grosickiet al, *Lancet* 2020;396:1563-73 – BOSTON; Chen CI, et al. *Blood* . 2020;136(Supplement 1):18–19
Gasparetto C, et al. Br J Cancer. 2022 Mar;126(5):718-725; Gasparetto C, et al. *eJHaem.* 2021;2:56–65

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Selinexor Efficacy Rates

Trial	STORM	BOSTON	STOMP		
Treatment	**Sd**	**SVd**	**SPd**	**SKd**	**SDd**
n	n=122	n=195	n=47 (evaluable for response)	n=32	n=32 (evaluable for response)
ORR	26%	76%	58%	78%	69%
CR	2% (sCR)	7%	2%	6% (sCR)	81% (clinical benefit rate)
VGPR	5%	28%	11%	28%	34%
Time to response	4.1 week (time to PR+)	1.1 months (time to first response)	1.1 month*	1 month	1 month
Median duration of response	4.4 months	20.3 months	N/A	22.7 months	11.4 months
PFS	3.7 months	14 months	8.8 months	15 months	11.4 months

Chari et al, N Engl J Med 2019;381(8):727-738; Grosickiet al, *Lancet* 2020;396:1563-73; Chen CI, et al. *Blood* . 2020;136(Supplement 1):18–19; Baljevic M, et al 2024 ASH abstract #1996
Gasparetto C, et al. Br J Cancer. 2022 Mar;126(5):718-725; Gasparetto C, et al. *eJHaem.* 2021;2:56–65 Gasparetto C, et al. *Blood* . 2018;132(Supplement 1) 599-599
Schiller GJ, et al. Clin Lymphoma Myeloma Leuk. 2023 Sep;23(9):e286-e296; White D, et al. Front Oncol. 2024 May 17:14:1352281 ;Baljevic M, et al. 2024 ASH abstract #1996

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Selinexor Toxicity Rates

Trial	STORM		BOSTON		STOMP							
Treatment	**Sd**		**SVd**		**SPd**		**SKd**				**SDd**	
n	All patients (n=122)		All patients (SVd n=195)		All patients (n=52)		All patients (n=32)		RP2D (n=18)		All patients (n=34) *[dose escalation n=3; RP2D n=31]*	
Toxicity	**All grade**	**Gr 3/4**	**All grade**	**Gr 3/4**	**All grade**	**Gr 3/4**	**All grade**	**Gr 3/4**	**All grade**	**Gr 3/4**	**All grade**	**Gr 3/4**
Thrombocytopenia	73%	58%	60%	39%	56%	35%	72%	47%	78%	50%	71%	47%
Neutropenia	40%	21%	15%	9%	62%	56%	28%	6 %	33%	6%	50%	27%
Nausea	72%	10%	50%	8%	62%	2%	72%	6%	78%	11%	71%	9%
Vomiting	38%	3%	21%	4%	23%	2%	16%	3%	22%	0%	29%	3%
Diarrhea	46%	7%	32%	6%	35%	0%	25%	0%	17%	0%	35%	3%
Fatigue	73%	25%	42%	13%	56%	12%	53%	9%	56%	6%	62%	18%
Decreased appetite	56%	5%	35%	4%	48%	2%	47%	3%	50%	6%	35%	0%
Weight loss	50%	1%	26%	2%	42%	0%	41%	0%	44%	0%	24%	3%
Hyponatremia	37%	22%	N/A	N/A	N/A	N/A	19%	6%	22%	6%	32%	12%

Chari et al, N Engl J Med 2019;381(8):727-738; Grosickiet al, *Lancet* 2020;396:1563-73; Chen CI, et al. *Blood* . 2020;136(Supplement 1):18–19
Gasparetto C, et al. Br J Cancer. 2022 Mar;126(5):718-725; Gasparetto C, et al. *eJHaem.* 2021;2:56–65; Gasparetto C, et al. *Blood* . 2018;132(Supplement 1) 599-599
Schiller GJ, et al. Clin Lymphoma Myeloma Leuk. 2023 Sep;23(9):e286-e296; White D, et al. Front Oncol. 2024 May 17:14:1352281; Baljevic M, et al. 2024 ASH abstract #1996

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Selinexor Toxicity Rates

Trial	STORM		BOSTON		STOMP							
Treatment	Sd		SVd		SPd		SKd				SDd	
n	All patients (n=122)		All patients (SVd n=195)		All patients (n=52)		All patients (n=32)		RP2D (n=18)		All patients (n=34) *[dose escalation n=3; RP2D n=31]*	
Toxicity	All grade	Gr 3/4										Gr 3/4
Thrombocytopenia	73%	58%										47%
Neutropenia	40%	21%										27%
Nausea	72%	10%										9%
Vomiting	38%	3%	21%	4%	25%	2%	16%	3%	22%	6%	29%	3%
Diarrhea	46%	7%	32%	6%	35%	0%	25%	0%	17%	0%	35%	3%
Fatigue	73%	25%	42%	13%	56%	12%	53%	9%	56%	6%	62%	18%
Decreased appetite	56%	5%	35%	4%	48%	2%	47%	3%	50%	6%	35%	0%
Weight loss	50%	1%	26%	2%	42%	0%	41%	0%	44%	0%	24%	3%
Hyponatremia	37%	22%	N/A	N/A	N/A	N/A	19%	6%	22%	6%	32%	12%

Weekly dosing improved tolerability without decreasing efficacy

Chari et al, N Engl J Med 2019;381(8):727-738; Grosickiet al, *Lancet* 2020;396:1563-73; Chen CI, et al. *Blood* . 2020;136(Supplement 1):18–19
Gasparetto C, et al. Br J Cancer. 2022 Mar;126(5):718-725; Gasparetto C, et al. *eJHaem*. 2021;2:56–65; Gasparetto C, et al. *Blood* . 2018;132(Supplement 1) 599-599
Schiller GJ, et al. Clin Lymphoma Myeloma Leuk. 2023 Sep;23(9):e286-e296; White D, et al. Front Oncol. 2024 May 17;14:1352281; Baljevic M, et al. 2024 ASH abstract #1996

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Selinexor Dose Modifications in Clinical Trials

Trial	STORM	BOSTON	STOMP				
Treatment	Sd	SVd	SPd	SKd		SDd	
n	All patients (n=122)	All patients (SVd n=195)	All patients (n=52)	All patients (n=32)	RP2D (n=18)	All patients (n=34) Dose escalation (n=3) RP2D (n=31)	
	All patients	All patients	All patients	All patients	RP2D	All pt	RP2D
Treatment discontinued d/t AEs	32.5%	21% (SVd) vs 16% (Vd)	9%	15.6%	11.1%	15%	N/A
Dose interruption	80% (dose interruption or modification	88% (SVd)	61%	53.1%	N/A	71%	68%
Dose reduction		89% (SVd) vs 76% (Vd)	44%	65.6%	N/A	65%	61%

Chari et al, N Engl J Med 2019;381(8):727-738;Grosickiet al, *Lancet* 2020;396:1563-73; Chen CI, et al. *Blood* . 2020;136(Supplement 1):18–19
Gasparetto C, et al. Br J Cancer. 2022 Mar;126(5):718-725; Gasparetto C, et al. *eJHaem*. 2021;2:56–6; Gasparetto C, et al. *Blood* . 2018;132(Supplement 1) 599-599
Schiller GJ, et al. Clin Lymphoma Myeloma Leuk. 2023 Sep;23(9):e286-e296; White D, et al. Front Oncol. 2024 May 17;14:1352281; Baljevic M, et al. 2024 ASH abstract #1996

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Nausea, Vomiting (N/V)

Median time to onset
- Nausea 3-6 days
- Vomiting 5-8 days

Causes
- Central nervous system, as crosses blood brain barrier

Incidence
- Decrease over time
- >90% of patient improved nausea after first 2 cycles and beyond

PREVENTION

- **5-HT3 antagonist**
  - Ondansetron 8mg every 8 hours 30 min before the first dose and continue 3 days. Other days, 8 mg every 8 hours PRN N/V
- **Olanzapine** 2.5-5mg daily for 3 days each week of selinexor. Start on same day of selinexor.
- Continued use of anti-emetics evaluated after first 8 weeks

XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020—US FDA; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440
Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Barbar A, et al. J Oncol Pharm Pract. 2024 Apr;30(3):535-546;Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7
Dev R, et al. Investigational New Drugs (2022) 40:124–133); Gasparetto C, et al. *eJHaem*. 2021;2:56–6; CTCAE version 5. Accessed at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

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Nausea, Vomiting (N/V)

MANAGEMENT

- Grade 1/2 nausea (oral intake decreased without significant weight loss, dehydration, or malnutrition) OR Grade 1/2 vomiting (≤5 episodes/day):
  - Maintain selinexor dose
  - Add anti-nausea meds
- Grade ≥ 3 nausea (inadequate oral caloric or fluid intake) **OR** Grade ≥ 3 vomiting (≥ 6 episodes per day):
  - Hold until resolved to grade ≤2 or baseline and dose reduce selinexor by 20 mg
  - Add NK1 receptor antagonist (e.g., aprepitant)
- May stop or reduce anti-emetics after first 8 weeks if tolerate selinexor

MEDICATIONS

Prophylaxis
- 5HT3 receptor antagonist (e.g., ondansetron)
- Olanzapine

Additive Options
- NK1 receptor agonist (e.g., aprepitant)
- Prochlorperazine
- Others
  - Benzodiazepines
  - Dronabinol

SUPPORTIVE CARE
- Hydration (oral, IV)
- Nutrition/dietary consult

XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020; NCCN antiemesis Version 1. 2020; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440; Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7; Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Barbar A, et al. J Oncol Pharm Pract. 2024 Apr;30(3):535-546 Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440; Dev R, et al. Investigational New Drugs (2022) 40:124–133); Gasparetto C, et al. eJHaem. 2021;2:56–65; CTCAE version 5. Accessed 2/2025
May MB, et al. Cancer Manag Res 2016; 8:49-55

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Anorexia, Weight Loss

Median time to onset
- Anorexia 8-35 days
- Weight loss 15-58 days

PREVENTION

- Dietary consultation
- Track weight at weekly office visit

MANAGEMENT

- Dietary consultation and nutritional supplements (Ensure, Boost), IV fluids, electrolyte replacement, supportive care meds (dronabinol, mirtazapine, olanzapine)
- Grade ≥2 weight loss (10% to <20%) **or** Grade ≥3 anorexia (associated with significant weight loss or malnutrition)
  - Hold until weight returns to >90% of baseline weight and restart at dose reduced by 20 mg

XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020—US FDA; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440
Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Barbar A, et al. J Oncol Pharm Pract. 2024 Apr;30(3):535-546; Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7
Dev R, et al. Investigational New Drugs (2022) 40:124–133); Gasparetto C, et al. eJHaem. 2021;2:56–65; CTCAE version 5. Accessed at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

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Diarrhea

Median time to onset
- 12-50 days

PREVENTION

Hydration (Oral and IV)
- Oral hydration with ≥ eight 8oz glasses of fluid per day
- Saline infusions weekly for the first month to maintain hydration, serum sodium levels

MANAGEMENT

- Anti-diarrheal treatment (loperamide)
- Grade 2 (increase of 4-6 stools per day over baseline)
  - 1st event: maintain selinexor dose and start supportive care
  - Subsequent event: dose reduce selinexor by 20mg and start supportive care
- Grade ≥3 (increase of ≥7 stools per day over baseline; hospitalization indicated)
  - Hold selinexor and start supportive care
  - Monitor until diarrhea resolves to grade ≤2
  - Restart selinexor, but dose reduce by 20 mg

XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020—US FDA; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440
Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Barbar A, et al. J Oncol Pharm Pract. 2024 Apr;30(3):535-546; Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7
Dev R, et al. Investigational New Drugs (2022) 40:124–133); Gasparetto C, et al. *eJHaem.* 2021;2:56–65; CTCAE version 5. Accessed at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

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Hyponatremia

Median time to onset
- 8-21 days

PREVENTION

Hydration (Oral +/- IV)
- Monitor Na levels
- Maintain fluid intake
- Salty foods/snacks
- Consider IV fluid weekly during first cycle

MANAGEMENT

Sodium level ≤130 mmol/L
- Explore other causes (e.g., diuretics, paraproteinemia)
- Hold selinexor
- Correct sodium level for concurrent hyperglycemia (serum glucose >150mg/dL)
- Provide supportive care (IV saline +/- salt tablets with dietary review)
- Monitor until sodium levels return to >130 mmol/L (grade 1) or baseline
- Restart selinexor, but dose reduced by 20mg

XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020—US FDA; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440
Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Barbar A, et al. J Oncol Pharm Pract. 2024 Apr;30(3):535-546; Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7
Dev R, et al. Investigational New Drugs (2022) 40:124–133); Gasparetto C, et al. eJHaem. 2021;2:56–65 ; CTCAE version 5. Accessed at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

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Thrombocytopenia

Median time to onset
- 22-28 days

Causes
Inhibit thrombopoietin (TPO) signaling and prevent stem cells differentiation into megakaryocytes

PREVENTION

Monitor CBC weekly in cycle 1, then day 1 of each cycle

MANAGEMENT
- Platelet 25-75K: dose reduce by 20mg
- Platelet 25-75K with concurrent bleeding:
  - Hold until platelet ≥50K and bleeding resolved
  - Dose reduce by 20mg
- Platelet <25K:
  - Hold until platelet ≥50K
  - Dose *reduce* by 20mg
- Consider platelet growth factor (romiplostim, eltrombopag)

XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020—US FDA; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440; Machlus KR, et al. Blood 2017; 130:1132-43
Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Barbar A, et al. J Oncol Pharm Pract. 2024 Apr;30(3):535-546; Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7
Dev R, et al. Investigational New Drugs (2022) 40:124–133); Gasparetto C, et al. eJHaem. 2021;2:56–65; CTCAE version 5. Accessed at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

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Neutropenia

Median time to onset
- 23-25 days

PREVENTION

Monitor CBC weekly in cycle 1, then day 1 of each cycle

MANAGEMENT

- Grade 3 (ANC 500-1000/mm^3) without fever:
  - Dose reduce selinexor by 20mg. Consider growth factor
- Grade 4 (ANC <500/mm^3) OR neutropenic fever:
  - Hold selinexor and when ANC ≥1000/mm^3, restart selinexor, but dose reduced by 20mg. Growth factor.

Fatigue

Median time to onset
- 7 days
- Grade 3 fatigue: 22 days

PREVENTION

Check other causes (depression, dehydration, anemia, hormonal imbalance)

MANAGEMENT

- Grade 2 (fatigue not relieved by rest, limit instrumental ADL) lasting >7 days OR Grade 3 (fatigue not relieved by rest, limit self-care ADL):
  - Hold selinexor until resolve to grade 1 (fatigue relieved by rest) or baseline
  - Restart selinexor, but dose reduced by 20mg
  - Consider methylphenidate 5mg PO BID

XPOVIOTM (selinexor). Prescribing information. Reference ID: 5014020—US FDA; Gavriatopoulou M, et al. Leukemia. 2020 Sep;34(9):2430-2440
Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):e526-e531; Barbar A, et al. J Oncol Pharm Pract. 2024 Apr;30(3):535-546; Mikhael J, et al. Clinical Lymphoma, Myeloma & Leukemia. 2020;20(6): 351-7
Dev R, et al. Investigational New Drugs (2022) 40:124–133); Gasparetto C, et al. eJHaem. 2021;2:56–65; CTCAE version 5. Accessed at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

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Talquetamab

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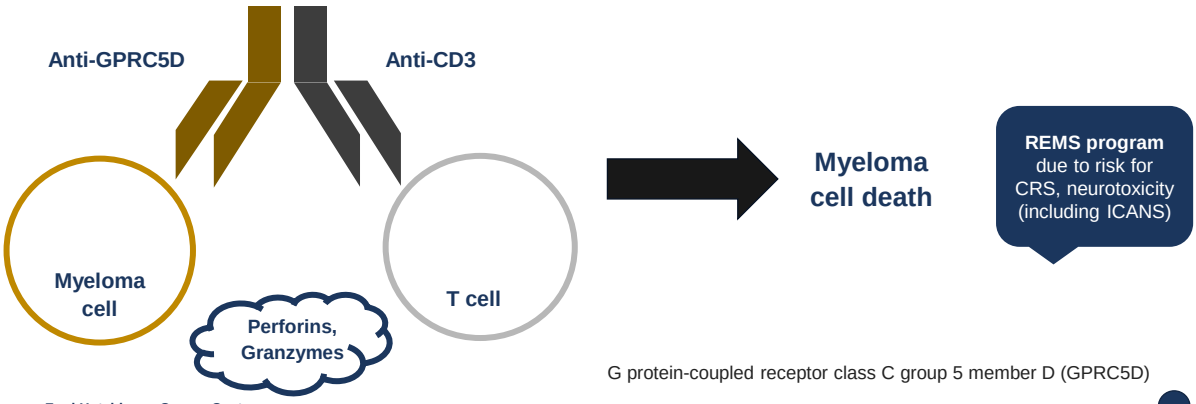
Talquetamab Background

- Indication: relapsed or refractory multiple myeloma after ≥4 prior lines of therapy, including proteasome inhibitor, immunomodulatory agent, and anti-CD38 monoclonal antibody
- Mechanism of action:



G protein-coupled receptor class C group 5 member D (GPRC5D)

Talquetamab Package Insert. Revised 8/2023.

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MonumenTAL-1

C1D1 0.01 mg/kg	C1D4 0.06 mg/kg	C1D7 0.4 mg/kg	C1D10 0.8 mg/kg	Every 2 weeks 0.8 mg/kg

- Phase 2 portion — N=44, subcutaneous, 0.8 mg/kg q2weeks dose level
  - Median 64yo. 68% penta-drug exposed. 22% HRCA. 34% >1 EMD plasmacytoma
  - Median follow-up 4.2 months --> 64% ORR (23% ≥CR rate).
    - Penta-refractory, 66.7% ORR; HRCA 56% ORR; EMD 40%
  - Median time to response 1.2 months (median time to ≥CR 2.3 months)
  - Median duration of response 7.8 months
  - Most common AEs:
    - CRS (80%; no Gr3-4); Neurotoxicity (5%; all Gr 1/2)
    - skin-related event (70%; Gr3-4 2%), rash-related event (30%; Gr3-4 16%)
    - dysgeusia (57%), dry mouth (57%), decreased weight (32%; Gr3-4 2%)
    - nail-related event (27%; Gr3-4 2%)
    - fatigue (27%), headache (25%), incr. ALT (30%; Gr3-4 7%), incr. AST (34%; Gr3-4 7%)

Chari A, et al. N Engl J Med. 2022;387:2232-2244.

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Talquetamab Toxicity Management

Toxicity	Prevention	Management
CRS	• Premedicate with dexamethasone, diphenhydramine, acetaminophen during step-up phase	• Gr1: Hold until resolves. Administer premeds for next dose of talq. • Gr2 – Gr3 (duration <48 hrs): Hold until resolve. Premeds prior to next dose and hospitalize for 48h. Tocilizumab, steroid • Gr3 (recurrent OR duration ≥48 hrs) – Gr4: Permanently d/c. Tocilizumab, steroid
ICANS		• ≥Gr1: Hold until resolves • ≥Gr2: Dexamethasone + Consider neurology consult + Anti-seizure prophylaxis + Consider ICU care. Hospitalization after next dose of talq • Gr3 (recurrent), grade 4 - permanantely d/c talq
Infection	• Prophylaxis for HSV/VZV, PJP • IVIG prophylaxis for IgG <400	• During step-up phase: Hold until resolves • After step-up phase, Gr3: Hold until infection improves to ≤Gr1 or baseline • After step-up phase, Gr4: Consider permanently discontinuing talq
Cytopenia	• Repletion as needed	• ANC < 0.5 x 10^9/L OR Hgb < 8 g/dL: Hold until above threshold(s) • Febrile neutropenia: Hold until ANC ≥ 1 x 10^9/L + fever resolves • PLT < 25k/mcL *OR* PLT 25-50k/mcL with bleeding: Hold until PLT > 25k/mcL and no bleeding

May need to repeat part or all of step-up phase if significant delay to next dose of talquetamab

Fred Hutchinson Cancer Center

Talquetamab Package Insert. Revised 8/2023.

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Talquetamab GPRC5D Related Toxicity MOA

- 'On target, Off tumor' effect
- GPRC5D RNA expressed on keratinized structures
  - Papillae of the tongue
  - Skin
  - Nail
- GPRC5D upregulated on clonal plasma cell vs normal plasma cells
  - Not much expression on normal B cells, T cells, natural killer cells, monocytes, granulocytes, bone marrow progenitors unlike BCMA

Fred Hutchinson Cancer Center

Talquetamab Package Insert. Revised 8/2023; Chari A, et al. N Engl J Med. 2022;387:2232-2244; Chari A, et al. Clin Lymphoma Myeloma Leuk 2024 Oct;24(10):665-693
Inoue S, et al. J Invest Dermatol . 2004;122(3):565–573; Pillarisetti K, et al. Blood . 2020;135(15):1232–1243; Kodama T, et al. Mol Cancer Ther . 2019;18(9):1555–1564; Verkleij CPM, et al. Blood Adv . 2021;5(8):2196–2215

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GPRC5D Related Toxicity Rates with Talquetamab

Toxicity	Any grade	Grade 3-4	Onset	Time to resolution	Resolution	Dose modification	Discontinue for toxicity
Oral toxicity			15 days	43 days	30%		
Dysgeusia	72%	N/A	13-20 days	95-102 days	38%	6-12%	1%
Dysphagia	24%	1%	21-29 days	73-109 days	66%	1-6%	0%
Dry mouth	36%	0%	19-26 days	57-89 days	39%	1-6%	0%
Weight loss	28%	1%	67 days	50 days	39%	N/A	1%
Skin-related Rash	60% 32%	1% 7%	24 days 21 days	39 days 17 days	46% 62%	1-8%	1%
Nail-related	39%	1%	51 days	74 days	29%	0-2%	0%

Chari A, et al. N Engl J Med 2022;387:2232-44. / Schinke C, et al. Curr Med Res Opin. 2024 Oct;40(10):1705-1711. / Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-693. / Catamero D, et al. Semin Oncol Nurs. 2024 Oct;40(5):151712 . Talquetamab Package Insert. Revised 8/2023. / Pan D, et al. Current Hematologic Malignancy Reports. 2024; 19:237–245. / Laheij, AMGA, et al. Supportive Care in Cancer. 2024; 32:20. / Fleischer A, et al. Blood. 2023; 142: 2403.

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Dose Modifications to Manage Toxicity

MonumenTAL-1

After ≥PR, switched to
- **reduced dose** (0.8 mg/kg to 0.4 mg/kg Q2W)
  OR
- **less frequent dose** (0.8 mg/kg Q2W to Q4W)

Dosing switch starting cycles 3-5

➢ **Deepened or maintained responses to talquetamab**

➢ **TEAEs improved or resolved**
- Oral: 25%, 1-6 months after switch
- Skin: 38%,1-3 months after switch
- Nail: 29%, 3-4 months after switch

Real-world experience

Changing dose frequency more effective than dose strength for managing TEAEs (e.g., 0.8mg/kg Q4W was more effective than 0.4mg/kg Q2W)

Dose modifications (reduction, delay, skip) can maintain clinical efficacy while reducing talquetamab related toxicity

Chari A, et al. Clin Lymphoma Myeloma Leuk 2024 Oct;24(10):665-693; Chari A, Oriol A, Krishnan A, et al. *Blood* (2023) 142 (Supplement 1): 1010-1011; Schinke C, et al. Curr Med Res Opin. 2024 Oct;40(10):1705-1711

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Oral Toxicity Prevention (Dysgeusia, Dry Mouth, Dysphagia)

- Saliva substitute
- Dexamethasone, nystatin mouth washes
- Vitamin B complex
- Sour citrus, sour candy, sugar-free candy/gum (e.g., sucking on sour candies before eating)
- Clonazepam, zinc

Patients should notify provider if
- Baseline appetite, nutritional status are difficult to maintain
- Weight significantly decreases

- Routine dental visits, regular teeth cleanings
- Early referral to nutrition consult

Schinke C, et al. Curr Med Res Opin. 2024 Oct;40(10):1705-1711.; Shono H, et al. Nutrients. 2021;13(9):2921. Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-69
Shin HI, et al. Sci Rep. 2023 May 4;13(1):7257; Lyckholm L, et al. J Pain Palliat Care Pharmacother. 2012;26(2):111–114

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Oral Toxicity Management (Dysgeusia, Dry Mouth, Dysphagia)

Dysgeusia **Dry Mouth** **Dysphagia**

Grade 1-2: Supportive care + Nutrition consult + Consider holding if not responsive to supportive care
Grade 3: Hold until resolution to ≥ grade 1 and provide supportive care
Grade 4: Permanently discontinue

- Stimulate/supplement salivation (artificial saliva)
- Ensure adequate hydration
- Replete with intravenous fluids and electrolytes as needed

- Corticosteroid mouth wash
- Baking soda/salt water/magic mouth rinse
- Ice packs

- Use sodium lauryl sulphate-free toothpaste
- Limit caffeine, alcohol intake
- Add flavoring to food

Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-69. Schinke C, et al. Curr Med Res Opin. 2024;40(10):1705-1711. Catamero D, et al. Semin Oncol Nurs. 2024;40(5):151712.
Chari A, et al. Blood. 2023;142(Suppl 1). Chari A, et al. N Engl J Med 2022;387:2232-44

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Weight Loss Management

Prophylaxis may overlap with Oral Toxicity Prevention

Grade 1-2: Supportive care + Nutrition consult + Consider holding if not responsive to supportive care
Grade 3: Hold until resolution to ≥ grade 1 and provide supportive care
Grade 4: Permanently discontinue

- Diet alterations - small frequent meals and snacks with protein, adding calorie-boosting foods (e.g., olive oil, nut butter), oral appetite stimulants
- Nutrition consult if weight loss

Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-69; Catamero D, et al. Semin Oncol Nurs. 2024;40(5):151712.

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Skin Toxicity Management

- Keep skin moisturized – short lukewarm showers; thick moisturizer daily after showers; avoid alcohol-containing fragrances; could consider ammonium lactate
- Sunscreen

- Patients should notify provider if
  - New-onset rash (maculopapular rash, erythematous rash, and erythema)
  - Other new-onset non-rash (skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome)

Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-69; Pan D, et al. Current Hematologic Malignancy Reports. 2024;19:237-245.; Schinke C, et al. Curr Med Res Opin. 2024;40(10):1705-1711.

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Skin Toxicity Management

Grade 1-2: Early intervention and treatment
Grade 3-4: Hold until improvement to ≤Gr1 or baseline

- Continue preventive supportive care interventions
- Emollient (e.g., thick moisturizer, ammonium lactate 12%) for **dry skin**
- Antihistamines and topical steroids (e.g., triamcinolone 0.1% twice daily) for **pruritic, maculopapular rashes**
- Consider short course of PO methylprednisolone with quick taper for **diffuse rashes**
- Referral to dermatology if persistent or grade 3-4 skin toxicity, refractory to emollients, low-potency corticosteroids

Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-69.; Pan D, et al. Current Hematologic Malignancy Reports. 2024;19:237-245.; Schinke C, et al. Curr Med Res Opin. 2024;40(10):1705-1711.
Chari A, et al. Blood. 2023;142(Suppl 1).

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Nail Toxicity Prevention

- Nail hydration, including to cuticles (hands and feet) – soaks, topical moisturizers, emollients, topical vitamin E, ammonium lactate
- Maintain short and clean nails to reduce infections (avoid imitation fingernails)
- Avoid activities involving nail breakage
- Utilize protective wear – socks, gloves at night; comfortable shoes; gloves during household tasks

- Patients should notify provider if
  - Nails thicken or discolor (may be signs of fungal infection)
  - Nails become brittle

- Consider podiatry referral if patient having difficulty maintaining nail hygiene or finding comfortable footwear
- Consider referral to dermatology

Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-69.; Pan D, et al. Current Hematologic Malignancy Reports. 2024;19:237-245. ;Schinke C, et al. Curr Med Res Opin. 2024;40(10):1705-1711.
Chari A, et al. Blood. 2023;142(Suppl 1).

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Nail Toxicity Management

Grade 3: Hold until resolution to ≥Gr1
Grade 4: Consider permanently discontinuing talq

- Continue preventive supportive care interventions
- Low-dose topical steroid (e.g., triamcinolone 0.025% ointment) for **peeling around nails or brittle nails**
- Fortifying nail lacquers and polishes (applied daily and removed once a week with an acetone-based nail polish remover) for **brittle nails**
- Urea-based treatment on hands/feet twice daily
- Biotin supplement
- Nail toxicity wax and wane and take time to resolve due to slow nail growth

Chari A, et al. Clin Lymphoma Myeloma Leuk 2024;24(10):665-69.; Pan D, et al. Current Hematologic Malignancy Reports. 2024;19:237-245; Schinke C, et al. Curr Med Res Opin. 2024;40(10):1705-1711. Catamero D, et al. Semin Oncol Nurs. 2024;40(5):151712; Chari A, et al. Blood. 2023;142(Suppl 1).

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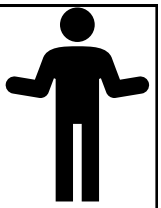
Case – Talquetamab



- 63 yo female with relapsed IgA kappa multiple myeloma with t(4;14) and deletion 13
- Prior treatment history: Daratumumab/bortezomib/dex, BCMA CAR T cells, Elo-Pd (elotuzumab, pomalidomide, dexamethasone), SKd (selinexor, carfilzomib, dexamethasone), then progressed and now on talquetamab
- KP has symptoms of dysgeusia with persistent sensitivity to spicy foods and dry mouth about 1.5 weeks after starting talquetamab. Now, one month afterward, KP reports a new-onset skin rash.
- Labs & Imaging
  - SCr 1.05, AST/ALT 15/7, wbc 4.37, Plt 176, Hgb 8
  - KLC 10, K/L >82.21, M spike 2 (decreased from 1 month ago)
- What supportive care medications would be appropriate to prescribe?
- What dose modifications would you consider?

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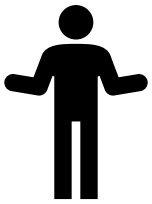
Case – Selinexor



- 76 yo male with relapsed IgA lambda multiple myeloma with 1q+ and t(14;16) who is transferring care to your institution. AJ reports low baseline appetite and oral hydration.
- Prior treatment history: RVD x4 cycles, autoHCT, DaraRD x8 cycles, KPD x6 cycles
- Labs & Imaging
  - SCr 2.1, AST/ALT 11/12, ANC 1.2, Plt 120, Hgb 8.7
  - LLC 81.2, L/K >120.34, M spike 6.1 (increased from 0.1 two months ago)
  - PET/CT with multiple new lytic lesions throughout femur
- Prior team was considering selinexor 80mg PO twice weekly and dexamethasone 20 mg PO twice weekly.

- How would you empirically modify selinexor dosing?
- What prophylactic medications and/or lifestyle modifications would be appropriate to recommend?

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Questions
Thank You!

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