Case Studies for Nurses:

NEW THERAPIES AND REGIMENS FOR PATIENTS WITH MULTIPLE MYELOMA

NURSE LEADERSHIP BOARD
A Division of International Myeloma Foundation

INTERNATIONAL MYELOMA FOUNDATION

New and Emerging Therapies for Multiple Myeloma: Case Studies for Nurses

Slides available for download at:
https://www.imf-ons.myeloma.org
password: ons2024

Please help us start on time.
Please do not save seats. Please silence cell phones.

Thank you for coming!

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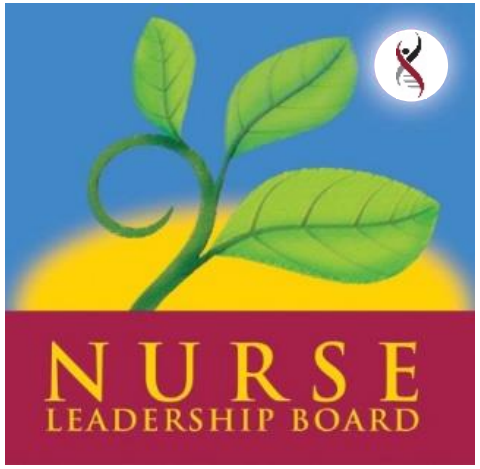

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A maximum of 1.5 contact hours may be earned for successful completion of this activity.

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Patient names, demographics, and identifying characteristics have been masked to be HIPAA compliant.

Off-label use of drugs may be discussed.

Slides available for download at:
https://www.imf-ons.myeloma.org

HIPAA = Health Insurance Portability and Accountability Act.

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Faculty Introductions

CHAIR

Beth Faiman, PhD, MSN, APRN-BC, AOCN®, BMTCN®, FAAN, FAPO
Cleveland Clinic Taussig Cancer Institute
Member, Population and Cancer Prevention Program, Case Comprehensive Cancer Center
Cleveland, OH

FACULTY

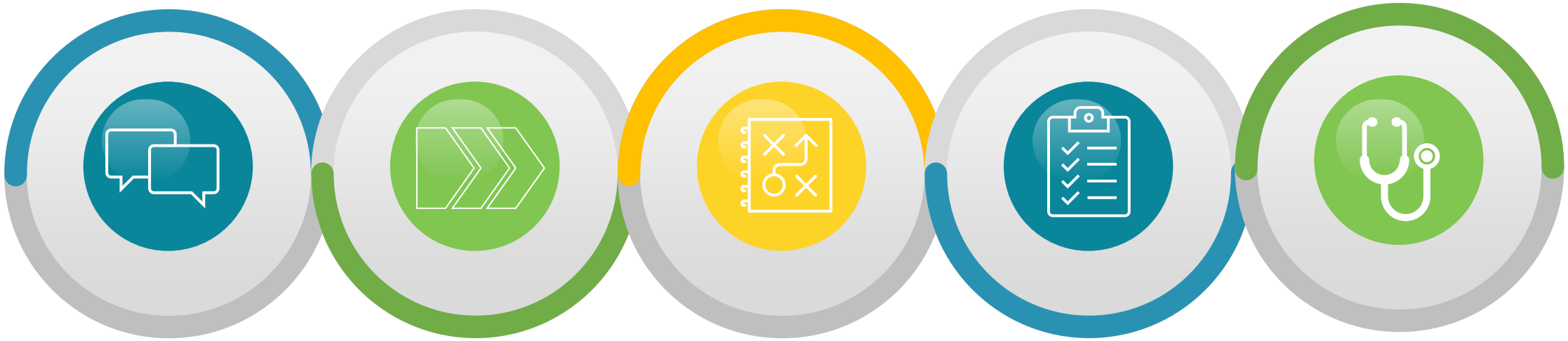
Kevin Brigle, PhD, NP
Massey Comprehensive Cancer Center
Virginia Commonwealth University, Richmond, VA

Donna D. Catamero, ANP-BC, OCN®, CCRC
Mount Sinai Health System
Multiple Translational Research, New York, NY

Patricia A. Mangan, RN, MSN, APRN-BC
Abramson Cancer Center
University of Pennsylvania, Philadelphia, PA

Learning Objectives

As a result of this program, you will be able to:



- Discuss **new and emerging therapies**, including CELMoDs®, CAR-T cell therapy, and T-cell engagers, such as bispecific antibodies, for patients with multiple myeloma, as well as **AE management and patient education**
- Explain the importance of **sequencing therapy**, including the use of **multidrug regimens and bridging therapy**
- Use strategies to support the attainment of **deep responses** by patients with myeloma, such as new therapies, multidrug regimens, ASCT, maintenance, adherence, shared decision-making, MRD, and other testing
- Summarize **disparities faced by patients** with multiple myeloma and **strategies to overcome** these (health equity)
- Use patient and care partner's (caregiver's) input in treatment decisions through shared decision-making

AE = adverse event; ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; CELMoD = cereblon E3 ligase modulatory drug; MRD = minimal residual disease.

Q1. Which of the following is TRUE about multiple myeloma (MM) in Black vs White patients?

1. Black patients tend to be diagnosed with myeloma at an older age
2. Black patients of African descent tend to have higher-risk disease
3. Black patients with MM have similar rates of mortality compared with White patients
4. Black patients may have superior outcomes when treated with standard-of-care
5. I don’t know

Q2. Which of the following is TRUE about strategies to attain deep minimal residual disease (MRD) negative responses to treatment in multiple myeloma (MM)?

1. Patients who achieve MRD-negative status do not relapse
2. Multidrug regimens produce higher MRD-negative rates than doublet regimens
3. Autologous stem cell transplant (ASCT) is no longer recommended as a strategy to achieve MRD-negative responses
4. A shorter duration of therapy with higher doses of chemotherapy will lead to deeper MRD-negative response rates
5. I don’t know

Q3. Which of the following is TRUE about sequencing and CAR T cell therapy for multiple myeloma (MM)?

1. A new line of therapy is defined as the discontinuation of 1 treatment regimen due to progression and the start of another therapy
2. Patients must have been treated with a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) before CAR T-cell therapy
3. CAR T cell therapies are indicated for patients with MM only after 3 or more prior lines of therapy
4. Patients treated with a bispecific antibody are not eligible to receive CAR T-cell therapy
5. I don’t know

Q4. Which of the following is TRUE about bispecific antibody therapies for multiple myeloma (MM)?

1. Skin and nail toxicities are common AEs experienced by patients receiving a BCMA-targeted bispecific antibody
2. Cytokine release syndrome (CRS) can occur in CART-cell therapy but does not occur in patients treated with bispecific antibodies
3. Patients are not eligible for a BCMA-directed bispecific antibody after a BCMA-directed CAR T-cell therapy
4. Atypical infections such as CMV, PJP, and fungal infections may occur at higher rates in patients receiving bispecific therapies for MM compared with standard therapy
5. I don’t know

International Myeloma Foundation
800-452-CURE (2873)
http://myeloma.org

Newly Diagnosed Multiple Myeloma, Including Treatment Disparities

CASE 1: CARL*

*HIPAA-compliant; not actual patient name.

Kevin Brigle, PhD, NP
Beth Faiman, PhD, RN, MSN, APRN-BC, AOCN, BMTCN, FAAN

HIPAA = Health Insurance Portability and Accountability Act.

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CASE 1

CARL*

PATIENT NOTES:

- 61-year-old man
- PMH: HTN; prostate cancer treated with XRT 1 year prior
- Back pain, lumbar and thoracic; visited PCP → prescribed NSAIDs
- Pain persisted × 1 week → wife and daughter encouraged him to return to PCP
- Prescribed lidocaine patch and physical therapy

PHYSICAL THERAPY	**Started twice-weekly sessions**

*HIPAA-compliant, not actual patient name, stock photo.

HIPAA = Health Insurance Portability and Accountability Act; HTN = hypertension; NSAID = nonsteroidal anti-inflammatory drug; PCP = primary care provider; PMH = past medical history; XRT = external beam radiotherapy.

Myeloma Is a Cancer of Plasma Cells

Bone Marrow of a Patient With MM

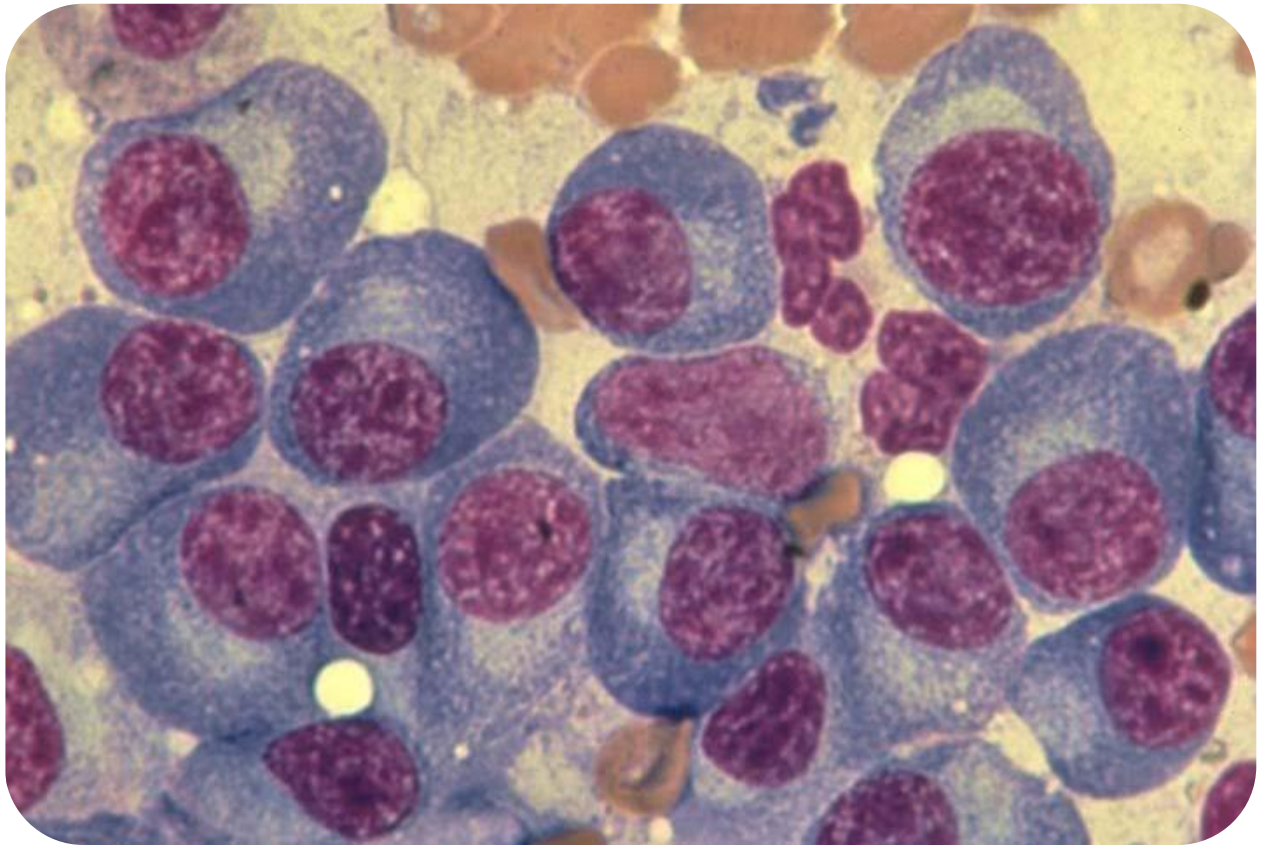


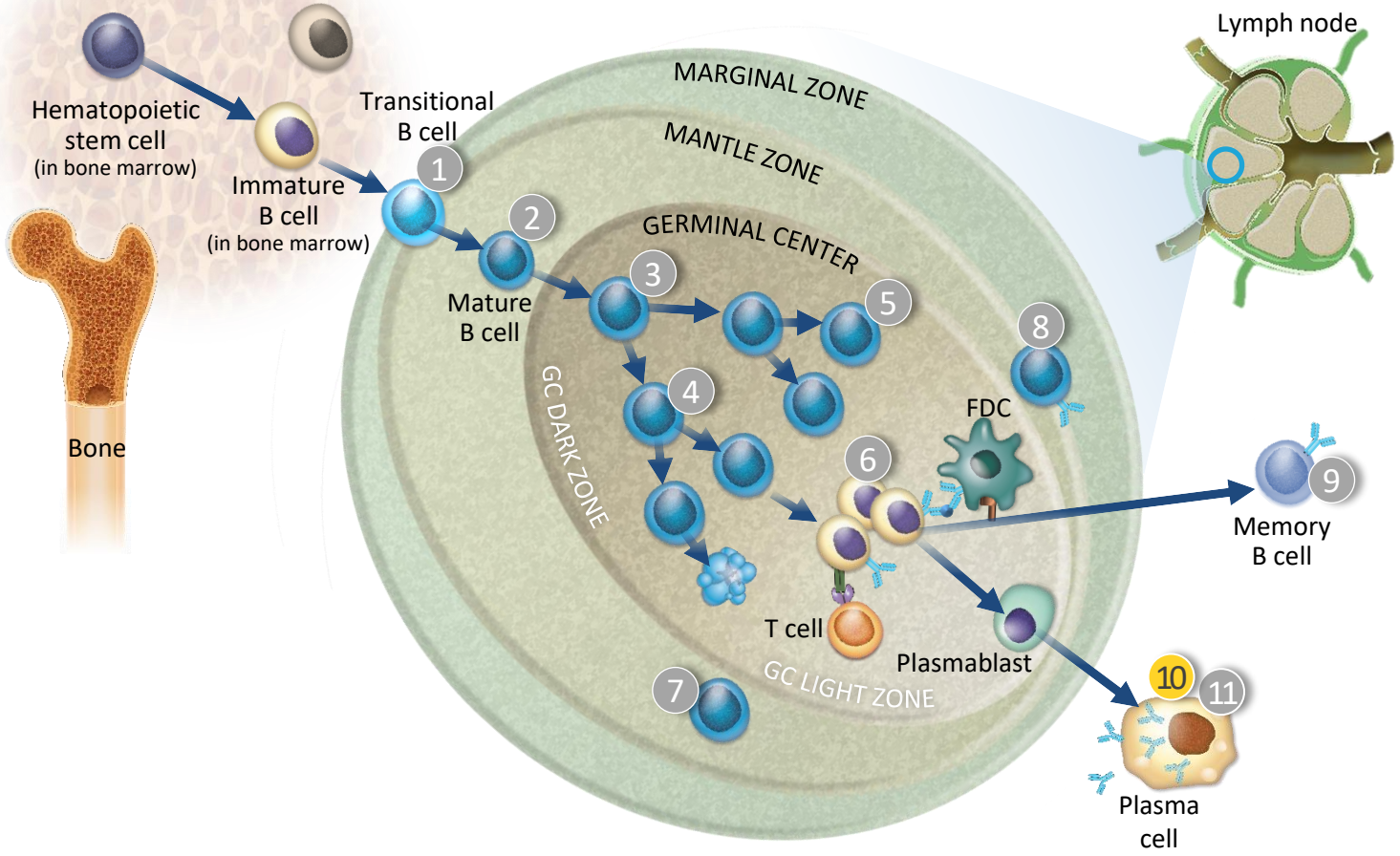
Image courtesy of American Society of Hematology

MM = multiple myeloma.

Kyle RA, et al. *Mayo Clin Proc.* 2003;78:21-33.

Plasma Cells Are Differentiated B Cells That Produce Antibodies

B-cell malignancies have characteristics similar to the stages of B-cell development



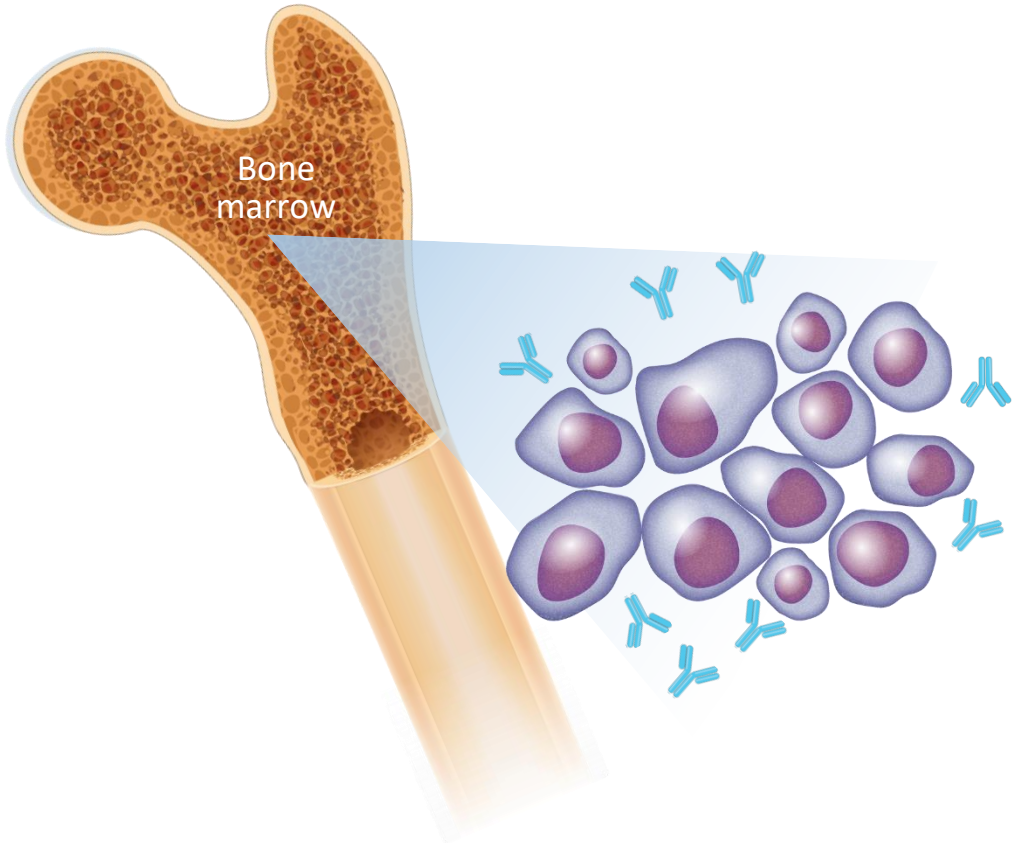
B-cell Malignancies

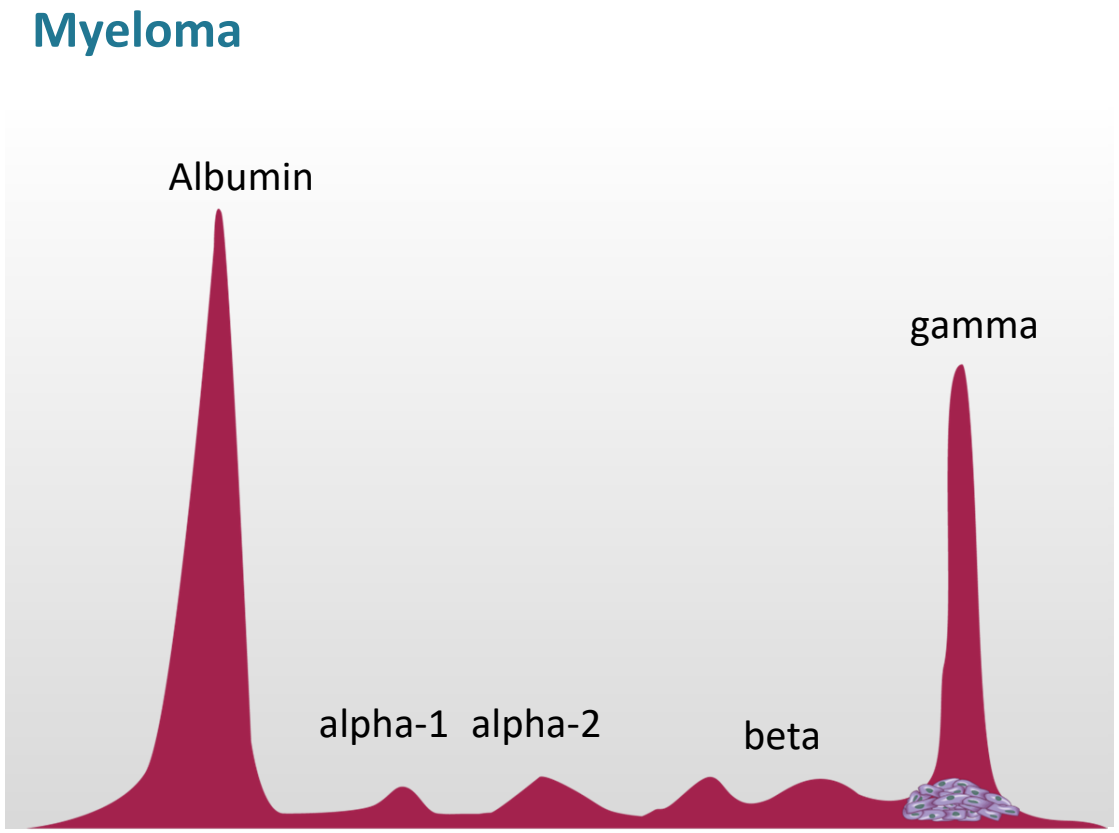
1. Pre-B acute lymphoblastic leukemia (ALL)
2. Chronic lymphocytic leukemia (CLL) with unmutated *IGHV*
3. Burkitt lymphoma (BL)
4. Follicular lymphoma (FL)
5. Diffuse large B-cell lymphoma (DLBCL)
6. Activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL)
7. Mantle cell lymphoma (MCL)
8. Marginal zone lymphoma (MZL)
9. Chronic lymphocytic leukemia (CLL with mutated *IGHV*)
10. **Multiple myeloma (MM)**
11. Waldenström macroglobulinemia (WM)

FDC = follicular dendritic cell; GC = germinal center; *IGHV* = immunoglobulin heavy chain variable.

Pal Singh S, et al. *Mol Cancer*. 2018;17(1):57. Pasqualucci L. *Immunol Rev*. 2019;288(1):240-261.

Myeloma Cells Can Produce Myeloma Protein Continually: Detectable in Plasma and Urine



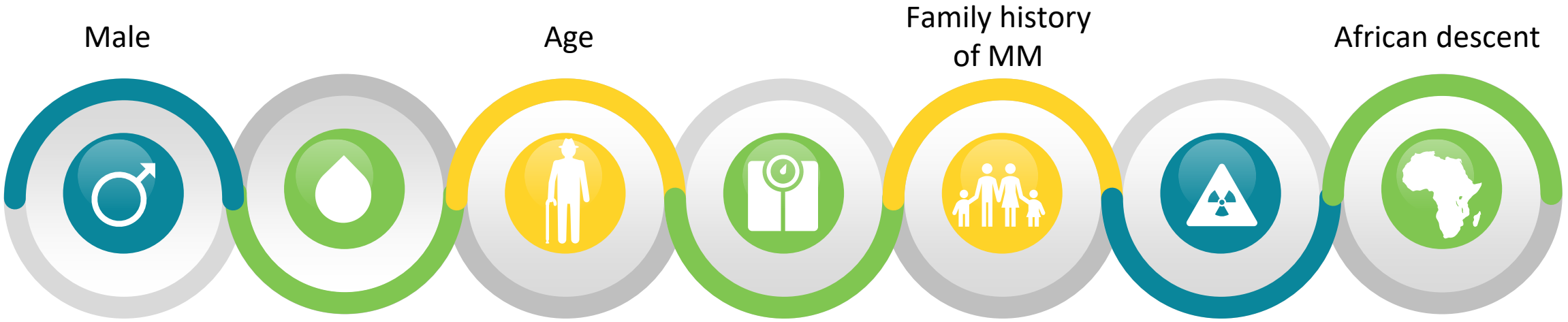


Note: Some patients have nonsecretory disease that does not produce detectable myeloma protein.

Understanding Your Test Results, International Myeloma Foundation 2018.

Characteristics Put Some People at Higher Risk for MM

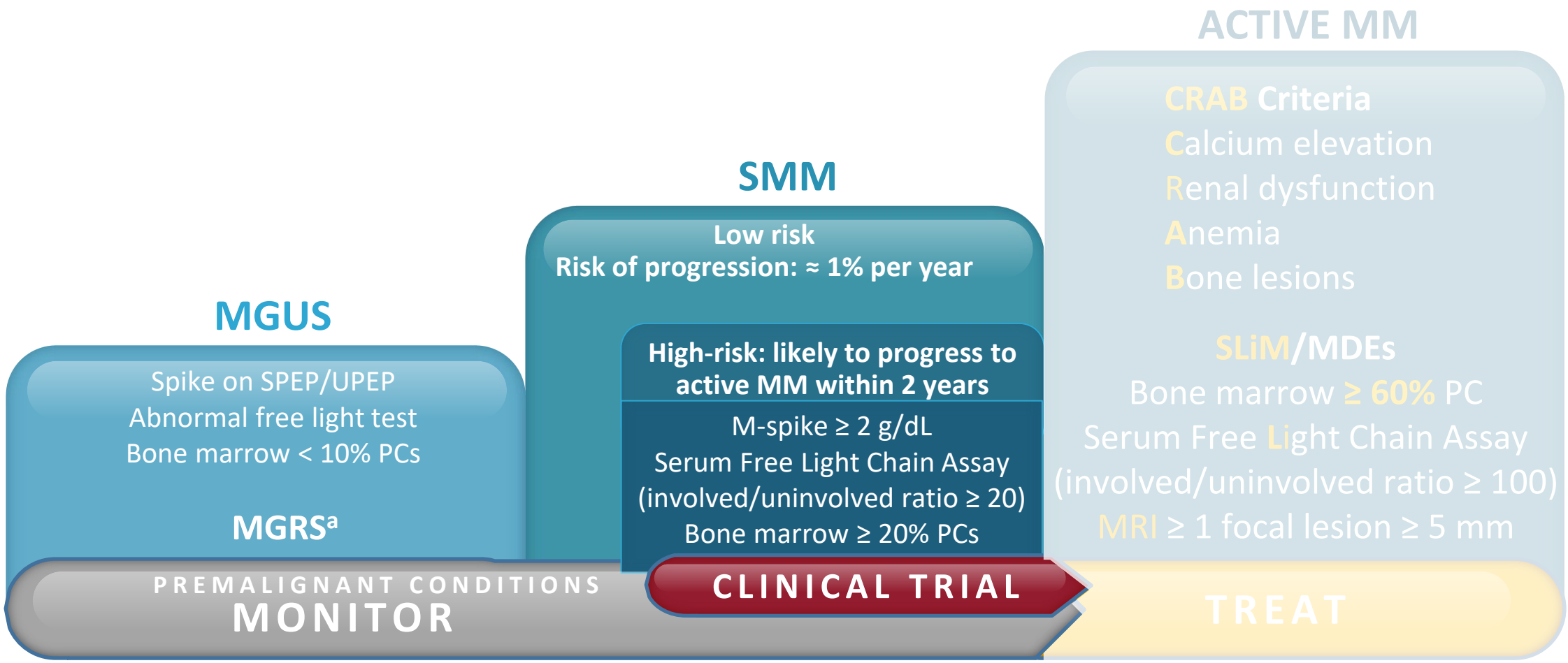
Risk Factors



MM = multiple myeloma; MGUS = monoclonal gammopathy of undetermined significance.

Plasma Cell Neoplasms (Including Multiple Myeloma) Treatment (PDQ®)–Patient Version - NCI. Published December 9, 2022. Accessed April 1, 2023. https://www.cancer.gov/types/myeloma/patient/myeloma-treatment-pdq. Tariman JD. Multiple myeloma. In: Yarbro CH, Frogge MH, Goodman M, eds. *Cancer Nursing: Principles and Practice*. Jones and Bartlett Publishers; 2005:1460-1489. Sergentanis TN, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15(10):563-577.

Multiple Myeloma Continuum: Premalignant Conditions



[a]MGRS does not meet criteria for myeloma but has kidney manifestation; kidney biopsy is the gold standard for diagnosis.

CRAB = calcium elevation, renal dysfunction, anemia, bone lesions; M-spike = monoclonal spike; MDE = myeloma-defining event; MGRS = monoclonal gammopathy of renal significance; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MRI = magnetic resonance imaging; PC = plasma clone; SLiM = PC ≥ sixty, light chain, MRI; SMM = smoldering multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Rajkumar SV, et al. *Lancet Oncol.* 2014;15(12):e538-e548. Bridoux F, et al. *Kidney Int.* 2015;87(4):698-711. Terpos E, et al. *Lancet Oncol.* 2021;22(3):e119-e130. Hillengass J, et al. *Lancet Oncol*. 2019;20(6):e302-e312. Ludwig H, et al. *Lancet*. 2023;58:101910.

iStopMM Clinical Study: New Insights About MGUS

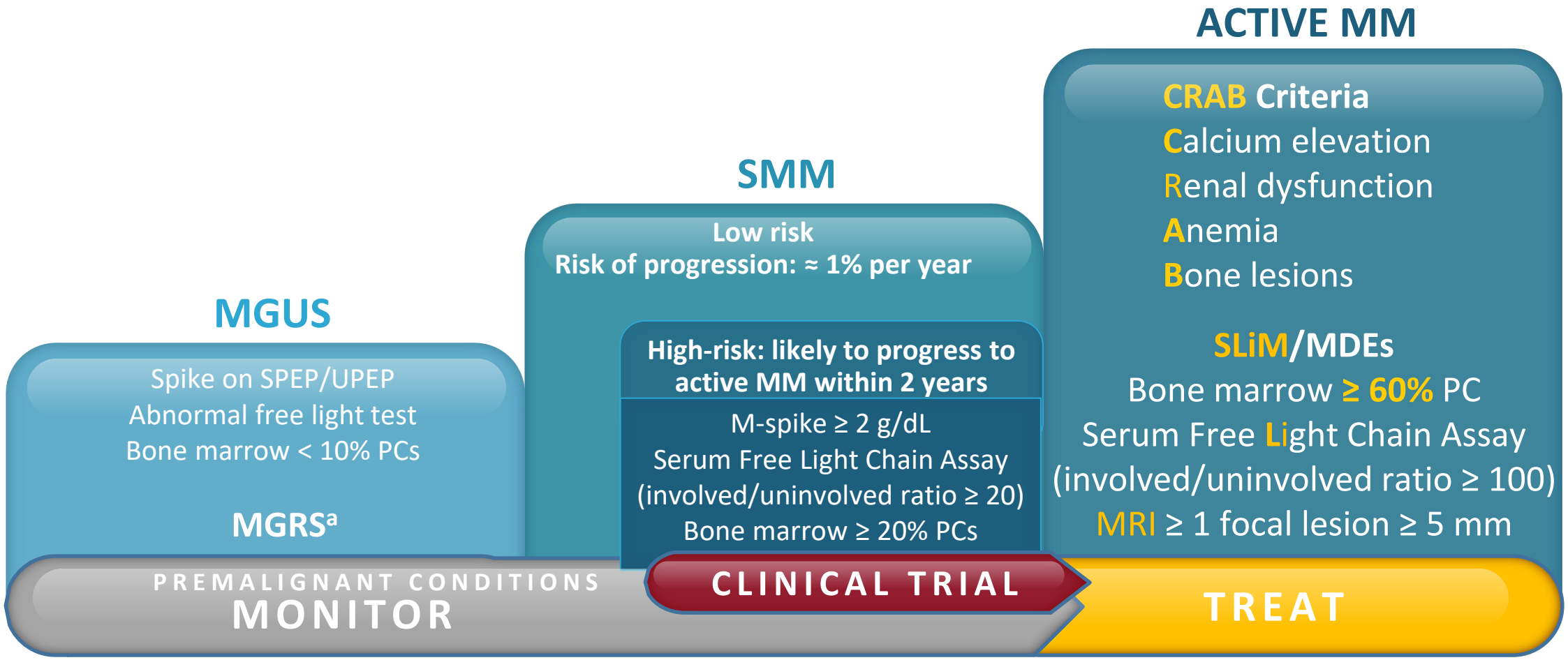
- **75,422** individuals screened in Iceland via serum sample
- Represents **54%** of all Icelanders aged ≥40
- Analysis of study data has provided new insights into MM and related premalignant conditions

- MGUS screening via feasible and leads to early diagnosis and treatment of MM and related disorders
- MGUS screening was not associated with any demonstrable harm
- 4.4% (3,353/75,422) of people had heavy chain MGUS and 0.4% had light chain MGUS
  - Increased rates of thrombotic events in patients with MGUS (especially non-IgM MGUS)
- New reference intervals for serum free kappa FLC, lambda FLC, and FLC ratio according to age for patients with preserved kidney function

WATCH FOR
New iStopMM results as analyses continue

FLC = free light chain; IgM = immunoglobulin M; iStopMM = Iceland Screens Treats or Prevents Multiple Myeloma; MGUS = monoclonal gammopathy of undetermined significance.
Rögnvaldsson S, et al. ASH 2023. Abstr #214. Rögnvaldsson S, et al. ASH 2023. Abstr #216. Long TE, et al . ASH 2023. Abstr #535.

Multiple Myeloma Continuum: Premalignant Conditions



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How Patients With Myeloma Commonly Present

ROUTINE PHYSICAL

- Patient with few/ no symptoms
- Abnormal bloodwork or test result

VISIT FOR SPECIFIC COMPLAINT

- Bone pain, fatigue, or injury
- Abnormal test result (eg, x-ray, blood test)

EMERGENCY ROOM

- Severe pain—often spinal fractures
- Kidney failure

NON-EMERGENCY;
More time for shared decision-making

MEDICAL EMERGENCY;
Need immediate treatment!

Brigle K, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):7-14. Brigle K, et al. *Clin J Oncol Nurs*. 2017;21(5 suppl):60-76. Faiman B, et al. *J Adv Pract Oncol.* 2016;2016:7(suppl 1):17-29. Kurtin S, et al. *J Adv Pract Oncol.* 2016;7(suppl 1):59-70.

CASE 1

CARL*

PATIENT NOTES:

- Pain worsened and he could only complete 10 days of physical therapy
- Returned to primary care → APP ordered imaging, CBC, CMP, and PSA
- Results suspicious for myeloma and APP ordered SPEP and IFE
- Referral to hematologist-oncologist who ordered full myeloma workup

CBC and CMP	CBC remarkable for low Hgb (10.3 g/dL) CMP remarkable for elevated calcium (11.7 mg/dL) Cr 1.1 mg/dL and elevated globulin (6.9 g/dL) PSA normal at 0.7 ng/mL
SPEP	3.1 g/dL IgG kappa monoclonal protein

*HIPAA-compliant, not actual patient name, stock photo.

APP = advanced practice provider; CBC = complete blood count; CMP = comprehensive metabolic panel; Cr = creatinine; Hgb = hemoglobin; HIPAA = Health Insurance Portability and Accountability Act; IFE = immunofixation electrophoresis; IgG = immunoglobulin G; PSA = prostate-specific antigen; SPEP = serum protein electrophoresis.

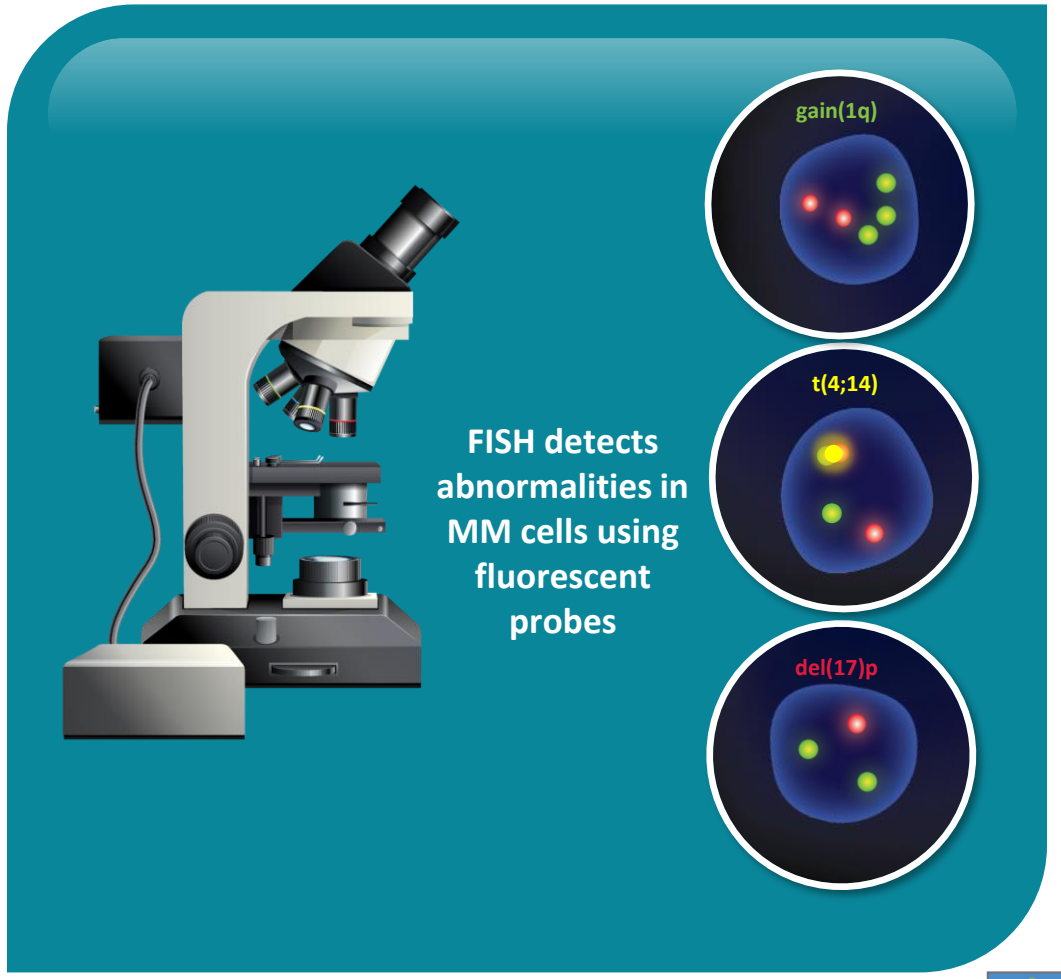
Diagnostic Workup for Multiple Myeloma

LAB TESTS

- Serum protein electrophoresis (SPEP)
- Immunofixation (IFE)
- Urine protein electrophoresis (UPEP)
- CBC + differential, CMP, including albumin, β2 microglobulin, and LDH
- Serum-free light chain assay
- Quantitative immunoglobulins

BONE MARROW BIOPSY

- FISH
- Cytogenetics
- Clonal plasma cell percentage
- Congo red for amyloid



CBC = complete blood count; CMP = comprehensive metabolic panel; del = deletion; FISH = fluorescence in situ hybridization; FLC = free light chain; LDH = lactate dehydrogenase; MM = multiple myeloma; t = translocation.

Ghobrial IM, et al. *Blood*. 2014;124:3380-3388. Rajkumar SV, et al. *Lancet Oncol*. 2014;15:e538-e3548. Faiman B. *Clin Lymphoma Myeloma Leuk*. 2014;14:436-440.

Imaging for Multiple Myeloma

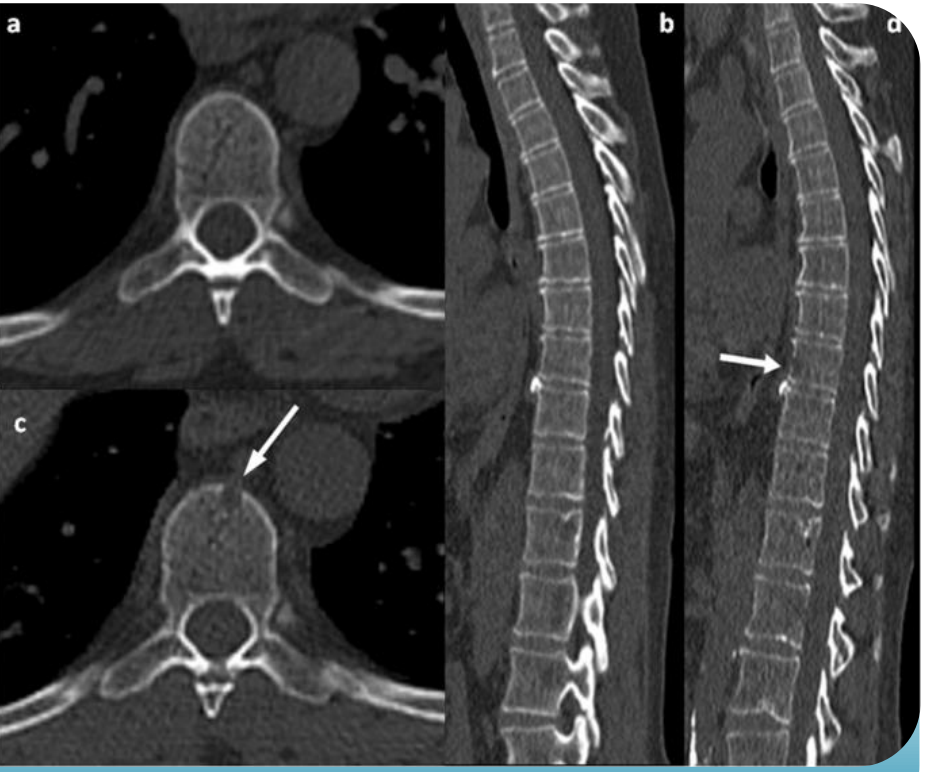


Image: Gavriatopoulou M, et al. *Blood Cancer J*. 2020;10:93

SEVERAL OPTIONS FOR BONE IMAGING

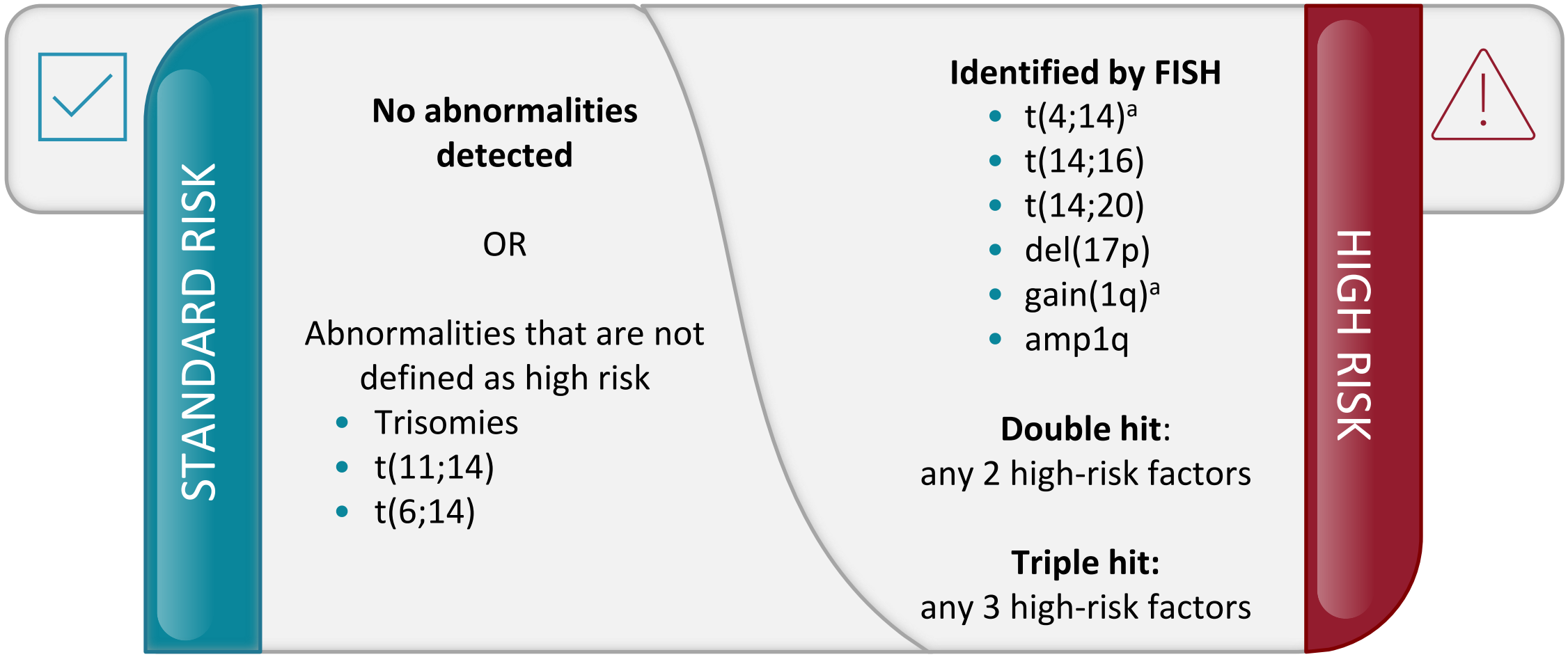
Whole Body Low-Dose CT (WBLDCT)	PET-CT	MRI Whole body (WB) or spine + pelvis
Best for early screening for bone disease	Response assessment: active residual disease	Gold standard to assess bone marrow involvement

Skeletal survey is no longer the standard of care in MM
Bone scan (DEXA) for bone density is not for MM

CT = computed tomography; DEXA = dual-energy x-ray absorptiometry; MM = multiple myeloma; MRI = magnetic resonance imaging; PET = positron emission tomography; WB = whole body; WBLDCT = whole-body low-dose computed tomography.

Brigle K, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):7-14. Hillengass J, et al. *Lancet Oncol*. 2019;20(6):e302-e312. Rome SI, et al. *Clin J Oncol Nurs*. 2017;21(5 suppl):47-59. Faiman B. *Clin Lymphoma Myeloma Leuk*. 2014;14:436-440. Dimopoulous M, et al. *Leukemia.* 2009;23(9):1545-1556.

Risk With Multiple Myeloma



[a]High risk if detected in SMM; intermediate risk in MM according to Rajkumar SV 2022.
del = deletion; FISH = fluorescence in situ hybridization; MM = multiple myeloma; SMM = smoldering multiple myeloma t = translocation.
Rajkumar SV. *Am J Hematol.* 2022;97(8):1086-1107.

R-ISS Staging System for Multiple Myeloma

STAGE	R-ISS	5-YEAR OS	5-YEAR PFS
I	• ISS stage I (serum B2M level < 3.5 mg/L and serum albumin ≥ 3.5 g/dL) • No high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)] • Serum LDH < ULN (varies by institution)	82%	55%
II	• Not R-ISS stage I or III	62%	36%
III	• ISS stage III (serum B2M level > 5.5 mg/L) • High-risk CA [del(17p) and/or t(14;4) and/or t(14;16)] or high serum LDH	40%	24%

Tip: R-ISS calculator available at https://www.mdcalc.com/calc/3842/revised-multiple-myeloma-international-staging-system-r-iss

WATCH FOR

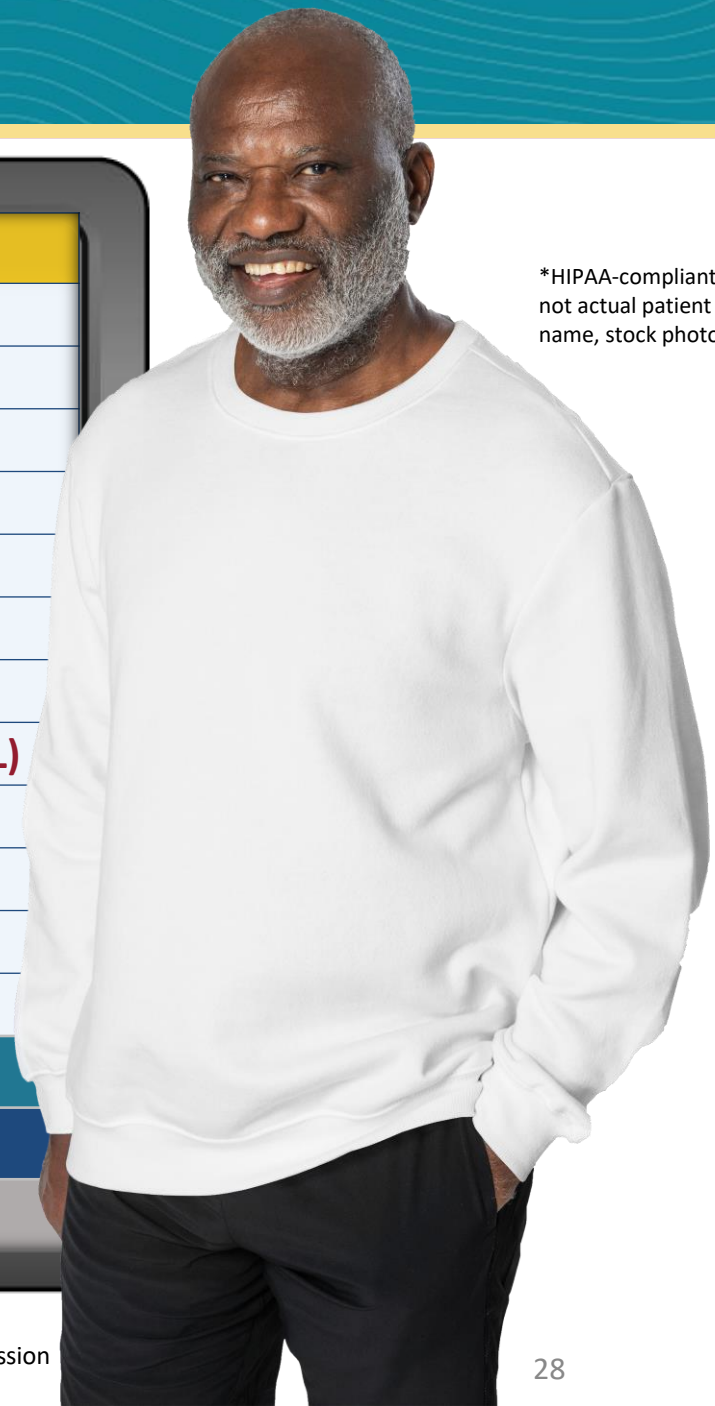
Adoption of the proposed revision to R-ISS: R2-ISS that includes gain 1q risk factor

B2M = β2 microglobulin; CA = chromosomal abnormality; ISS = International Staging System; LDH = lactate dehydrogenase; MM = multiple myeloma; OS = overall survival; PFS = progression-free survival; R-ISS = Revised-ISS; R2-ISS = ISS second revision; ULN = upper limit of normal.

Palumbo A, et al. *J Clin Oncol.* 2015;33:2863-2869. D'Agostino M, et al. *J Clin Oncol.* 2022;40(29):3406-3418.

CASE 1

MYELOMA WORKUP		
Bone Marrow	**Plasma Cells:**	**30% kappa restricted**
	FISH:	No abnormalities detected
Blood	**Calcium:**	**11.7 mg/dL (ULN: 10.6 mg/dL)**
	Albumin:	3.3 mmol/L (LLN: 3.5 mmol/L)
	B2M:	**4.0 mg/dL (ULN: 2.64 mg/dL)**
	LDH:	150 U/mL (ULN: 250 U/mL)
	Creatinine:	1.1 mg/dL (ULN: 1.3 mg/dL)
	Hgb:	**10.3 g/dL (normal range: 13.8-17.2 g/dL)**
	SPEP	**3.1 g/dL IgG kappa monoclonal protein**
	Kappa light chain	**250 g/dL (normal range: 3.3-19.4 g/dL)**
	Lambda light chain	9.8 g/dL (normal range 5.7 to 26.3 g/dL)
	κ/λ-light-chain ratio:	**25.2 (ULN: 1.65)**
Whole Body PET-CT	FDG-avid lesions: T10-T12, L2, lateral right ribs; right humerus	
Whole Spine MRI	T10-T12 lesions, L2 lesion, intact spinal canal	
Diagnosis	**Active MM Stage 2**	



*HIPAA-compliant, not actual patient name, stock photo.

B2M = β2 microglobulin; CT = computed tomography; FDG = 18F-fluorodeoxyglucose; FISH = fluorescence in situ hybridization; GFR = glomerular filtration rate; Hgb = hemoglobin; HIPAA = Health Insurance Portability and Accountability Act; κ/λ = kappa to lambda; κFs = kappa free serum; L = lumbar; LDH = lactate dehydrogenase; LLN = lower limit of normal; MM = multiple myeloma; MRI = magnetic resonance imaging; PET = positron emission tomography; T = thoracic; ULN = upper limit of normal.

IMF: Raising Awareness via Public Service Announcement

Ice-T Talks Health Equity: Real Facts About Multiple Myeloma in the Black Community

International Myeloma Foundation
12.4K subscribers
Subscribe

"Myeloma is among the worst of all cancers for delayed diagnosis."

Drayson M, et al. *Br J Haematol*. 2024;204(2):476-486.

IMF = International Myeloma Foundation.

Actor and Artist ICE-T Raises Awareness of Myeloma in the Black Community. IMF website. Accessed April 2, 2024. https://www.myeloma.org/videos/actor-artist-ice-t-raises-awareness-myeloma-black-community. ICE-T Sets the Record Straight on Multiple Myeloma, It's Not Melanoma. IMF website. Accessed April 2, 2024. https://www.myeloma.org/videos/psa-2-ice-t-sets-record-straight-multiple-myeloma-its-not-melanoma.

Median Age at Diagnosis of MM Varies by Race/Ethnicity

THE MEDIAN AGE AT DIAGNOSIS FOR ALL PATIENTS IS 69 years

62 63 64 **65** **66** 67 68 **69** 70 **71** 72

Hispanic Patients **65** YEARS

Black Patients **66** YEARS

Asian Patients **69** YEARS

White Patients **71** YEARS

MM = multiple myeloma.

Ailawadhi S, et al. *Br J Haematol*. 2012;158:91-98. National Cancer Institute. SEER Stat Fact Sheets: Myeloma. Surveillance, Epidemiology, and End Results Program website. Accessed February 11, 2021. http://seer.cancer.gov/statfacts/html/mulmy.html.

Health Disparities in Multiple Myeloma Among Black Patients

Black patients with MM have **more than double the mortality** compared with White patients

MM is a malignancy with one of the **greatest disparities:** **2- to 3-fold higher incidence of MM** in Black vs White Americans[a]

≈ 10% of Black patients have MGUS; **MM is the most common blood cancer** in Black patients

Black patients are **less likely to receive life-extending therapies,** such as ASCT, IMiDs, and PIs

Black patients tend to achieve better outcomes when they receive equal therapy

Patients of African descent **tend to have lower-risk disease** due to biologic differences in MM

ASCT = autologous stem cell transplant; IMiD = immunomodulatory drug; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; PI = protease inhibitor.

[a]Data derived by calculating the ratio of the average age-adjusted incidence rates for Black and White patients from 2000 to 2013 for the 8 most common malignancies in Black patients, plus all cancer sites and MM. Incidence rates were obtained from National Cancer Institute. Fast stats. Surveillance, Epidemiology, and End Results Program website. Accessed March 3, 2022. https://seer.cancer.gov/.

Dong J, et al. *Blood Cancer J*. 2022;12(2):34. El-Khoury H, et al. ASH 2021. Abstr #152. Pierre A, Williams TH. *Clin J Oncol Nurs.* 2020;24(4):439-443. Greenberg AJ, et al. *Blood Cancer J*. 2015;4:e2713. Baker A, et al. *Blood*. 2013;12(16):3147-3152. Waxman AJ, et al. *Blood*. 2010;116(25):5501-5506. Hari PN, et al. *Biol Blood Marrow Transplant*. 2010;16:395-402. Saraf SL, et al. *Bone Marrow Transplant*. 2013;48:319-320. Rhotagi N, et al. *Am J Clin Oncol*. 2007;30(5):540-548. Ailawadhi S, et al. *Br J Haematol*. 2012;158:91-98. Doroshow D, et al. *Ann Oncol.* 2020;31:S1204. Hultcrantz M, et al. *Blood Cancer Discov.* 2020;1:234-243.

What Can Nurses Do to Combat Disparities in MM Care?

BE AWARE of higher rates and earlier age of onset of MGUS and MM in Black patients

STRIVE to become aware of potential conscious or unconscious biases

ENSURE equal access to centers of excellence and treatments (eg, ASCT, IMiDs, PIs, clinical trials) and supportive care

ENGAGE each patient; be aware of cultural differences

ENCOURAGE Black patients with MM to connect with IMF https://mpower.myeloma.org/

M-POWER CHANGING THE COURSE OF MYELOMA

FREE patient engagement tools from AHRQ: https://www.ahrq.gov/health-literacy/patient-education/index.html

AHRQ = Agency for Healthcare Research and Quality; ASCT = autologous stem cell transplant; IMiD = immunomodulatory drug; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; PI = protease inhibitor.

Dong J, et al. *Blood Cancer J*. 2022;12(2):34. El-Khoury H, et al. ASH 2021. Abstr #152. Pierre A, Williams TH. *Clin J Oncol Nurs.* 2020;24(4):439-443. Greenberg AJ, et al. *Blood Cancer J*. 2015;4:e2713. Baker A, et al. *Blood*. 2013;12(16):3147-3152. Waxman AJ, et al. *Blood*. 2010;116(25):5501-5506. Hari PN, et al. *Biol Blood Marrow Transplant*. 2010;16:395-402. Saraf SL, et al. *Bone Marrow Transplant*. 2013;48:319-320. Rhotagi N, et al. *Am J Clin Oncol*. 2007;30(5):540-548. Ailawadhi S, et al. *Br J Haematol*. 2012;158:91-98. Doroshow D, et al. *Ann Oncol*. 2020;31:S1204. Hultcrantz M, et al. *Blood Cancer Discov*. 2020;1:234-243. International Myeloma Foundation website. Accessed March 4, 2022. http://www.myeloma.org.

CASE 1

CARL*

PATIENT NOTES:

- Felt overwhelmed by cancer diagnosis
- Concerned about side effects of “chemotherapy”
- Concerned about out-of-pocket costs, loss of work, impact on family
- Concerned about long-term survival

*HIPAA-compliant, not actual patient name, stock photo.

HIPAA = Health Insurance Portability and Accountability Act.

Knowledge Is Power: Steep Learning Curve for Newly Diagnosed Patients With Multiple Myeloma

- Patient education is crucial but can be overwhelming
- The shock of diagnosis makes understanding and retaining information difficult
  - Tell patients, but also give written or electronic information they can refer to
  - Engage care partners or extended family
  - Focus on crucial information

NIH NATIONAL CANCER INSTITUTE

https://www.cancer.gov

American Cancer Society®

https://www.cancer.org

Multiple Languages

Free Download or Order From myeloma.org

IMF Videos

IMF Patient and Family Seminar 2024 — Boca Raton,

IMF Website

http://myeloma.org

Leukemia & Lymphoma Society

https://www.lls.org

IMF = International Myeloma Foundation.

Important Health Protection Education for Newly Diagnosed Patients With Multiple Myeloma

INFECTION PREVENTION

- Ensure handwashing, hygiene
- Growth factor (eg, filgrastim)
- IVIG for hypogammaglobulinemia
- Immunizations (NO live vaccines)
  - NEW RSV vaccine
  - Shingles vaccine: zoster vaccine recombinant, adjuvanted
  - COVID-19 vaccination + booster(s)
  - Pneumococcal 20-valent conjugate vaccine
  - Seasonal inactivated influenza vaccine (× 2 or high dose)
- Avoid contact with sick people

KIDNEY HEALTH

Risks

- Active MM (M-protein, casts)
- High calcium

Prevention

- Avoid certain medications (contrast dyes, NSAIDs)
- Hydration

Treatment

- Address underlying myeloma causing kidney dysfunction
- Dose adjustments may be needed for reduced kidney function

BONE HEALTH

- Hypercalcemia from bone destruction can affect the kidneys
- ≈ 85% of patients with MM develop bone disease

Monitor

- Report new or worsening bone pain

Medical testing or intervention

- Monitor serum calcium levels
- Imaging may be needed depending on type and location of pain (eg, MRI, PET-CT)
- Bone-modifying agents

CT = computed tomography; IVIG = intravenous immunoglobulin; M-protein = monoclonal protein; MM = multiple myeloma; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PET = positron emission tomography; RSV = respiratory syncytial virus.

Brigle K, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):7-14. Hillengass J, et al. *Lancet Oncol*. 2019;20(6):e302-e312. Faiman B, et al. *Clin J Oncol Nurs.* 2017;21(5 suppl):19-36. Faiman B, et al. *Clin J Oncol Nurs.* 2011;15(suppl):66-76. Miceli TS, et al. *Clin J Oncol Nurs.* 2011;15(4):9-23. Rome SI, et al. *Clin J Oncol Nurs*. 2017;21(5 suppl):47-59. Dimopoulous M, et al. *Leukemia.* 2009;23(9):1545-1556. Brigle K, et al. *Clin J Oncol Nurs.* 2017;21(5 suppl):60-76.

Bone-Modifying Agents

IMWG
INTERNATIONAL MYELOMA WORKING GROUP
A Research Division of International Myeloma Foundation

Recommendation: Bone-strengthening agents should be administered for <u>at least 12 months</u> to all patients with newly diagnosed MM, with or without bone disease

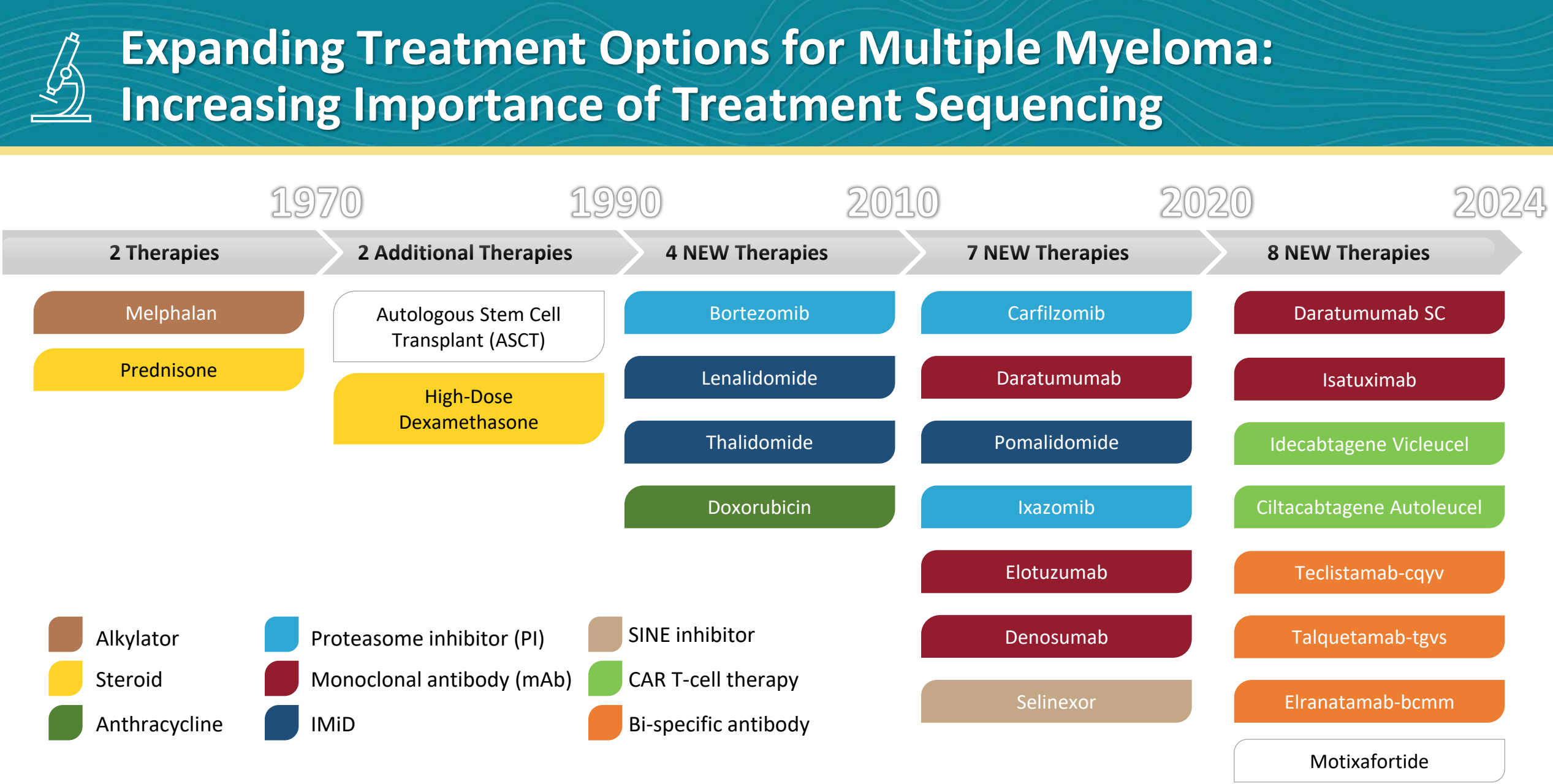
Agent	Notes
Zoledronic acid	• Preferred agent • Also indicated for MM-related hypercalcemia • PFS and OS benefit
Denosumab	• May also be used, particularly in patients with kidney impairment • May prolong PFS in patients who are newly diagnosed with MM and are ASCT-eligible • Discontinuation can be challenging due to rebound effect
Pamidronic acid	• May be used if other agents are not available

ASCT = autologous stem cell transplant; MM = multiple myeloma; OS = overall survival; PFS = progression-free survival.

Terpos E, et al. *Lancet Oncol.* 2021;22(3):e119-e130.

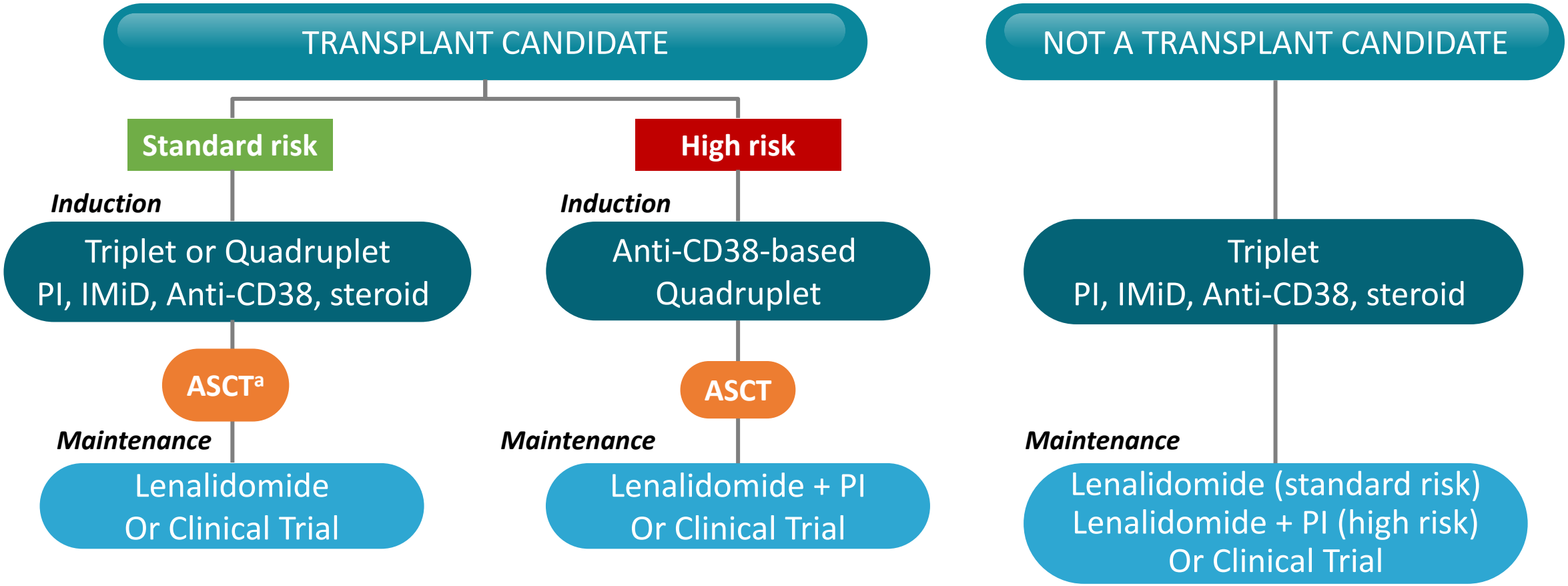
NURSE LEADERSHIP BOARD

Expanding Treatment Options for Multiple Myeloma: Increasing Importance of Treatment Sequencing



CAR = chimeric antigen receptor; IMiD = immunomodulatory drug; SC = subcutaneous; SINE = selective inhibitor of nuclear export.
Tariman J. *Nurs Clin North Am.* 2017;52(1):65-81. DRUGS@FDA.gov.

Newly Diagnosed MM: Frontline Therapy Sequence



[a]ASCT may be delayed until first relapse.

ASCT = autologous stem cell transplant; IMiD = immunomodulatory drug; PI = proteosome inhibitor.

Rajkumar SV. 2024 Myeloma Algorithm. Accessed March 25, 2024. https://clinicaloptions.com/CE-CME/oncology/2024-mm-algorithm/18440-26989. Rajkumar SV. *Am J Hematol.* 2022;97(8):1086-1107. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024.

Daratumumab: Anti-CD38 Monoclonal Antibody

- **Monoclonal antibody targeting CD38**
  - Original IV dosing and SC formulation
- **Multiple indications for MM**
  - See prescribing information for details
- **Clinical pearls**
  - SC dose form for SC only; IV for IV only
  - Antibody interference—type and cross BEFORE starting
  - Premeds: corticosteroids, antipyretics, antihistamine, and montelukast
  - IRR with IV: ≈ 50% (mostly grade 1 and 2, in first or second infusion)
  - IRR with SC: ≈ 9%; systemic reactions 10%
  - Post-med: oral corticosteroid for 2 days
  - Herpes prophylaxis
  - Screen for hepatitis titers if HepB core antibody prophylaxis with entecavir
  - Remember appropriate prophylaxis for combination partner drugs
  - Educate patients/care partners about expectations

SC injection

Dara-Rd, Dara-VMP
(First-line non-transplant)

Dara-VTd
(First-line transplant eligible)

Dara-Vd, Dara-Pd, Dara-Kd
(1-3 prior therapies)

Dara monotherapy
(3 prior therapies or refractory to PI and IMiD)

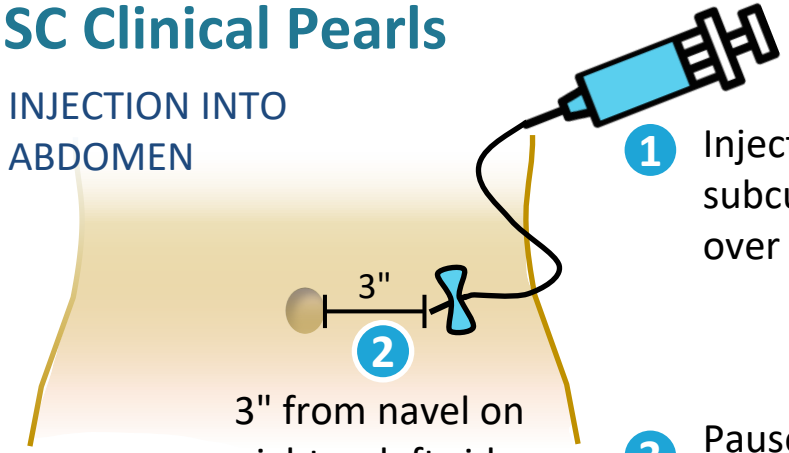
Dara = daratumumab; Kd = carfilzomib dexamethasone; IMiD = immunomodulatory drug; IRR = infusion-related reaction; IV = intravenous; MM = multiple myeloma; Pd = pomalidomide dexamethasone; PI = proteasome inhibitor; Rd = lenalidomide dexamethasone; SC = subcutaneous; Vd = bortezomib dexamethasone; VMP = bortezomib melphalan prednisone; VTd = bortezomib thalidomide dexamethasone.

DARZALEX® (daratumumab) Prescribing Information. DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) Prescribing Information. Gleason C, et al. *J Adv Pract Oncol.* 2016;7(suppl 1):53-57.

Daratumumab: Anti-CD38 Monoclonal Antibody (cont.)

SC Clinical Pearls

INJECTION INTO ABDOMEN

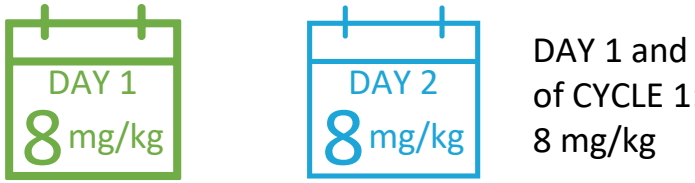


1. Inject 15 mL into subcutaneous tissue over 3 to 5 minutes
3. Pause or slow if patient experiences pain

IV Clinical Pearls

SLOW FIRST INFUSION

ALTERNATIVE: DIVIDED FIRST INFUSION



SC or IV: SCHEDULES DEPEND on REGIMEN: CHECK PRESCRIBING INFORMATION

Example: 4-week cycle with Rd

- Injection/infusion becomes less frequent
- If no injection/infusion reaction after 3 doses, consider discontinuing corticosteroid pre/post medications

IV = intravenous; Rd = lenalidomide dexamethasone; SC = subcutaneous.

DARZALEX® (daratumumab) Prescribing Information. DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) Prescribing Information.

PERSEUS: Phase 3 VRd ± Daratumumab in Transplant-Eligible Patients With Newly Diagnosed MM

Multi-drug regimens produce deeper responses

Study Design: Multicenter, Randomized, Open Label

- N = 709 patients with NDMM, aged 18-70 years, ECOG PS ≤ 2
- Randomized to

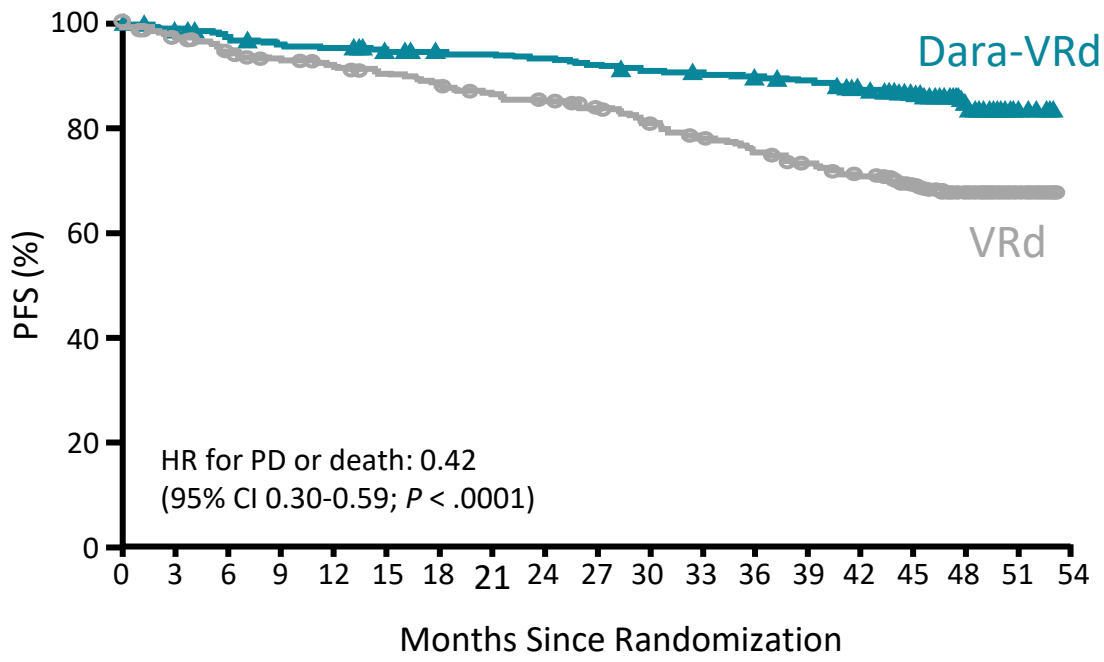
  Dara-VRd → ASCT → Dara-VRd → Dara-R → Dara-R (if MRD+) or R (MRD-)

  VRd → ASCT → VRd → Dara-R → R

Secondary Endpoints

- **Improvements in CR or better rates with Dara-VRd vs VRd across all subgroups**
- 64% of patients in Dara-VRd arm + Dara-R maintenance discontinued Dara after reaching sustained MRD negativity per protocol
- OS data immature
  - Current mortality rate with Dara-VRd vs VRd: 9.6% vs 12.4% (HR: 0.73)

PFS (Primary Endpoint)



Patients at Risk, n

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

ASCT = autologous stem cell transplant; CR = complete response; Dara = daratumumab; Dara-R = daratumumab lenalidomide; Dara-VRd = daratumumab bortezomib lenalidomide dexamethasone; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PD = progressive disease; PFS = progression-free survival; R = lenalidomide; VRd = bortezomib lenalidomide dexamethasone.

Sonneveld P, et al. ASH 2023. Abstr #LBA-1. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313.

Real-World Data: Dara-VRd vs VRd

Study Design: Retrospective Analysis

- N = 1326 patients with NDMM transplant-eligible disease; either standard risk or high risk

  Dara-VRd → ASCT → R (std risk) OR PI + IMiD (high risk)

  VRd → ASCT → R (std risk) OR PI + IMiD (high risk)

Conclusions

- Response rates improved from post-induction to post-transplant phase
- Median follow-up: Dara-VRd 18 months; VRd 87 months
- MRD assessment is ongoing
- **Real-world data on Dara-VRd are generally consistent with clinical trial results**

Outcome	Dara-VRd	VRd
PFS rate, %		
1 year	98	93
2 years	93	82
3 years	91	69
4 years	85	61
OS rate, %		
1 years	99	97
2 years	94	91

ASCT = autologous stem cell transplant; Dara-R = daratumumab lenalidomide; Dara-VRd = daratumumab bortezomib lenalidomide dexamethasone; IMiD = immunomodulatory drug; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression-free survival; PI = proteosome inhibitor; std = standard; VRd = bortezomib lenalidomide dexamethasone.

Joseph NS, et al. ASH 2023. Abstr #647.

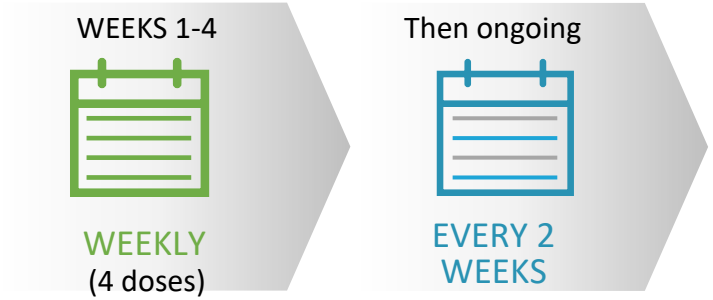
Isatuximab: Anti-CD38 Monoclonal Antibody

Safety

- IRR (38%): the most-common AR specific to isatuximab
- Isa-Pd common ARs: cytopenias, IRR, infections, dyspnea, GI ARs

Dosing

- Slower first and second infusions
- Weekly for 4 weeks then every 2 weeks



- Discontinue if IRR grade ≥ 3

WATCH FOR

New indication(s) for patients with newly diagnosed MM expected this summer

Isa-Kd
(1-3 prior therapies)

Isa-Pd
(≥ 2 prior therapies: IMiD and PI)

Clinical Pearls

- IRR protection: premedicate with
  - Dexamethasone: 40 mg oral or IV (or 20 mg for patients aged ≥ 75 years)
  - Acetaminophen: 650 mg to 1000 mg
  - H2 antagonists
  - Diphenhydramine: 25 mg to 50 mg oral or IV; IV preferred for at least the first 4 infusions
- Antibody interference—type and cross BEFORE starting
- Prophylaxis for herpes virus and DVT
- No dose adjustments for isatuximab

AR = adverse reaction; dex = dexamethasone; DVT = deep vein thrombosis; GI = gastrointestinal; H = histamine; IMiD = immunomodulatory drug; Isa = isatuximab; IRR = infusion-related reaction; IV = intravenous; Kd = carfilzomib dexamethasone; MM = multiple myeloma; Pd = pomalidomide dexamethasone; PI = proteasome inhibitor.

Wilmoth J, et al. *Clin J Oncol Nurs.* 2021;25(6):706-712. SARCLISA® (isatuximab) Prescribing Information. Goldschmidt H, et al. ASH 2021. Abstr #463.

Isatuximab: IsKia Phase 3 in Patients With Newly Diagnosed MM

WATCH FOR

IMROZ phase 3 clinical trial results in patients with NDMM (non-transplant)

Study Design: Multicenter, Open-Label

- Transplant-eligible NDMM
- N = 302 randomized to

  Isa-KRd → ASCT → Isa-KRd (n = 151)

  KRd → ASCT → KRd (n = 151)

Results

- **Increase in MRD-negativity rate in patients treated with Isa-KRd observed across all subgroups**

Multi-drug regimens produce deeper responses

Outcome	Isa-KRd (n = 151)	KRd (n = 151)
MRD negativity, by cytogenic risk (NGS 10^{-5} cutoff), %		
0 HRCAs	79	72
1 HRCA	78	65
2+ HRCAs	77	53
MRD negativity, by cytogenic risk (NGS 10^{-6} cutoff), %		
0 HRCA	65	48
1 HRCA	69	53
2+ HRCA	77	27

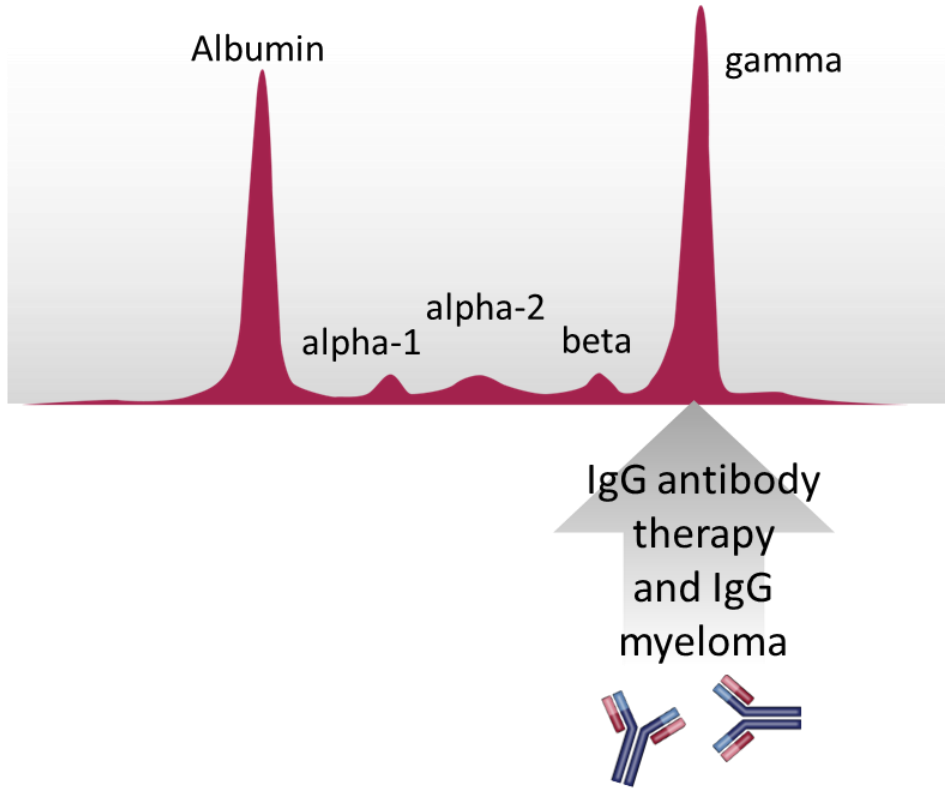
HRCA defined as presence of del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3q23), gain (1q21) or amp(1q21); 2+ HRCA categorized as very high risk.

amp = amplification; ASCT = autologous stem cell transplant; del = deletion; Isa-KRd = isatuximab carfilzomib lenalidomide dexamethasone; HRCA = high-risk cytogenetic abnormality; Isa = isatuximab; KRd = carfilzomib lenalidomide dexamethasone; MM = multiple myeloma; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; NGS = next-generation sequencing.

Gay F, et al. ASH 2023. Abstr #4.

Special Considerations With Antibody Therapy

- Potential interference with laboratory tests
  - Co-migration of therapeutic antibodies with M-protein: overestimation of M-protein and reduced apparent CR rates
- Solutions
  - Awareness
  - Laboratory assays to minimize effects (eg, high-resolution mass spectrometry)



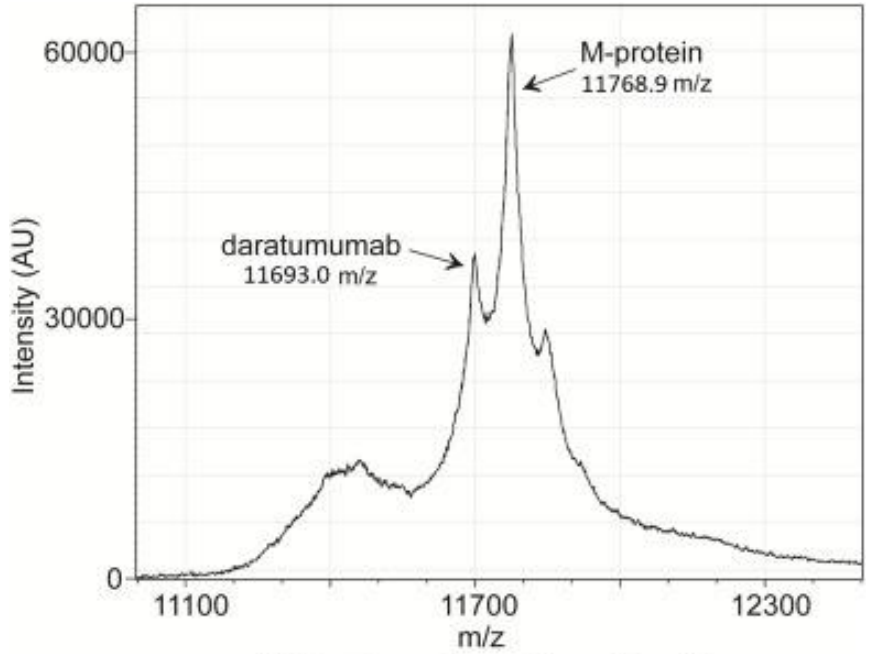
Daratumumab, isatuximab, and elotuzumab (to be discussed later) are all IgG antibodies

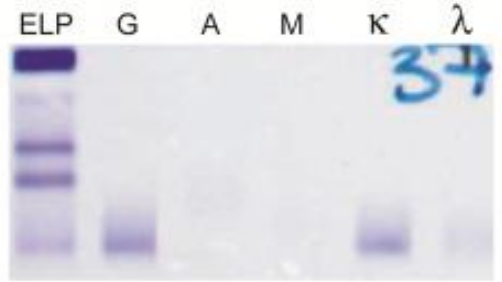
CR = complete response; IgG = immunoglobulin G; M-protein = monoclonal protein.
Mills JR, Murray DL. *J Appl Lab Med.* 2017;1(4):421-431.

Mass Spectrometry: Coming Soon

- Some centers already have mass spectrometry testing in routine clinical use
- Patients with multiple myeloma can be followed by newer mass spectrometric methods → replaces SPEP and IFE
- Mass spectrometry provides improved specificity in finding M-proteins
- Mass spectrometry provides improved specificity in discriminating between therapeutic monoclonal drugs and m-proteins than other techniques
- Mass spectrometry also has a role in amyloidosis (eg, it has improved accuracy for typing amyloid plaques and has led to the discovery of new types of amyloid)

Mass spectrometry can resolve antibody interference





IFE cannot distinguish between therapeutic IgG antibodies and IgG M-protein

IFE = immunofixation electrophoresis; IgG = immunoglobulin G; SPEP = serum protein electrophoresis.

Murray DL, Dasari S. *Clin Lab Med.* 2021;41(2):203-219. Deulofeu M, et al. *ACS Chem Neurosci.* 2023;14(2):300-311. Moore LM, et al. *Clin Chim Acta.* 2019;492:91-94.

Maintenance Therapy Recommended for Patients With MM

Multiple clinical studies have confirmed the benefits of maintenance therapy in

- Patients with MM after ASCT
- Patients with MM after induction therapy (delayed transplant)
- Patients with MM after induction (no transplant)

Questions remain

- How long?
- Which drug(s)?

WATCH FOR

New studies that aim to

- Provide new options for maintenance
- Optimize length of maintenance therapy

ASCT = autologous stem cell transplant; HR = hazard ratio; ISS = International Staging System; Len = lenalidomide; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression-free survival.

McCarthy PL, et al. *J Clin Oncol.* 2017;35(29):3279-3289. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024.

Maintenance Therapy Nursing Implications

- Patients on therapy for a long time: AE management, adherence, treatment fatigue, no pregnancy with lenalidomide
  - Most common reasons for early discontinuation AEs (56%), patient preference (23%)
- May encounter reimbursement challenges with maintenance therapy (begin authorization early, follow up)
- Short-term vs long-term effects
  - Many AEs subside after the first few months
  - Health screening related to long-term use
- Patients living longer: survivorship care, coordination with PCP, emphasis on healthy behaviors
- Patient advocacy: understanding patient's changing needs/desires; advocating with extended health care team

Minimum Standard of Care

Lenalidomide maintenance:
10 or 15 mg on
days 1 to 28 of a 28-day cycle

Lenalidomide + bortezomib
Recommended for high-risk

Bortezomib maintenance:
1.3 mg/m^2 every 2 weeks

Ixazomib maintenance:
3 or 4 mg, days 1, 8, and 15 in
a 28-day cycle in TOURMALINE-MM3

AE = adverse event; PI = proteasome inhibitor; PCP = primary care provider.

Bilotti E, et al. *Clin J Oncol Nurs.* 2011;15(4 suppl). Kurtin S. In: Tariman JD, et al, eds. *Multiple Myeloma: A Textbook for Nurses*. 2nd ed. 2015. Dimopoulous MA, et al. *Lancet*. 2019;393(10168):253-264. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024. Zhang S, et al. *Blood Cancer J.* 2020;10:33. Rajkumar SV. *Am J Hematol.* 2022;97(8):1086-1107. Nunnelee J, et al. *J Clin Med.* 2022 Oct; 11(19): 5794.

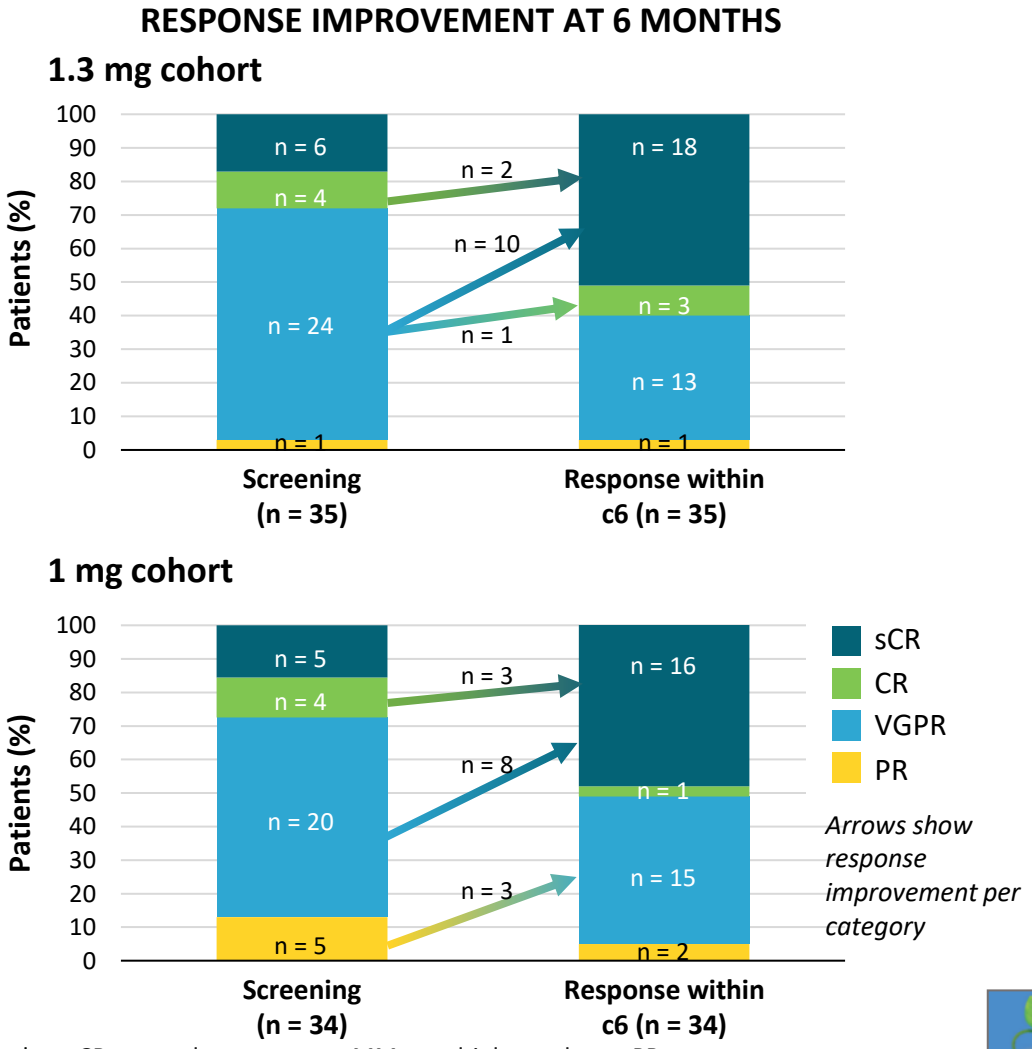
Iberdomide: CELMoD in Development

Study Design: Phase 2 Iberdomide Maintenance

- Post-ASCT patients with MM treated with iberdomide on days 1 to 21 of 28-day cycle
  - 1.0 mg n = 34
  - 1.3 mg n = 35
- 14% had high-risk disease[a]

Results

- Deepening of responses after 6 months of iberdomide maintenance
- Most common grade 3+ AEs: neutropenia (21% in 1.0 mg cohort and 46% in 1.3 mg cohort), infections (3% and 14%), fatigue/asthenia (12% and 14%)
- No ≥ grade 3 thrombocytopenia, anemia, diarrhea, VTE, or neuropathy



[a]High-risk defined as del(17p), t(4;14), and/or t(14;16).

AE = adverse event; ASCT = autologous stem cell transplant; C6 = cycle 6; CELMoD = cereblon E3 ligase modulatory drug; CR = complete response; MM = multiple myeloma; PR = partial response; sCR = stringent complete response; VGPR = very good partial response; VTE = venous thromboembolism.

Van de Donk NWCJ, et al. ASH 2023 #208.

SHARE Approach to Shared Decision-Making

Benefits to Healthcare Professionals

- Improved quality of care delivered
- Increased patient satisfaction

Benefits to Patients

- Improved patient experience of care
- Improved patient adherence to treatment recommendations using the SHARE Approach builds a trusting and lasting relationship between healthcare professionals and patients

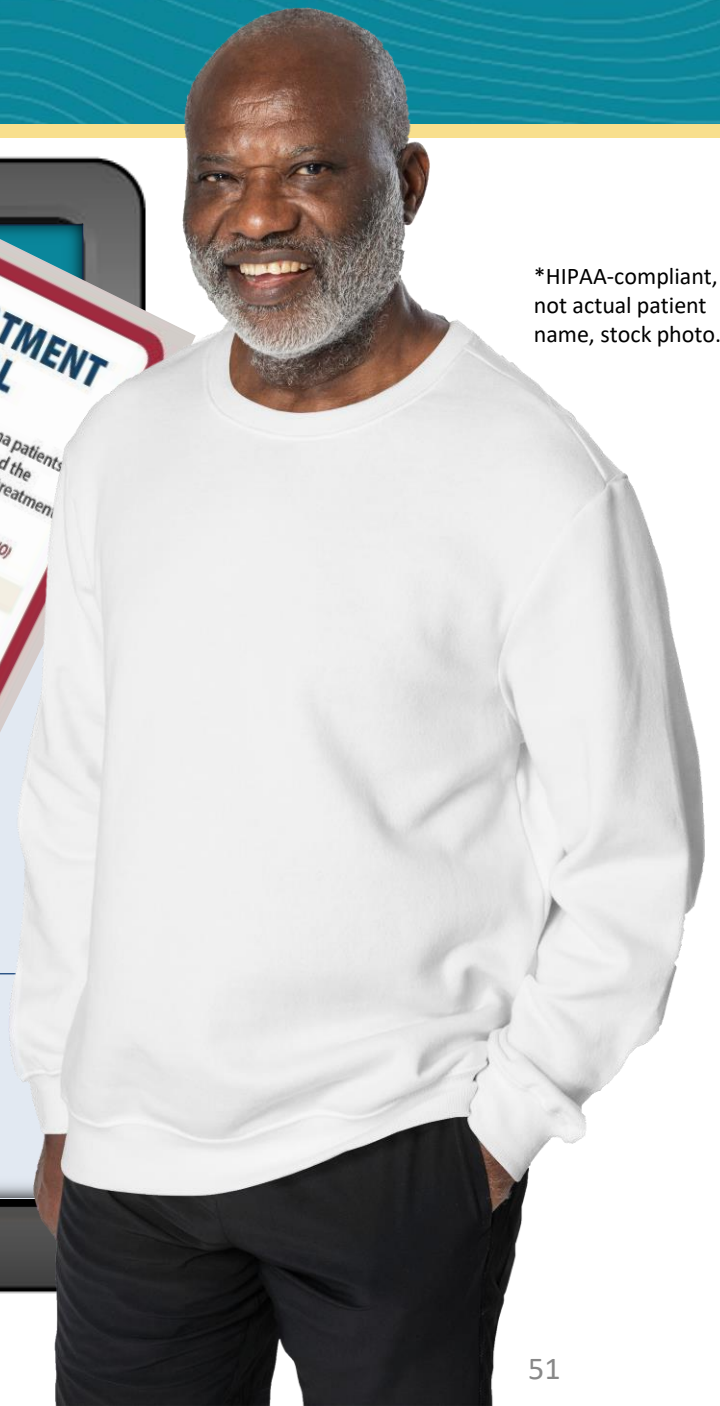
FREE professional education and training
https://www.ahrq.gov/health-literacy/professional-training/index.html

Agency for Healthcare Research and Quality website. Accessed March 25, 2024. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html.

CASE 1

CARL*

- Shared decision-making:
  - Treatment goals discussion
  - Explore treatment options:
    - Clinical trial options
    - Treatment risk vs benefit
    - Side effects
  - Priorities and preferences
  - Agree on a treatment plan



*HIPAA-compliant, not actual patient name, stock photo.

HIPPA = Health Insurance Portability and Accountability Act; IMF = International Myeloma Foundation.

IMF Myeloma Treatment Discussion Tool. Accessed March 28, 2023. https://m-powercharlotte.myeloma.org/wp-content/uploads/Myeloma-Treatment-Discussion-Tool.pdf.

CASE 1

CARL*

TREATMENT	Dara-VRd Shared decision-making
ASCT	Referral for consult with transplant center
MAINTENANCE	Planned: R or clinical trial

Remember:
- ✓ Shingles prevention
- ✓ DVT prophylaxis
- ✓ Monitor sugars

*HIPAA-compliant, not actual patient name, stock photo.

ASCT = autologous stem cell transplant; Dara = daratumumab; DVT = deep vein thrombosis; HIPAA = Health Insurance Portability and Accountability Act; Dara-VRd = daratumumab bortezomib lenalidomide dexamethasone. R = lenalidomide.

How Well Treatment Is Working: IMWG Myeloma Response and Relapse Criteria Assessment

CR	CR: **myeloma protein undetectable** in serum or urine (negative immunofixation); **no more than 5% plasma cells** in bone marrow; no new lytic lesions; plasmacytomas resolved
VGPR	**90% reduction** in myeloma protein
PR	At least **50% reduction** in myeloma protein
MR	
SD	
PD	

Further categorization of CR: sCR, MRD-negative

For Nurses:

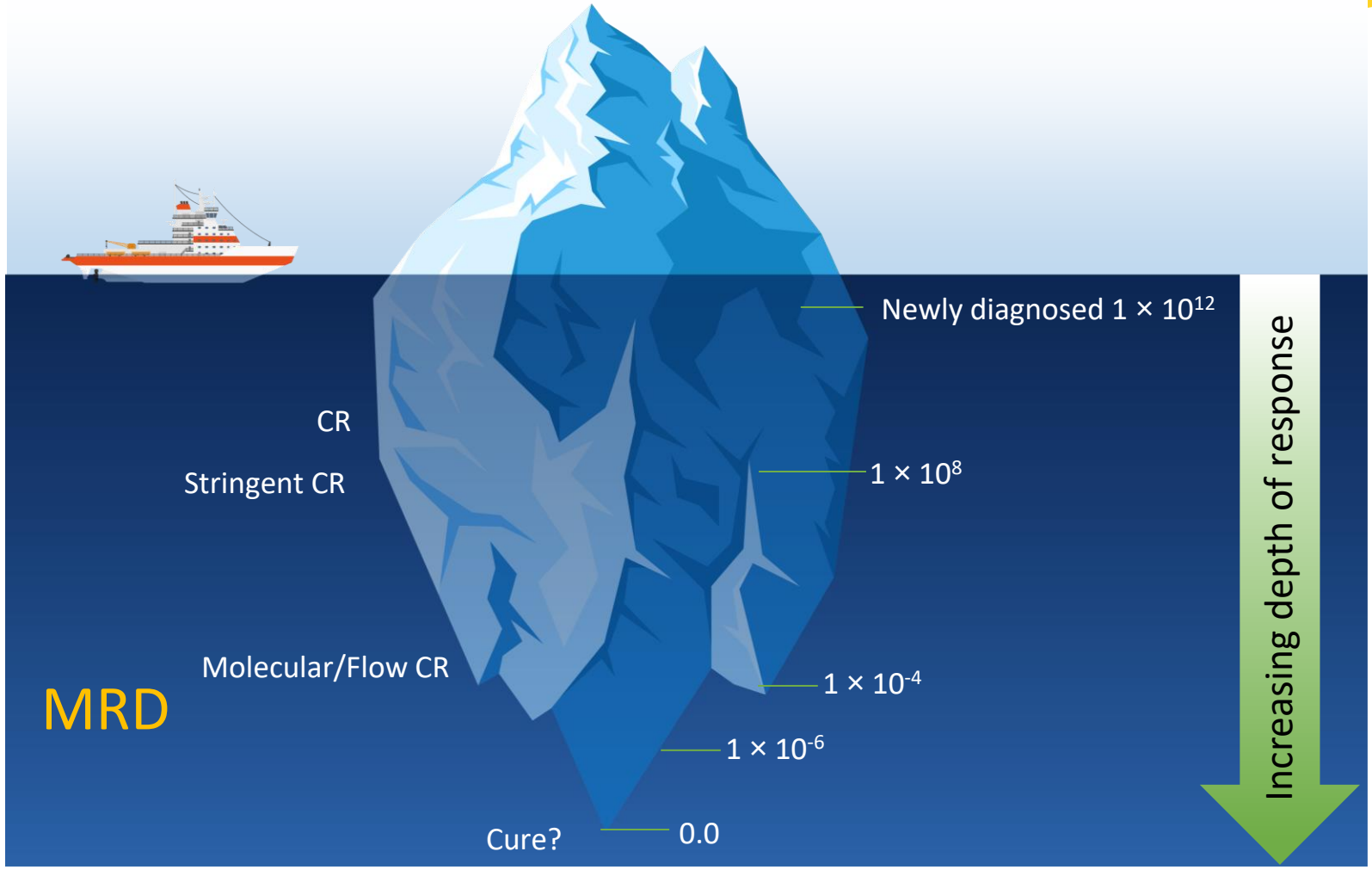
- ✓ Order labs regularly
- ✓ Encourage patients to know who is monitoring
- ✓ Monitor for relapse
  - CRAB symptoms OR increase of 25% in M-protein from the lowest point

CR = complete response; CRAB = calcium elevation, renal dysfunction, anemia, bone lesions; IMWG = International Myeloma Working Group; M-protein = monoclonal protein; MR = minimal response (only in relapsed); MRD = minimal residual disease; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

Palumbo A, et al; International Myeloma Working Group. *J Clin Oncol.* 2014;32:587-600. Durie BM, et al; International Myeloma Working Group. *Leukemia.* 2006;20(9):14671473. Kumar S, et al. *Lancet Oncol.* 2016;17(8):e328-e346.

No Detectable MRD Is Predictive of Better Outcomes

The FDA ODAC committee voted unanimously on April 12, 2024 that data supports the use of MRD as an endpoint for accelerated approval of new treatments for MM



Key concept:
Deeper responses
(less residual disease)
generally means better patient outcomes

MANY ways to get to deeper responses:

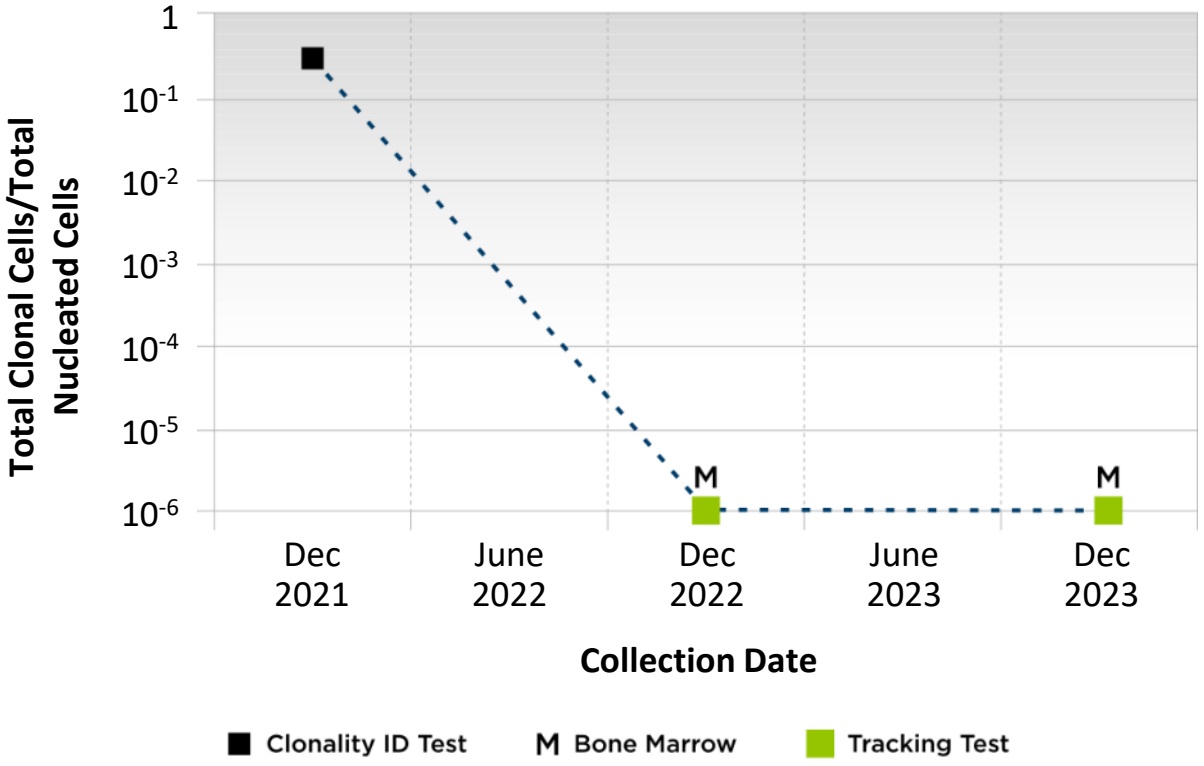
- Multidrug regimens
- ASCT
- Longer therapy duration (eg, continuous regimens or maintenance)
- New therapies that produce deep responses

ASCT = autologous stem cell transplant; CR = complete response; MRD = minimal residual disease.

Kumar S, et al. *Lancet Oncol.* 2016;17(8):e328-e346. Medina-Herrera A, et al. *Cancers (Basel).* 2023;15(14):3687.

MRD Testing

ClonoSEQ MRD Results



Role of the Nurse in MRD Testing:

The Why, When, How, and What

WHY?	• Predict outcomes • Support treatment decisions?
WHEN?	• VGPR or better • Often prior to transplant or cellular therapy • Often retest at set intervals (eg, every 6 months or annually)
HOW?	• ClonoSEQ—FDA cleared for diagnostic use • Within a clinical trial protocol
WHAT DO THE TESTS MEAN FOR PATIENTS?	• Nice-to-know vs need-to-know information

ASCT = autologous stem cell transplant; FDA = US Food and Drug Administration; MRD = minimal residual disease; VGPR = very good partial response.

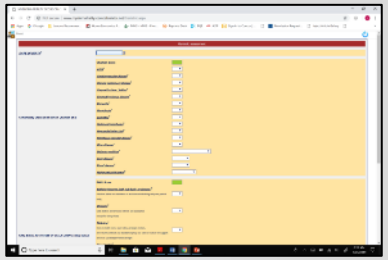
Munshi N, et al. *Blood Adv.* 2020;4(23):5988-5999. ClonoSEQ website. Accessed March 15, 20224. https://www.clonoseq.com/. ClonoSEQ® [technical summary]. Seattle, WA. Adaptive Biotechnologies; 2020. Accessed March 23, 2024. https://www.clonoseq.com/technical-summary/.

Consider Frailty of Patients With MM and Individualize Care

Fitness evaluation → Adapted treatment

Online myeloma frailty score calculator at
http://www.myelomafrailtyscorecalculator.net/

Calculates frailty score based on age, comorbidities, and ability to manage daily activities



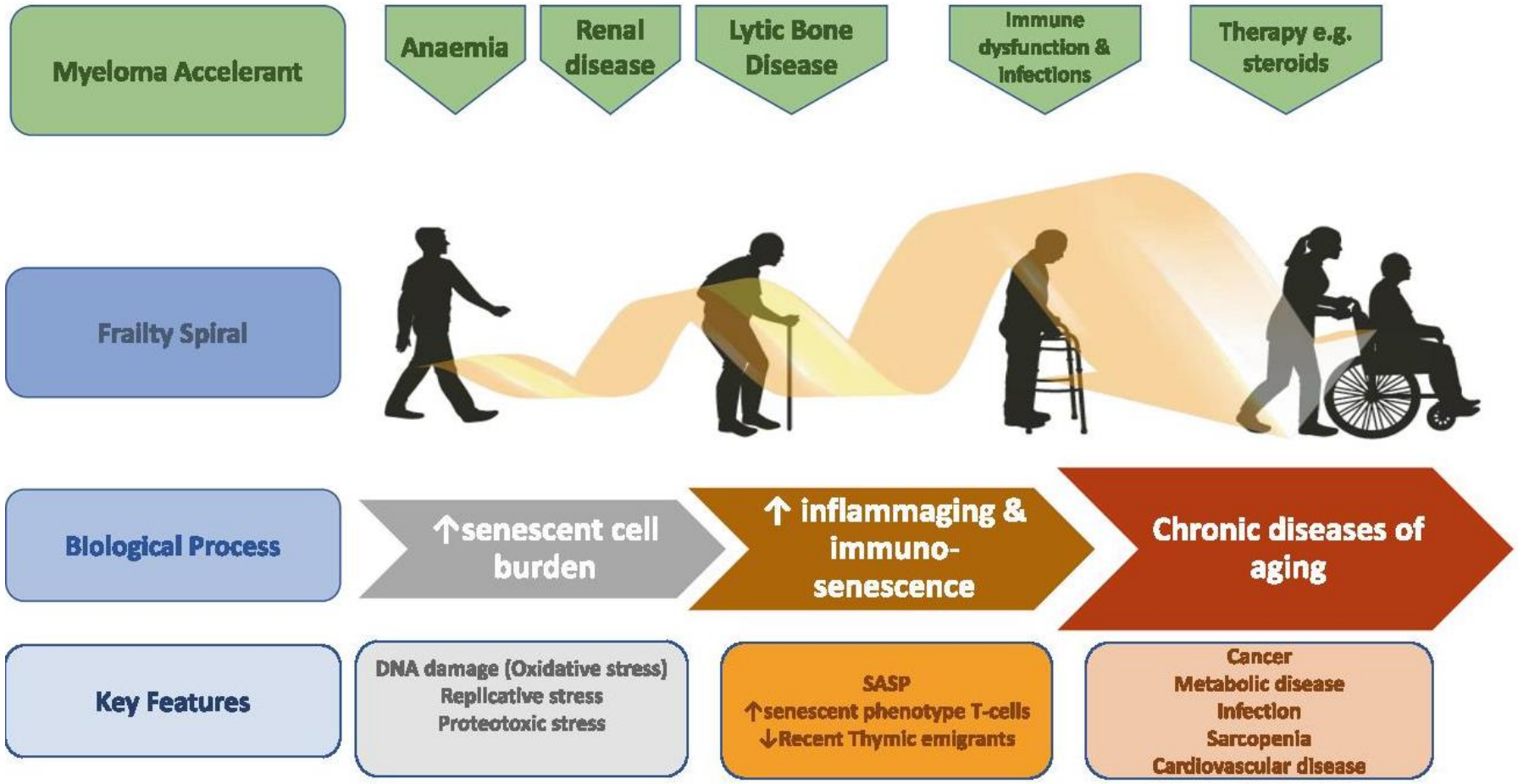
Score	Patients (%)	3-Year Survival (%)	Treatment Discontinuation (%)
0 (fit)	39	84	17
1 (intermediate)	31	76	22
≥ 2 (frail)	31	57	25

- Consider the appropriateness of ASCT
- Dose adjustments for tolerability (eg, low-dose dexamethasone)
- Anti-CD38 mAb-containing regimens or reduced intensity regimens like RVD-lite
- Proactive AE management to avoid disability and downward spiral

AE = adverse event; ASCT = autologous stem cell transplant; mAb = monoclonal antibody; RVD = lenalidomide bortezomib dexamethasone.

Grant SJ, et al. *Hematology Am Soc Hematol Educ Program (2021).* 2021(1):46-54. O' Donnell EK, et al. *Br J Haematol.* 2018;182(2):222-230.Palumbo A, et al. *Blood.* 2015;125(13):2068-2074. International Myeloma Working Group. Myeloma Frailty Score Calculator. Accessed April 5, 2024. http://www.myelomafrailtyscorecalculator.net/

Frailty Spiral: MM May Accelerate Age-related Physiological Decompensation



Cook G, et al. *Leukemia.* 2020;34(9):2285-2294.

Survivorship Care Plans Are Important and Recommended for Each Survivor

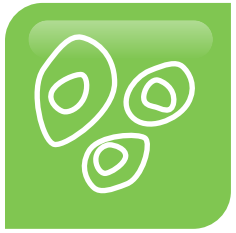
National Academy of Medicine Recommendation: A Survivorship Care Plan for Each Survivor

- **Record of care**
  - Diagnosis, including diagnostic tests and results
  - Treatments received, total dosage, responses, toxicities
  - Other supportive services (psychosocial, etc)
  - Contact information for key providers
  - Point of contact for continuing care
- **Follow-up plan**
  - Ongoing health maintenance therapy/testing
  - Recommended screenings
  - Late/Long-term effects of treatments
  - Recommendations/Resources for healthy behaviors, support, etc

PCP = primary care provider.

Institute of Medicine. Cancer Survivorship Care Planning. Fact Sheet Nov 2005. Accessed March 17, 2023. https://apos-society.org/wp-content/uploads/2016/06/factsheetcareplanning.pdf.
Salz T, et al. *Cancer.* 2014;120(5):722-730. Bilotti E, et al. *Clin J Oncol Nurs.* 2011;15(4 suppl):25-40. Kurtin S. In: Tariman JD, et al, eds. *Multiple Myeloma: A Textbook for Nurses*. 2nd ed. 2015.

Summary



MM is a cancer of the plasma cells. Active MM, defined by **CRAB criteria** and/or myeloma-defining events (**SLiM**), requires treatment. **MGUS and SMM are premalignant conditions** associated with MM.

The **workup for MM** includes laboratory blood work, genetic testing (bone marrow biopsy), and imaging for bone involvement.

Disparities exist among patients with MM. **Black patients tend to have lower-risk disease and can achieve superior outcomes when treated with standard of care**. Nurses are important to reducing disparities.

Frontline multidrug regimens including those containing an anti-CD38 antibody produce deep responses and are becoming standard of care.

Maintenance treatment is recommended for all patients (both transplant eligible and ineligible) with MM.

Nurses can support shared decision-making by using the SHARE model and encouraging patients to discuss their priorities and preferences with the healthcare team.

CRAB = calcium elevation, renal dysfunction, anemia, bone lesions; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; SLiM = plasma clones ≥ sixty percent, light chain ratio, focal lesions by MRI; SMM = smoldering multiple myeloma.

Kyle RA, et al. *Mayo Clin Proc.* 2003;78:21-33. Greenberg AJ, et al. *Blood Cancer J*. 2015;4:e271. Baker A, et al. *Blood*. 2013;12(16):3147-3152. Brigle K, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):7-14. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024. O'Donnell EK, et al. *Blood.* 2019;134(suppl 1):3178. Pierre A, Williams TH. *Clin J Oncol Nurs.* 2020;24(4):439-443. O'Donnell EK, et al. *Br J Haematol.* 2018;182(2):222-230. Gerber L. *Nursing*. 2018;48(4):55-58. Agency for Healthcare Research and Quality website. Accessed March 25, 2024. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html.

International Myeloma Foundation
800-452-CURE (2873)
http://myeloma.org

Relapsed Multiple Myeloma
CASE 2: Margaret*

*HIPAA-compliant; not actual patient names.

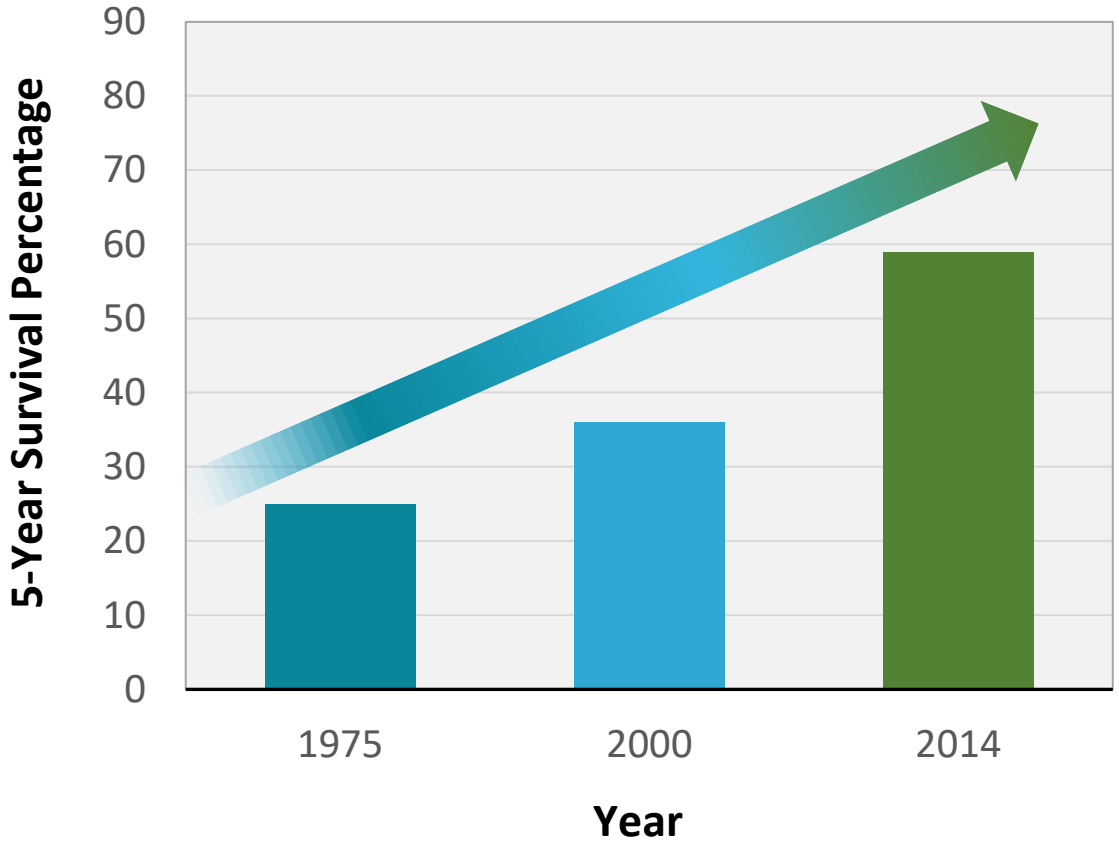
Patricia A. Mangan, RN, MSN, APRN-BC
Beth Faiman, PhD, RN, MSN, APRN-BC, AOCN, BMTCN, FAAN

HIPAA = Health Insurance Portability and Accountability Act.

NURSE LEADERSHIP BOARD

INTERNATIONAL MYELOMA FOUNDATION

Patients With Multiple Myeloma Are Living Longer Than Ever



≈ 60%

LIVE MORE THAN

5 YEARS

after their diagnosis

Many patients are living

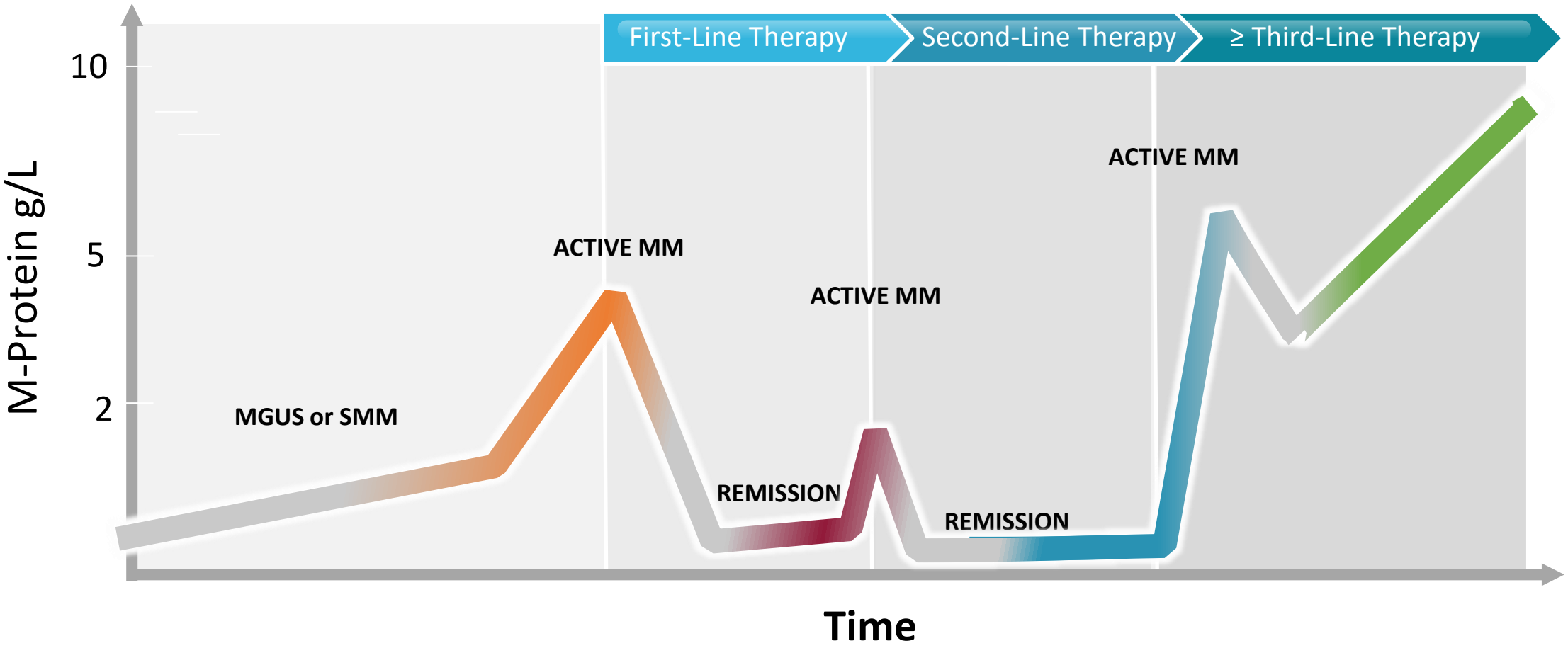
10+ YEARS

after their diagnosis!

Particularly those who are younger and/or have standard-risk disease

Rajkumar SV. *Am J Hematology.* 2022;97(8):1086-1107. SEER Cancer Stat Facts: Myeloma. Accessed March 19, 2024. https://seer.cancer.gov/statfacts/html/mulmy.html.

Clonal Evolution: The Relapsing Nature of Multiple Myeloma as Dominant Clones Change Over Time

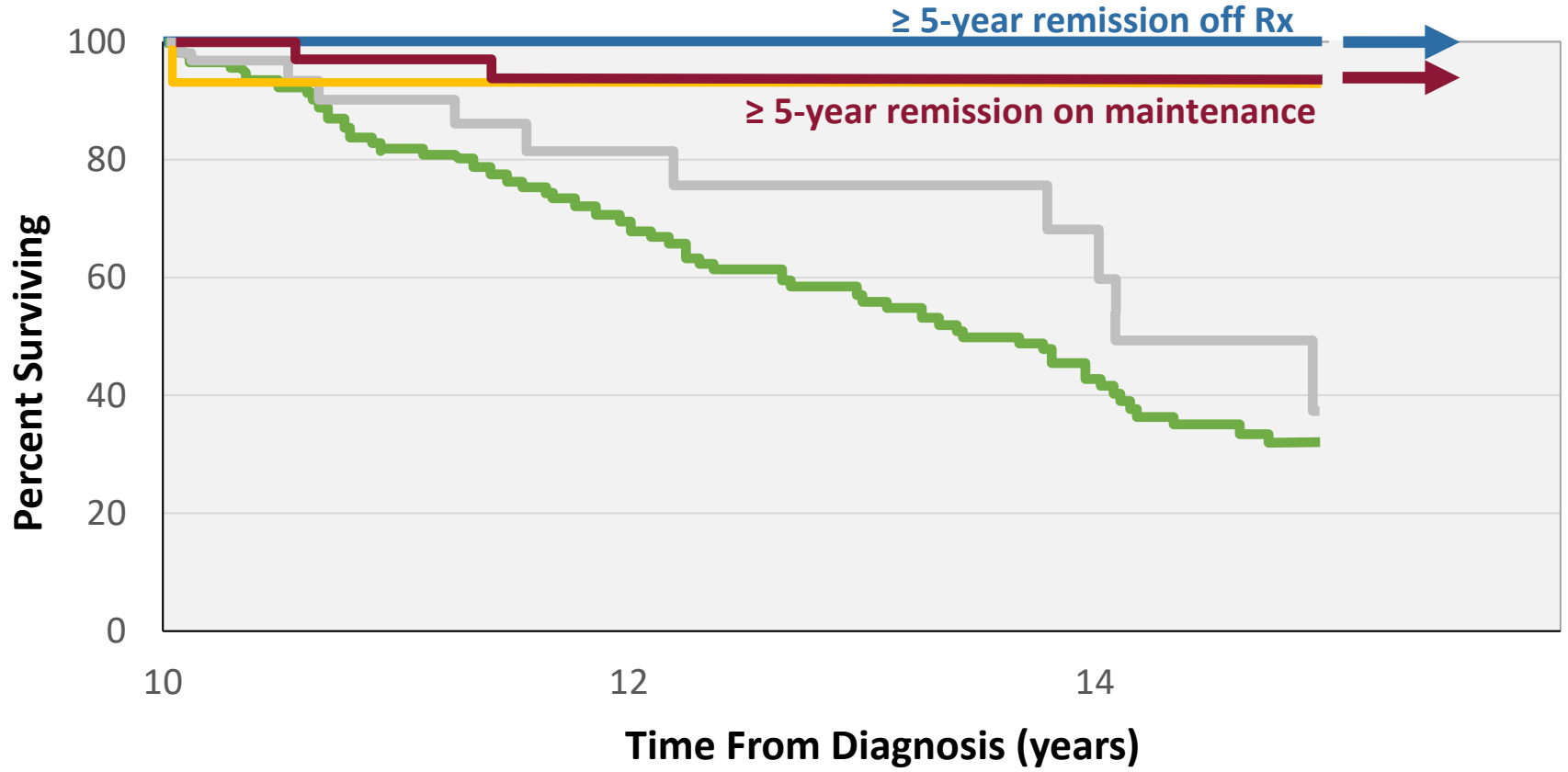


M-protein = monoclonal protein; MGUS = monoclonal gammopathy of undetermined significance; misc = miscellaneous (no dominant clone); MM = multiple myeloma; SMM = smoldering multiple myeloma.

Adapted from Durie B. Keats JJ, et al. *Blood*. 2012;120(5):1067-1076.

Some Patients (≈ 17%) Do Not Relapse After Their First Treatment for MM

Mayo Clinic Follow-Up of 2125 Patients With MM at ≥ 10 Years

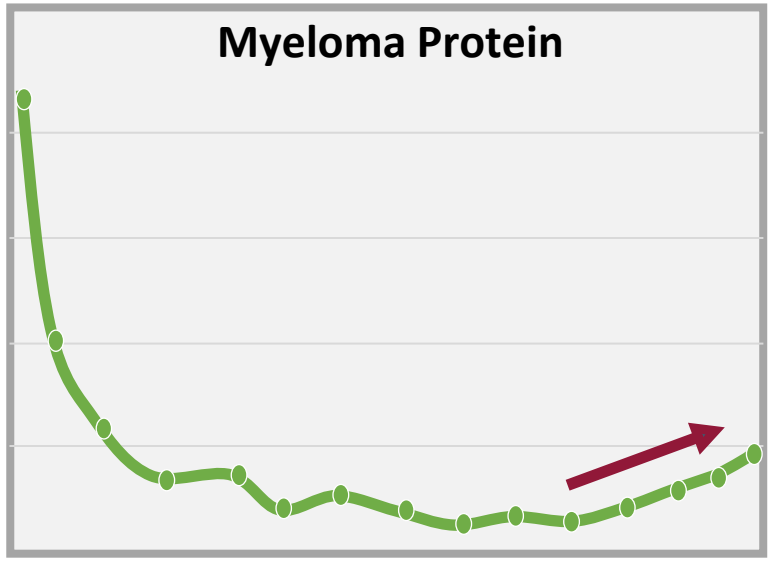


≈ 17%

of long-term survivors of MM may represent patients "operationally cured"

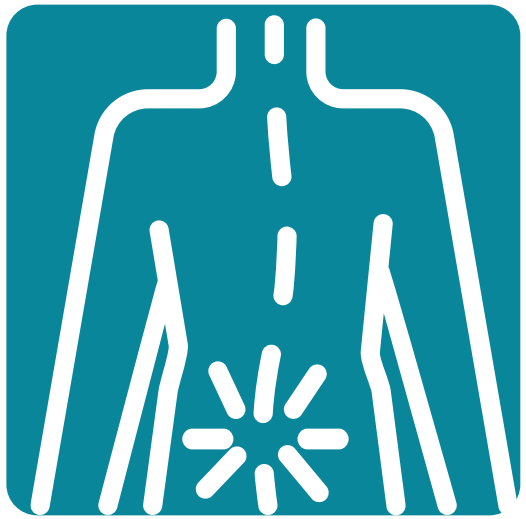
MM = multiple myeloma; Rx = prescription.
Grieb B, et al. ASH 2018. Abstr #1912.

How Patients With Myeloma Relapse



Asymptomatic Biochemical Relapse

- Sequentially rising myeloma protein or free light chain (> 25% increase from low point)
- No other symptoms
- Decisions: if, when, how to treat



Symptomatic

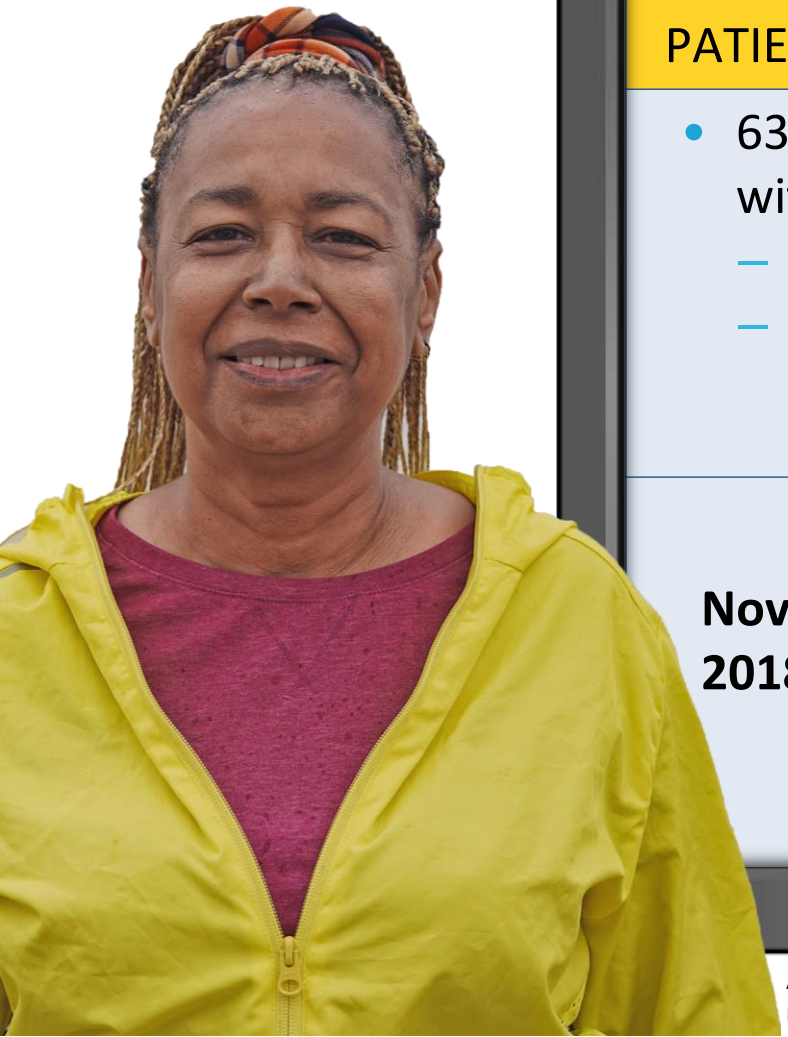
- New or worsening bone pain
- Increasing fatigue, anemia
- Next step: relapse workup; many therapy choices

Psychologically, many patients find their first relapse harder than their initial diagnosis. Nurses are essential for supporting patients!

Noonan K, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):15-21. Faiman B, et al. *J Adv Pract Oncol.* 2016:7(suppl 1):17-29. Kurtin S, et al. *J Adv Pract Oncol.* 2016;7(suppl 1):59-70. Gerber L. *Nursing*. 2018;48(4):55-58.

CASE 2

*HIPAA-compliant, not actual patient name, stock photo.



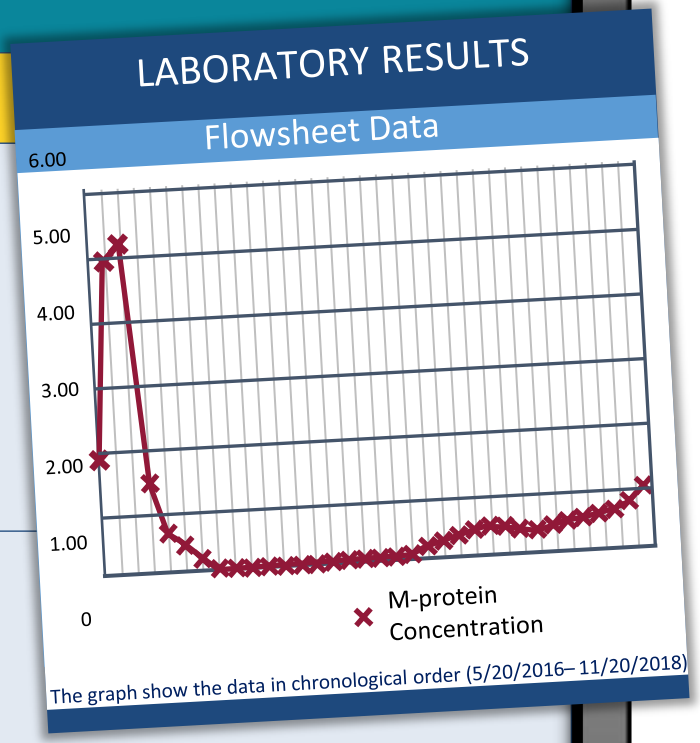
MARGARET*

PATIENT NOTES

- 63-year-old woman diagnosed with MM in 2016
  - High risk: del 17p
  - RVd → ASCT → R maintenance

November 2018

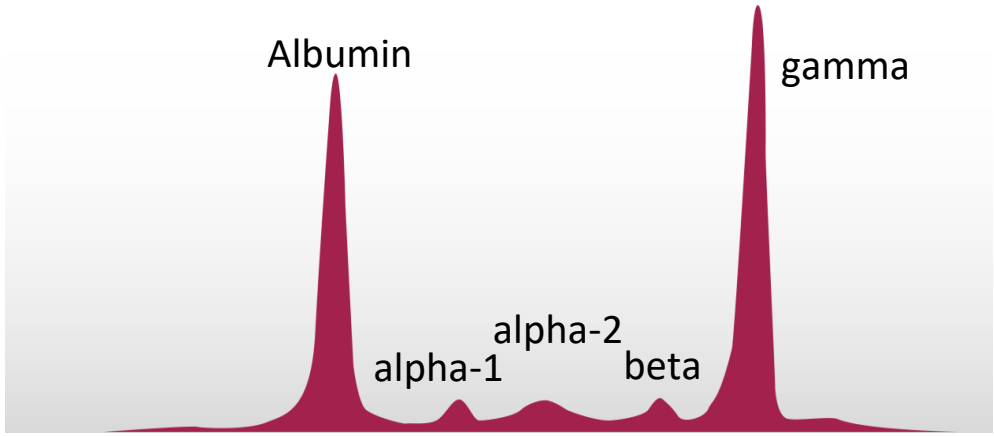
- 65 years old, biochemical relapse
  - Light chains increasing > 25% above the lowest point

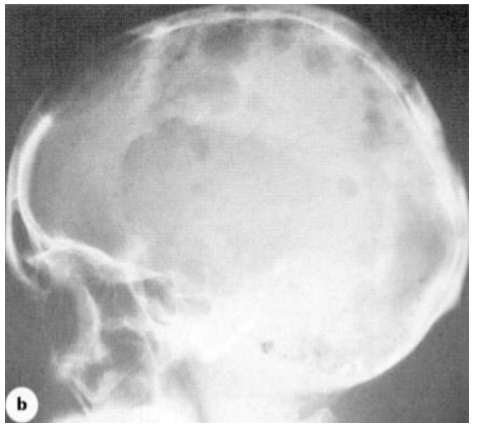


ASCT = autologous stem cell transplant; HIPAA = Health Insurance Portability and Accountability Act; M-protein = monoclonal protein; MM = multiple myeloma; R = lenalidomide; RVd = lenalidomide bortezomib dexamethasone.

Relapse Workup

LAB TESTS	• CBC + differential + chemistry (metabolic panel) • Serum free light chain (FLC) assay • Serum protein electrophoresis (SPEP) • Urine protein electrophoresis (UPEP)	
CONSIDER BONE MARROW BIOPSY	Cytogenetics and FISH	
IMAGING	• PET/CT • WBLDCT • MRI	Imaging type depends on individual's symptoms and available testing options





CBC = complete blood count; CT = computed tomography; FISH = fluorescence in situ hybridization; FLC = free light chain; MRI = magnetic resonance imaging; PET = positron emission tomography; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBLDCT = whole-body low-dose computed tomography.

Noonan K, et al. *J* Adv *Pract Oncol.* 2022;13(suppl 4):15-21. Rome SI, et al. *Clin J Oncol Nurs.* 2017;21(5 suppl):47-59. Hillengass J, et. *Lancet Oncol.* 2019;20(6):e302-e312. Ghobrial IM, et al. *Blood.* 2014;124:3380-3388. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548. Faiman B. *Clin Lymphoma Myeloma Leuk*. 2014;14:436-440.

Practical Approach to the Treatment of Patients With Relapsed Myeloma

Disease-Related Factors

- Duration of response to initial therapy
- High-risk vs low-risk status
- Molecular relapse vs symptomatic relapse
- Other comorbid conditions, patient frailty

Treatment-Related Factors

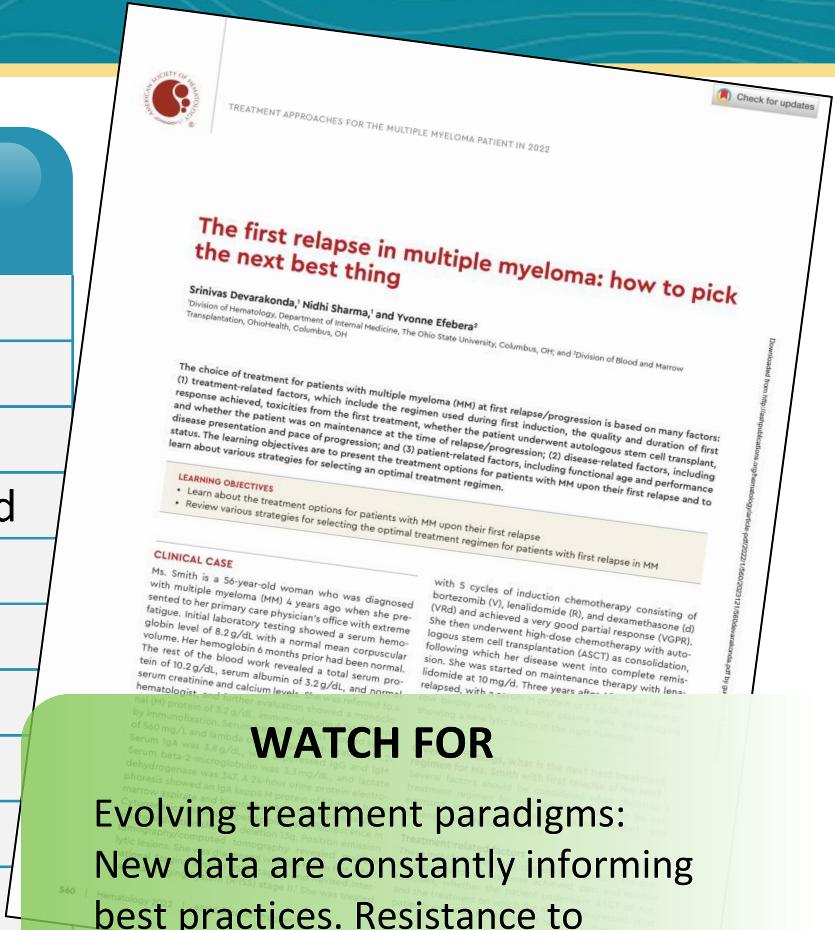
- Previous/Current therapy exposure and response (relapsed vs refractory)
- Toxicity/Tolerability of the previous regimen
- Mode of administration (ie, PO or IV)
- Cost and convenience (out-of-pocket co-pays for IV vs PO)
- Patient preference

IV = intravenous; PO = by mouth.

Noonan K, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):15-21. Faiman B, et al. *J Adv Pract Oncol.* 2016;2016:7(suppl 1):17-29.

Many Treatment Options at Early Relapse (1-3 Prior Therapies):

FDA-Approved Myeloma Therapies	Common Combinations
Bortezomib (SQ admin)	VRd, Vd, VCd
Carfilzomib	KRd, Kd, Dara-Kd, Isa-Kd
NEW Ciltacabtagene Autoleucel	--
Daratumumab	Dara-Rd, Dara-Vd, Dara-Pd, Dara-VMp, Dara-Kd
Elotuzumab	ERd, EPd[a]
NEW Idecabtagene Vicleucel[a]	--
Isatuximab	Isa-Pd[a], Isa-Kd
Ixazomib	IRd
Lenalidomide	VRd, Rd, KRd, Dara-Rd, ERd, IRd
Pomalidomide[a]	Pd[a], Dara-Pd, EPd[a], PCd[b]
Selinexor	Xd, XVd, XKd[b], Dara-Xd[b]
New agents or regimens in clinical trials are always an option	


TREATMENT APPROACHES FOR THE MULTIPLE MYELOMA PATIENT IN 2022

Check for updates

The first relapse in multiple myeloma: how to pick the next best thing

Srinivas Devarakonda,[1] Nidhi Sharma,[1] and Yvonne Efebera[2]

[1]Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus, OH; and [2]Division of Blood and Marrow Transplantation, OhioHealth, Columbus, OH

The choice of treatment for patients with multiple myeloma (MM) at first relapse/progression is based on many factors: (1) treatment-related factors, which include the regimen used during first induction, the quality and duration of first response achieved, toxicities from the first treatment, whether the patient underwent autologous stem cell transplant, and whether the patient was on maintenance at the time of relapse/progression; (2) disease-related factors, including disease presentation and pace of progression; and (3) patient-related factors, including functional age and performance status. The learning objectives are to present the treatment options for patients with MM upon their first relapse and to learn about various strategies for selecting an optimal treatment regimen.

LEARNING OBJECTIVES
- Learn about the treatment options for patients with MM upon their first relapse
- Review various strategies for selecting the optimal treatment regimen for patients with first relapse in MM

CLINICAL CASE

Ms. Smith is a 56-year-old woman who was diagnosed with multiple myeloma (MM) 4 years ago when she presented to her primary care physician's office with extreme fatigue. Initial laboratory testing showed a serum hemoglobin level of 8.2 g/dL with a normal mean corpuscular volume. Her hemoglobin 6 months prior had been normal. ...

with 5 cycles of induction chemotherapy consisting of bortezomib (V), lenalidomide (R), and dexamethasone (d) (VRd) and achieved a very good partial response (VGPR). She then underwent high-dose chemotherapy with autologous stem cell transplantation ...

Downloaded from http://ashpublications.org/hematology/article-pdf/2022/1/560/2023121/560devarakonda.pdf

WATCH FOR

Evolving treatment paradigms: New data are constantly informing best practices. Resistance to lenalidomide and/or anti-CD38 informs treatment sequencing

[a]2 or more prior therapies. [b]Off-label; not currently FDA-approved.

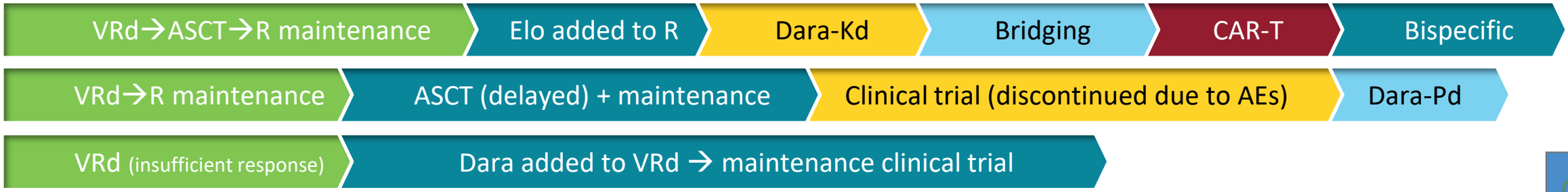
C = cyclophosphamide; d = dexamethasone; Dara = daratumumab; FDA = US Food and Drug Administration; E = elotuzumab; Isa = isatuximab; I = ixazomib; K = carfilzomib; M = melphalan; p = prednisone; P = pomalidomide; R = lenalidomide; SQ = subcutaneous; V = bortezomib; X = selinexor.

Rajkumar SV. 2024 Myeloma Algorithm. https://clinicaloptions.com/CE-CME/oncology/2024-mm-algorithm/18440-26989. Accessed March 25, 2024. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024. Noonan K, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):15-21. Steinbach M, et al. *J Adv Pract Oncol*. 2022;13(suppl 4):23-30. Moreau P, et al. *Lancet Oncol*. 2021;22(3):e105-e118. O'Donnell EK, et al. *Br J Haematol*. 2018;182(2):222-230. Mo CC, et al. *EJHaem*. 2023;4(3):792-810.

Guidelines For Counting Lines of Therapy in Myeloma

Definition of New Line of Therapy	Comment
Discontinuation of 1 treatment regimen and start of another[a]	The reasons for discontinuation, addition, substitution, or SCT do not influence how lines are counted. It is recognized that reasons for change may include end of planned therapy, toxicity, progression, lack of response, inadequate response, etc.
Unplanned addition or substitution of 1 or more drugs in a regimen	
In patients undergoing >1 SCT, each SCT (autologous or allogeneic) is considered a new line of therapy	Note that a planned tandem SCT is an exception and is considered 1 line. Planned induction and/or consolidation, maintenance with any SCT (frontline, relapse, autologous or allogeneic) is considered 1 line.

[a]A discontinued regimen restarted at a later date will be counted as a new line of therapy if there were 1 or more other regimens administered in between. Restarting the same regimen (even with dose modifications) without any other intervening regimen is not considered a new line.



Rajkumar SV, et al. *Blood.* 2015;126(7):921-922.

Carfilzomib Clinical Pearls

IV Proteasome Inhibitor

- Active in bortezomib refractory; common agent in regimens for MM, including trials
- Dosing
  - Premedication with dexamethasone
  - Hydration but not overhydration
  - First dose @ 20 mg/m^2 then escalate
  - Dose-dependent 10-min or 30-min infusion
- Full anticoagulation, especially for patients with high risk of VTE
- Herpesvirus prophylaxis
- Diuretic (furosemide or torsemide) or inhalers if needed
- Know cardiac and pulmonary status
  - Optimize heart failure and blood pressure management
- Monitor
  - Blood counts
  - Response
  - Signs of infection
- TIP: Avoid dyspnea over the weekend: start new patients' first dose early in the week
- Patient education

Kd or Dara-Kd
≥ 1 prior line[a]
20/70 mg/m^2
Once weekly
30-min infusion

Kd, Dara-Kd, K
≥ 1 prior line[a]
20/56 mg/m^2
Twice weekly
30-min infusion

KRd or K
≥ 1 prior line[a]
20/27 mg/m^2
Twice weekly
10-min infusion

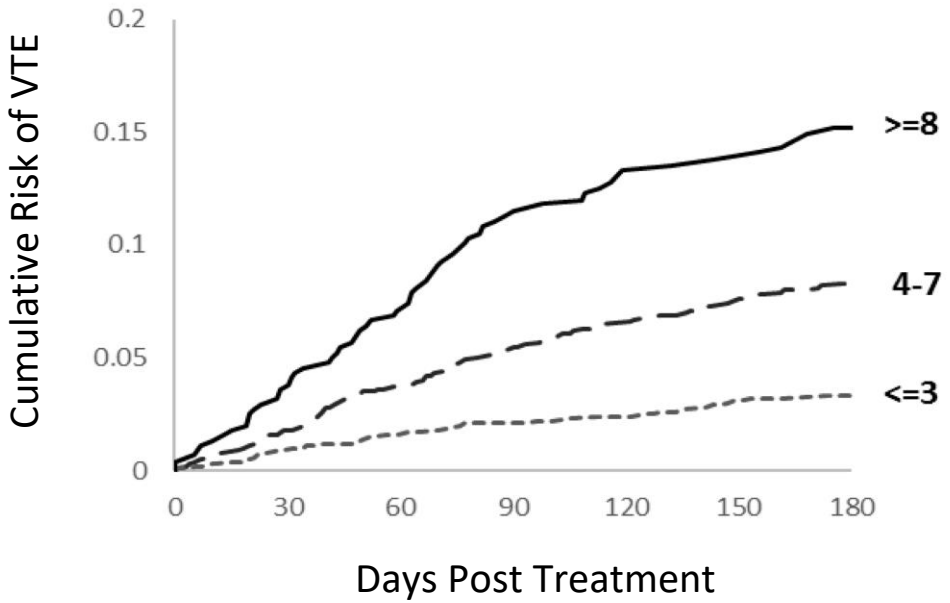
[a]1 to 3 prior lines of therapy for Dara-Kd, KRd, or Kd.
Dara = daratumumb; IV = intravenous; K = carfilzomib; Kd = carfilzomib dexamethasone; KRd = carfilzomib lenalidomide dexamethasone; MM = multiple myeloma; Rd = lenalidomide dexamethasone; VTE = venous thromboembolism.
KYPROLIS® (carfilzomib) Prescribing Information. Stewart K, et al. *N Engl J Med.* 2015;372:142-152.

IMPEDE VTE Score Can Assess VTE Risk in Patients With Multiple Myeloma

IMPEDE VTE Score

Predictor	Acronym	Score
Immunomodulatory Drug	I	4
Body **M**ass Index ≥ 25 kg/m^2	M	1
Pelvic, Hip or Femur Fracture	P	4
Erythropoiesis-stimulating Agent	E	1
Doxorubicin	D	3
Dexamethasone High-Dose Low-Dose		 4 2
Ethnicity/Race = Asian/Pacific Islander	E	–3
History of **V**enous Thromboembolism before MM	V	5
Tunneled Line Central Venous Catheter	T	2
Existing Thromboprophylaxis: Therapeutic LMWH or Warfarin	E	–4
Existing Thromboprophylaxis: Prophylactic LMWH or Aspirin		–3

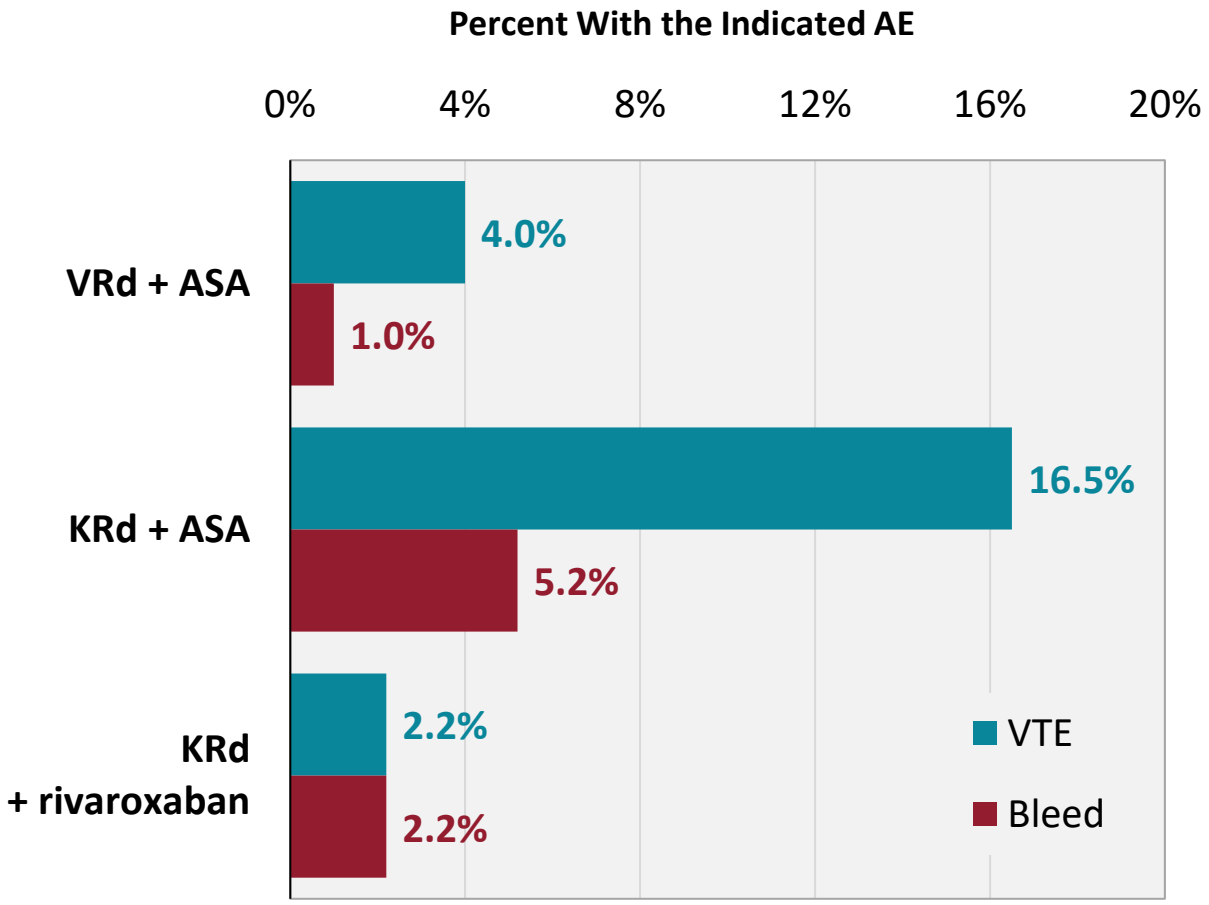
…the IMPEDE VTE score outperformed IMWG guidelines and NCCN Guidelines® and could be considered the new risk stratification standard for VTE in MM



IMWG = International Myeloma Working Group; LWMH = low molecular weight heparin; MM = multiple myeloma; NCCN = National Comprehensive Cancer Network; VTE = venous thromboembolism.

Sanfilippo KM, et al. *Am J Hematol*. 2019;94(11):1176-1184.

Consider Full Anticoagulation for Patients on Carfilzomib Regimens



Tip: rivaroxaban co-pay may be covered by an LLS grant or other cancer-related assistance IF indicated that it is necessary for myeloma treatment

Rivaroxaban may be a more-effective antithrombotic agent for patients receiving carfilzomib- or lenalidomide-based regimens

AE = adverse event; ASA = aspirin; KRd = carfilzomib lenalidomide dexamethasone; LLS = Leukemia & Lymphoma Society; VRd = bortezomib lenalidomide dexamethasone; VTE = venous thromboembolism.

Piedra KM, et al. ASH 2019. Abstr #1835.

Pomalidomide Clinical Pearls

Oral Immunomodulatory Agent

- Active in R-refractory patients; common agent in regimens for MM, including trials
- Monitor
  - Blood counts—neutropenia most frequent grade 3/4 AE
  - Liver function
  - Response
- REMS program
- Proactive AE management
- Patient education
  - Oral adherence
  - REMS process for refills
  - DVT prophylaxis
  - Common AEs: low blood counts, infection, GI
  - Refrain from smoking (reduces pomalidomide exposure)
  - Protect renal health (renal excretion of pomalidomide)
    - Hydration
    - Avoid NSAIDS, IV contrast, other drugs with renal interactions

Dara-Pd
(1 or more prior therapies)

EPd
(≥ 2 prior therapies)

Pd
(≥ 2 prior therapies)

Clinical Pearl:
can often be started at 2mg instead of 4mg

AE = adverse event; Dara = daratumumab; DVT = deep vein thrombosis; GI = gastrointestinal; IV = intravenous; EPd = elotuzumab pomalidomide dexamethasone; MM = multiple myeloma; NSAID = nonsteroidal anti-inflammatory drug; Pd = pomalidomide dexamethasone; R = lenalidomide; REMS = Risk Evaluation and Mitigation Strategy.

POMALYST® (pomalidomide) Prescribing Information. Faiman B, et al. *J Adv Pract Oncol.* 2016;7:45-52. EMPLICITI™ (elotuzumab) Prescribing Information. DARZALEX® (daratumumab) Prescribing Information.

Elotuzumab: Anti–*SLAMF-7* Monoclonal Antibody

- IV monoclonal antibody targeting *SLAMF-7*
- Prescribed with Rd or Pd
  - DVT prophylaxis (for R or P)
  - Steroid side effects and schedule (AM vs PM)
- **Clinical pearls**
  - Prophylaxis for infusion reactions
  - Infuse at a rate of 0.5 mL/min and escalate to 5 mL/min over time
  - Give weekly for 8 weeks, then twice monthly until progressive disease
  - Multiple dosing regimens—check prescribing information
- **Monitoring**
  - Blood counts (hold/adjust the dose if needed)
  - Response assessment (monthly); interference
  - Glucose (dexamethasone can affect)
  - Kidney and liver function

ERd
(1-3 prior therapies)

EPd
(≥ 2 prior therapies)

WATCH FOR

Clinical trials with elotuzumab in combination with other MM drugs such as iberdomide

DVT = deep vein thrombosis; EPd = elotuzumab pomalidomide dexamethasone; ERd = elotuzumab lenalidomide dexamethasone; IV = intravenous; MM = multiple myeloma; R = lenalidomide; Rd = lenalidomide dexamethasone; P = pomalidomide; Pd = pomalidomide dexamethasone; *SLAMF-7* = signaling lymphocytic activation molecule 7 (also CD319, CS1).

EMPLICITI™ (elotuzumab) Prescribing Information. Gleason C, et al. *J Adv Pract Oncol.* 2016;7(suppl 1):53-57. Clinical trials.gov website. Accessed March 15, 2023. https://clinicaltrials.gov/.

Selinexor: Oral Selective Inhibitor of Nuclear Export (SINE)

- Oral selective inhibitor of nuclear export (SINE) compound XPO1 inhibitor
- Standard practice is to dose Selinexor weekly
- Consider sequencing before MM therapies such as CAR T-cell therapy and bispecific antibodies, which rely on T-cell fitness for activity
- Watch for new regimens that optimize dosing, such as all-oral XPd with selinexor dosed at 40 mg weekly (ASCO 2023 e20006)
- **Clinical pearls**
  - Patient education and expectations
  - Proactive AE management is crucial
    - Patients must be given **2 anti-nauseants prophylactically** for the management of nausea and anorexia (start ondansetron day 1; add olanzapine and/or aprepitant)
    - Thrombocytopenia and neutropenia (weekly blood counts in cycle 1)
    - Hyponatremia (salty snacks, oral hydration)
    - Diarrhea (oral hydration)

XVd
(≥ 1 prior therapy)

Xd
(≥ 4 prior therapies: refractory to 2 PIs, 2 IMiDs, anti-CD38 mAb)

NEW DATA

Selinexor has the potential to lessen T-cell exhaustion, which may improve the effectiveness of some MM therapies and reduce infections

AE = adverse event; ASCO = American Society of Clinical Oncology; IMiD = immunomodulatory drug; mAb = monoclonal antibody; MM = multiple myeloma; PI = proteasome inhibitor; SINE = selective inhibitor of nuclear export; Xd = selinexor dexamethasone; XPd = selinexor pomalidomide dexamethasone; XPO1 = exportin 1; XVd = selinexor bortezomib dexamethasone.

XPOVIO™ (selinexor) Prescribing Information. Mikhael J, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20(6):351-357. White D, et al. ASCO 2023. Abstr#e20006. Binder AF, et al. *Front Immunol.* 2023;14:1275329.

Ixazomib: Oral Proteasome Inhibitor

- Oral proteasome inhibitor
  - Indication: patients with MM who have received at least 1 prior therapy
  - In combination with Rd
- Administration
  - Oral capsule 1 × per week; do not crush, chew, or open the capsule
  - Empty stomach: 1 hour before or 2 hours after food
- **Clinical pearls**
  - Adherence, schedule, viral prophylaxis
  - Rapid response (1.1 months); fast absorption (if vomit, do NOT repeat dose)
  - Monitor blood counts: cyclic thrombocytopenia
  - Less peripheral neuropathy, peripheral edema
  - In combination with Rd, so DVT prophylaxis

Ixazomib + Rd
(≥ 1 prior therapy)

All-oral regimen

WATCH FOR

- New regimens
- Clinical trials
  - IR in SMM
  - IPd in MM
  - Others

DVT = deep vein thrombosis; IR = ixazomib lenalidomide; IPd = ixazomib pomalidomide dexamethasone; MM = multiple myeloma; Rd = lenalidomide dexamethasone; SMM = smoldering MM.

NINLARO® (ixazomib) Prescribing Information. Faiman B, et al. *J Adv Pract Oncol.* 2016;7:45-52. Clinical trials.gov.

CASE 2

*HIPAA-compliant, not actual patient name, stock photo.

Margaret*

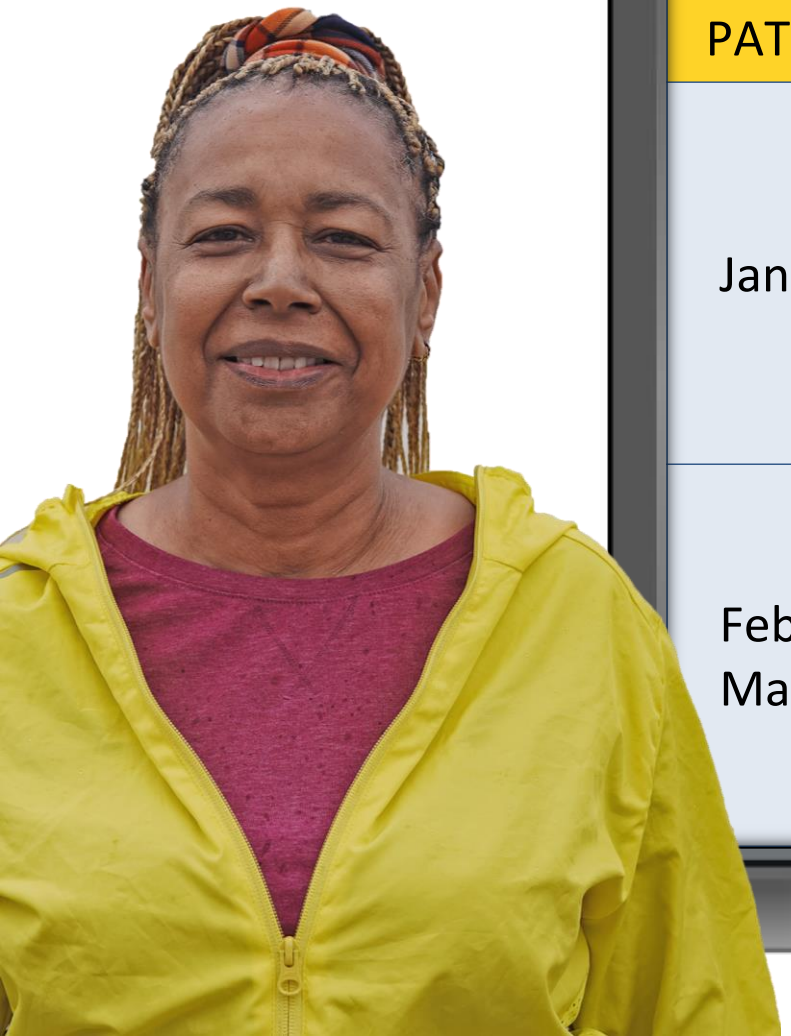
PATIENT NOTES

November 2018	• Shared decision-making → KRd • 90% reduction in light chains (VGPR)
November 2019	• Biochemical relapse • Shared decision-making → Dara pom dex • 90% reduction in light chains (VGPR)
April 2020	• Shared decision-making during pandemic → converted to an all-oral regimen – Ixazomib pom dex

Dara = daratumumab. dex = dexamethasone; HIPAA = Health Insurance Portability and Accountability Act; KRd = carfilzomib lenalidomide dexamethasone; MM = multiple myeloma; pom = pomalidomide; VGPR very good partial response.

CASE 2

*HIPAA-compliant, not actual patient name, stock photo.



MARGARET*

PATIENT NOTES

January 2022	• Shared decision-making: Discussed possibility that CAR T-cell therapy could be next therapy
February-March 2022	• Financial and medical consult at CAR T-cell therapy center

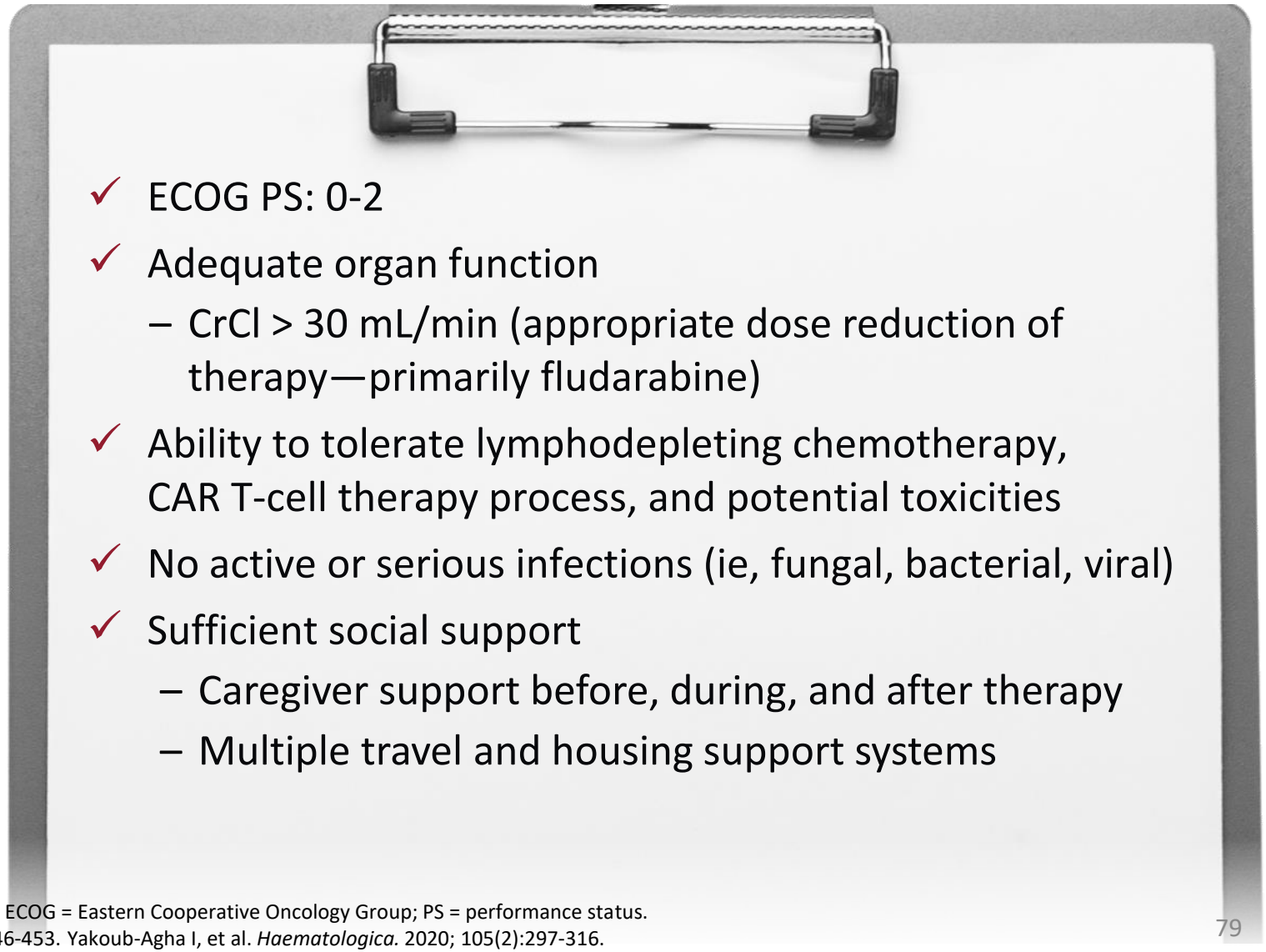
Provide tools and resources to enhance decision-making

CAR = chimeric antigen receptor; HIPAA = Health Insurance Portability and Accountability Act.

Patient Eligibility for CAR T-Cell Therapy: General Criteria

Available CAR T-cell therapies may be appropriate for patients with advanced disease and …

Specific criteria may vary depending on CAR T-cell therapy center



- ✓ ECOG PS: 0-2
- ✓ Adequate organ function
  - CrCl > 30 mL/min (appropriate dose reduction of therapy—primarily fludarabine)
- ✓ Ability to tolerate lymphodepleting chemotherapy, CAR T-cell therapy process, and potential toxicities
- ✓ No active or serious infections (ie, fungal, bacterial, viral)
- ✓ Sufficient social support
  - Caregiver support before, during, and after therapy
  - Multiple travel and housing support systems

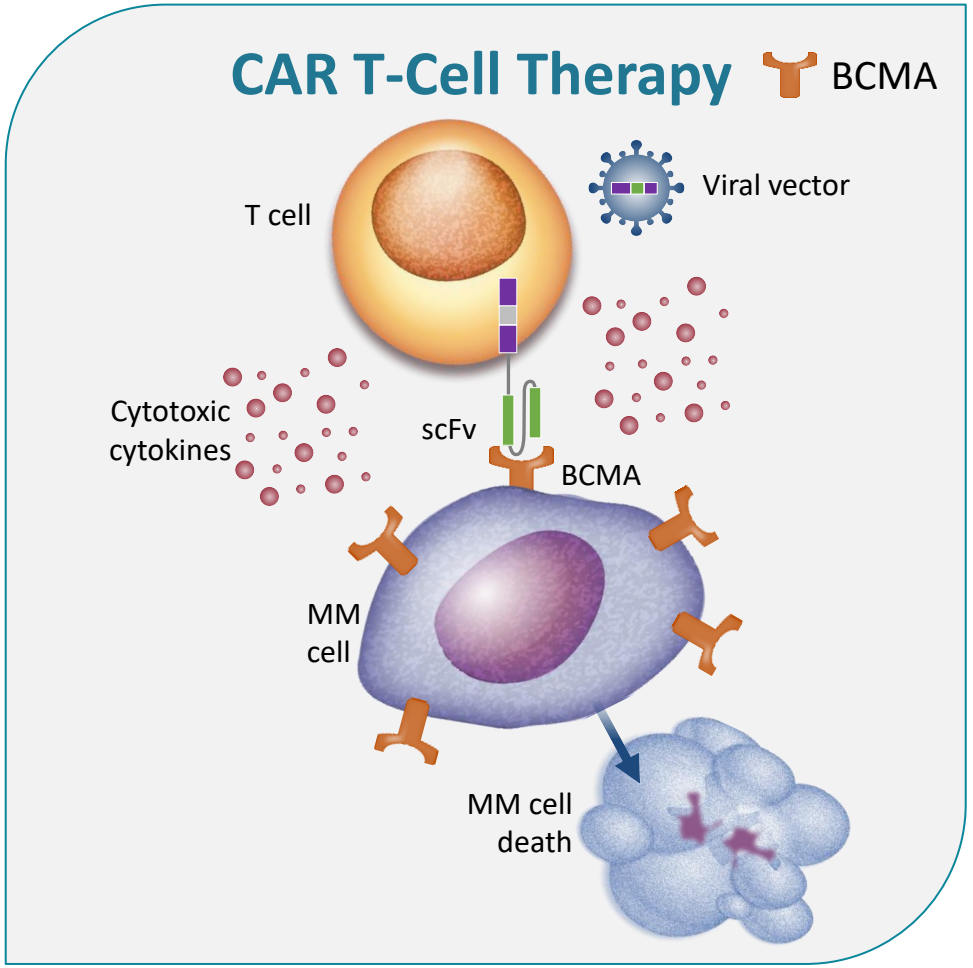
CAR = chimeric antigen receptor; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Abramson, JS, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:446-453. Yakoub-Agha I, et al. *Haematologica.* 2020; 105(2):297-316.

BCMA Is the Target for FDA-Approved CAR T-Cell Therapies

BCMA (B-Cell Maturation Antigen)

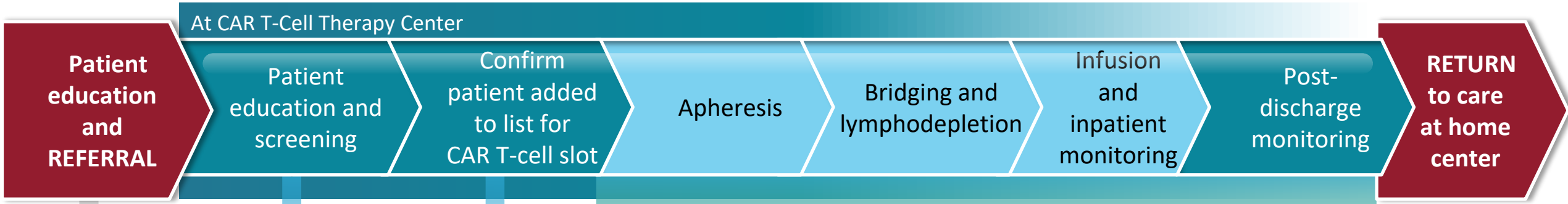
- Member of TNF receptor superfamily
- BCMA is expressed on late memory B cells committed to PC differentiation and PCs
- BCMA plays a role in survival of long-lived PCs
- BCMA is expressed more abundantly on malignant PCs than on normal ones



BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; FDA = US Food and Drug Administration; MM = multiple myeloma; PC = plasma cell; scFv = single chain fragment variable; TNF = tumor necrosis factor.

Shah N, et al. *Leukemia*. 2020;34(4):985-1005. Yu B, et al. *J Hematol Oncol.* 2020;13:125.

CAR T-Cell Therapy: A New Treatment Approach



Refer patients to CAR T-cell therapy center early: Slots are limited

Most centers require several screening steps, including financial consultation

Allocation of slots is institution specific—UNDERSTAND their process to help your patients navigate

CAR T-cell therapy takes a couple of months once a patient receives a CAR T-cell therapy slot!

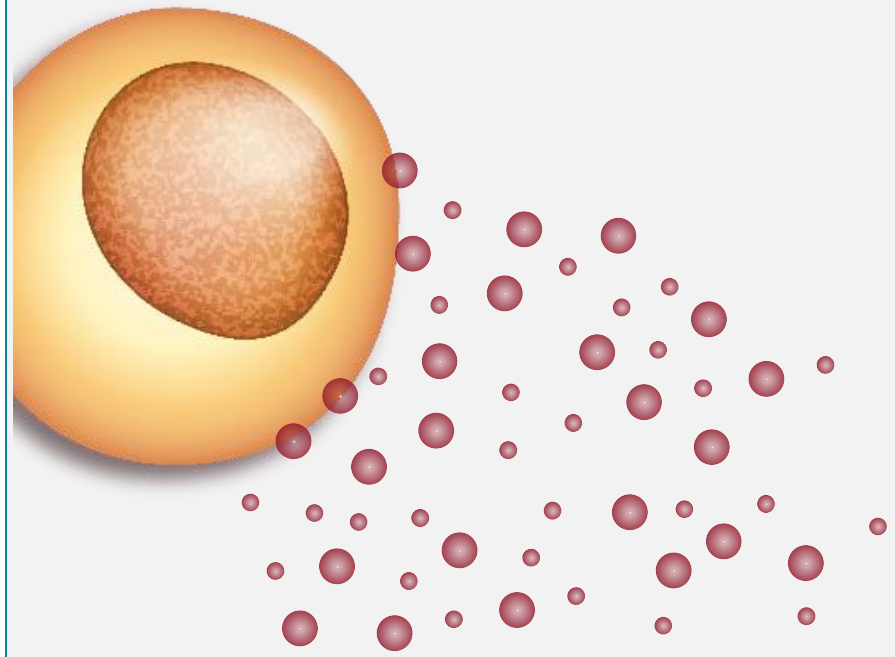
- Extensive care partner support is typically required (especially for month after CAR T-cell infusion)
- Patients usually need to remain in proximity to the CAR T-cell therapy center for ≈ 4 weeks after CAR T-cell infusion
- Patients should not drive for ≈ 2 months after CAR T-cell infusion

CAR = chimeric antigen receptor.

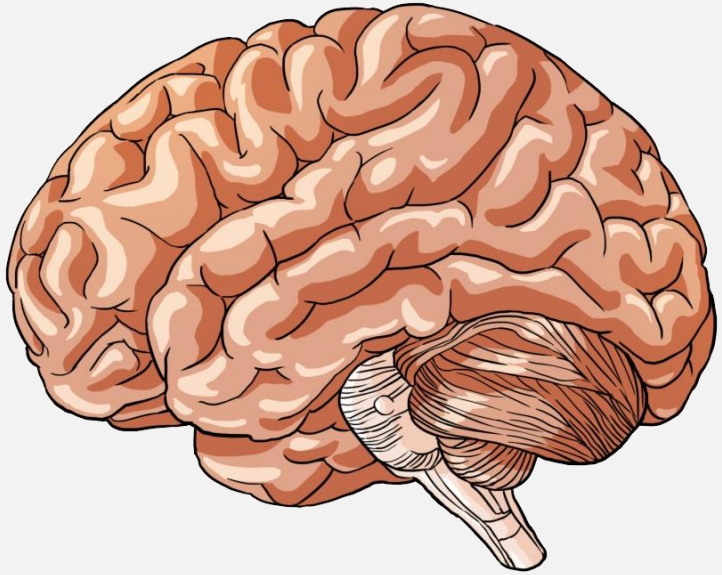
Catamero D, et al. *J Adv Pract Oncol.* 2022;13(suppl 4):31-43. Teoh PJ, Chng WJ. *Blood Cancer J.* 2021;11(4):84. Shah UA, Mailankody S. *BMJ.* 2020;370:m3176.

Immune Activity–Specific Side Effects

Cytokine release syndrome (CRS)



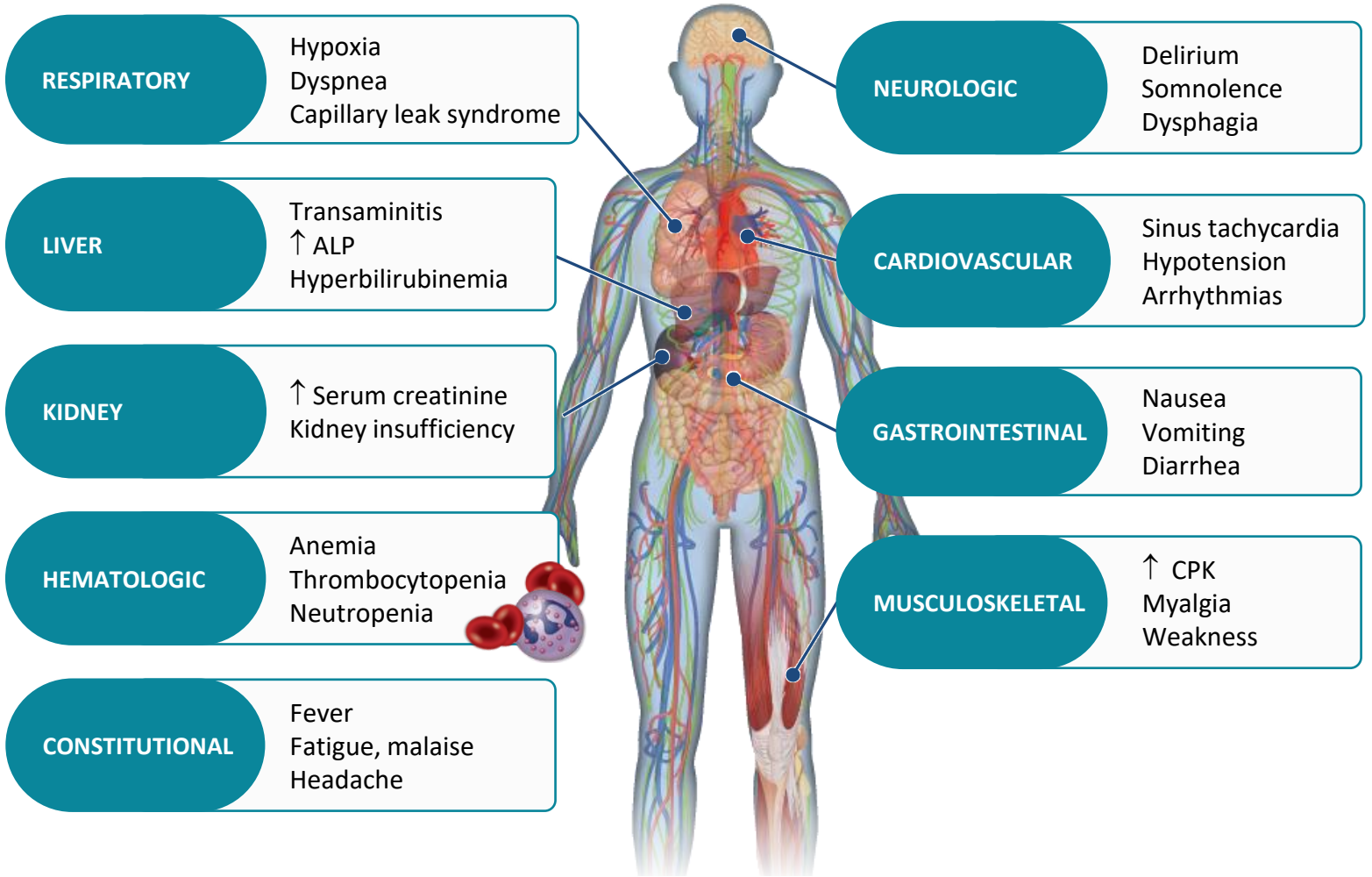
Immune effector cell–associated neurotoxicity syndrome (ICANS)



Neurotoxicity

CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome.

CRS Severity Ranges From Mild to Life-Threatening: Early Recognition and Treatment



Monitoring for CRS

- Vital signs (temperature, O_2 saturation, etc)
- Review of systems and physical exam
  - Focus on cardiovascular, pulmonary, and neurologic systems
- Rule out infection
- Laboratory monitoring
  - CRP
  - Cytokines
  - Ferritin
  - LDH

ALP = alkaline phosphatase; CPK = creatine phosphokinase; CRP = C-reactive protein; CRS = cytokine release syndrome; LDH = lactate dehydrogenase; O_2 = oxygen.

Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265-1272. June CH, et al. *Science*. 2018;359:1361-1365. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019:34:45-55. Shimabukuro-Vornhagen, et al. *J Immunother Cancer.* 2018;6:56. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

ASTCT CRS Consensus Grading

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

Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events v5.0 but not influence CRS grading.

[a]Fever is defined as temperature ≥ 38° C not attributable to any other cause. In patients who have CRS and receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. [b]CRS grade is determined by the more-severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. [c]Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome.

Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638.

Managing CRS Is Institution Specific

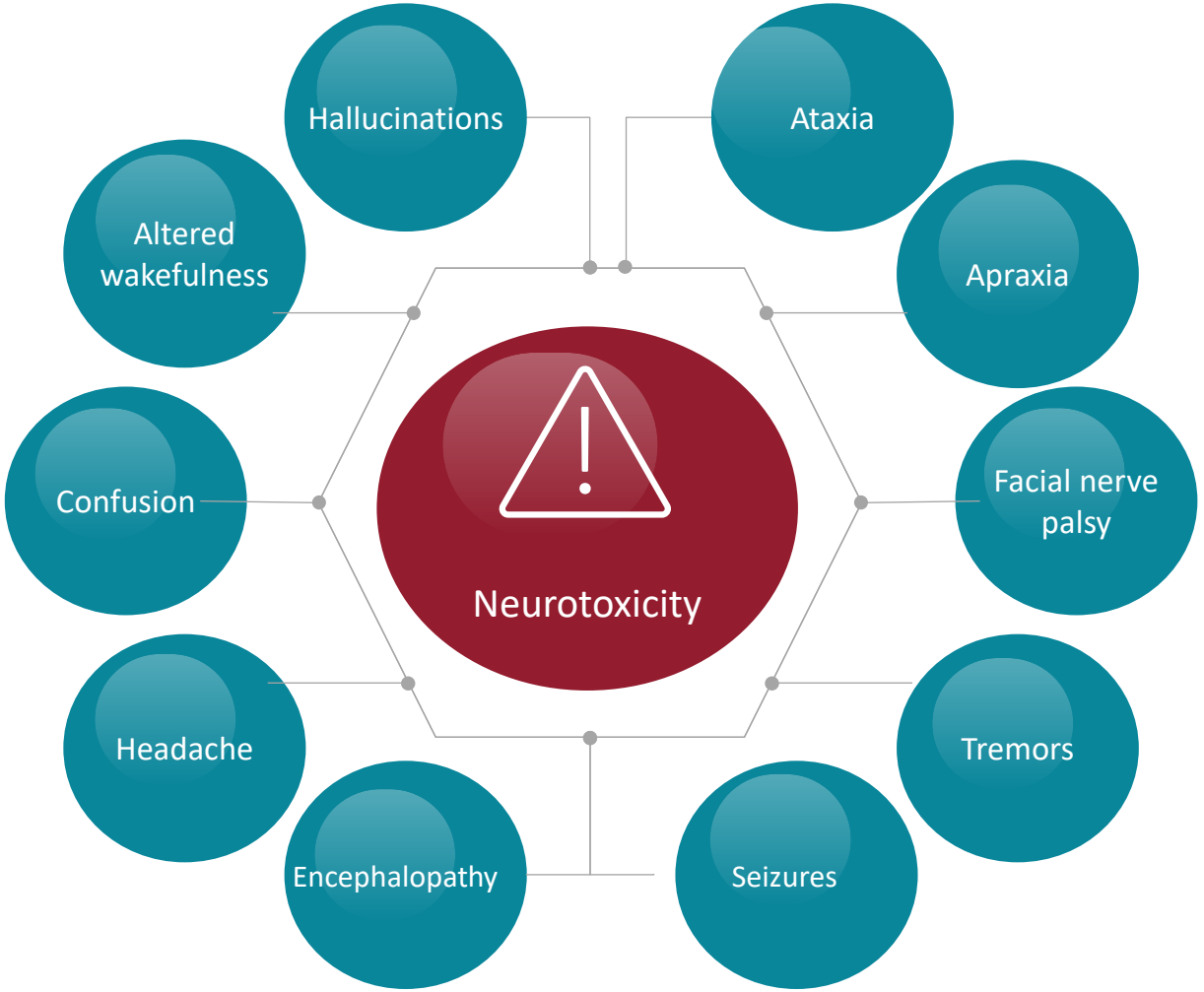
Clinical Pearl:
Institution-specific guidelines for managing CRS vary.

ASTCT CRS Grade	Management (Example Guideline)
1	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Antibiotics if neutropenic
2	• Supportive care as in grade 1 • IV fluid boluses and/or supplemental oxygen • **Tocilizumab** +/- **dexamethasone (or its equivalent of methylprednisolone)**
3	• Supportive care as in grade 1 • Consider monitoring in ICU • Vasopressor support and/or supplemental oxygen • **Tocilizumab** + **dexamethasone 10 to 20 mg IV every 6 hours (or its equivalent of methylprednisolone)**
4	• Supportive care as in grade 1 • Monitoring in ICU • Vasopressor support and/or supplemental oxygen via positive-pressure ventilation • **Tocilizumab** + **methylprednisolone 1,000 mg/day**

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; ICU = intensive care unit; IV = intravenous; O_2 = oxygen.

Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47-62. Neelapu SS, et al. *Hematol Oncol.* 2019;37(Suppl 1):48-52.

Neurotoxicity: Rare but Potentially Serious AE



Monitoring for Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- ICE screening tool
- Review of systems and physical exam
  - Focus on neurologic systems
- Rule out infection
- If ICANS suspected
  - Neuroimaging (ideally MRI)
  - Diagnostic lumbar puncture for opening pressure and infection tests
- Corticosteroids are typically indicated for ICANS ≥ grade 2
- Patient and care partner information

AE = adverse event; ICANS = immune effector cell–associated neurotoxicity syndrome; ICE = immune effector cell encephalopathy; MRI = magnetic resonance imaging.
Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

ICE Screening Tool for Neurologic Assessment

Assessment		Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects (eg, point to clock, pen, button)	3
Following Commands	Ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1
Writing	Ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1
Attention	Ability to count backwards from 100 by 10	1
Total Points		10

Scoring	
10	No impairment
7-9	Grade 1 ICANS
3-6	Grade 2 ICANS
0-2	Grade 3 ICANS
0 due to patient unarousable and unable to perform ICE assessment	Grade 4 ICANS

ICANS = immune effector cell–associated neurotoxicity syndrome; ICE = immune effector cell encephalopathy.

Santomasso B, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:433-444. Lee DW, et al. *Biol Blood Marrow Transplant.* 2018;15:47-62.

CAR T-Cell Therapy AEs

Nurses are critical for coordination of care between CAR T center and community center!

Acute AEs

- Cytokine-release syndrome
- Immune effector cell–associated neurotoxicity syndrome
- Cytopenias
- Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome

Typically managed by CAR T-cell therapy center

Delayed AEs

- B-cell aplasia/**hypogammaglobulinemia**
- **Prolonged cytopenias**
- Long-term **neurologic** events/ movement and neurocognitive treatment-emergent AEs
- Transient cardiac toxicities
- **Late infections**

Typically managed by primary oncology team

AE = adverse event; CAR = chimeric antigen receptor.

Maus MV, et al. *J Immunother Cancer*. 2020;8(2):e001511. Cohen AD, et al. *Blood Cancer J*. 2022;12(2):32. Chakraborty R, et al. *Transplant Cell Ther*. 2021;27:222-229.

Medications Can Reduce Infection Risk

Some people receiving BCMA-targeting CAR T cell therapy have experienced infections that are less common, such as CMV, PJP, and fungal infections

Type of Infection Risk	Medication Recommendation(s)
Viral: herpes simplex (HSV/VZV); CMV	Acyclovir prophylaxis
Viral: influenza, COVID-19	Consider antiviral therapy if exposed or positive for influenza or COVID-19, per institution recommendations
Hepatitis B virus (HBV) reactivation	**Entecavir prophylaxis in patients positive for chronic HBV infection** (defined as serologically positive for hepatitis B surface antigen [HBsAg]) **if treated with CAR T,** bispecific antibodies, or daratumumab
Bacterial: blood, pneumonia, and urinary tract infection	Consider prophylaxis with levofloxacin
PJP (*P jirovecii* pneumonia)	Consider prophylaxis with trimethoprim-sulfamethoxazole
Pneumococcal infection	The CDC recommends pneumococcal vaccination (1 dose of PCV20 or 1 dose of PCV 15 followed by 1 dose of PPSV23 at least one year later); CAR T or ASCT: revaccinate 3-6 months after treatment; **Bispecific: Update vaccination status prior to starting therapy**
Fungal infections	Consider prophylaxis with fluconazole
IgG < 400 mg/dL (general infection risk)	IVIG replacement (400 mg/kg once every 4 weeks) is indicated; **IVIG replacement during CAR T-cell and bispecific antibody therapy is not guided by the presence of infections[a]** CAR T: Day +30 through 1 year. After 1 year continue until serum IgG > 400 mg/dL Bispecific: start at the second cycle of therapy and continue until the end of therapy or serum IgG > 400
ANC < 1000 cells/µL (general infection risk)	Consider GCSF 2 or 3 times/week (or as frequently as needed) to maintain ANC > 1000 cells/µL and treatment dose intensity; **CAR-T: Start levofloxacin at 500 mg PO daily[b] or per clinician discretion and continue through neutrophil recovery;** Bispecific: consider starting with therapy and administer throughout the first cycle.

[a]IVIG is indicated in all patients with MM with IgG < 400 and recurrent life-threatening infections. [b]Alternatives: cefdinir 300 mg PO twice a day or amoxicillin/clavulanate 875 mg PO twice a day.
ANC = absolute neutrophil count; BCMA = B-cell maturation antigen; CMV, cytomegalovirus; GCSF = granulocyte colony-stimulating factor; HSV = herpes simplex virus; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; PJP = *Pneumocystis jirovecii* pneumonia; VZV = varicella zoster virus.

Raje NS, et al. *Lancet Haematol*. 2022;9(2):143-161. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024. Cao W, et al. *Blood.* 2020;136(4):516-519.

Idecabtagene Vicleucel (Ide-cel)

CAR T-Cell Therapy Targeting BCMA

- ORR = 72%; median DoR = 11 months
- Offered only in qualified centers (get on list)
- REMS program
- CRS (N = 349)
  - Median time to onset: 1 day (range: 1-27)
  - Median duration: 5 days (range 1-63)
  - CRS rates: 89% all grades
    7% grade ≥3
    0.9% grade 5 (n = 3)

Common Manifestations of CRS With Ide-cel (N = 349)	
Pyrexia	87%
Hypotension	30%
Tachycardia	26%
Chills	19%
Hypoxia	16%

- Neurotoxicity (N = 349)
  - Median time to onset: 2 days (range: 1-148)
  - Median duration: 5 days (range 1-245); 123/139 resolved
  - NT rates: 40% all grades
    4.6% grade 3-4
    1 grade 5 event
- Hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS)
- Prolonged cytopenias
  - Prolonged neutropenia: 40%; median time to recovery 1.9 months
  - Prolonged thrombocytopenia: 42%; median time to recovery 1.9 months

NEW

R/R MM after
2 or more prior lines
of therapy
(including a PI, an IMiD, and an anti-CD38 mAb)

Find a Treatment Center
at AbecmaFinder.com

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DoR = duration of response; IMiD = immunomodulatory drug; mAb = monoclonal antibody; MM = multiple myeloma; ORR = overall response rate; PI = proteasome inhibitor; REMS = Risk Evaluation and Mitigation Strategy; R/R = relapsed/refractory.

ABECMA® (idecabtagene vicleucel) Prescribing Information. ABECMA® website Accessed April 11,.2024. https://www.abecmahcp.com/safety

KarMMa-3: Ide-cel Improved PFS and OS vs Standard of Care in Patients With R/R MM (1-3 Prior Lines of Therapy)

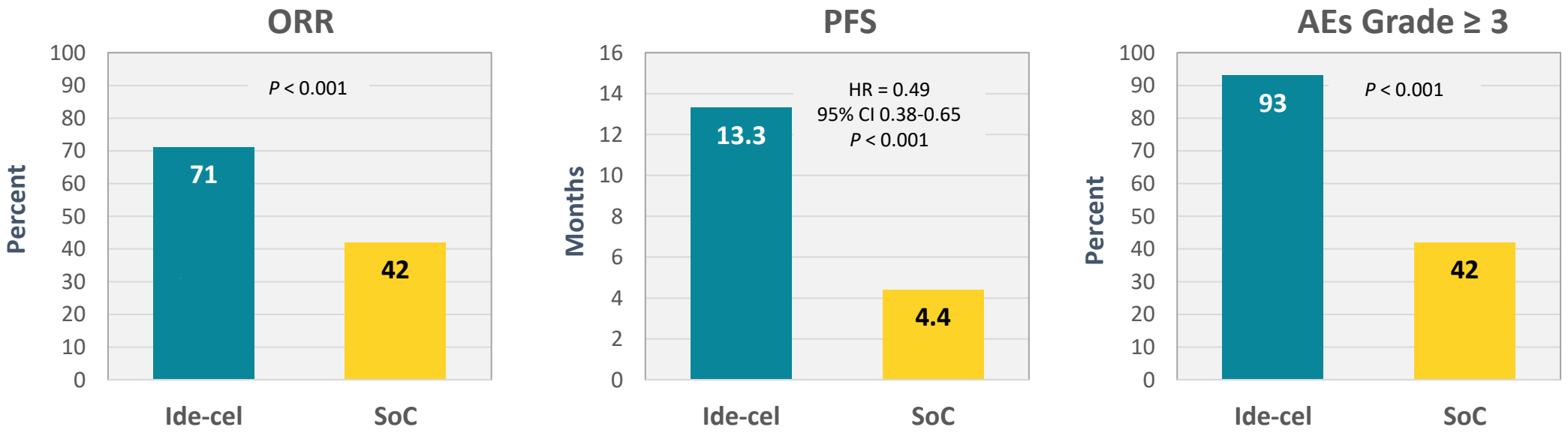
KarMMa-3 Phase 3 Clinical Trial

- 386 patients with R/R MM (ide-cel n = 254; standard regimen [5 options] n = 132)
  - 66% triple-class refractory
  - 95% daratumumab refractory

Among those treated with ide-cel (n = 225)

- 88% any-grade CRS (5% grade ≥ 3)
- 15% any-grade neurotoxicity (3% grade ≥ 3)

Results



AE, adverse event; CRS = cytokine release syndrome; HR = hazard ratio; ide-cel = idecabtagene vicleucel; MM = multiple myeloma; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; R/R = relapsed/refractory; SoC = standard of care.

Rodriguez-Otero P, et al. *N Engl J Med.* 2023;388:1002-1014.

Ciltacabtagene Autoleucel (Cilta-cel)

CAR T-Cell Therapy With 2 BCMA-Targeting Domains

- ORR = 97.9%; DoR = 21.8 months
- Offered only in qualified centers (get on list)
- REMS program
- CRS (N = 97)
  - Median time to onset: 7 days (range: 1-12)
  - Median duration: 4 days (range 1-40 days with 1 patient extending out to 97 days)
  - CRS rates: 95% any grade
    4% grade 3 or 4
    1% grade
- Neurotoxicity (N = 97)
  - 26% any grade
  - 11% grade 3 or higher
- ICANs
  - During (n = 16), before (n = 3), or after CRS (n = 3)
  - Median time to onset: 8 days (range: 1-28)
  - Median duration: 7.5 days (range: 2-1229)
  - Resolution in 77% (17/22); median time 6 days (range: 2-143)
  - ICANS rates: 23% any grade (n = 22); 3% grade 3 or 4 (n =3); 2% grade 5 (n=2)
- Hemophagocytic lymphohistiocytosis (HLH); macrophage activation syndrome (MAS)
- Prolonged cytopenias
  - Neutropenia grade 3 or 4: 30% (n=29)
  - Thrombocytopenia grade 3 or 4: 41% (n=40) not resolved by day 30

NEW

R/R MM after **at least 1 prior line** of therapy of therapy (including a PI, an IMiD, and refractory to lenalidomide)

Find a Treatment Center at https://www.carvyktihcp.com/treatment-centers

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DoR = duration of response; ICANS = immune effector cell–associated neurotoxicity syndrome; IMiD = immunomodulatory drug; mAb = monoclonal antibody; MM = multiple myeloma; ORR = overall response rate; PI = proteasome inhibitor; REMS = Risk Evaluation and Mitigation Strategy; R/R = relapsed/refractory.

CARVYKTI™ (ciltacabtagene autoleucel) Prescribing Information. CARVYKTI™ website. Accessed April 11, 2024. https://www.carvyktihcp.com/safety.

CARTITUDE-4: Cilta-cel Improved PFS and OS vs Standard of Care in Patients With R/R MM (1-3 Prior Lines of Therapy)

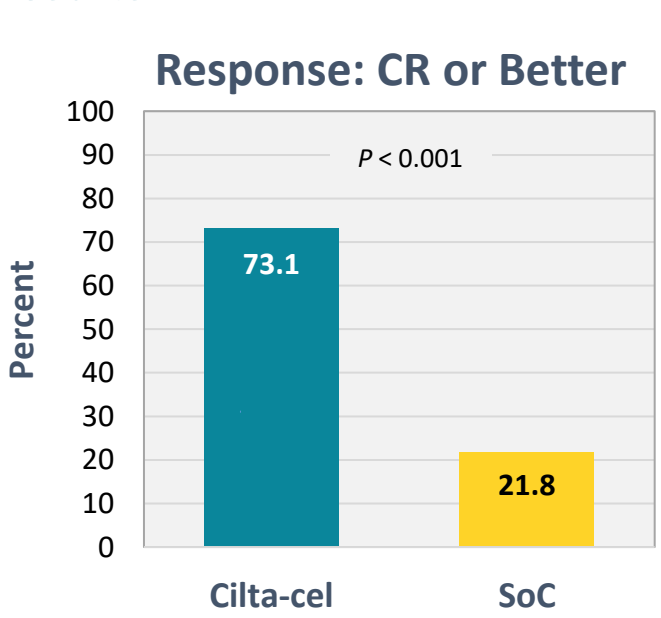
CARTITUDE-4 Phase 3 Clinical Trial

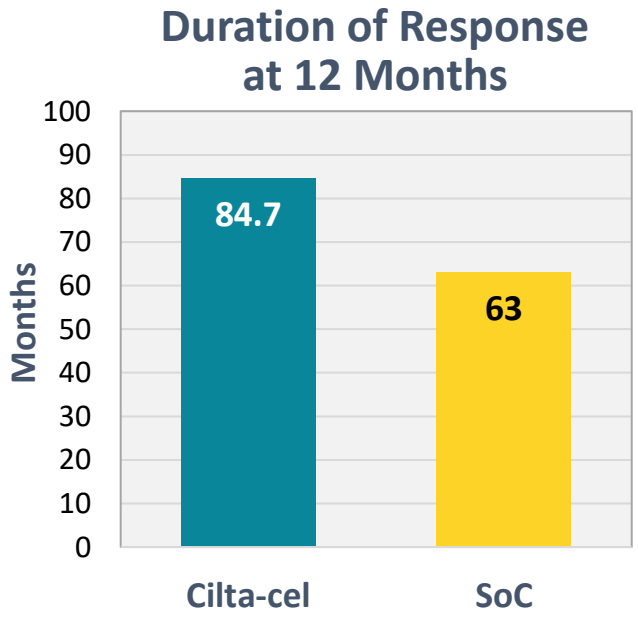
- 419 patients with R/R MM (1-3 prior lines of therapy)
  - Cilta-cel n = 208
  - Standard regimen n = 211 (Dara-Pd [n = 183] or PVd [n = 28])

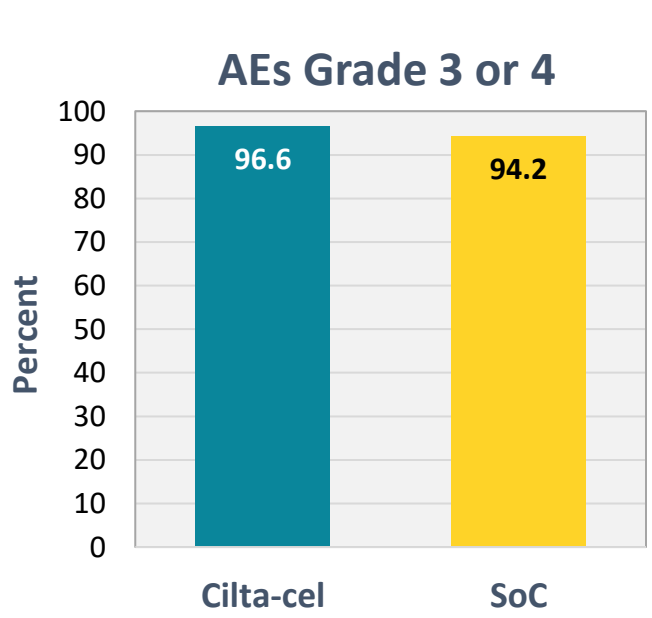
Among those treated with cilta-cel on trial (n = 176)

- 76.1% any-grade CRS (grade 3, n = 2)
- 20.5% any-grade neurotoxicity (grade 3 or 4, n = 5)
- ICANS n = 8; all grade 1 or 2

Results





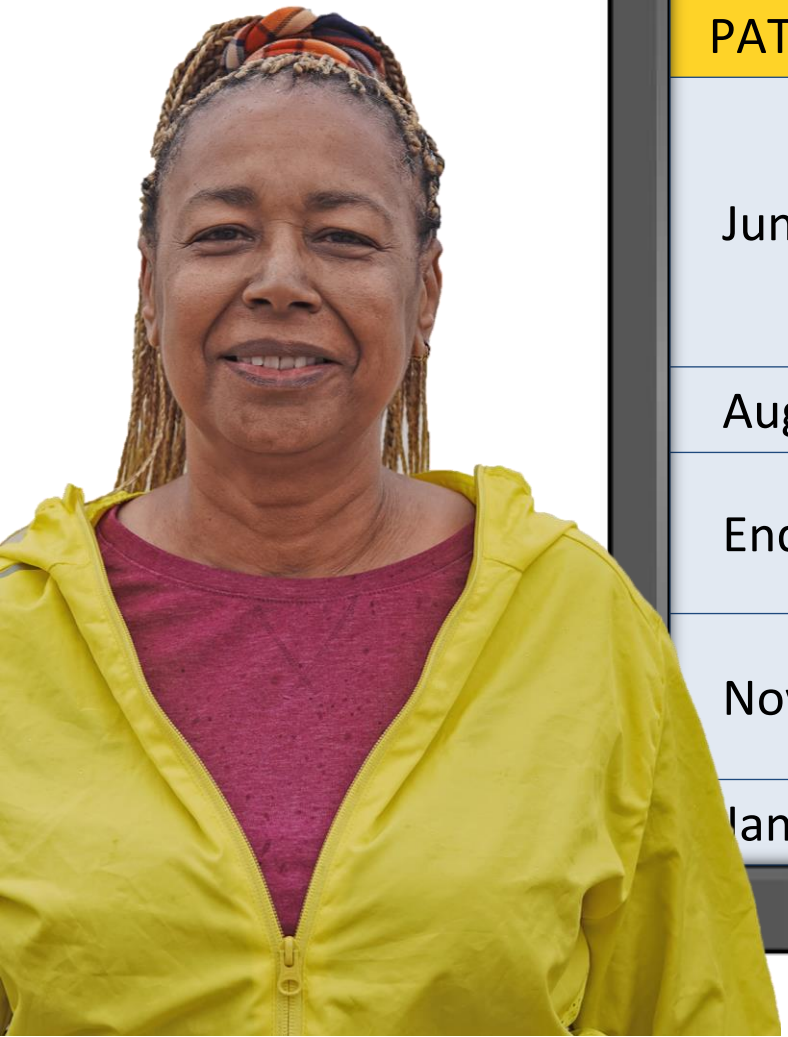


AE = adverse event; cilta-cel = ciltacabtagene autoleucel; CR = complete response; CRS = cytokine release syndrome; Dara-Pd = daratumumab pomalidomide dexamethasone; ICANS = immune effector cell–associated neurotoxicity syndrome; MM = multiple myeloma; OS = overall survival; PFS = progression-free survival; PVd = pomalidomide bortezomib dexamethasone; R/R = relapsed/refractory; SoC = standard of care.

San-Miguel J, et al. *N Engl J Med.* 2023;389:335-347.

CASE 2

*HIPAA-compliant, not actual patient name, stock photo.



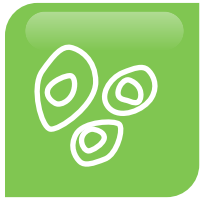
MARGARET*

PATIENT NOTES

June 2022	• Symptomatic MM relapse (anemia, new bone lesions) • Pre CAR-T therapy: Selinexor-bortezomib-dexamethasone (XVd)
August 2022	• Received CAR T slot
End of September 2022	• T cells harvested • Resumed XVd as bridging therapy
November 2022	• BCMA-directed CAR T cells infused • Grade 2 CRS, cytopenias
January 2023	• CR

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CR, complete response; CRS = cytokine release syndrome; HIPAA = Health Insurance Portability and Accountability Act; MM = multiple myeloma.

Summary



MM clones evolve over time and can become resistant to therapy.

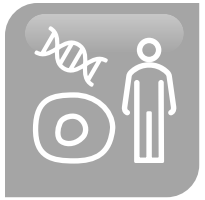
The **relapse workup for MM** includes laboratory blood work, genetic testing (FISH of bone marrow biopsy), and imaging for bone involvement and/or extramedullary disease.

There are **many options** for treating patients with relapsed MM; many considerations for treatment (eg, prior therapies, sequencing, **patient preference → provide tools and resources to aid decision-making**).

Anticoagulation is important for patients receiving certain myeloma therapies, **including IMiD-, doxorubicin-, or carfilzomib-containing regimens.**

Selinexor is a novel selective nuclear export (SINE) inhibitor that, in addition to treating MM, **does not impair T-cell function**, potentially improving the effectiveness of MM therapies that depend on T-cell function.

Cilta-cel and ide-cel are CAR T-cell therapies that now approved for earlier lines of after at least a proteasome inhibitor and IMiD therapy



CRS, neurotoxicity, cytopenias, and infection are AEs associated with CAR T-cell therapy; acute toxicities are managed at the CAR T-cell therapy center; delayed toxicities may be managed by the primary oncology practice.

AE, adverse event; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; cilta-cel = ciltacabtagene autoleucel; CRS = cytokine release syndrome; FISH = fluorescence in situ hybridization; ICANS = immune effector cell–associated neurotoxicity syndrome; IMiD = immunomodulatory drug; ide-cel = idecabtagene vicleucel; MM = multiple myeloma.

Keats JJ, et al. *Blood*. 2012;120(5):1067-1076. Hillengass J, et al. *Lancet Oncol*. 2019;20(6):e302-e312. Ghobrial IM, et al. *Blood*. 2014;124:3380-3388. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-3548. Faiman B, et al. *J Adv Pract Oncol.* 2016;2016:7(suppl 1):17-29. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024. XPOVIO™ (selinexor) Prescribing Information. Binder AF, et al. *Front Immunol.* 2023;14:1275329. ABECMA™ (idecabtagene vicleucel) Prescribing Information. CARVYKTI™ (ciltacabtagene autoleucel) Prescribing Information. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. Maus MV, et al. *J Immunother Cancer*. 2020;8(2):e001511. Cohen AD. *Blood Cancer J*. 2022;12:32. Chakraborty. *Transplant Cell Ther*. 2021;27:222. Raje NS, et al. *Lancet Haematol*. 2022;9(2):143-161.

International Myeloma Foundation
800-452-CURE (2873)
http://myeloma.org

Relapsed Multiple Myeloma: Immunotherapies and Emerging Therapies

CASE 2: MARGARET* (continued)

CASE 3: ROBERT*

*HIPAA-compliant; not actual patient names.

Donna Catamero, ANP-BC, OCN, CCRC

Beth Faiman, PhD, RN, MSN, APRN-BC, AOCN, BMTCN, FAAN

HIPAA = Health Insurance Portability and Accountability Act.

NURSE LEADERSHIP BOARD

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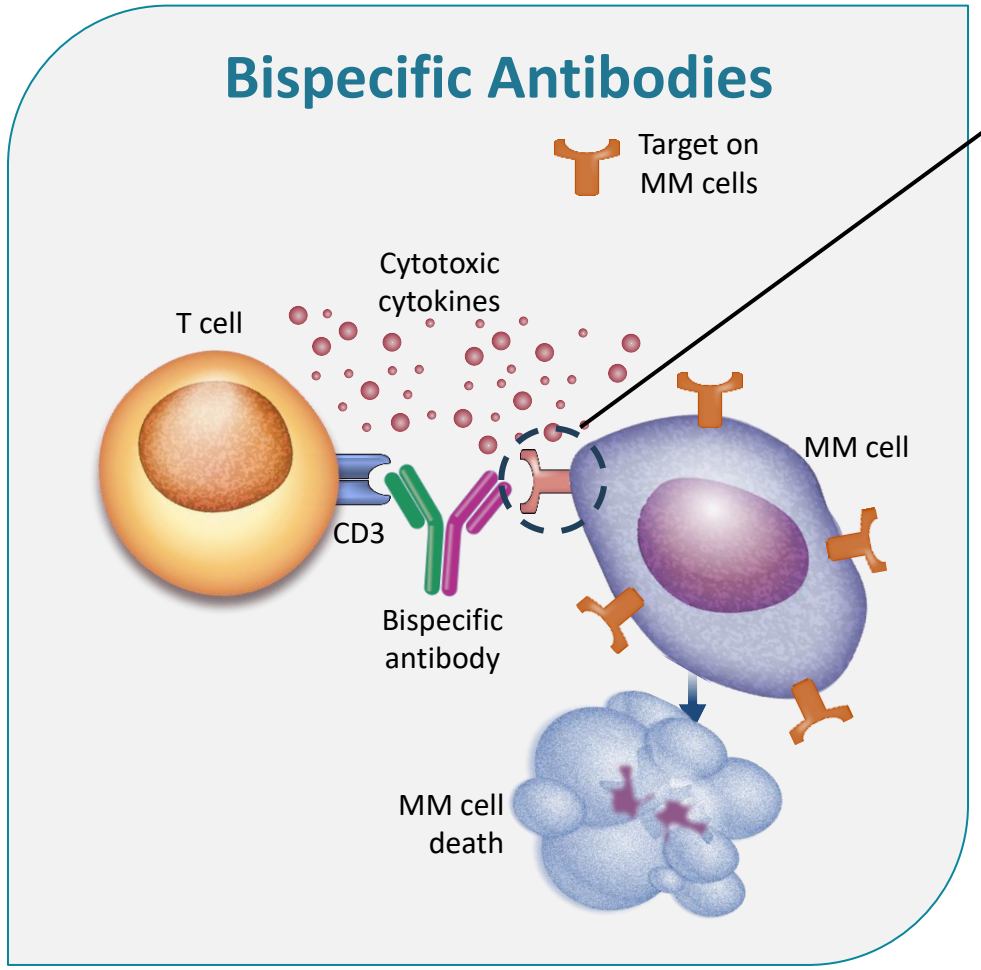
Mechanism of Action for Bispecific Antibodies: T-Cell Immune Activity Triggered Killing of Myeloma Cells



Target on Myeloma Cells	Bispecific Antibody	Administration	FDA Approval
BCMA	Teclistamab-cqyv	SC	October 2022
BCMA	Elranatamab-bcmm	SC	August 2023
GPRC5D	Talquetamab-tgvs	SC	August 2023

Target on Myeloma Cells	Bispecific Antibody in Development
BCMA	ABBV-383 (TNB-383B)
	Alnuctamab
	Linvoseltamab
GPRC5D	Forimtamig (RG6234)
FcRH5	Cevostamab

BCMA = B-cell maturation antigen; FcRH5 = Fc receptor-homolog 5; IV = intravenous; FDA = US Food and Drug Administration; GPRC5D = G-protein coupled receptor family C group 5 member D; MM = multiple myeloma; SC = subcutaneous.

O'Neill C, van de Donk NWCJ. *EJHaem*. 2023;4(3):811-822.Cho S-F, et al. *Front Oncol.* 2022;12:1032775. TECVAYLI® (teclistamab-cqyv) Prescribing Information. ELREXFIO™ (elranatamab-bcmm) Prescribing Information. TALVEY™ (talquetamab-tgvs) Prescribing Information.

Bispecific Antibody Clinical Pearls

- CRS and neurotoxicity management important for all bispecific antibodies
  - More likely during step-up and early doses; unlikely later
- Particular AEs tend to be related to target; individualize support
- Assess care partner needs (formal or informal)
- Step-up dosing is specific to each bispecific antibody
  - May need to repeat step-up dosing after a dose delay
- REMS program for each bispecific antibody:
  - Prescribers and institutions must be certified
  - Nurses must be trained on AE monitoring requirements
  - Driving restrictions for patient during step-up dosing and if patient has neurologic AEs that would interfere with driving
  - Start REMS training early
- Consider inpatient vs outpatient reimbursement

AE = adverse event; CRS = cytokine release syndrome; IV = intravenous; REMS = Risk Evaluation and Mitigation Strategy; SC = subcutaneous.

IMF Nurse Leadership Board experience. TECVAYLI® (teclistamab-cqyv) Prescribing Information. ELREXFIO™ (elranatamab-bcmm) Prescribing Information. TALVEY™ (talquetamab-tgvs) Prescribing Information.

Suggested Interventions With Grade 1 CRS Following Bispecific Antibody (Institution Specific)

- Administer tocilizumab 8 mg/kg IV
  - May repeat dose up to 3 times; however, this patient cohort did not require additional doses
- Administer acetaminophen 1000 mg
- Monitor vital signs every 15 minutes until resolution
  - If no improvement in 1 hour, consider administering steroids
- Until ruled out, manage for infection
  - IV antibiotics
- IV fluids for hypotension
  - Consider vasopressors if no resolution (Brudno JN, Kochenderfer JN. *Blood Rev.* 2019:34:45-55)

Order set in place at the time of bispecific administration

Nurses are trained to recognize symptoms

Nurses notify APP or MD, who authorizes release of the orders

Patients are admitted to the APP service for CRS management

APP = advanced practice provider; CRS = cytokine release syndrome; IV = intravenous.

Catamero D, et al. Presented at: 20th International Myeloma Society (IMS) Annual Meeting Nurse Symposium. September 27-30, 2023; Athens, Greece.

Neurotoxicity

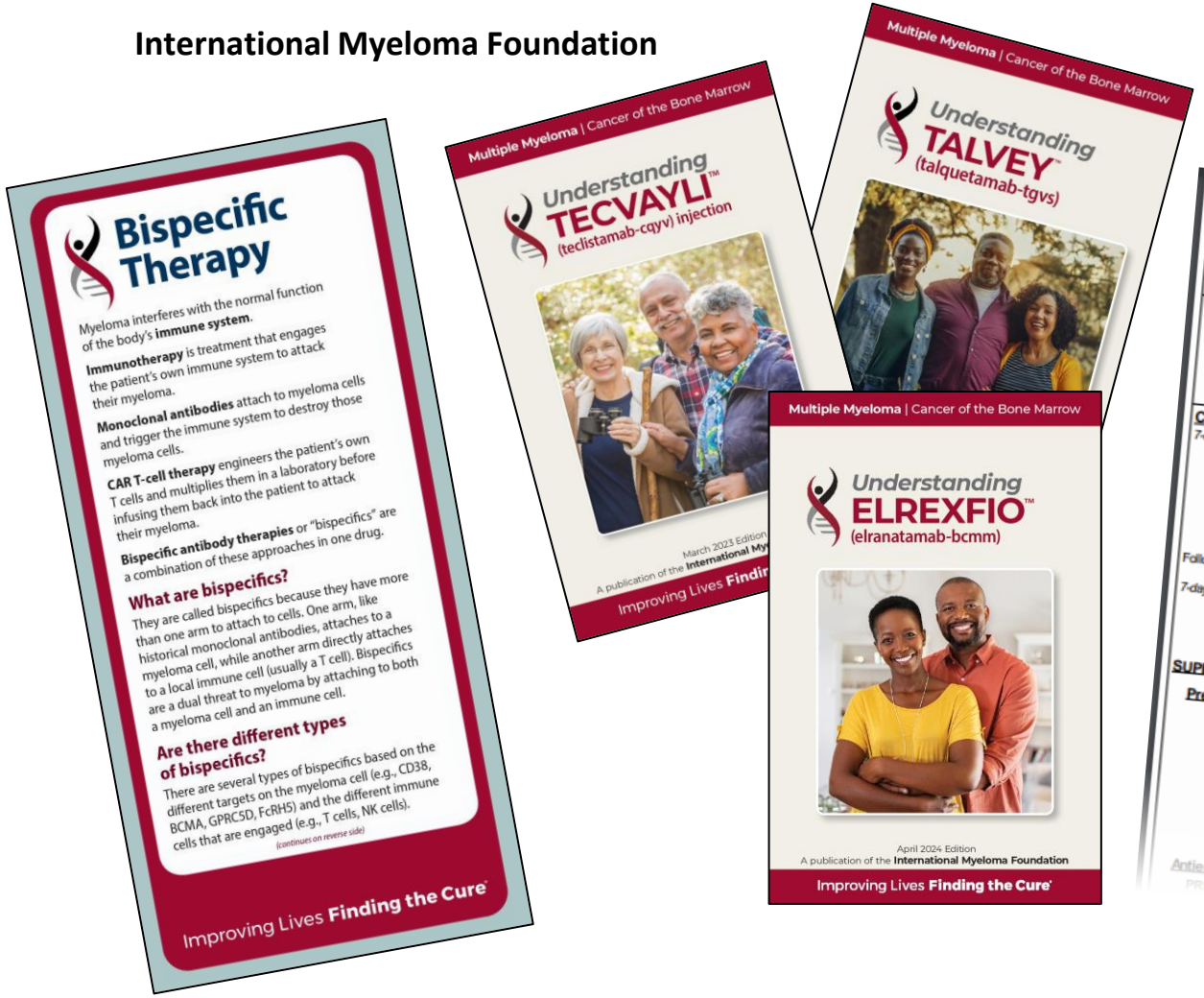
- Can occur:
  - In the absence of CRS
  - Concurrent with CRS
  - More commonly, after CRS
- Considered to be a distinct process from CRS
- The exact mechanism of neurologic toxicity is not known
- Endothelial injury, possibly resulting from pro-inflammatory cytokines, may contribute
- Onset can vary widely and can be acute or chronic
  - Short-term acute (eg, palsy) vs delayed onset (eg, lack of focus, or “chemo brain”)
- Toxicities tend to be self-limited and reversible

CRS = cytokine release syndrome.

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265-1272. June CH, et al. *Science*. 2018;359:1361-1365. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019:34:45-55. Catamero D, et al. Presented at: 20th International Myeloma Society (IMS) Annual Meeting Nurse Symposium. September 27-30, 2023; Athens, Greece.

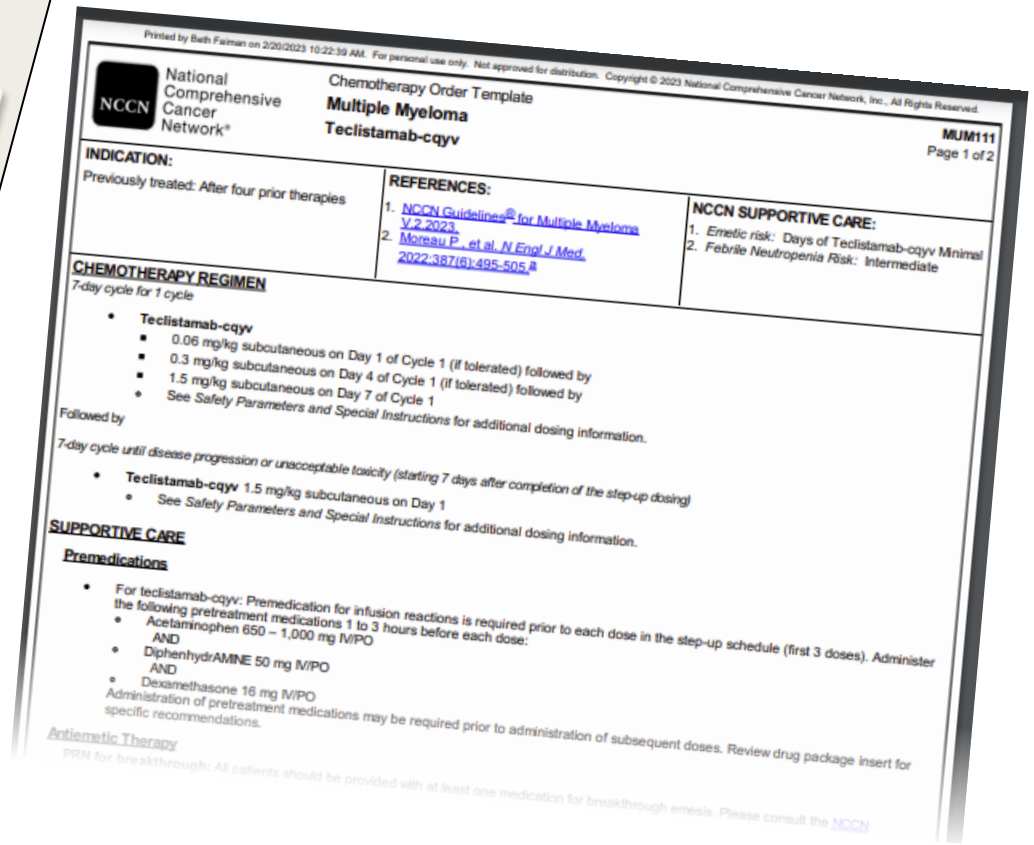
Resources for Bispecific Antibodies

International Myeloma Foundation



Prescribing Information and Drug-Specific Websites

NCCN



International Myeloma Foundation Website. Accessed March 15, 2024. https://www.myeloma.org/publications-videos/download-our-publications/tip-cards.
NCCN Website. Accessed March 15, 2024. https://www.nccn.org/compendia-templates/compendia/drugs-and-biologics-compendia.

Teclistamab: BCMA-Directed Bispecific Antibody

- Bispecific antibody targeting BCMA
- SC administration
- Step-up dosing → weekly for 6 months → **biweekly (every 2 weeks) after 6+ months for patients with a CR or better**
- Recommended premedication:
  - Corticosteroid (oral or IV dexamethasone 16 mg)
  - Histamine-1 (H1) receptor antagonist (oral or IV diphenhydramine 50 mg or equivalent)
  - Antipyretics (oral or IV acetaminophen 650 mg to 1000 mg or equivalent)
- Infection prophylaxis
- See prescribing information for dose modifications
  - CRS, neurotoxicity, hematologic AEs, infections, other
  - For restarting after dose delays (may need to repeat step-up dosing)

R/R MM after
≥ 4 lines of therapy
(including a PI, an IMiD, and an anti-CD38 mAb)

Dosing Schedule	Day		Dose	
Step-up dosing schedule	Day 1	Many institutions do step up doses every 48 hours	Step-up dose 1	0.06 mg/kg
	Day 4*		Step-up dose 1	0.3 mg/kg
	Day 7*		First treatment dose	1.5 mg/kg
Weekly dosing schedule	One week after first treatment dose and weekly thereafter		Subsequent treatment doses	1.5 mg/kg once weekly
Patients who have achieved and maintained a CR or better for a minimum of 6 months				
Biweekly	The dosing frequency may be decreased to 1.5 mg/kg every 2 weeks			

*May be given between 2 to 4 days after the prior step-up dose and up to 7 days after the prior step-up dose to allow for resolution of AEs

AE = adverse event; BCMA = B-cell maturation antigen; CR = complete response; CRS = cytokine release syndrome; IMiD = immunomodulatory drug; mAb = monoclonal antibody; MM = multiple myeloma; PI = proteasome inhibitor; R/R = relapsed/refractory.

TECVAYLI® (teclistamab-cqyv) Prescribing Information. Nurse Leadership Board.

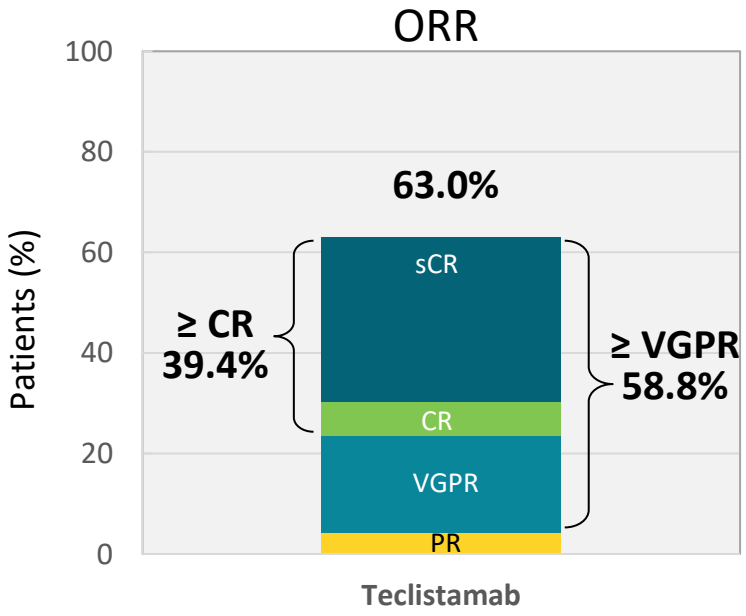
MajesTEC-1: Teclistamab in Patients With R/R MM

MajesTEC-1: Phase 1/2

- N = 165 patients with R/R MM with a median of 5 prior lines of therapy (no prior BCMA-directed)
  - 100% triple-class exposed; 77.6% triple-class refractory
  - 70.3% penta-drug exposed; 30.3% penta-drug refractory

WATCH FOR

Data from other MajesTEC clinical trials



- Median PFS: 11.3 months (95% CI, 8.8-17.1)
- Median DoR: 18.4 months (95% CI 14.9-NE)
- 46% MRD negative among pts with ≥CR
- Notable AEs
  - 76.4% infection (grade 3 or 4, 44.8%)
  - 72.1% CRS (grade 3, 0.6%; no grade 4)
  - 70.9% neutropenia (grade 3 or 4, 64.2%)
  - 52.1% anemia (grade 3 or 4, 37.0%)
  - 40% thrombocytopenia (grade 3 or 4, 21.2%)
  - 14.5% neurotoxic events (occurred in 24 patients, including ICANS in 5 patients [3.0%; all grade 1 or 2])

AE = adverse event; CR = complete response; CRS = cytokine release syndrome; DoR = duration of response; ICANS = immune effector cell–associated neurotoxicity syndrome; MM = multiple myeloma; MRD = minimal residual disease; NE = not estimable; ORR = overall response rate; PFS = progression free survival; PR = partial response; R/R = relapsed/refractory; sCR = stringent complete response; VGPR = very good partial response.

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

Elranatamab: BCMA-Directed Bispecific Approved for MM

- Bispecific antibody targeting BCMA
- SC administration
- Step-up dosing → weekly (for 24+ weeks) → **biweekly (every 2 weeks) after 25 weeks for responders**
- Recommended premedication:
  - Acetaminophen (or equivalent) 650 mg orally
  - Dexamethasone (or equivalent) 20 mg orally or IV
  - Diphenhydramine (or equivalent) 25 mg orally
- See prescribing information for dose modifications
  - For CRS, neurotoxicity, hematologic AEs, infections, other
  - For restarting after dose delays (may need to repeat step-up dosing)

R/R MM after
≥ 4 lines of therapy
(including a PI, an IMiD, and an anti-CD38 mAb)

Dosing Schedule	Day	Dose	
Step-up dosing schedule	Day 1	Step-up dose 1	12 mg
	Day 4	Step-up dose 2	32 mg
	Day 8	First treatment dose	76 mg
Weekly dosing schedule	One week after first treatment dose and weekly thereafter, through week 24	Subsequent treatment doses	76 mg 1× weekly
Biweekly (every 2 weeks) for responders	Week 25 and every 2 weeks thereafter	Subsequent treatment doses	76 mg every 2 weeks

AE = adverse event; BCMA = B-cell maturation antigen; CRS = cytokine release syndrome; IMiD = immunomodulatory drug; IV = intravenous; IVIG = intravenous immune globulin; mAb = monoclonal antibody; MM = multiple myeloma; PI = proteasome inhibitor; R/R = relapsed/refractory; SC = subcutaneous.
ELREXFIO™ (elranatamab-bcmm) Prescribing Information.

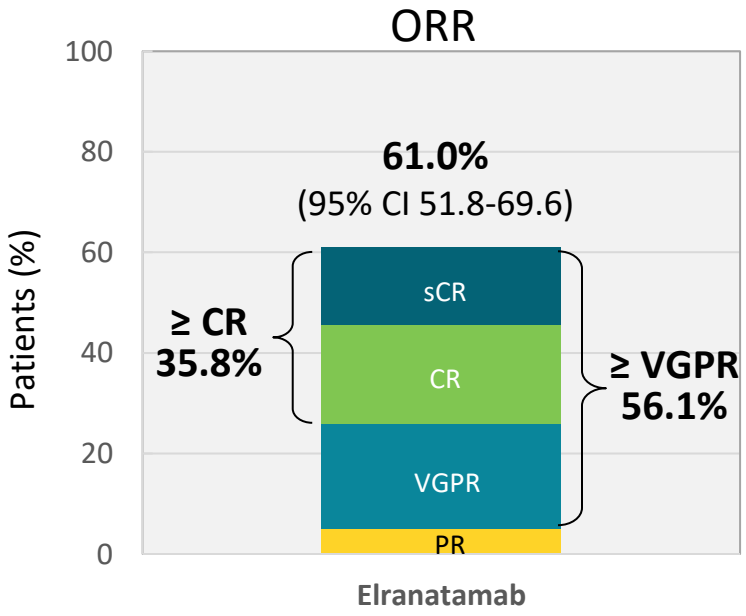
MagnetisMM-3: Elranatamab in Patients With R/R MM

MagnetisMM-3 Phase 2

- N = 123 patients with R/R MM with a median of 5 prior lines of therapy (no prior BCMA-directed)
  - 100% triple-class exposed; 96.7% triple-class refractory
  - 70.7% penta-drug exposed; 42.3% penta-drug refractory

WATCH FOR

Data from other MagnetisMM clinical trials



- Median PFS, median DoR, and OS have not been reached (median follow up 15.9 months)
- Notable AEs
  - 69.9% infection (grade 3 or 4, 40.7%)
  - 57.7% CRS grade 1 or 2 (no grade 3 or 4); median onset @ 2 days
  - 48.8% anemia (grade 3 or 4, 37.4%)
  - 48.8% neutropenia (grade 3 or 4, 48.8%)
  - 31.7% thrombocytopenia (grade 3 or 4, 23.6%)
  - 3.4% (4/119) ICANS grade 1 or 2 (no grade 3 or 4)
- 80% of pts who switched to biweekly dosing improved or maintained their response for ≥6 months

AE = adverse event; BCMA = B-cell maturation antigen; CR = complete response; CRS = cytokine release syndrome; DoR = duration of response; ICANS = immune effector cell–associated neurotoxicity syndrome; IMiD = immunomodulatory drug; mAb = monoclonal antibody; MM = multiple myeloma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI = proteasome inhibitor; PR = partial response; R/R = relapsed/refractory; sCR = stringent complete response; VGPR = very good partial response.

Lesokhin AM, et al. *Nat Med*. 2023;29(9):2259-2267. Tomasson MH, et al. ASH 2023. Abstr #3385.

Medications Can Reduce Infection Risk (RECAP)

Some people receiving bispecific antibody therapy have experienced infections that are less common, such as CMV, PJP, and fungal infections

Type of Infection Risk	Medication Recommendation(s)
Viral: herpes simplex (HSV/VZV); CMV	Acyclovir prophylaxis
Viral: influenza, COVID-19	Consider antiviral therapy if exposed or positive for influenza or COVID-19, per institution recommendations
Hepatitis B virus (HBV) reactivation	**Entecavir prophylaxis in patients positive for chronic HBV infection** (defined as serologically positive for hepatitis B surface antigen [HBsAg]) if treated with CAR T, **bispecific antibodies,** or daratumumab
Bacterial: blood, pneumonia, and urinary tract infection	Consider prophylaxis with levofloxacin
Pneumococcal infection	The CDC recommends pneumococcal vaccination (1 dose of PCV20 or 1 dose of PCV 15 followed by 1 dose of PPSV23 at least one year later); CAR T or ASCT: revaccinate 3-6 months after treatment; **Bispecific: Update vaccination status prior to starting therapy**
PJP (*P jirovecii* pneumonia)	Consider prophylaxis with trimethoprim-sulfamethoxazole
Fungal infections	Consider prophylaxis with fluconazole
IgG < 400 mg/dL (general infection risk)	IVIG replacement (400 mg/kg once every 4 weeks) is indicated; **IVIG replacement during CAR T-cell and bispecific antibody therapy is not guided by the presence of infections**[a] CAR T: Day +30 through 1 year. After 1 year continue until serum IgG > 400 mg/dL **Bispecific: start at the second cycle of therapy and continue until the end of therapy or serum IgG > 400**
ANC < 1000 cells/µL (general infection risk)	Consider GCSF 2 or 3 times/week (or as frequently as needed) to maintain ANC > 1000 cells/µL and treatment dose intensity; CAR-T: Start levofloxacin at 500 mg PO daily[b] or per clinician discretion and continue through neutrophil recovery; **Bispecific: consider starting with therapy and administer throughout the first cycle.**

[a]IVIG is indicated in all patients with MM with IgG < 400 and recurrent life-threatening infections. [b]Alternatives: cefdinir 300 mg PO twice a day or amoxicillin/clavulanate 875 mg PO twice a day.
ANC = absolute neutrophil count; BCMA = B-cell maturation antigen; CMV, cytomegalovirus; GCSF = granulocyte colony-stimulating factor; HSV = herpes simplex virus; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; PJP = *Pneumocystis jirovecii* pneumonia; VZV = varicella zoster virus.

Raje NS, et al. *Lancet Haematol*. 2022;9(2):143-161. NCCN Guidelines®. Multiple Myeloma. V3.2024. Accessed March 15, 2024. Cao W, et al. *Blood.* 2020;136(4):516-519.

Talquetamab: GPRC5D-Directed Bispecific Antibody

- **NEW target by bispecific antibodies: G protein-coupled receptor family C group 5 member D (GPRC5D)**, which has limited expression in normal human tissue but is highly expressed on malignant plasma cells
- SC administration
- Step-up dosing based on body weight →
  - Weekly 0.4 mg/kg (doses at least 6 days apart) OR
  - Biweekly (every 2 weeks) 0.8 mg/kg (at least 12 days apart)
- Recommended premedication:
  - Corticosteroid (oral or intravenous dexamethasone, 16 mg or equivalent)
  - Antihistamines (oral or intravenous diphenhydramine, 50 mg or equivalent)
  - Antipyretics (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)
- See prescribing information for dose modifications
  - For oral toxicity/weight loss, infections, cytopenias, skin reactions, other
  - For restarting after dose delays (may need to repeat step-up dosing)

R/R MM after
≥ 4 lines of therapy
(including a PI, an IMiD, and an anti-CD38 mAb)

Dosing Schedule	Day	Dose	
Step-up dosing	Day 1	Step-up dose 1	0.01 mg/kg
	Day 4*	Step-up dose 2	0.06 mg/kg
First weekly treatment dose OR step-up dose for biweekly	Day 7*	Weekly: first treatment dose Biweekly: step up dose 3*	0.4 mg/kg
First biweekly dose	Day 10* (only for biweekly dosing)	Biweekly: first treatment dose	0.8 mg/kg

Many institutions do step up doses every 48 hours

*May be given between 2 to 4 days after the prior step-up dose and up to 7 days after the prior step-up dose to allow for resolution of AEs

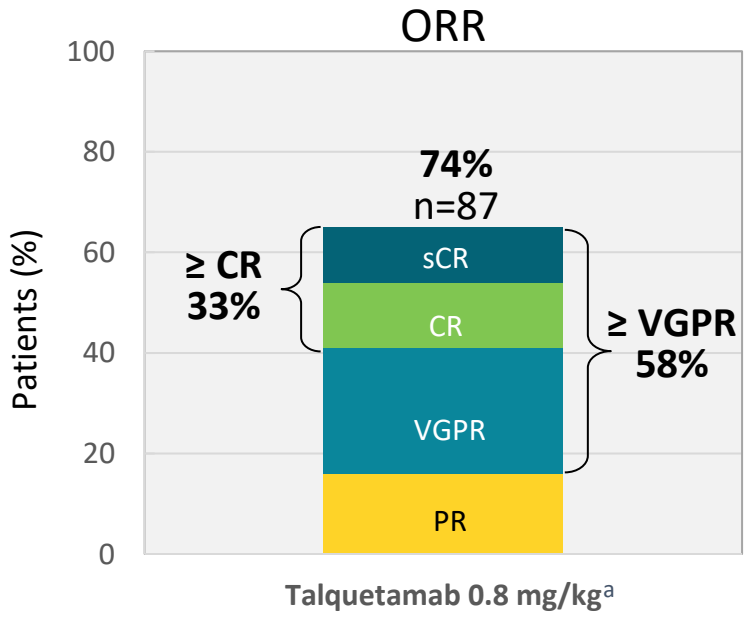
GPRC5D = G protein-coupled receptor, class C group 5 member D; IMiD = immunomodulatory drug; mAb = monoclonal antibody; MM = multiple myeloma; PI = proteasome inhibitor; R/R = relapsed/refractory; SC = subcutaneous.

TALVEY™ (talquetamab-tgvs) Prescribing Information. Nurse Leadership Board.

MonumenTAL-1: Talquetamab in Patients With R/R MM

MonumenTAL-1: Phase 1/2

- Patients with R/R MM received talquetamab IV or SC 0.4 mg/kg weekly (n=100) OR 0.8 mg/kg (n = 100) biweekly
- At least 3 prior lines of therapy (median ~6 prior lines of therapy (range 2-20); some with prior BCMA-directed bispecific or CAR T-cell therapy
- SC doses: Triple-class: 99% exposed, 97% refractory; penta-drug: 77% exposed, 25% refractory



- Median time to first response 1.2-1.3 months
- 72% ORR in Pts with prior T cell redirection therapy with at least 4 prior lines of therapy
- 40% ORR in pts with plasmacytomas (0.8 mg/kg biweekly SC dosing)
- Notable AEs
  - 76% CRS (grade 3 in 1.5%, NO grade 4)
  - 70% dysgeusia
  - 50% nail-related (NO grade 3 or 4)
  - 41% skin-related (grade 3, 0.3% NO grade 4)
  - 34% infections (grade 3 or 4, 7%) 0.8 mg/kg SC biweekly
  - 9% ICANS
  - Most GPRC5D-related AEs trended toward improvement or resolution except for weight loss

Skin, nail, and taste changes are AEs associated with targeting GPRC5D

[a]ORR was similar for 0.4 mg/kg weekly dose at 70% (2/30).

AE = adverse event; CAR = chimeric antigen receptor; CR = complete response; CRS = cytokine release syndrome; GPRC5D = G protein-coupled receptor, class C group 5 member D; ICANS = immune effector cell–associated neurotoxicity syndrome; MM = multiple myeloma; ORR = overall response rate; PR = partial response; R/R = relapsed/refractory; SC = subcutaneous; sCR = stringent complete response; VGPR = very good partial response.

TALVEY™ (talquetamab-tgvs) Prescribing Information. Chari A, et al. *N Engl J Med.* 2022;387(24):2232-2244. Chari A, et al. ASH 2023. Abstr #1010.

Management of Oral Toxicities

Clinical Pearl: If patients are not tolerating due to oral toxicities, have a low threshold for dose reduction or dosing interval

Taste Changes

Dexamethasone oral solutions "swish and spit" have been tried but with no proven benefit yet. Sour citrus or candies before meals are recommended.

Dry Mouth

OTC dry mouth rinse, gel, spray are recommended. Advise patients to avoid hot beverages.

Dysphagia

Dietary modifications, including taking small bites, eating upright, and sips of beverage with food, can help manage symptoms.

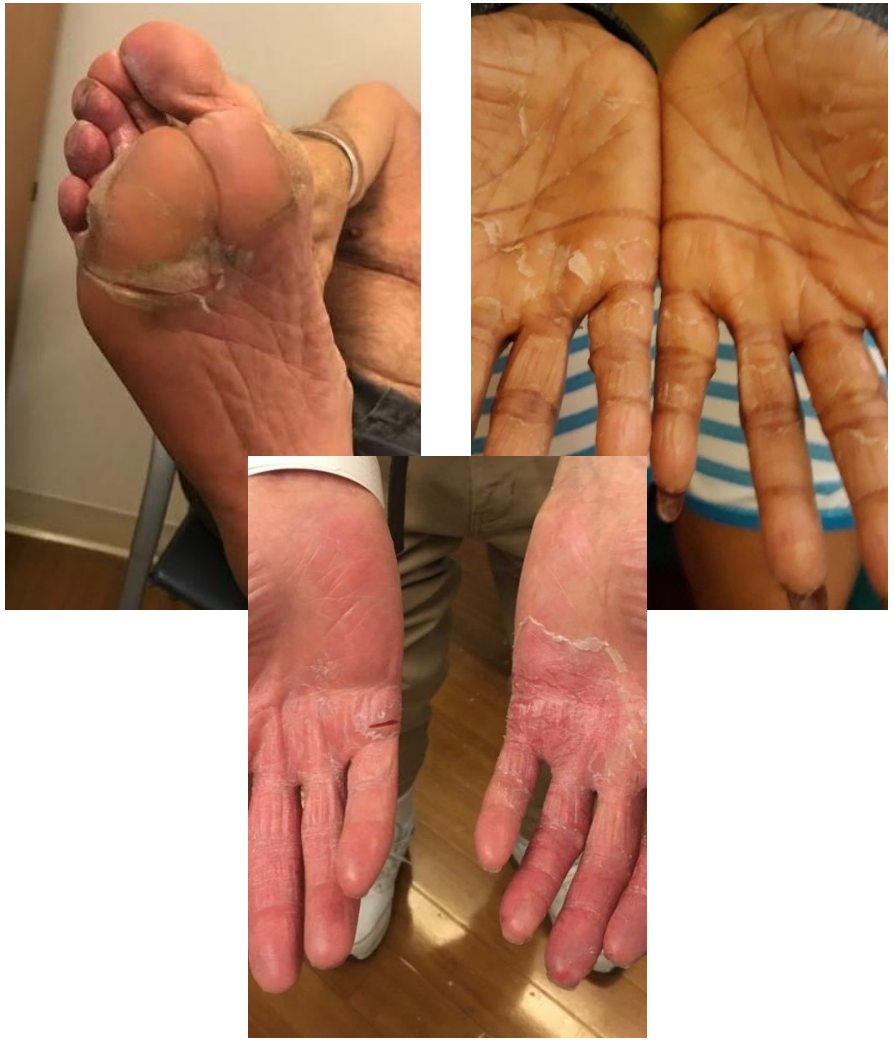
Glossitis and Thrush

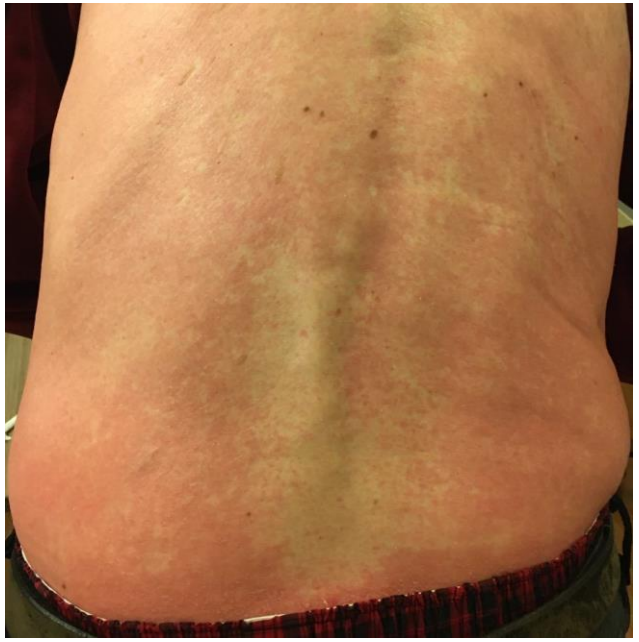
EARLY initiation of nystatin or clotrimazole is key to managing symptoms.

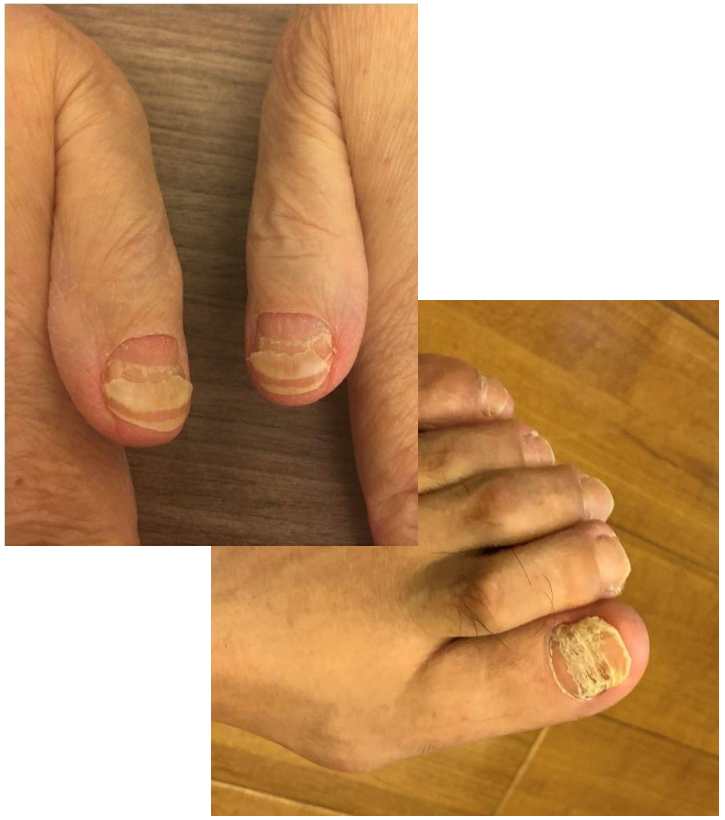
- **Weight loss and anorexia** are associated with taste changes. **Nutritionist** involvement and dietary modifications are recommended to support patients. An appetite stimulant with dronabinol, if indicated, can also be utilized.
- **Education and emotional support are key strategies for managing oral toxicities.**

Catamero D, et al. Presented at: 20th International Myeloma Society (IMS) Annual Meeting Nurse Symposium. September 27-30, 2023; Athens, Greece. Chari A, et al. ASH 2023. Abstr #1010.

Examples of Skin/Nail AEs With Talquetamab







Photos: Mount Sinai Hospital, NY, NY
AE = adverse event.

Management of Dermatologic AEs

Clinical Pearl: dermatologic AEs can be difficult to manage; dose adjustment may be needed

Dry Skin	Heavy moisturizers
Hand and/or Foot Peeling	Ammonium lactate 12% lotion to soles and palms twice daily
Nail Thinning and Peeling	Nail hardeners, topical vitamin E oil, and triamcinolone 0.025% ointment
Pruritus	Loratadine 10 mg by mouth daily for 3 to 5 days after talquetamab dose and triamcinolone 0.1% cream twice daily
Injection Site Reaction	
Body Rash/ Drug Rash	Above, plus consider methylprednisolone taper and betamethasone 0.05% cream twice daily

- Consider dose HOLD for other grade 3 dermatologic AEs
- Dermatology consults may be helpful as an early strategy
- **With experience, dermatologic AEs can be managed more easily than oral AEs**
- These interventions were successful at reducing or resolving dermatologic AEs

AE = adverse event.

Catamero D, et al. Presented at: 20th International Myeloma Society (IMS) Annual Meeting Nurse Symposium. September 27-30, 2023; Athens, Greece.

Teclistamab + Talquetamab Combination in Development

Study Design: Phase 1b

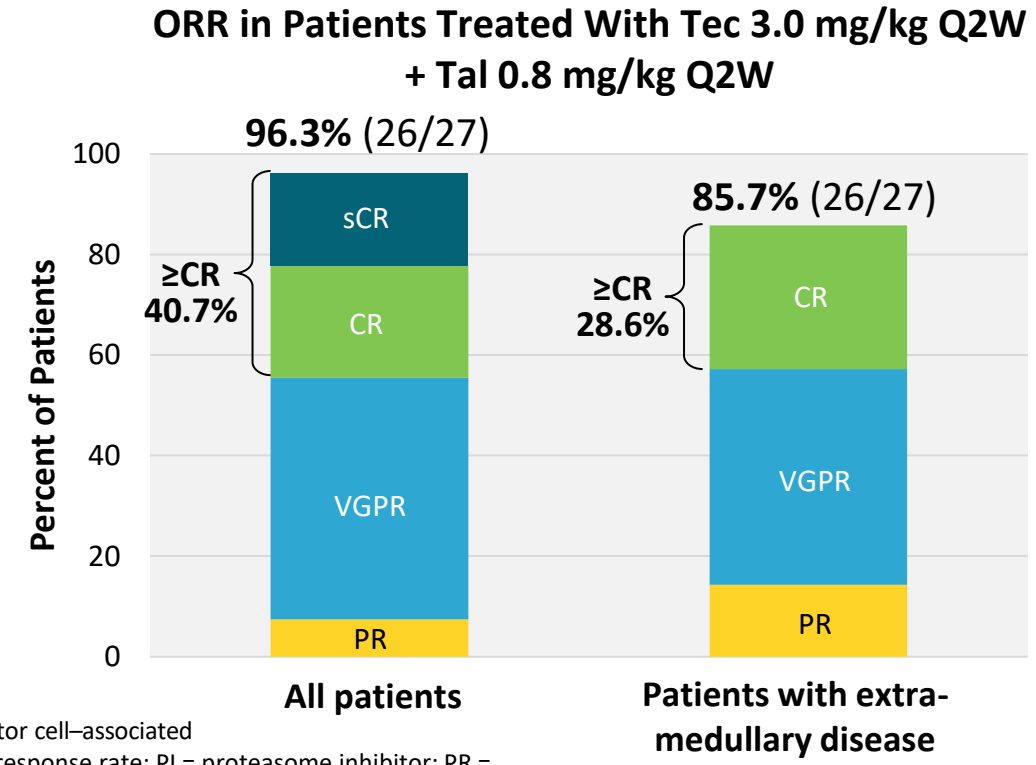
- Tec 3.0 mg/kg Q2W + Tal 0.8 mg/kg Q2W (n = 34)
- All had exposure to PI, IMiD, anti-CD 38 mAb
- 32% with extramedullary disease

Results

- AE profile was consistent with both monotherapy profiles
  - 65% any-grade neutropenia (61.3% grade 3/4)
  - 73.5% grade 1/2 CRS (NO grade 3 or 4)
  - 5 ICANS events in 3/93 patients
  - 8.8% febrile neutropenia
  - 47.1% dysgeusia
  - 52.9% skin toxicity
  - 41% nail disorders

WATCH FOR

New combination regimens with bispecific antibodies in clinical trials

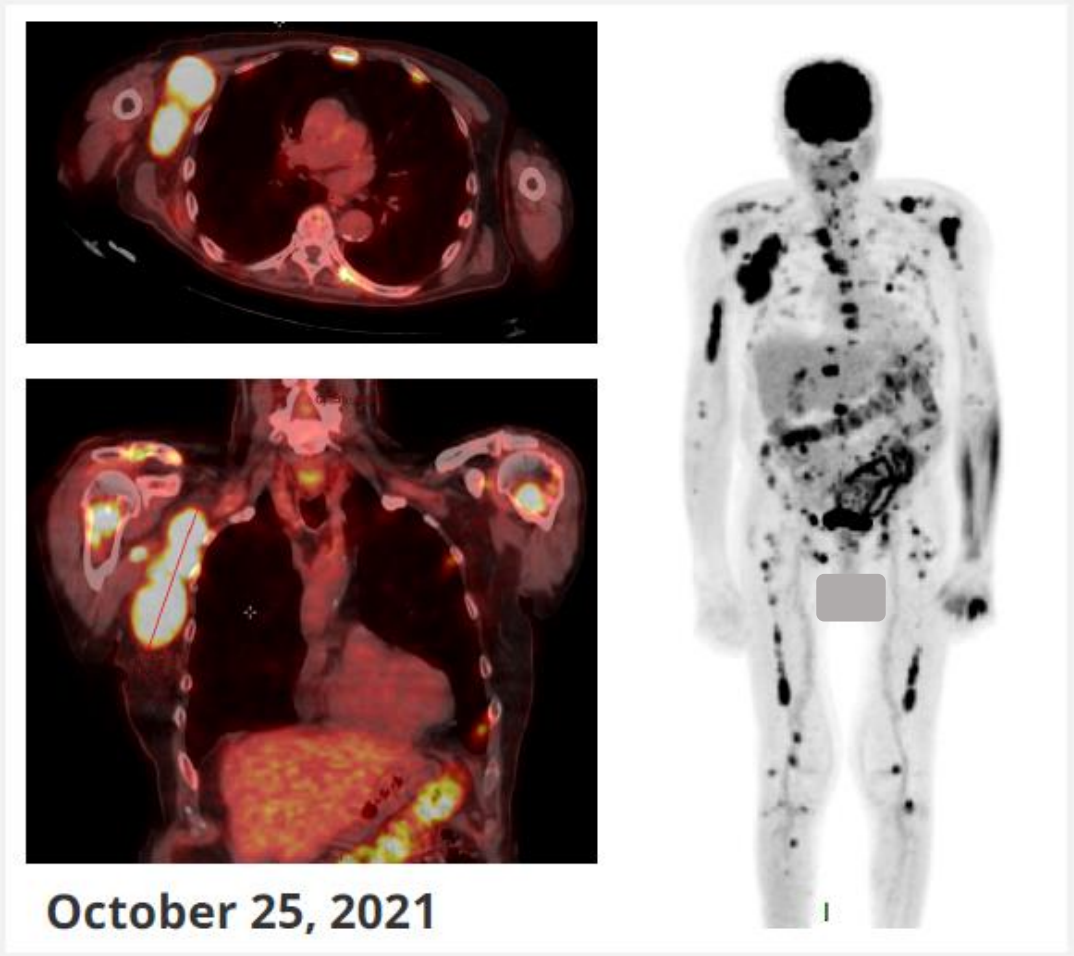


AE = adverse event; CR = complete response; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; IMiD = immunomodulatory drug; mAb = monoclonal antibody; ORR = overall response rate; PI = proteasome inhibitor; PR = partial response; Q2W = every 2 weeks; sCR = stringent complete response; Tal = talquetamab; Tec = teclistamab; VGPR = very good partial response.

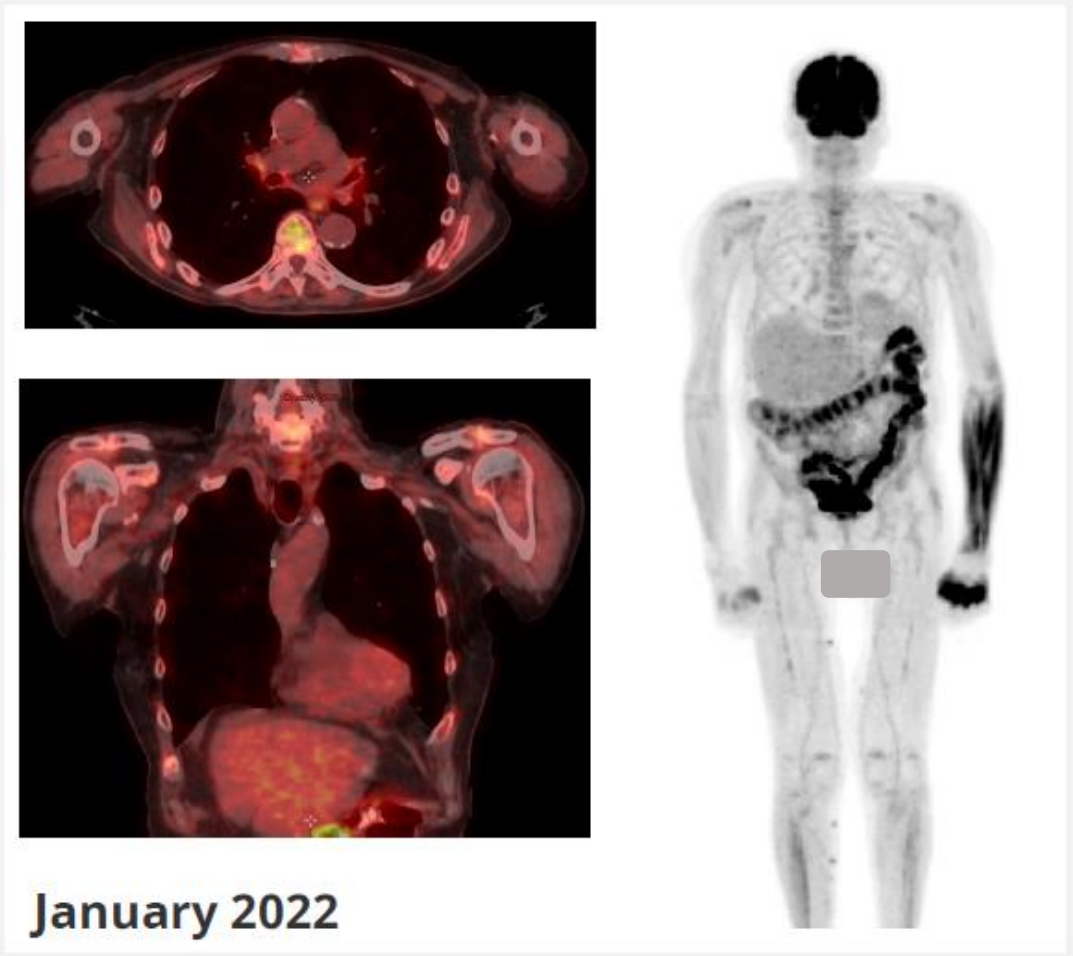
Mateos M-V, et al. EHA 2023. Abstr #S190. RedirecTT-1 (MMY1003) Study - TECVAYLI and TALVEY™ Cohort. Accessed March 27, 2024. https://www.janssenscience.com/products/talvey/medical-content/redirectt1-mmy1003-study-tecvayli-and-talvey-cohort.

Case Study: Teclistamab + Talquetamab Combination

- 74-year-old male, penta refractory, 6 prior LOT including ASCT, belantamab mafodotin, and prior RT to humerus



October 25, 2021



January 2022

ASCT = autologous stem cell transplant; LOT = line of therapy; RT = radiotherapy.
Mateos M-V, et al. EHA 2023. Abstr #S190.

Sequencing: BCMA-directed and GPRC5D-directed Bispecifc Antibodies Are Both Active Post BCMA-directed CAR T

HEMATOLOGIC MALIGNANCIES—PLASMA CELL DYSCRASIA

Check for updates

e20049 Publication Only

Sequencing bispecific antibodies and CAR T cell therapy in multiple myeloma with prior exposure to BCMA-targeted therapies.

Urvi Patel, Olalekan O. Oluwole, Adetola Kassim, Reena Jayani, Paul Belliveau, Bipin Savani, Bhagirathbhai R. Dholaria; Massachusetts College of Pharmacy and Health Sciences, Boston, MA; Vanderbilt University Medical Center, Nashville, TN; Massachusetts College of Pharmacy and Health Sciences, Worcester, MA; Vanderbilt-Ingram Cancer Center, Division of Hematology and Oncology, Nashville, TN

Background: In patients with heavily pretreated relapse and refractory multiple myeloma (MM), novel

REGULAR ARTICLE

blood advances

Sequencing T-cell redirection therapies leads to deep and durable responses in patients with relapsed/refractory myeloma

Tarek H. Mouhieddine,[1] Oliver Van Oekelen,[1,2] David T. Melnekoff,[1,2] Jeanne Li,[3] Yogita Ghodke-Puranik,[1] Guido Lancman,[1] Santiago Thibaud,[1] Darren Pan,[1] Sridevi Rajeeve,[1] Sarita Agte,[1] Adolfo Aleman,[1,4] Larysa Sanchez,[1] Shambavi Richard,[1] Adriana Rossi,[1] Joshua Richter,[1] Hearn Jay Cho,[1] Cesar Rodriguez,[1] Alessandro Lagana,[1,2,5] Erin Mosher,[3] Ajai Chari,[1] Sundar Jagannath,[1] and Samir Parekh[1]

[1]Division of Hematology and Medical Oncology, Tisch Cancer Institute; [2]Department of Genetics and Genomic Sciences; [3]Department of Population Health Science and Policy, Tisch Cancer Institute; [4]Graduate School of Biomedical Sciences; and [5]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

Key Points

- After treatment with a BiAb and disease relapse, patients with myeloma can be salvaged using sequential T-cell redirection therapy.
- Sequential T-cell redirection therapy led to a >80% response rate and a median OS that was not reached at a 30.5-month follow-up.

T-cell redirection therapy using chimeric antigen receptor (CAR) T cells and bispecific antibodies (BiAbs) has shown promising efficacy in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM), leading to the approval of 2 CAR T-cell products and numerous BiAb trials. Data on the outcomes after relapse following BiAbs are urgently required to develop strategies for sequencing salvage therapies. We identified 58 patients progressing after a BiAb trial at Mount Sinai Hospital. Progression-free survival (PFS) to the first salvage (PFS1), second salvage therapy (PFS2), and overall survival (OS) were estimated using the Kaplan-Meier method. The median age of the patients was 67 years, and 78% had high-risk cytogenetics. They had a median of 6 prior therapy lines, 89% were triple-class refractory, and 44% were penta-drug refractory. After the BiAb trial, patients were followed for a median of 30.5 months and received a median of 2 additional salvage therapies (range, 1-9). The most common first salvage was T-cell redirection in 19 patients (10 BiAb and 9 CAR T cells). Ten patients underwent T-cell redirection as a second salvage treatment. T-cell redirection therapy as first or second salvage was feasible and associated with a median PFS1 of 28.9 months, PFS2 of 30.9 months, and an OS of 62% at 2 years. The sequential use of different T-cell redirection therapies is possible and may lead to deep and durable responses following the relapse after BiAb therapy in RRMM.

Introduction

Over the past decade, the clinical outcomes of patients with multiple myeloma (MM) have substantially improved with the introduction of newer generations of immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, selective nuclear export inhibitors, B-cell maturation antigen (BCMA) antibody-drug conjugates (ADCs), and T-cell redirection therapies, including chimeric antigen receptor (CAR) T cells and bispecific antibodies (BiAbs).[1-5]

Submitted 21 April 2022; accepted 8 August 2022; prepublished online on *Blood Advances* First Edition 26 August 2022. https://doi.org/10.1182/bloodadvances.2022007923.
Presented as an oral presentation at the 63rd annual meeting of the American Society of Hematology, Atlanta, GA, 13 December 2021.
Data are available on request from the corresponding author, Samir Parekh (samir.parekh@mssm.edu).

"This analysis indicates that sequencing BsAbs and CAR -T cell therapy after previous BCMA-targeted treatments offers meaningful clinical benefit with durable response rates in patients who have few other options."

"Changing targets after relapse from a BCMA—targeted therapy (e.g., switching to a GPRC5D—targeted therapy) appears to work well."

Cancer Immunology, Immunotherapy (2023) 72:3931–3937
https://doi.org/10.1007/s00262-023-03559-4

REVIEW

Beyond BCMA, why GPRC5D could be the right way: treatment strategies with immunotherapy at relapse after anti-BCMA agents

Maria Livia Del Giudice[1] · Sara Galimberti[1] · Gabriele Buda[1]

Received: 21 August 2023 / Accepted: 6 October 2023 / Published online: 4 November 2023

Abstract
Multiple Myeloma remains incurable, and there is a need for therapies with novel mechanisms of action. Recently, B cell maturation antigen targeted therapy has demonstrated deep and durable responses in a largely treated population. However, the relapse rate of myeloma patients after anti-BCMA treatment strategies is increasing worldwide, and one of the most challenging issues for them is to choose the best therapy sequencing. After anti-BCMA treatment, retreatment with anti-BCMA drugs remains an option, but new targets are emerging strongly. One of them is G protein-coupled receptor, class C group 5 member D (GPRC5D), that due to the very promising data from the use of chimeric antigen receptor T-cells (CAR-T) and bispecific antibodies (BsAb) seems to be the ideal candidate in the relay of myeloma treatment at relapse. In this literature review, we discuss data from treatment with the new drugs at relapse after anti-BCMA therapies, observing an undeniable benefit from the use of drugs directed against GPRC5D.

Keywords Multiple myeloma · BCMA · GPRC5D · Talquetamab · Car-t · Therapy sequencing

Introduction

Multiple myeloma (MM) is a tumor of the plasma cells. Its clinical course is characterized by relapses over time, with the progression-free interval decreasing with each relapse. More than 12,000 myeloma-related deaths are expected in 2023 in the USA, and despite increasing survival rates worldwide [1], the disease remains incurable. In particular, the estimated survival of a myeloma patient is dramatically reduced after the use of the major available drugs [2, 3]. Only recently, however, therapies directed against B cell maturation antigen (BCMA) have been approved and they have yielded unhoped-for results in triple-class exposed patients, who otherwise would have had very poor overall survival.

B cell maturation antigen, also known as TNFRSF17 or CD269, is a member of the tumor necrosis factor receptor family [4]. BCMA gene is located on chromosome 16 (16p13). It was first characterized from human malignant T-cell lymphoma cells; it was later shown that BCMA gene is preferentially expressed in mature B cells, suggesting a role for this gene in the B-cell developmental process [5, 6]. BCMA is indeed highly expressed by mature B cells, with upregulation in the late stages of normal B-cell differentiation and also on MM plasma cells [7, 8]; it is also essential for the survival of long-lived bone marrow plasma cells [9].

Ligands for BCMA include B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), and they act as growth and proliferation signals, attenuating cell death mechanism associated with NF-κB activation and playing as a survival factor, with maintenance and survival of malignant MM cells [10, 11]: this is probably why therapeutic strategies for blocking the BCMA pathway have proven to be so effective in MM. Recently, there has been a wide availability of different drugs and classes against BCMA: antibody–drug conjugates (ADC), bispecific antibodies (BsAb), chimeric antigen receptor T-cells (CAR-T) products, mainly used in randomized trials and also in clinical practice in advanced stages of MM, following the most common drugs, such as proteasome inhibitors (PI), immunomodulatory drugs (IMiD), anti-CD38 and anti-signaling lymphocyte activation molecule F7 (SLAMF7) monoclonal antibodies (mAb).

The use of therapies directed against BCMA has shown revolutionary results in heavily pretreated relapse and/or

✉ Maria Livia Del Giudice
mliviadelgiudice@gmail.com

[1] Department of Clinical and Experimental Medicine, Hematology, University of Pisa, 56126 Pisa, Italy

Patel U, et al. ASCO 2023. Abstr #e20049. Mouhieddine TH, et al. *Blood Adv.* 2023;7(6):1056-1064. Del Giudice ML, et al. *Cancer Immunol Immunother*. 2023;72(12):3931-3937.

IMWG Immunotherapy Registry: Real-World Research to Answer Questions About Sequencing MM Therapies

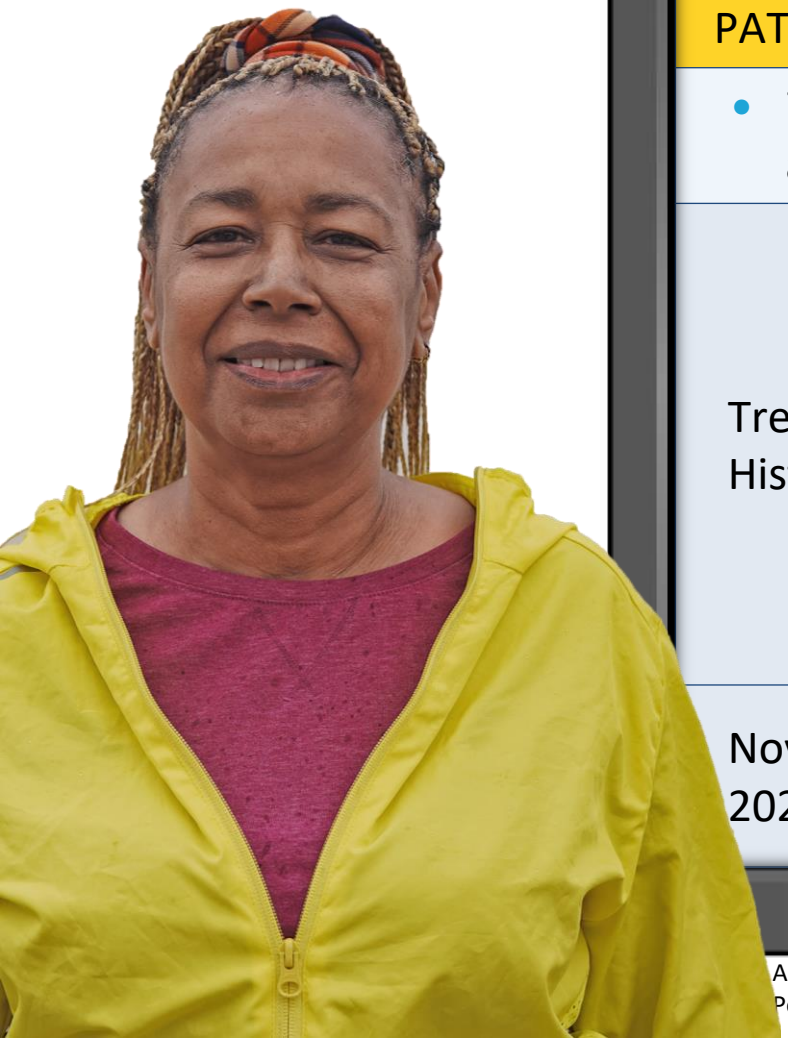
- Real-world data from IMWG-affiliated sites
- Prospectively follow 6000 participants, including “controls”
- Collect risk status, lines of therapy, drug exposure and refractoriness
- Evaluate sequencing of immunotherapies
- Asses global differences in practice patterns
- Analyze treatment response, toxicities, and outcomes

IMWG = International Myeloma Working Group; MM = multiple myeloma.

The IMF’s Immune Therapy Registry. Accessed March 27, 2024. https://www.myeloma.org/international-myeloma-working-group/imfs-immune-therapy-registry.

CASE 2 Continued

*HIPAA-compliant, not actual patient name, stock photo.



MARGARET*

PATIENT NOTES

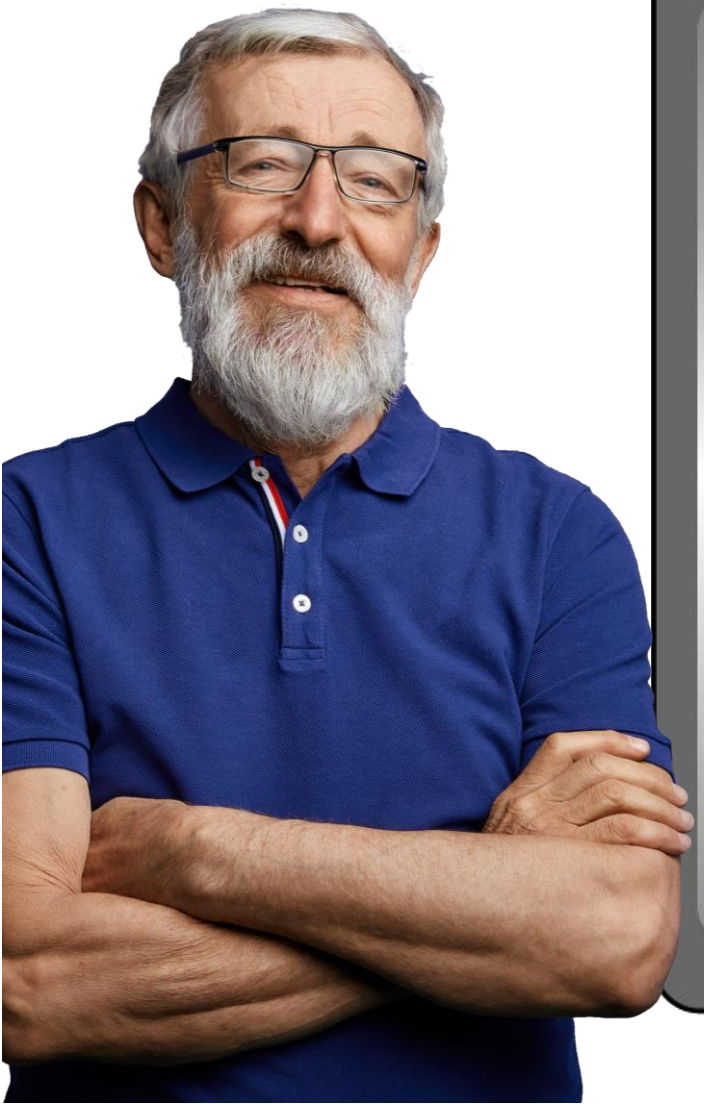
- 70 years old woman; diagnosed with high-risk MM in 2016 at age 63 years

Treatment History	• VRd→ASCT→R maintenance • Carfilzomib lenalidomide dexamethasone • Daratumumab pomalidomide dexamethasone • Ixazomib pomalidomide dexamethasone • Selinexor bortezomib dexamethasone (pre-CAR T) • CAR T-cell therapy (BCMA-directed)
November 2023	• Symptomatic relapse • Shared decision-making: talquetamab

ASCT = autologous stem cell transplant; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; HIPAA = Health Insurance Portability and Accountability Act; MM = multiple myeloma; R = lenalidomide; VRd = bortezomib lenalidomide dexamethasone.

CASE 3

*HIPAA-compliant, not actual patient name, stock photo.



ROBERT*

- 72-year-old man, diagnosed with standard-risk MM in 2015 at age 63 years

TREATMENT HISTORY

Treatment History	• VRd then transplant + R maintenance (2 years) • Carfilzomib/pomalidomide/dexamethasone • Elotuzumab/lenalidomide/dexamethasone • Daratumumab/pomalidomide/dexamethasone
January 2023 (71 Years Old)	• Symptomatic relapse • Shared decision-making: elranatamab

HIPAA = Health Insurance Portability and Accountability Act; MM = multiple myeloma; R = lenalidomide; VRd = bortezomib lenalidomide dexamethasone.

Clinical Trials: The Reason We Have So Many Therapies for MM

Preclinical

ANIMAL STUDIES: Examine safety and potential for efficacy

PHASE 1

FIRST INTRODUCTION OF AN INVESTIGATIONAL DRUG INTO HUMANS

- Determine metabolism and PK/PD actions, MTD, and DLT
- Identify AEs
- Gain early evidence of efficacy, studied in many conditions; typically, 20 to 80 patients; everyone gets agent

PHASE 2

EVALUATION OF EFFECTIVENESS IN A CERTAIN TUMOR TYPE

- Determine short-term AEs and risks; closely monitored
- Includes up to 100 patients, typically

PHASE 3

GATHER ADDITIONAL EFFECTIVENESS AND SAFETY INFORMATION COMPARED TO STANDARD OF CARE

- Placebo may be involved if no standard of care exists; hundreds to several thousand patients
- Often multiple institutions; single or double blind; sometimes open label

PHASE 4

APPROVED AGENTS IN NEW POPULATIONS OR NEW DOSE FORMS

AE = adverse event; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; PD = pharmacodynamics; PK = pharmacokinetics.

Faiman B, et al. *Adv Pract Oncol.* 2016;7:17-29.

Importance of Participation by Diverse Populations in Clinical Trials

> [P]eople from racial and ethnic minorities and other diverse groups are underrepresented in clinical research. This is a concern because people of different ages, races, and ethnicities may react differently to certain medical products.
> – FDA

US Cancer Centers of Excellence Strategies for Increased Inclusion of Racial and Ethnic Minorities in Clinical Trials

FDA = US Food and Drug Administration.

Regnante JM, et al. *J Oncol Pract.* 2019;15(4):e289-e299. FDA website. Clinical Trial Diversity. Accessed March 27, 2024. https://www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity.

Clinical Trial Myths: Importance of Dispelling Inaccuracies

MYTH: If I participate in a clinical trial, I might get a placebo, not active treatment

MYTH: If I participate in a clinical trial, I can't change my mind

- Phase 1 and 2, everyone gets active treatment
- Phase 3 standard of care vs new regimen: often standard regimen with/without additional agent in MM trials
- Patients can withdraw their consent for clinical trial participation at any time

MYTH: Patients (whatever demographic/ distance from clinic/etc) never participate in clinical trials so I won't mention it

- Mention the option and give the patient the opportunity; implicit and explicit biases can limit participation
- Some groups may need more information about clinical trials to feel comfortable with participation

MYTH: Clinical trials are dangerous because they have new medicines and practices

- Some risk is involved with every treatment, but medicines are used in clinical trials with people only after they have gone through testing to indicate that the drug is likely to be safe and effective for human use

MYTH: Clinical trials are expensive and not covered by insurance

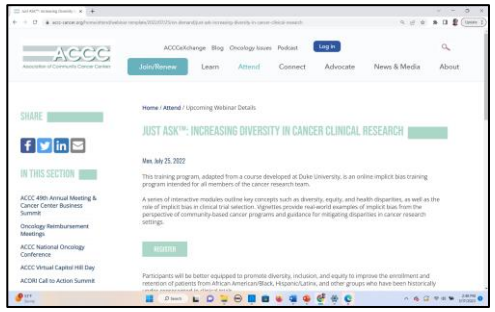
- Research costs are typically covered by the sponsoring company
- Standard patient care costs are typically covered by insurance
- Check with clinical trial team/insurers; costs such as transportation, hotel, etc may not be reimbursed and are paid by patient

MM = multiple myeloma.

PhRMA website. Accessed March 25, 2024. https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/A-C/CLINICAL-TRIALS-MYTH-FACT-PRINT.pdf?hsCtaTracking=f6689b95-1626-40d9-8c87-c6b8d31600a4%7C35221aa8-d487-4db3-9416-b9c3c35e3bac.

Resources to Find Clinical Trials and Avoid Bias

Clinicaltrials.gov
https://clinicaltrials.gov/



Just ASK™ Implicit Bias Training from Association of Community Cancer Centers website. Accessed March 15, 2024. https://www.accc-cancer.org/home/attend/webinar-template/2022/07/25/on-demand/just-ask-increasing-diversity-in-cancer-clinical-research

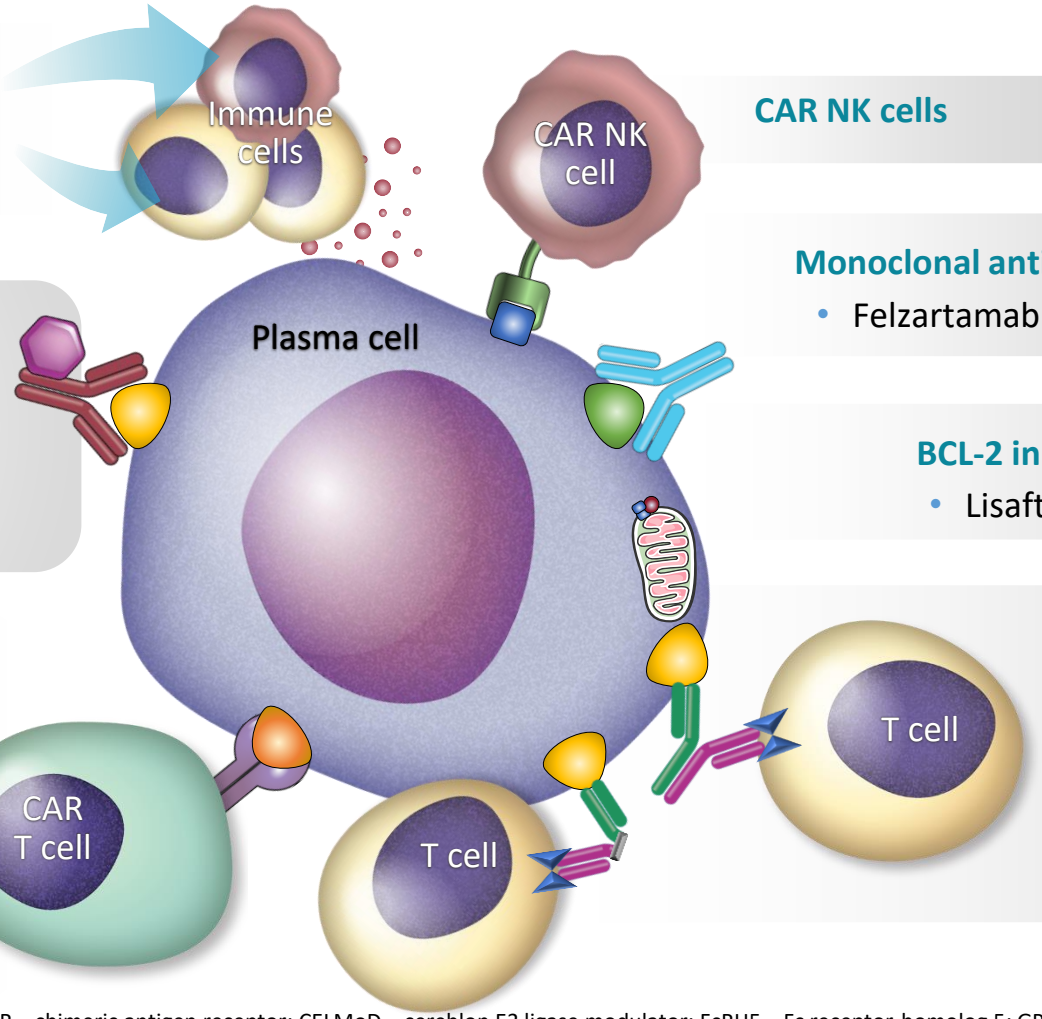
IMF Infoline
US & Canada: 800-452 CURE (2873)
Worldwide: 1-818-487-7455
infoline@myeloma.org

Therapies in Development for Treatment of Multiple Myeloma

CELMoD agents
- Iberdomide (cereblon E3 ligase)
- Mezigdomide (cereblon E3 ligase)

Antibody-drug conjugates
- Belantamab mafodotin (BCMA)
- STRO-001 (CD74)
- STI-6129 (CD38)
- CC-99712 (BCMA)

CAR T-cell therapies
- BMS-986393 (GPRC5D)
- CB-011 (BCMA)
- CART-ddBCMA (BCMA)
- P-BCMA-101 (BCMA)
- PHE885 (BCMA)
- GC012F (BCMA and CD19)



CAR NK cells

Monoclonal antibodies
- Felzartamab (CD38)

BCL-2 inhibitor
- Lisaftoclax

Bispecific antibodies
- ABBV-383 (BCMA)
- Alnuctamab (BCMA)
- Linvoseltamab (BCMA)
- Cevostamab (FcRH5)
- Forimtamig (GPRC5D)

BCL-2 = B-cell lymphoma 2; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CELMoD = cereblon E3 ligase modulator; FcRH5 = Fc receptor-homolog 5; GPRC5D = G-protein coupled receptor family C group 5 member D; HPC = hematopoietic progenitor cell; MM = multiple myeloma; NK = natural killer.

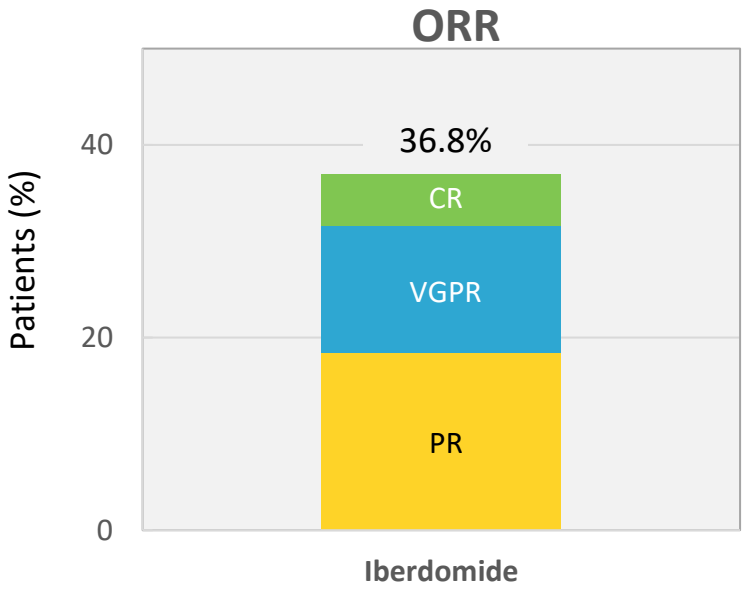
O'Neill C, van de Donk NWCJ. *EJHaem*. 2023;4(3):811-822. Hartley-Brown M, Richardson P. *Explor Target Antitumor Ther.* 2022;3(1):1-10. Ray U, Orlowski RW. Pharmaceuticals (Basel). 2023;16(4):590. Vu SH, et al. *Front Oncol.* 2023; 13: 1275076. Frigault MJ, et al. *Blood Adv.* 2023;7(5):768-777. van de Donk NWCJ, et al. ASH 2023. Abstr #208. Richardson PG, et al. ASH 2023. Abstr #1013. Chiu H, et al. ASH 2023. Abstr #335. Bal S, et al. ASH 2023. Abstr #219.

Iberdomide + Dexamethasone in R/R MM With Prior BCMA Therapy Exposure

- Mechanism: greater tumoricidal and immune-stimulatory effects compared with IMiDs; marked synergy with dexamethasone and other antimyeloma therapies in preclinical models
- Patients with R/R MM ≥ 3 lines of therapy (including IMiDs, a PI, an anti-CD38 mAb, and an anti-BCMA therapy) and progressive disease ≤ 60 days after last therapy* (n = 38)
  - Reference ORRs in similar populations: CAR T-cell therapy 36.8%; antibody-drug conjugate 34.2%; T-cell engager 13.7%; other 10.5%

WATCH FOR

- Clinical trials with iberdomide
- Combinations with iberdomide



Iberdomide showed encouraging activity and safety in patients with triple-class-exposed R/R MM and prior anti-BCMA therapy

- Median DoR: 7.5 months (95% CI 3.2-not reached)
- Median PFS: 2.4 months (95% CI 3.2-6.3)
- Hematologic toxicities
- Low rate of grade 3/4 nonhematologic toxicities
- No discontinuations due to treatment-emergent AEs

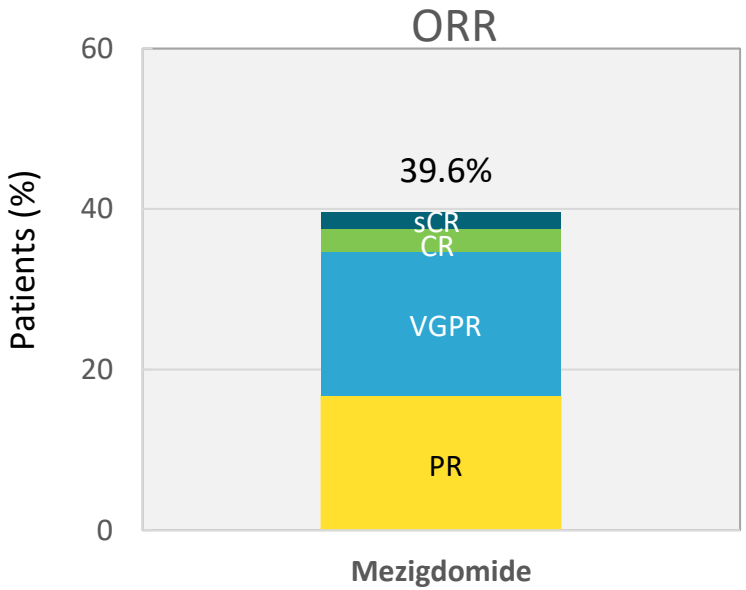
*Documented progressive disease if CAR T-cell therapy was the last therapy.
AE = adverse event; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CR = complete response; DoR = duration of response; IMiD = immunomodulatory drug; mAb = monoclonal antibody; MM = multiple myeloma; ORR = overall response rate; PFS = progression-free survival; PI = proteasome inhibitor; PR = partial response; R/R = relapsed/refractory; VGPR = very good partial response.
Lonial S, et al. ASH 2022. Abstr #1918.

Mezigdomide (MEZI), a Novel Oral CELMoD With Promising Activity

- Mechanism: enhanced tumoricidal and immune-stimulatory effects compared to IMiDs. MEZI induced maximal degradation of Ikaros and Aiolos, leading to increased apoptosis in myeloma cells
- Patients with R/R MM treated with MEZI + dexamethasone (n = 101)
  - ≥ 3 prior lines of therapy; progression ≤ 60 days of last myeloma therapy
  - Refractoriness to IMiDs, a PI, a glucocorticoid, and an anti-CD38 mAb

WATCH FOR

- Combinations with mezigdomide
- Evidence that mezigdomide reverses T-cell exhaustion



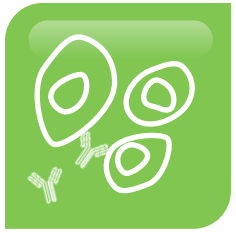
MEZI showed promising activity in heavily pretreated patients with MM

- Preliminary median DoR: 8.3 months (95% CI 5.4-not reached)
- Median PFS: 4.6 months (95% CI 3.2-6.3)
- ORR in patients with prior anti-BCMA therapy: 50% (n = 30)
- Hematologic toxicities
- Low rate of grade 3/4 nonhematologic toxicities: gastrointestinal disorders (5.9%), fatigue (4.0%), and rash (1.0%)
- 5.9% discontinuation due to treatment-emergent AEs

AE = adverse event; BCMA = B-cell maturation antigen; CELMoD = cereblon E3 ligase modulator; CR = complete response; DoR = duration of response; IMiD = immunomodulatory drug; Kd = carfilzomib dexamethasone; mAb = monoclonal antibody; MEZI = mezigdomide; MM = multiple myeloma; ORR = overall response rate; PI = proteasome inhibitor; PR = partial response; R/R = relapsed/refractory; sCR = stringent complete response; Vd = bortezomib dexamethasone; VGPR = very good partial response.

Richardson PG, et al. ASH 2022. Abstr #568. Chiu H, et al. ASH 2023. Abstr #335.

Summary



Bispecific antibodies act as a bridge between T cells and myeloma cells to use a patient's immune system to target myeloma. **Teclistamab**, **elranatamab**, and **talquetamab** are currently FDA approved; more are in development.

CRS, neurotoxicity, and hematological toxicities are important AEs for all **bispecific antibodies**.

BCMA-directed bispecific antibodies carry heightened **infection risk**. **GPRC5D-directed** bispecific antibodies carry the **possibility of skin, nail, and oral AEs**.

Optimal sequencing of MM therapies is evolving. The IMF immunotherapy registry attempts to answer questions of sequencing using real-world data.

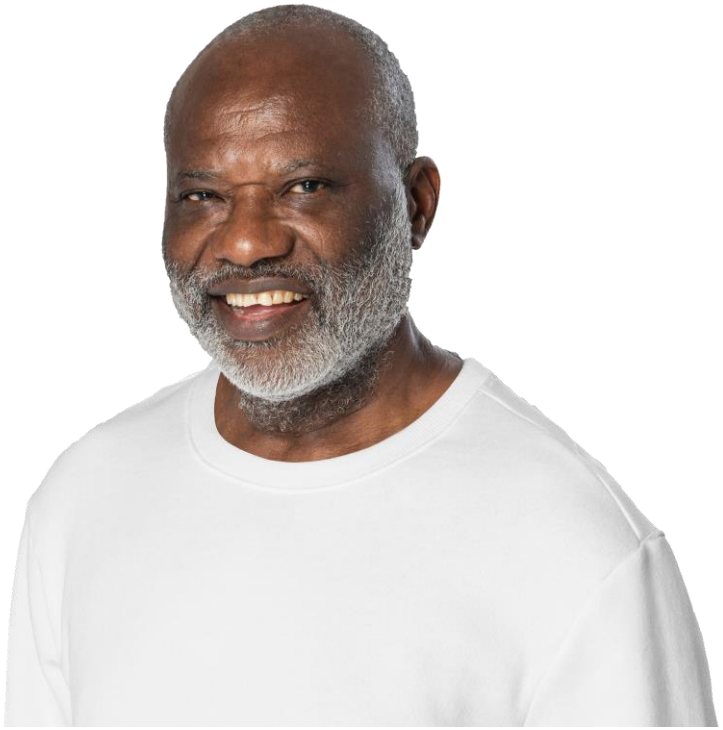
Many new drugs are in development with different targets, including CELMoD agents, monoclonal antibodies, bispecific monoclonal antibodies (T-cell engagers), and antibody-drug conjugates.

Clinical trial participation by diverse populations is essential to ensure that new drugs are appropriate for diverse populations.

AE = adverse event; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CELMoD = cereblon E3 ligase modulator; FDA = US Food and Drug Administration; GPRC5D = G-protein coupled receptor family C group 5 member D; IMF = International Myeloma Foundation; MM = multiple myeloma.

O'Neill C, van de Donk NWCJ. *EJHaem*. 2023;4(3):811-822. Cho S-F, et al. *Front Oncol.* 2022;12:1032775. TECVAYLI® (teclistamab-cqyv) Prescribing Information. ELREXFIO™ (elranatamab-bcmm) Prescribing Information. TALVEY™ (talquetamab-tgvs) Prescribing Information. Catamero D, et al. Presented at: 20th International Myeloma Society (IMS) Annual Meeting Nurse Symposium. September 27-30, 2023; Athens, Greece. Patel U, et al. ASCO 2023. Abstr #e20049. Mouhieddine TH, et al. *Blood Adv.* 2023;7(6):1056-1064. Del Giudice ML, et al. *Cancer Immunol Immunother*. 2023;72(12):3931-3937. The IMF's Immune Therapy Registry. Accessed March 27, 2024. https://www.myeloma.org/international-myeloma-working-group/imfs-immune-therapy-registry. Catamero D, et al. *J Adv Pract Oncol.* 2022;13(suppl 4):31-43. O'Neill C, van de Donk NWCJ. *EJHaem*. 2023;4(3):811-822. Hartley-Brown M, Richardson P. *Explor Target Antitumor Ther.* 2022;3(1):1-10. Ray U, Orlowski RW. Pharmaceuticals (Basel). 2023;16(4):590. Vu SH, et al. *Front Oncol.* 2023; 13: 1275076. Frigault MJ, et al. *Blood Adv.* 2023;7(5):768-777. van de Donk NWCJ, et al. ASH 2023. Abstr #208. Richardson PG, et al. ASH 2023. Abstr #1013. Chiu H, et al. ASH 2023. Abstr #335. Regnante JM, et al. *J Oncol Pract.* 2019;15(4):e289-e299. FDA website. Clinical Trial Diversity. Accessed March 27, 2024. https://www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity.

Thank You For Sharing in the Stories of Our Patients



CARL*

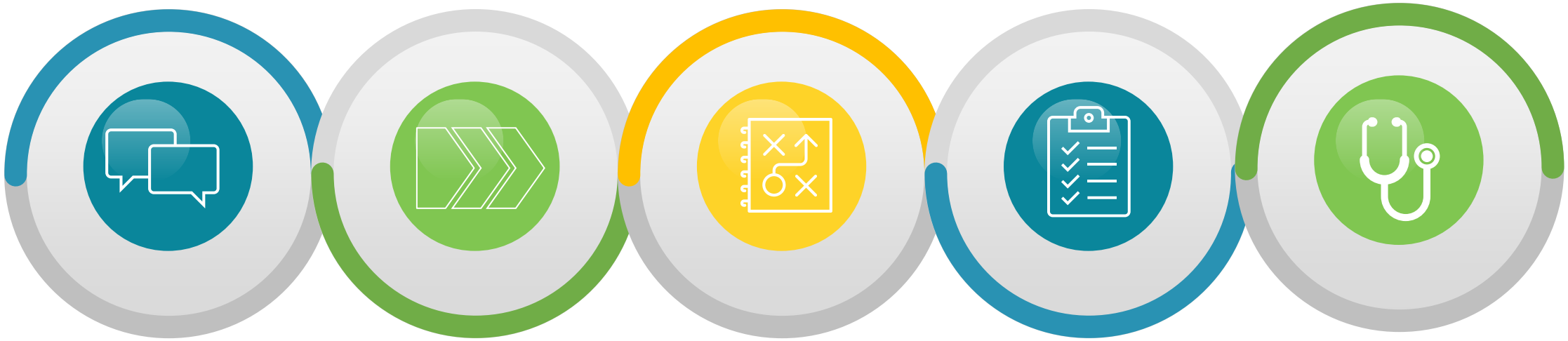
MARGARET*

ROBERT*

*HIPAA-compliant, not actual patient name, stock photo.
HIPAA = Health Insurance Portability and Accountability Act.

Learning Objectives

As a result of this program, you will be able to:



- Discuss **new and emerging therapies**, including CELMoDs®, CAR-T cell therapy, and T-cell engagers, such as bispecific antibodies, for patients with multiple myeloma, as well as **AE management and patient education**
- Explain the importance of **sequencing therapy**, including the use of **multidrug regimens and bridging therapy**
- Use strategies to support the attainment of **deep responses** by patients with myeloma, such as new therapies, multidrug regimens, ASCT, maintenance, adherence, shared decision-making, MRD, and other testing
- Summarize **disparities faced by patients** with multiple myeloma and **strategies to overcome** these (health equity)
- Use patient and care partner's (caregiver's) input in treatment decisions through shared decision-making

AE = adverse event; ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; CELMoD = cereblon E3 ligase modulatory drug; MRD = minimal residual disease.

Q1. Which of the following is TRUE about multiple myeloma (MM) in Black vs White patients?

1. Black patients tend to be diagnosed with myeloma at an older age
2. Black patients of African descent tend to have higher-risk disease
3. Black patients with MM have similar rates of mortality compared with White patients
4. Black patients may have superior outcomes when treated with standard-of-care
5. I don’t know

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Q2. Which of the following is TRUE about strategies to attain deep minimal residual disease (MRD) negative responses to treatment in multiple myeloma (MM)?

1. Patients who achieve MRD-negative status do not relapse
2. Multidrug regimens produce higher MRD-negative rates than doublet regimens
3. Autologous stem cell transplant (ASCT) is no longer recommended as a strategy to achieve MRD-negative responses
4. A shorter duration of therapy with higher doses of chemotherapy will lead to deeper MRD-negative response rates
5. I don’t know

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Q3. Which of the following is TRUE about sequencing and CAR T cell therapy for multiple myeloma (MM)?

1. A new line of therapy is defined as the discontinuation of 1 treatment regimen due to progression and the start of another therapy
2. Patients must have been treated with a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) before CAR T-cell therapy
3. CAR T cell therapies are indicated for patients with MM only after 3 or more prior lines of therapy
4. Patients treated with a bispecific antibody are not eligible to receive CAR T-cell therapy
5. I don’t know

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4. Patients treated with a bispecific antibody are not eligible to receive CAR T-cell therapy
5. I don't know

Q4. Which of the following is TRUE about bispecific antibody therapies for multiple myeloma (MM)?

1. Skin and nail toxicities are common AEs experienced by patients receiving a BCMA-targeted bispecific antibody
2. Cytokine release syndrome (CRS) can occur in CART-cell therapy but does not occur in patients treated with bispecific antibodies
3. Patients are not eligible for a BCMA-directed bispecific antibody after a BCMA-directed CAR T-cell therapy
4. Atypical infections such as CMV, PJP, and fungal infections may occur at higher rates in patients receiving bispecific therapies for MM compared with standard therapy
5. I don’t know

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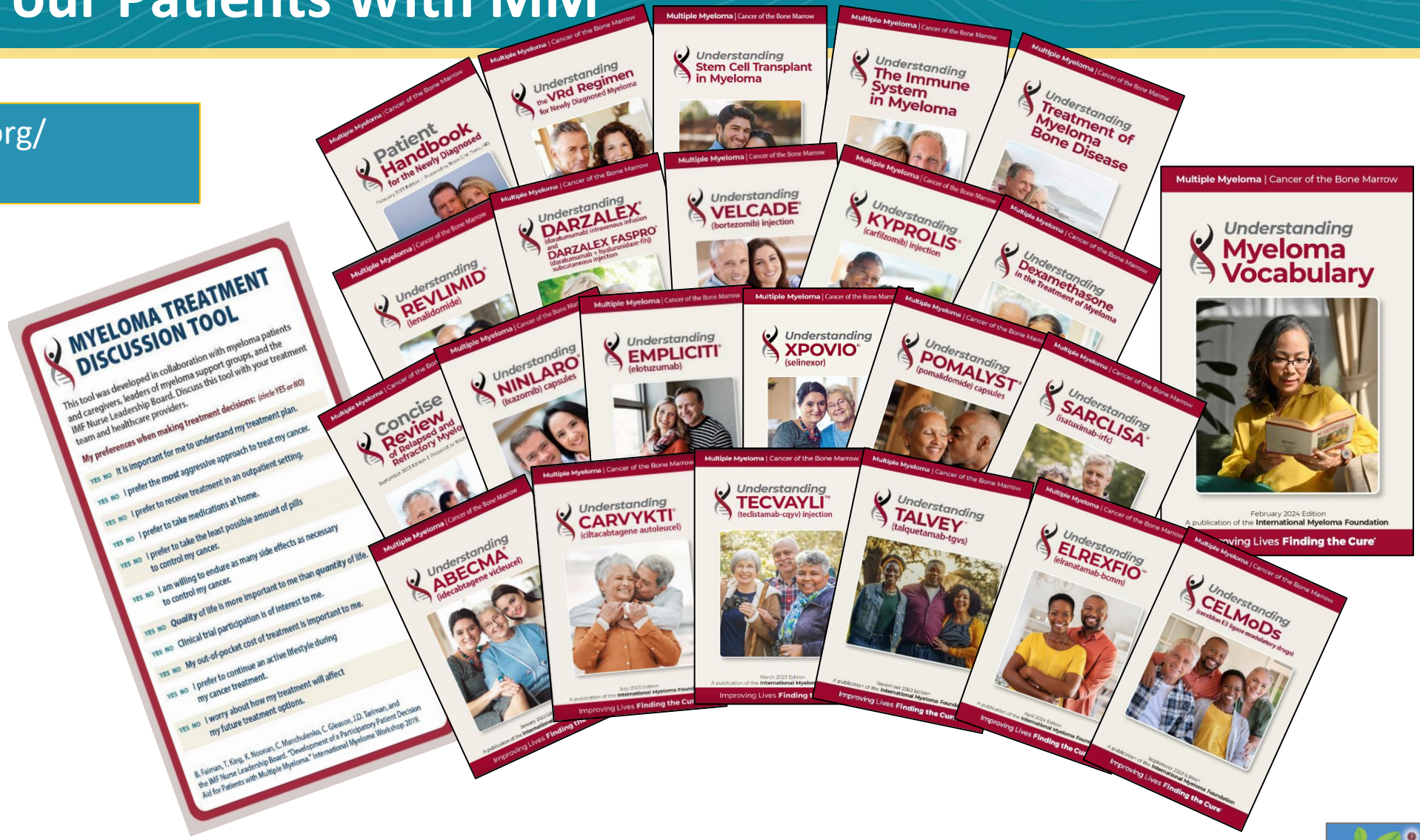
Remember the Resources to Enhance Your Ability to Care for Your Patients With MM

https://imf-ons.myeloma.org/
password: ons2024

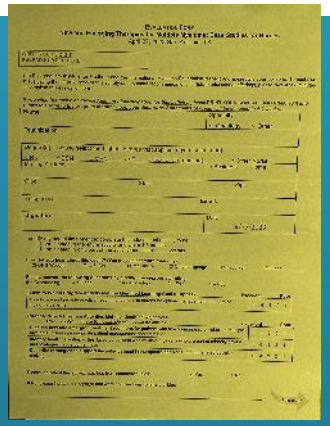


…and Much, Much, More!

MM = multiple myeloma.

Thank You for Your Attendance and Participation

On behalf of the IMF with the generous support from AbbVie, Inc.; Bristol Myers Squibb Company; Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; Karyopharm Therapeutics; Pfizer Inc.; and Sanofi, ***we thank you****.*



Don't forget to turn in your YELLOW eval for CNE credit

Please Contact IMF for Further Information and Resources:

1-800-452-CURE
(1-800-452-2873)

TheIMF@myeloma.org
http://myeloma.org

Slides and Resources available at:

http://imf-ons.myeloma.org

Password: ons2024

IMF = International Myeloma Foundation.