Southeastern Multidisciplinary Approaches to Cancer Symposium

Multiple Myeloma: Evolving Standards of Care 2026

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Disclosures

- Consultant for GSK & Sanofi. On the Speaker's Bureau for GSK & Sanofi. Grant/Research Support for Poseida Therapeutics, Pfizer, Gilead Sciences.

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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Address disparities in multiple myeloma incidence and outcomes among diverse populations.*
- *Promote equitable access to advanced therapies regardless of race or socioeconomic status.*

Objectives

- Review current standards of care for newly diagnosed and relapsed multiple myeloma.
- Discuss individualized treatment selection.
- Integrate cellular therapies and bispecific antibodies into treatment sequencing.
- Review supportive care to optimize patients outcomes

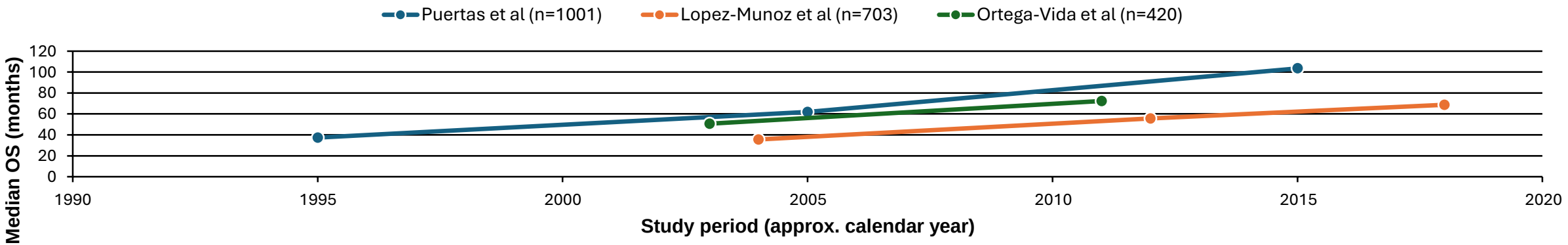
"How has the standard of care for multiple myeloma changed, and what should we be doing differently in 2026?“

What's New in 2026?

Then (2023–2024)	Now (2026)
Triplet induction	Quadruplet induction is standard for many transplant-eligible patients
CAR-T in late relapse	CAR-T moving earlier in the disease course
Bispecifics after multiple relapses	Increasing use in earlier relapses
MRD primarily research	MRD is standard for prognosis and increasingly informs management
Risk based on R-ISS	Genomic staging and frailty now shape individualized therapy

Median Overall Survival Rising Across Treatment Eras

Three independent real-world cohorts show consistent, significant OS gains over time



Cohort	Period	mOS	Clinical Evidence
Puertas et al, Cancers 2023 n = 1001 (1980-2020)	1991 - 2000	**37.4 mo**	Single institution; OS gains novel agents incorporated (p < 0.001)
	2001 - 2010	**61.8 mo**	Captures early PI/IMiD era; Provides pre-anti-CD38 “baseline” for the last 20 yr
	2011 - 2020	**103.6 mo**	Reflects broader access to combination/maintenance and later line novel agents (p < 0.001)
Lopez-Munoz,et al, J Hematol Oncol. 2023 n = 703; plus TriNetX validation	1999 - 2009	**35.61 mo**	Calendar-period analysis with significant improvement over time (p=0.0001); also reports increasing 5-year OS rates.
	2010 - 2014	**55.59 mo**	Demonstrates mid-decade improvement with broader PI/IMiD use
	2015 – 2020	**68.67 mo**	Late-decade improvement consistent with anti-CD38 era impact; still limited by follow-up for the newest period
Ortega-Vida et al, Cancers 2025 n = 420 (2000 – 2020)	2000 - 2007	**50.7 mo**	Era-grouped real-world cohort; steady OS improvement (p=0.008)
	2008 - 2015	**72.4 mo**	Continued gains with increasing novel-class use
	2016 – 2022	**Not reached**	Suggests further improvement in the anti-CD38 era; median not yet estimable due to follow up

Evaluation and Risk Assessment

Diagnosis — stable since IMWG 2014 • SLiM-CRAB framework remains the standard diagnostic foundation

SLiM Biomarkers

Myeloma-defining — any one

- ≥ 60% clonal plasma cells in marrow
- Involved / uninvolved FLC ratio ≥ 100 (involved FLC > 100 mg/L)
- > 1 focal lesion on MRI

CRAB Criteria

End-organ damage

C Calcium > 11.5 mg/dL

R Creatinine > 2 mg/dL or CrCl < 40 mL/min

A Anemia — hemoglobin < 10 g/dL

B Bone — osteolytic lesion

FISH Panel at Diagnosis

CD138-selected marrow • subtyping & prognosis

- **t(4;14) • t(14;16) • t(14;20)**
- **t(11;14)**
- **del(17p13)**
- **1q21+ (gain / amplification)**
- **del(1p32)**

**Significant when present in > 20% of cells*

Staging R2-ISS refines R-ISS

ISS

β2-microglobulin + albumin only — no cytogenetics or LDH

↓

R-ISS (2015)

ISS + LDH + high-risk cytogenetics: t(4;14), t(14;16), del(17p)

↓

R2-ISS (2022)

Adds 1q21 gain/amp; weights each feature into an additive score → 4 risk groups

Additive risk-feature points

Risk feature	Points
ISS stage III	1.5
ISS stage II	1
del(17p)	1
High LDH	1
t(4;14)	1
1q21 gain / amplification	0.5

Prognosis by total score

Score	R2-ISS risk group	Median OS
0	R2-ISS I · Low	Not reached
0.5–1	R2-ISS II · Low-intermediate	109.2 mo
1.5–2.5	R2-ISS III · Intermediate-high	68.5 mo
3–5	R2-ISS IV · High	37.9 mo

Calculate R-ISS in all newly diagnosed patients; R2-ISS refines the large intermediate group, but interpret alongside the new IMS/IMWG Consensus Genomic Staging (CGS).

Source: D'Agostino et al, J Clin Oncol 2022;40(29):3406–3420.

2025 IMS/IMWG Consensus Genomic Staging redefines High-Risk Multiple Myeloma (HRMM)

Defining Criteria

1. del(17p) > 20% clonal fraction and/or TP53 mutation
2. IgH translocation [t(4;14), t(4;16), or t(14;20)]
3. Monoallelic del(1p32) + 1q+, or biallelic del(1p32)
4. β2-macroglobulin ≥ 5.5 mg/L with creatinine < 1.2 mg/dL.

Key Changes

- TP53 mutation [not just del(17p)] now constitutes HRMM
- Biallelic del(1p32) is independently high risk
- β2 macroglobulin ≥ 5.5 with normal creatinine
- Combinatorial logic: individual intermediate-risk lesions [1q+, t(4;14), t(14;16), monoallelic del(1p32)] become high-risk when ≥ 2 co-occur (“double hit”).
- This schema identifies about 20% of patients as HRMM – clinically actionable vs the > 50% classified by the R2-ISS

Individualizing Therapy

Factors influencing treatment:

- Age
- Frailty
- Renal dysfunction
- Peripheral neuropathy
- High-risk cytogenetics
- Patient preference
- Distance from treatment center
- Insurance/access

There's no "one size fits all"

Common Frailty Models

IMWG Frailty Index

What it looks at:

- Age
- Everyday self-care tasks, such as bathing and dressing (ADL)
- More involved daily tasks, such as managing money and medications (IADL)
- Other ongoing health conditions (Charlson Comorbidity Index)

Sorts people into three groups:
Fit, somewhat fit, or frail.

Revised IMWG Frailty Index (R2-IMWG)

Adds measurable health factors:

- Age
- How well a person can carry out daily activities (ECOG performance status)
- Other ongoing health conditions
- A check of frailty and how well a person functions

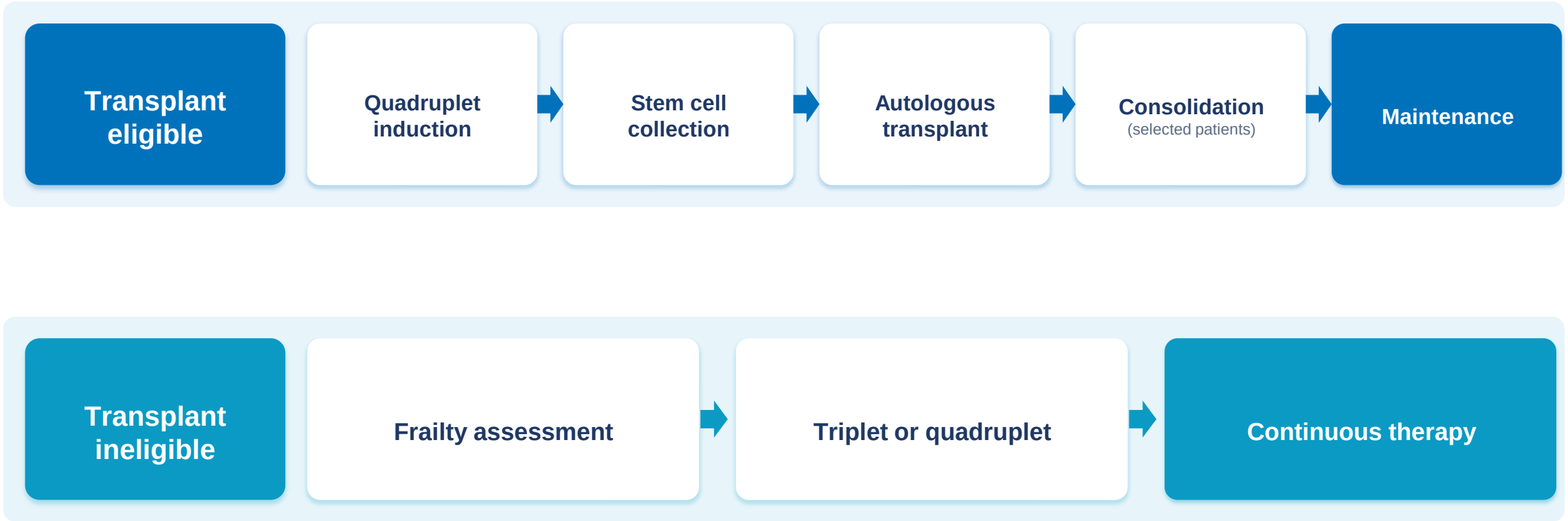
Gives a clearer picture of:

- Side effects from treatment
- How long a person lives before the disease gets worse
- How long a person lives overall

Take-Home Message

A person's frailty (not their age) should guide how intensive treatment is for older adults with multiple myeloma. Checking for frailty is now recommended as a regular part of the first evaluation, so care can be tailored to each person and lead to better outcomes.

Treatment Algorithm for Newly Diagnosed Disease



Current Frontline Regimens

Newly Diagnosed Multiple Myeloma

Transplant-Eligible

Dara-VRd *GRIFFIN, PERSEUS trials*

Isa-VRd

OUTCOMES

Higher sCR, MRD negativity, and improved depth of response

Transplant-Ineligible

Isa-VRd *IMROZ trial*

Dara-Rd *MAIA trial*

Dara-VRd

OUTCOMES

Improved PFS and OS vs Rd

Maintenance Therapy & MRD-Directed Strategies

Factors Influencing Maintenance

- Lenalidomide
- Proteasome inhibitor–based maintenance
- Doublet maintenance
- Duration of therapy
- MRD-guided approaches

Should maintenance ever stop?

MRD-Directed Strategies

- Dara + lenalidomide post-transplantation
- Using MRD status to guide duration / intensity of therapy
- Treating sustained MRD positivity with immune-based approaches

Post-transplant strategies incorporating anti-CD38 antibodies are being studied to determine whether deeper remission translates into longer survival.

MRD in Multiple Myeloma: Standard Prognostic Tool, Emerging Treatment Decision Tool

STANDARD OF CARE

Clinical Trials

✓ Established primary endpoint in frontline and relapsed/refractory MM trials

✓ One of the strongest validated prognostic markers

✓ Sustained MRD negativity is associated with better outcomes:

✓ **Longer progression-free survival**

✓ **Longer overall survival**

EMERGING — CLINICAL PRACTICE

Response & Risk Stratification

✓ Assess depth of response after induction/consolidation

✓ Prognostic assessment after autologous transplant

✓ Refine prognosis discussions

✓ Identify patients achieving exceptionally deep responses

Informs individualized treatment decisions

Sequencing Modern Therapies: A Roadmap

1. Frontline	Induction chosen by risk status and transplant eligibility; depth and durability of response set the baseline.
2. First relapse	Move on progression — driven by lenalidomide and anti-CD38 refractoriness and how fast the disease returns.
3. Second+ relapse	Switch drug class once options within the current class are exhausted; prior exposure narrows the field.
4. Cellular therapy (CAR T)	Refer early — before patients grow refractory across major classes and lose eligibility for the best responses.
5. Bispecific antibodies	Off-the-shelf option after or instead of CAR T; immediately available when disease pace leaves no time to wait.
6. Clinical trials	Consider at every step for access to next-generation agents and novel combinations.

Management at 1st Relapse

Factors to weigh at first relapse — across three dimensions:

Treatment history

Previous therapies
Which drug classes were used, and depth and duration of response

Lenalidomide refractory
Refractoriness reshapes the choice of next regimen

Prior anti-CD38 exposure
Earlier daratumumab limits CD38 re-treatment options

Disease behavior

Time to relapse
Early relapse (<18 months) signals higher-risk biology

Aggressive disease
Rapid, symptomatic relapse needs faster disease control

Extramedullary disease
Soft-tissue plasmacytomas predict poorer outcomes

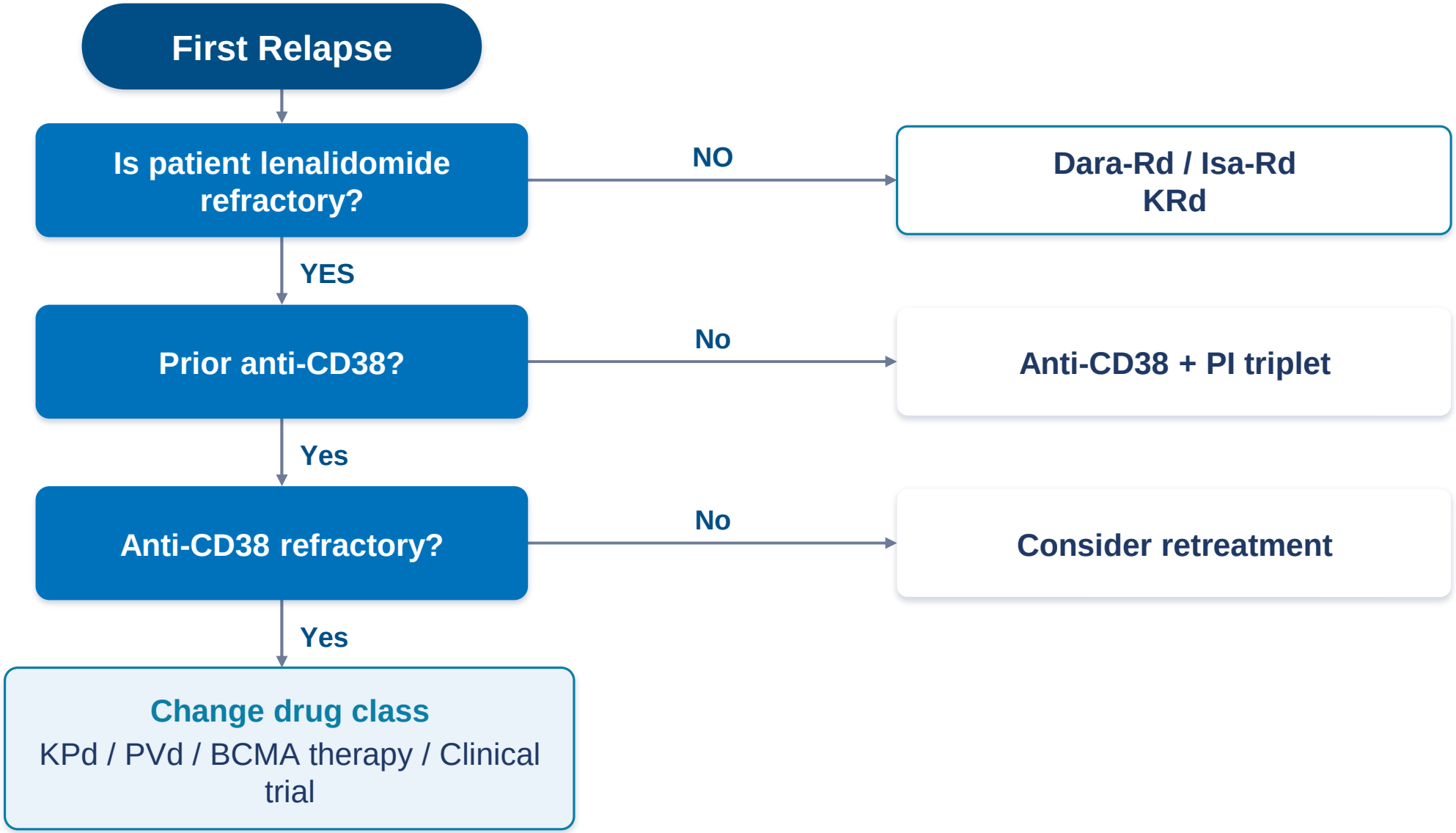
Patient & biology

Fitness & frailty
Age, performance status and comorbidities guide intensity

Renal function
Impaired clearance shapes drug selection and dosing

High-risk cytogenetics
Re-assess del(17p), t(4;14) and 1q21 gain/amp at relapse

Treatment Algorithm at First Relapse



Cellular Therapy in Multiple Myeloma: Where Are We in 2026?

Available BCMA-directed therapies

CAR T	Bispecific antibodies	Antibody-drug conjugate
Ide-cel Cilta-cel	Teclistamab Elranatamab Linvoseltamab*	Belantamab mafodotin Belantamab combinations

Moving earlier in the treatment journey

Cellular therapy is no longer “last-line” treatment.
Referral should occur **well before patients become refractory to multiple drug classes.**

Patient Selection for CAR T-Cell Therapy

Who benefits, when to refer, and the practical checks before manufacturing

Ideal candidate

- Triple-class exposed (IMiD, PI, anti-CD38)
- Good performance status (ECOG 0–1)
- Adequate organ and marrow function
- Disease controllable through the manufacturing window
- No uncontrolled infection
- Reliable caregiver and support
- Able to stay near the treatment center

Relative contraindication

- Rapidly progressive, high-burden disease
- Active or prior CNS involvement
- Borderline performance status (ECOG 2)
- Significant frailty or comorbidity
- Limited caregiver or social support
- Recent prior BCMA-targeted therapy

Absolute contraindication

- Uncontrolled active infection (incl. sepsis)
- Inadequate / irreversible organ dysfunction
- Active severe autoimmune disease
- Poor performance status (ECOG 3–4)
- Unable to comply with monitoring / logistics

Bridging therapy controls disease during the vein-to-vein manufacturing window. **Prior BCMA-targeted therapy** should factor into sequencing and expected depth of response.

Refer at first or second relapse — not after exhausting all options.

Sequencing CAR-T, Bispecifics, and ADC

Early relapse › Standard triplet/quadruplet › Triple-class exposed › Evaluate for CAR-T immediately

OPTION 1
CAR-T

Preferred when feasible

- ✓ Deepest responses
- ✓ Treatment-free interval

OPTION 2
Bispecifics

If CAR-T not eligible

- ✓ Immediately available
- ✓ Continuous therapy

OPTION 3
ADC

Later-line option

- ✓ Useful after CAR-T or bispecifics
- ✓ No T-cell dependence

Supportive Care in Multiple Myeloma

Preventing Treatment-Related Complications

SKELETAL
Bone Health & Skeletal Disease

✓ Zoledronic acid or denosumab to reduce skeletal-related events

✓ Optimize calcium/vitamin D, dental evaluation, and monitor for osteonecrosis of the jaw

THROMBOSIS
Thrombosis Prevention (VTE)

✓ IMiD-based regimens increase venous thromboembolism risk

✓ Aspirin or anticoagulation selected by individual thrombotic risk

IMMUNIZATION
Vaccinations

Recommended vaccines

Annual influenza, updated COVID-19, pneumococcal, and recombinant zoster

Avoid live vaccines in immunocompromised patients

ANTIVIRAL
Antiviral Prophylaxis

Herpesvirus reactivation prevention with

- Proteasome inhibitors
- Anti-CD38 antibodies
- CAR T-cell and other immune-based therapies

Infection Prevention & Long-Term Survivorship in Modern Myeloma

FOUNDATION

Infection Prevention

Elevated infection risk

Driven by disease-related immune dysfunction and therapy-induced immunosuppression

PROPHYLAXIS

PJP Prophylaxis (TMP-SMX)

Indicated with

- Prolonged corticosteroids
- Intensive combination therapy
- CAR T-cell therapy
- Bispecific antibodies

IMMUNE SUPPORT

Hypogammaglobulinemia

✓ Monitor IgG levels

✓ Consider IVIG replacement

SURVIVORSHIP

Secondary Malignancies

✓ Surveillance for therapy-related malignancies

✓ Maintain age-appropriate cancer screening

Risk factors: long-term lenalidomide, alkylator therapy

Equity in Multiple Myeloma: Closing the Gap Between Innovation and Access

Advances only improve outcomes if patients can access them

Disparities in Multiple Myeloma	Clinical Impact
African Americans have approximately **2-fold higher incidence** of MM than White individuals	Larger disease burden but historically underrepresented in clinical trials
Earlier age at diagnosis	Greater lifetime treatment needs
Lower rates of autologous stem cell transplantation	Inferior long-term outcomes
Reduced access to CAR-T cells and bispecific antibodies	Missed opportunities for disease long-term control
Socioeconomic and geographic barriers	Delays in referral to specialized centers and clinical trials

What can be done?

1 Earlier Recognition

- Improve awareness in high-risk populations
- Prompt evaluation of unexplained anemia, renal dysfunction, or MGUS

2 Equitable Referral

- Early referral to transplant/cellular therapy centers
- Standardized referral pathways regardless of insurance or zip code

3 Clinical Trial Access

- Increase enrollment of underrepresented populations
- Community-academic partnerships
- Reduce logistical and financial barriers

4 Shared Decision Making

- Discuss all FDA-approved options
- Consider patient preferences, caregiver support, transportation, and financial toxicity

Key Takeaways

1. Risk-adapted therapy remains essential.
2. Quadruplets have become standard for many newly diagnosed patients.
3. Treatment sequencing has become increasingly complex.
4. Early referral for cellular therapy improves options.
5. Shared decision-making and individualized care are central to optimal outcomes.

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