



**Brigham and Women's Hospital**

Founding Member, Mass General Brigham

# Multiple Myeloma

Omar Nadeem, MD

Senior Physician

Division of Plasma Cell Neoplasias

Dana-Farber Cancer Institute

Assistant Professor of Medicine

Harvard Medical School



## Omar Nadeem, MD



- Medical School: Ross University
- Internal Medicine Residency: Dartmouth-Hitchcock Medical Center
- Hematology/Oncology Fellowship: Brown University
- Assistant Professor of Medicine at HMS
- Clinical focus: Multiple myeloma

# DISCLOSURES

Advisory Boards: JNJ, BMS, Sanofi, GPCR therapeutics, Kite, AstraZeneca

Research funding: BMS, JNJ



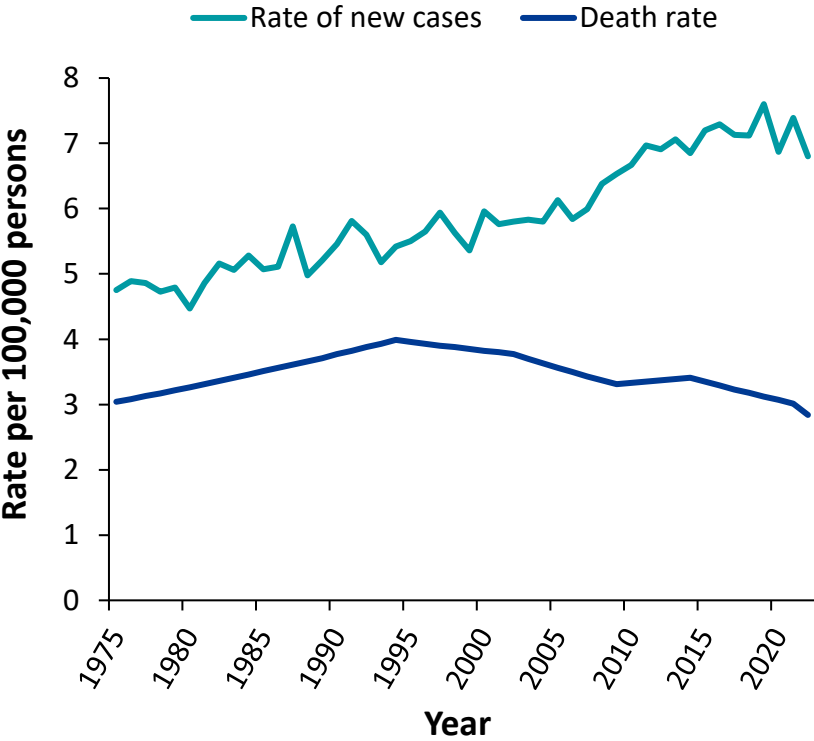
# OBJECTIVES

- Review classification and epidemiology of plasma cell disorders
- Review clinical presentation, diagnostic workup and risk stratification
- Discuss treatment approaches in newly diagnosed multiple myeloma
- Discuss evolving role of T-cell redirecting therapies in management of multiple myeloma



# Multiple Myeloma Epidemiology

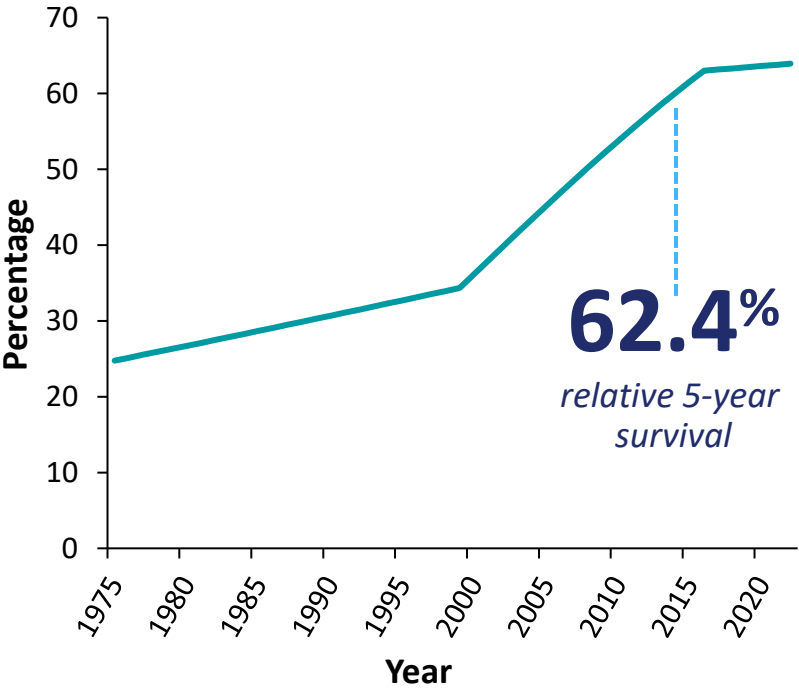
Rates of new cases and death



69  
Median age at diagnosis

76  
Median age at death

5-year survival rate



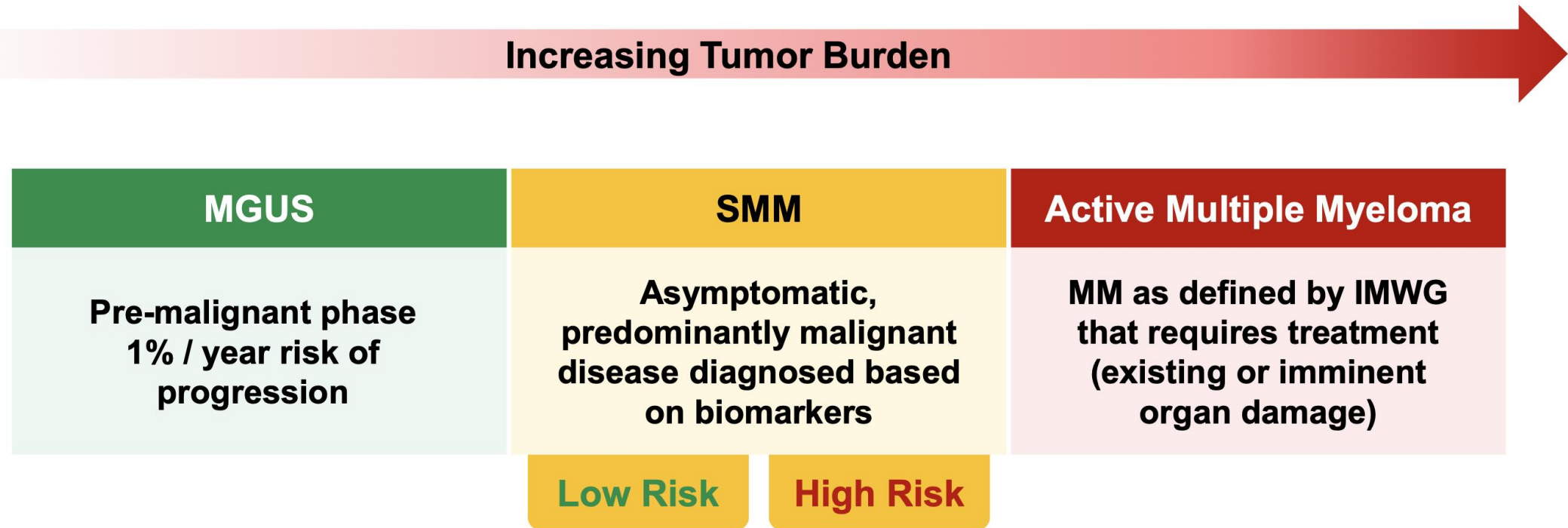
62.4%  
relative 5-year survival

MM represents 1.8% of all new cancer cases in the US, with the highest incidence being among non-Hispanic Black males

Though MM invariably relapses, the 5-year survival rate has risen to >60% due to the advent of more effective therapies and approaches



# Plasma Cell Dyscrasias Continuum



# Plasma Cell Disorders: Classification

## Updated IMWG criteria for diagnosis of multiple myeloma

### MGUS

- M protein <3 g/dL
- Clonal plasma cells in bone marrow <10%
- No myeloma-defining events

### Smoldering myeloma

- M protein  $\geq 3$  g/dL (serum) or  $\geq 500$  mg/24 hrs (urine)
- Clonal plasma cells in bone marrow  $\geq 10\%$  to 60%
- No myeloma-defining events

### Multiple myeloma

- Underlying plasma cell proliferative disorder
- AND**
- 1 or more myeloma-defining events:
- $\geq 1$  CRAB\* feature
  - Clonal plasma cells in bone marrow  $\geq 60\%$
  - Serum free light chain ratio  $\geq 100$
  - $>1$  MRI focal lesion

\***C**: Calcium elevation ( $>11$  mg/dL or  $>1$  mg/dL higher than ULN)

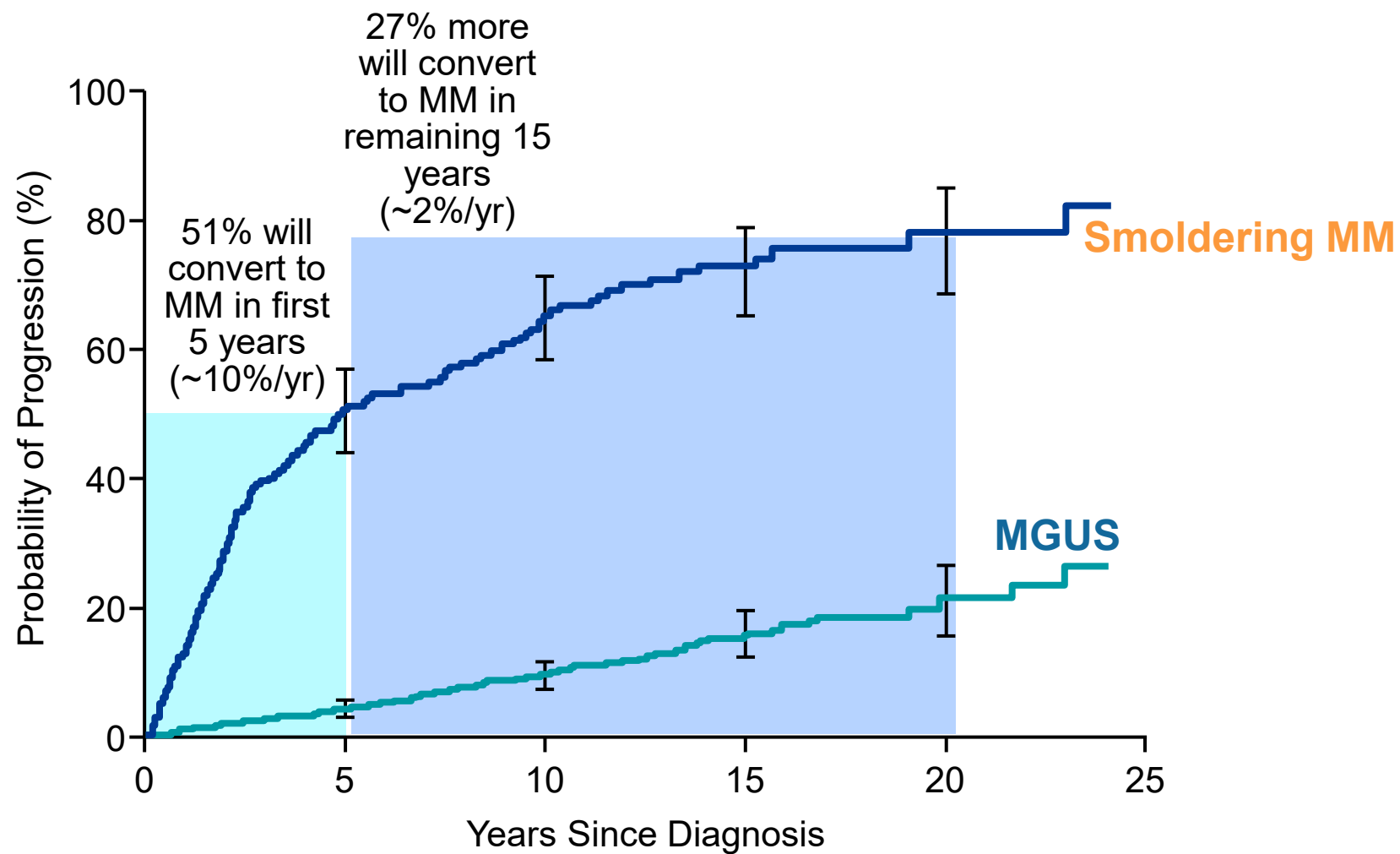
**R**: Renal insufficiency (creatinine clearance  $<40$  mL/min or serum creatinine  $>2$  mg/dL)

**A**: Anemia (Hb  $<10$  g/dL or 2 g/dL  $<$  normal)

**B**: Bone disease ( $\geq 1$  lytic lesions on skeletal radiography, CT, or PET-CT)



# Smoldering Multiple Myeloma: Heterogeneous Disease

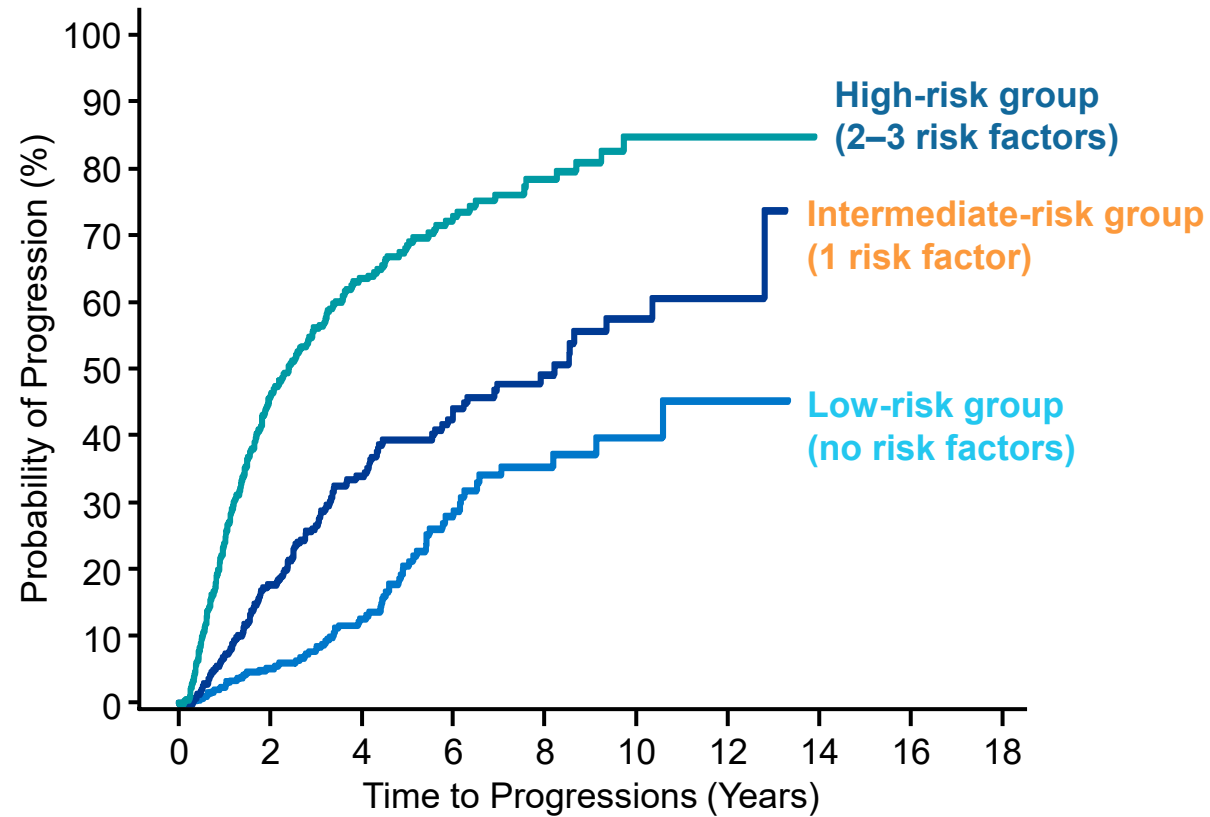


## 2/20/20 Model to Identify High-Risk SMM Patients

### 2/20/20 Risk assessment for SMM

- 2** >2 g/dL M protein
- 20** >20 free light chain ratio
- 20** >20% bone marrow plasma cells

Model does not include any biological or immune factors that may account for interpatient heterogeneity.



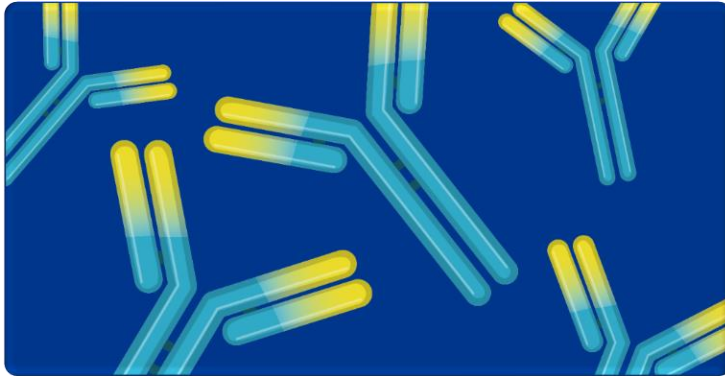
Risk of progression  
at 2 Years

**44.2%**

**17.9%**

**6.2%**

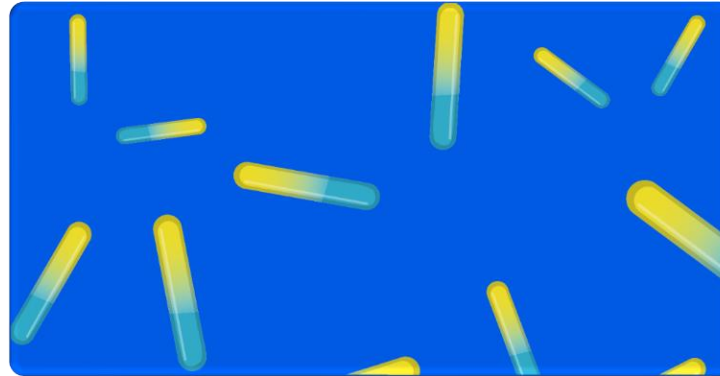
# Types of Multiple Myeloma



## Intact M protein

- Named for the type of immunoglobulin and light chain pair; for example, IgG kappa ( $\kappa$ ) or IgG lambda ( $\lambda$ )

**80%**



## Light chain only

- Also known as Bence Jones protein
- Renal failure more common in light chain multiple myeloma

**20%**



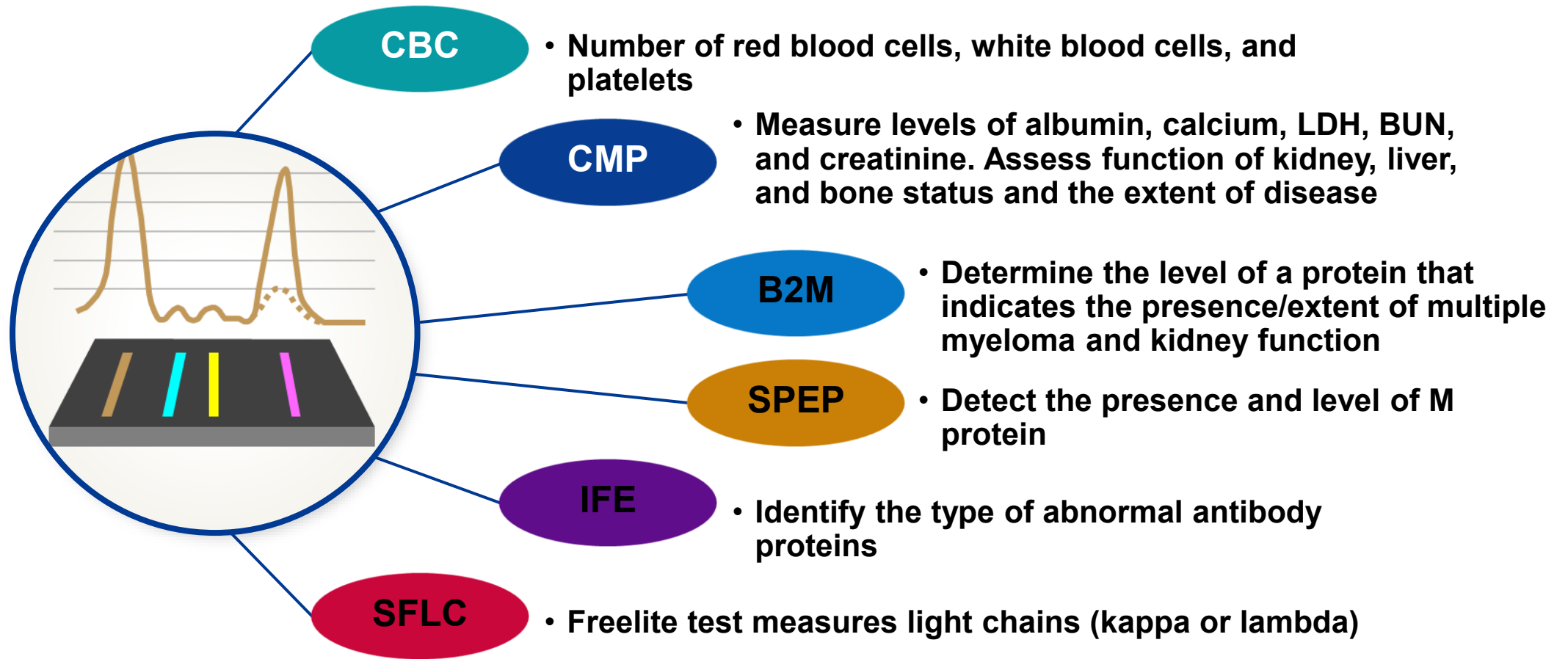
## Non-secretory

- No M protein present

**3%**



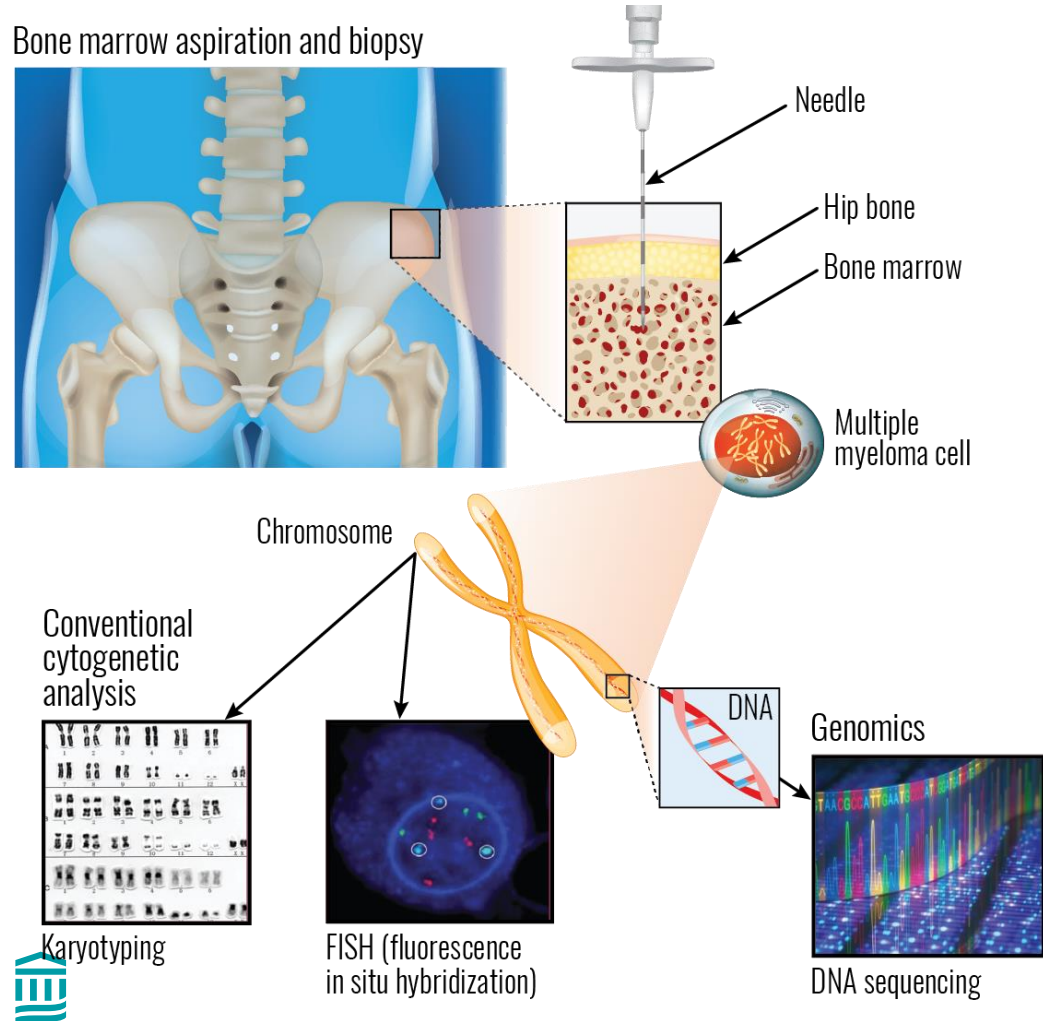
# Diagnosis: Laboratory Assessments



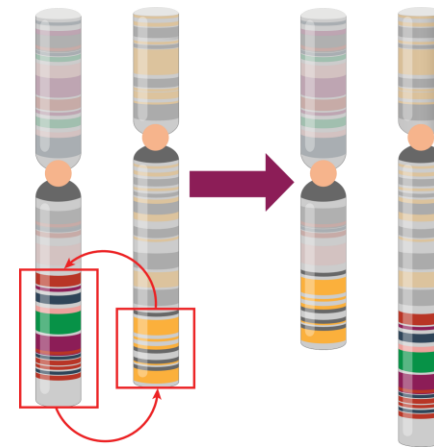
CBC, complete blood count; CMP, complete metabolic panel; B2M; beta-2 microglobulin; SPEP, serum protein electrophoresis; IFE, immunofixation electrophoresis; SFLC, serum free light chain assay; LDH, lactate dehydrogenase; BUN, blood urea nitrogen



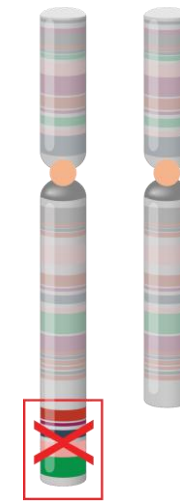
# Diagnosis: Bone Marrow Tests



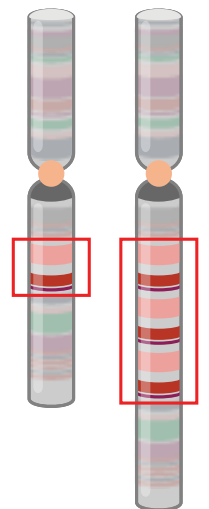
## Types of chromosomal abnormalities



Translocation



Deletion



Gain or amplification

# Diagnosis: Imaging Tests

**Assess changes in the bone structure and determine the number and size of tumors in the bone**

**X-ray**



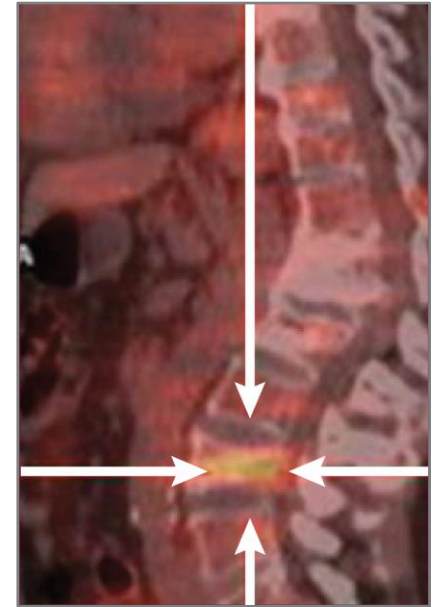
**MRI**



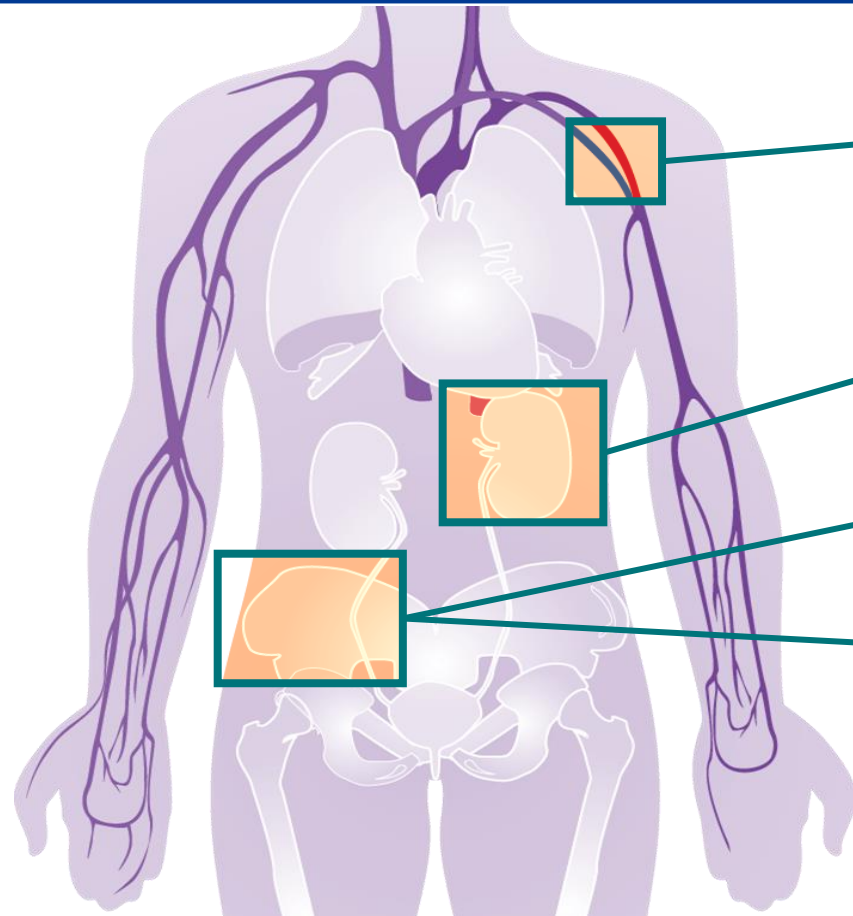
**CT scan**



**PET scan**



# Effects of Myeloma and Common Symptoms



Low blood counts

- Weakness
- Fatigue
- Infection

Decreased kidney function

Weakness

Bone damage

Bone pain

Bone turnover

- Loss of appetite
- Weight loss

***About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.***

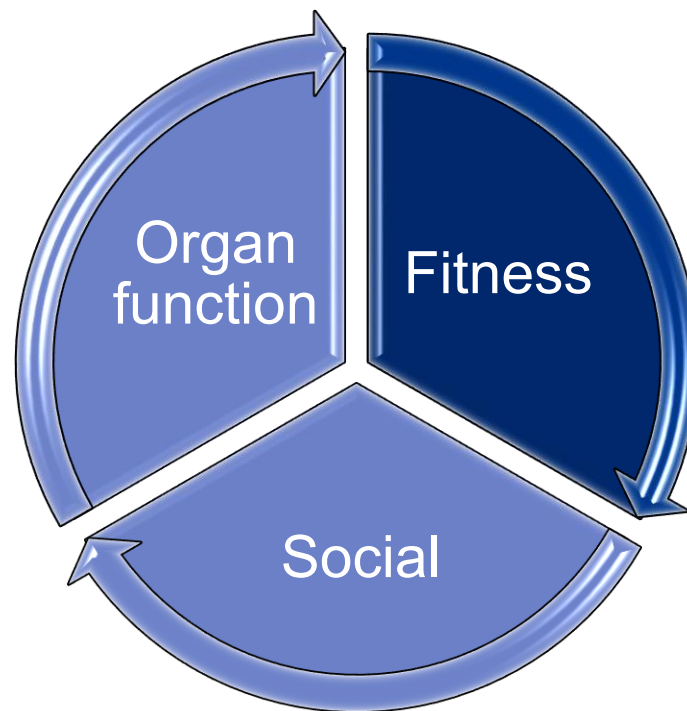




# Multiple Myeloma Risk Stratification

## Disease Factors

- Cytogenetics/molecular (R-ISS)
- CRAB criteria (renal injury)
- Plasma cell leukemia
- Extramedullary disease
- Coexisting amyloidosis
- Response to treatment

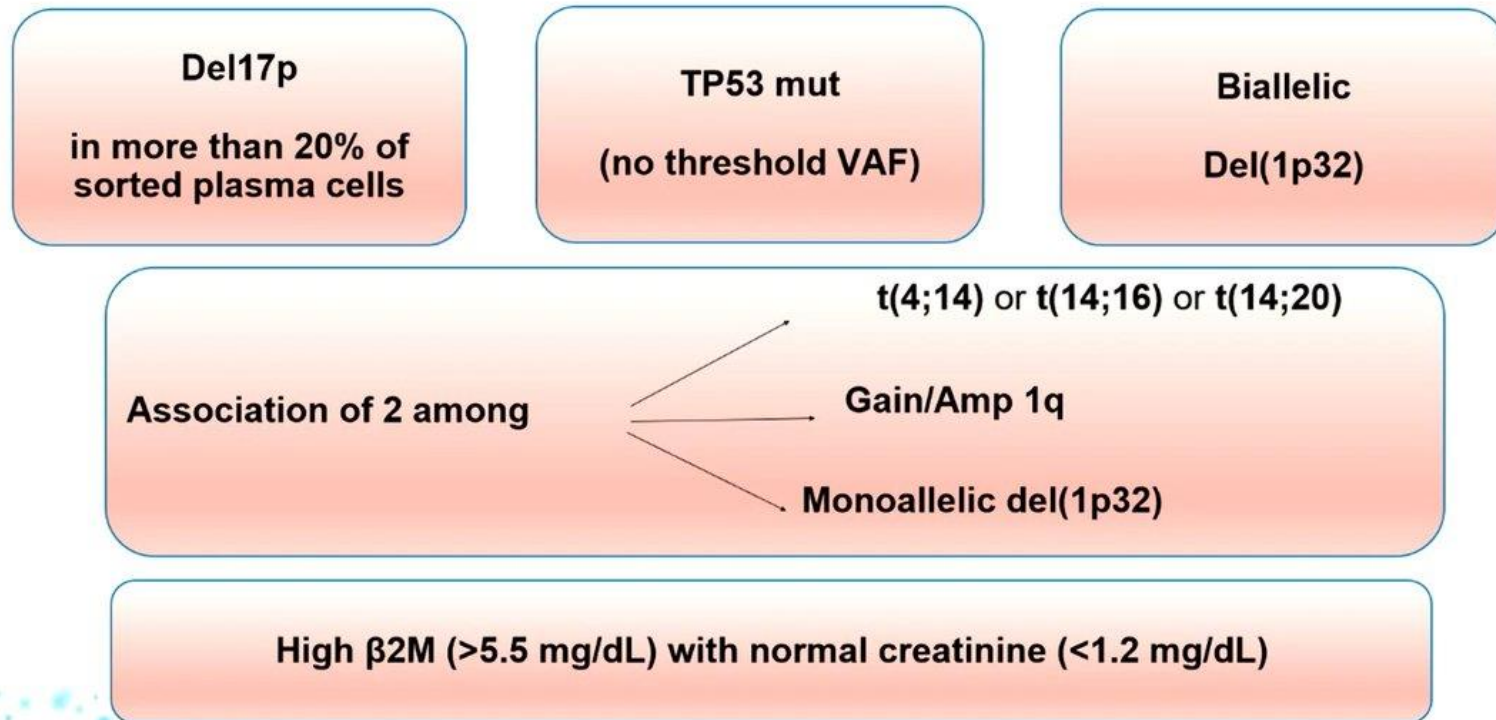


## Patient Factors

- Performance status
- Frailty index
- Comorbid conditions
- Caregiver support
- Financial toxicity
- Barriers to healthcare access

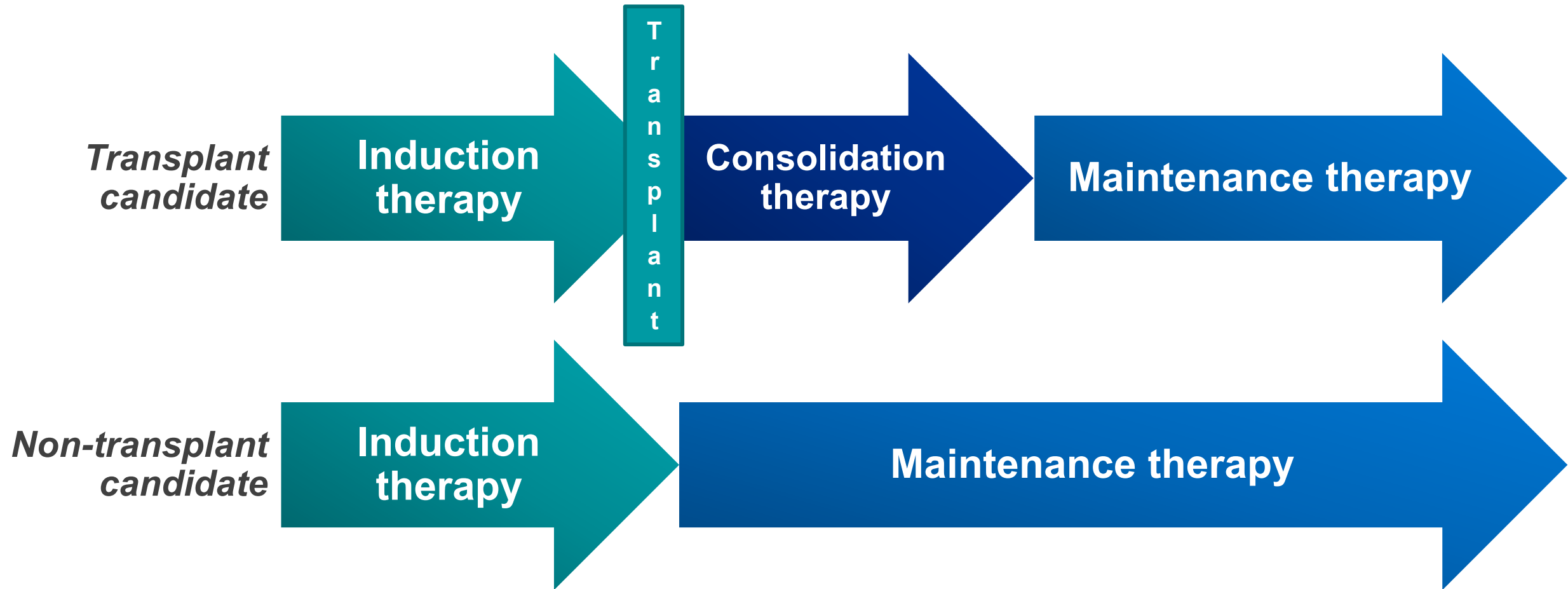


## Novel Data on High-Risk Myeloma (IMS/IMWG consensus)



Avet-Loiseau H, et al. J Clin Oncol 2025; accepted

# Treatment Paradigm for Newly Diagnosed Multiple Myeloma



# Goals of Multiple Myeloma Therapy



**Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible.**



**Eliminate myeloma cells from the bone marrow (as measured via minimal residual disease [MRD] testing).**



**Improve quality of life with as few treatment side effects as possible.**



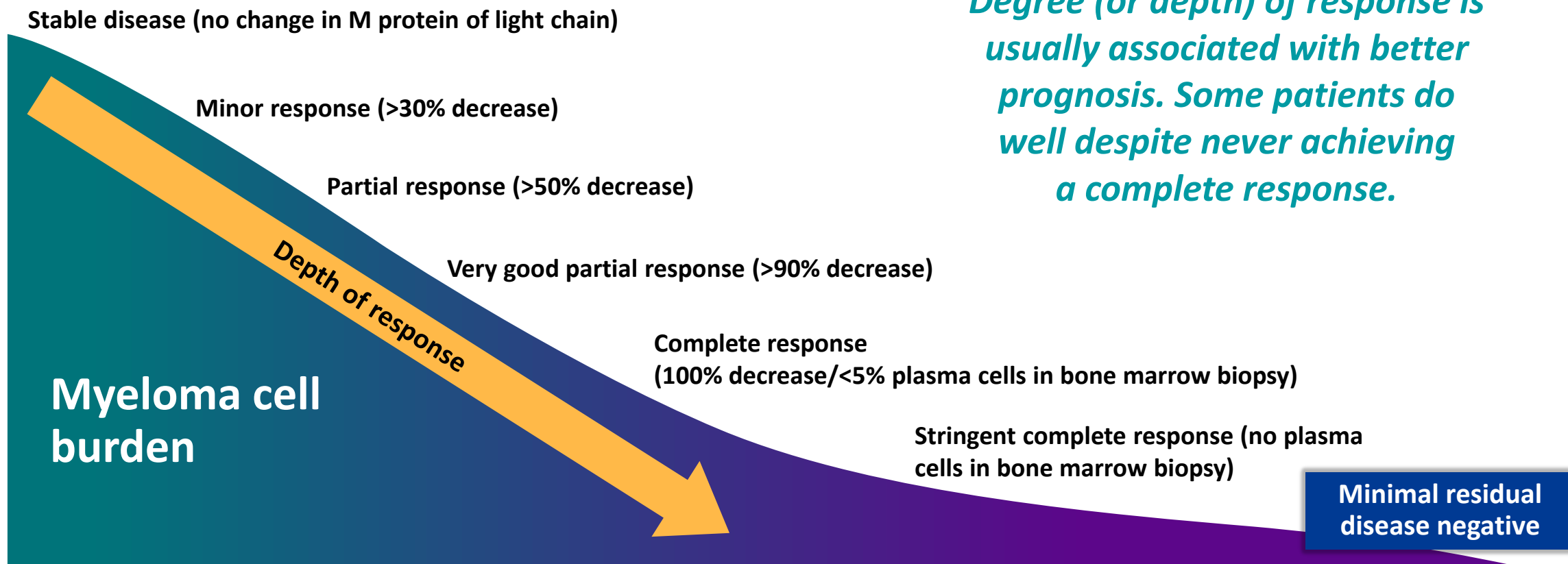
**Provide the longest possible period of response before first relapse.**



**Prolong overall survival.**



# Measuring Response to Therapy



ClonoSEQ is an FDA-approved next-generation sequencing (NGS) test to measure MRD in MM patients.

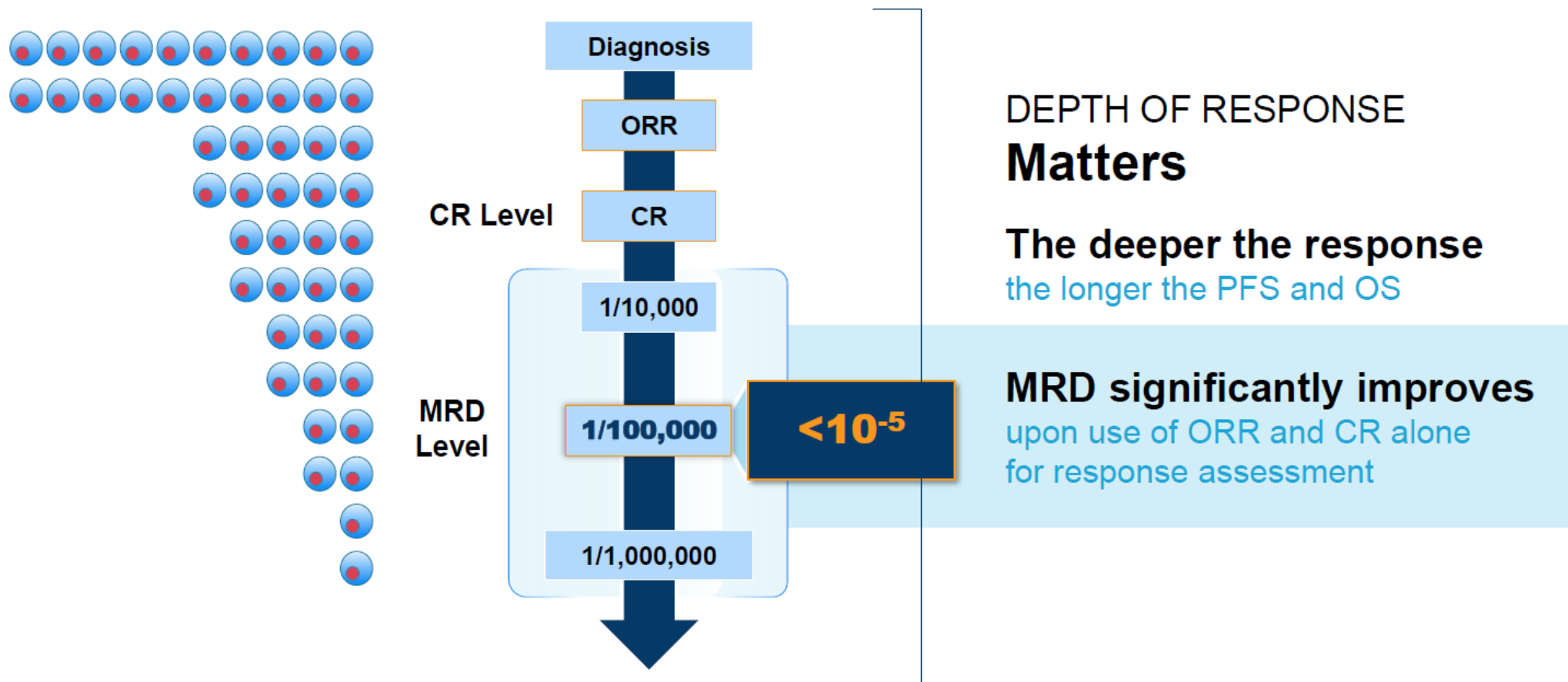
Palumbo A et al. *J Clin Oncol*. 2014;32:587.

Kumar S et al. *Lancet Oncol*. 2016;17:e328.

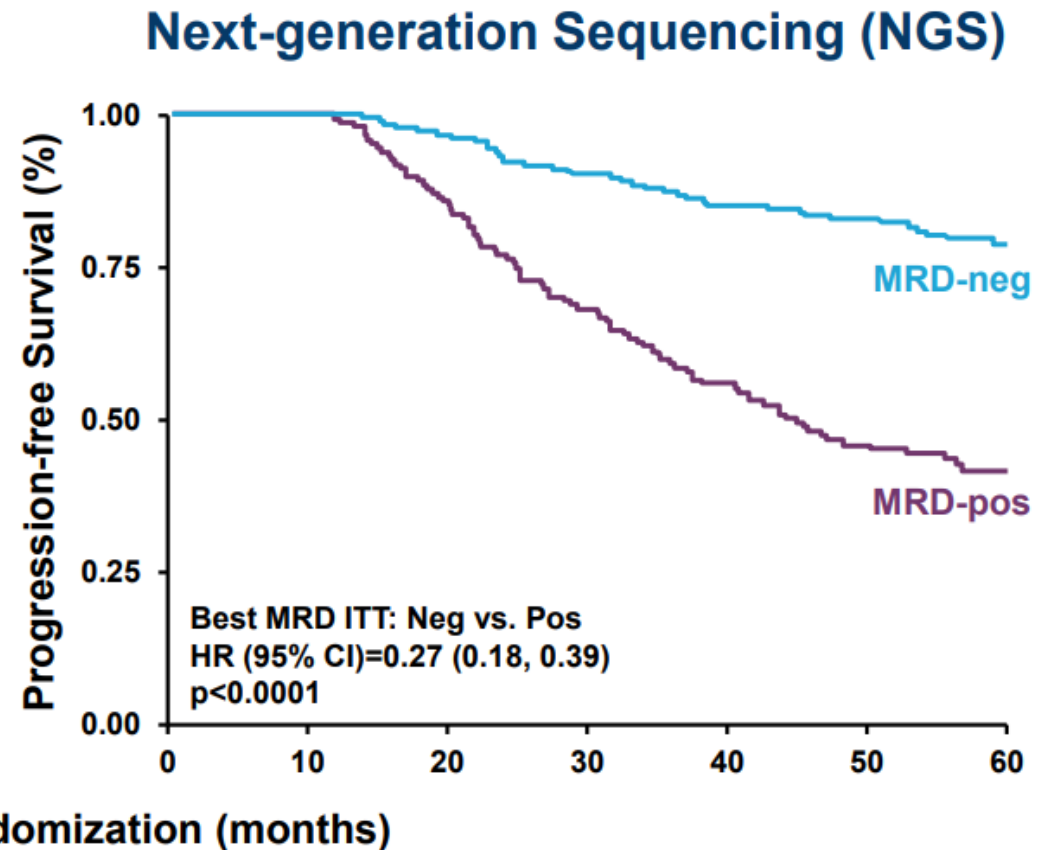
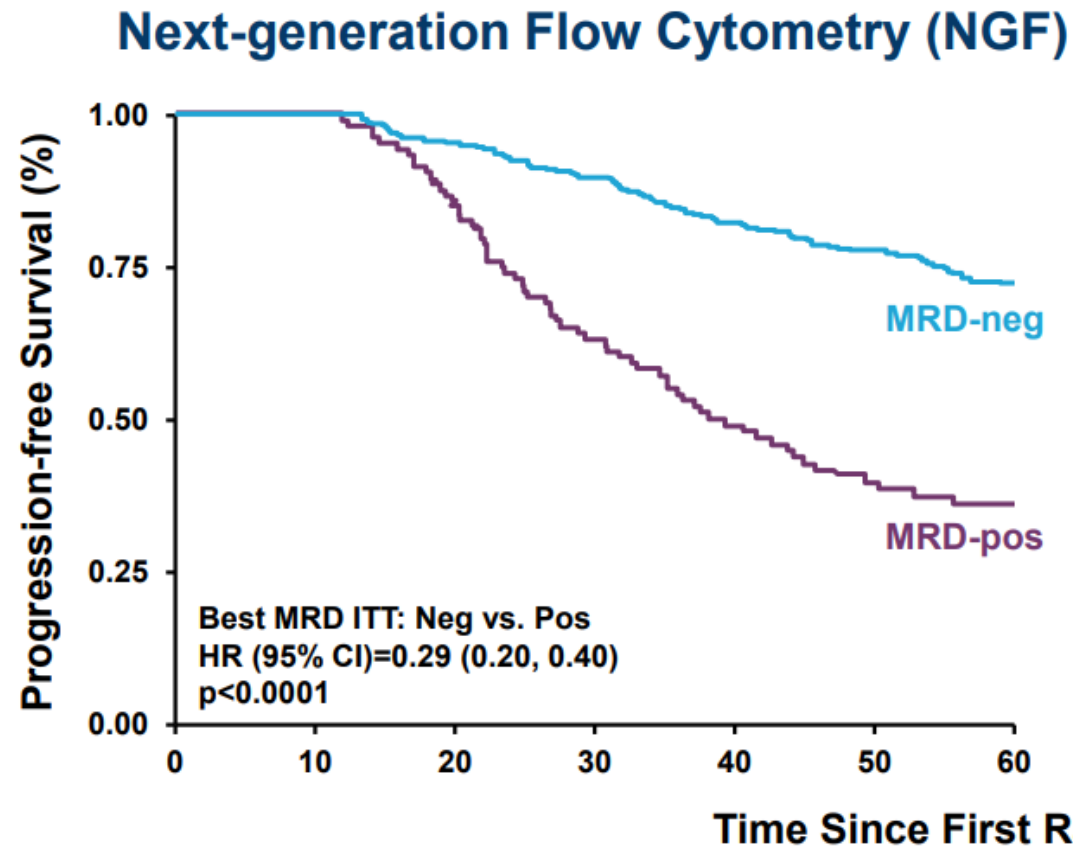


# Why Do We Need MRD?

## Depth of Response Predicts Longer PFS and OS



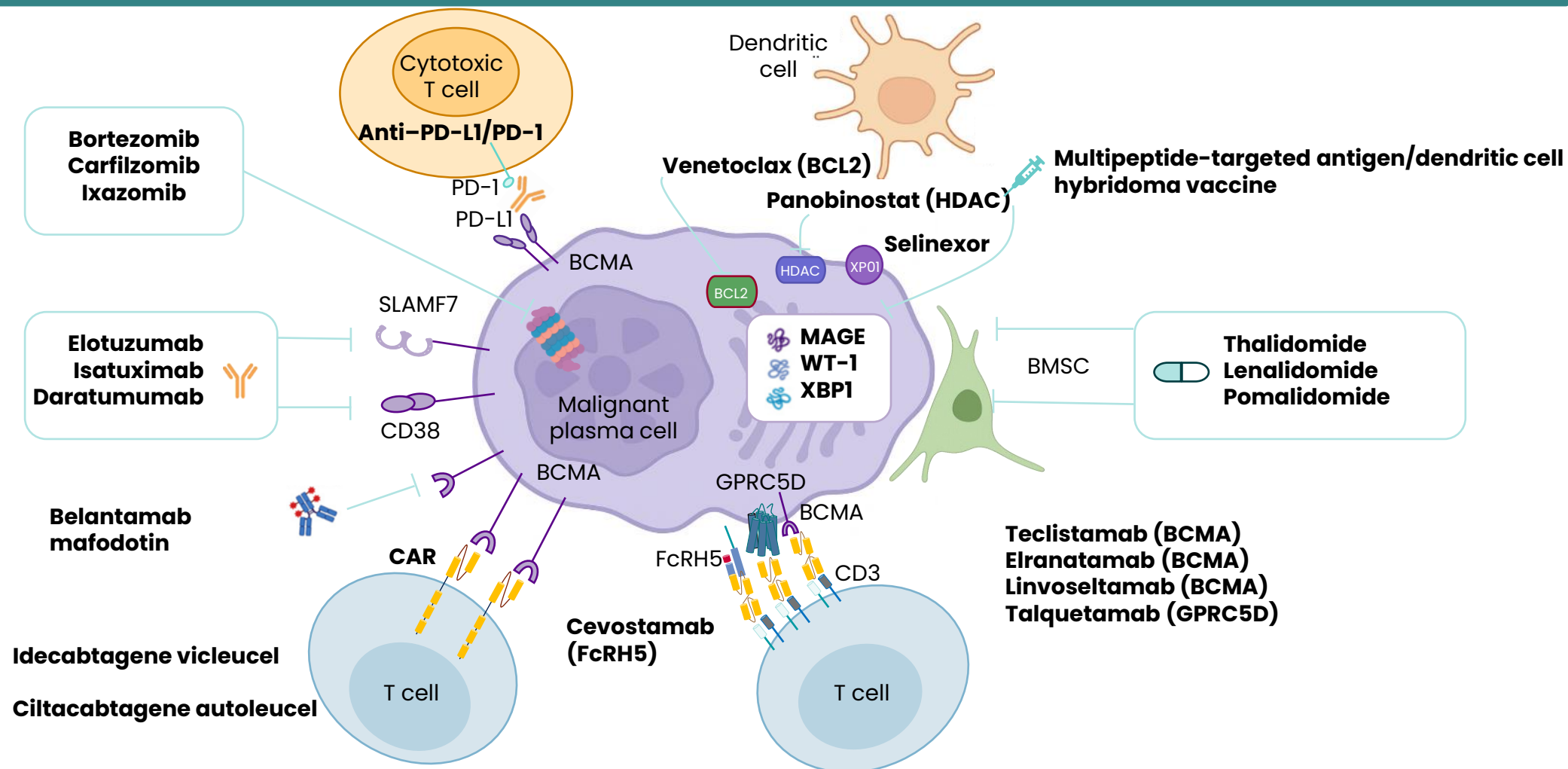
# We Now Have Two Next-Generation MRD Methods Detect MRD at $10^{-5}$ Threshold<sup>1</sup>



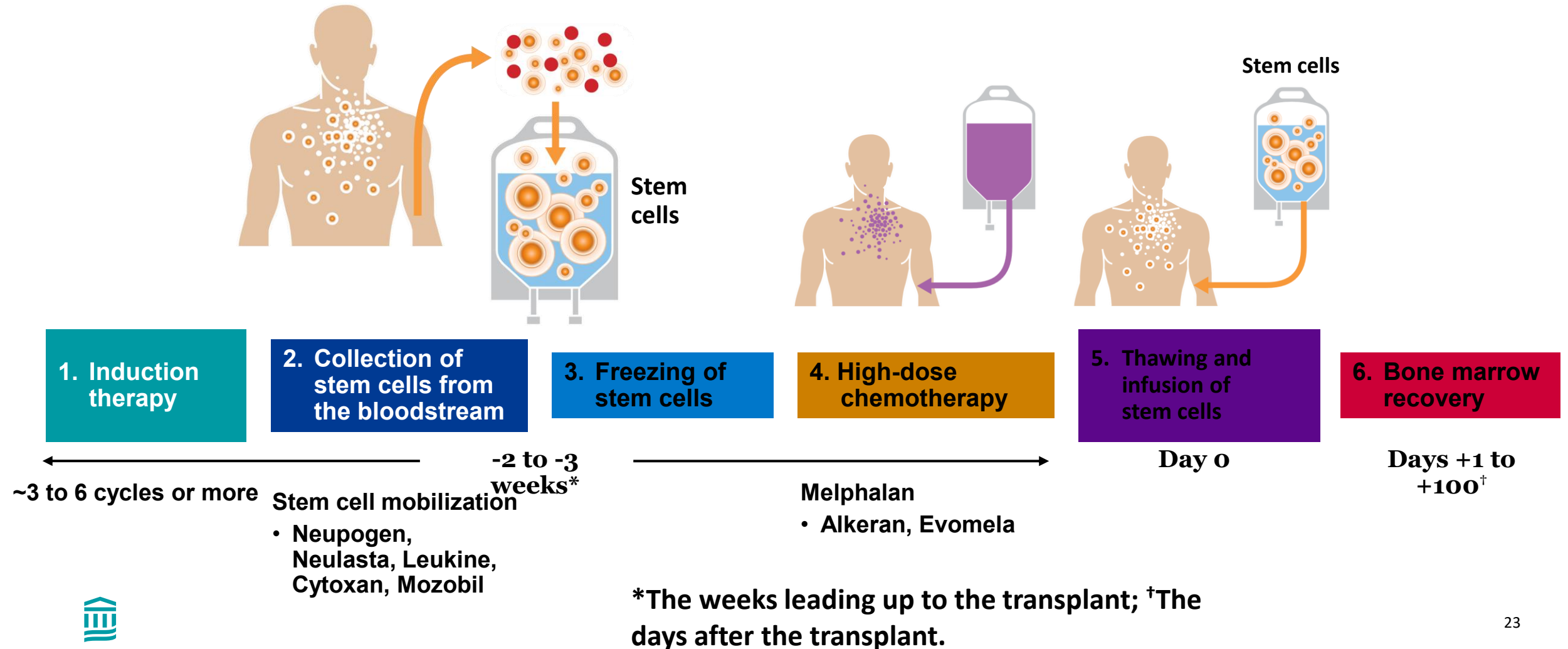
<sup>1</sup>Oliva S, et al. EClinicalMedicine. 2023 Jun 9;60:102016.

# Modern Therapeutic Targets for MM

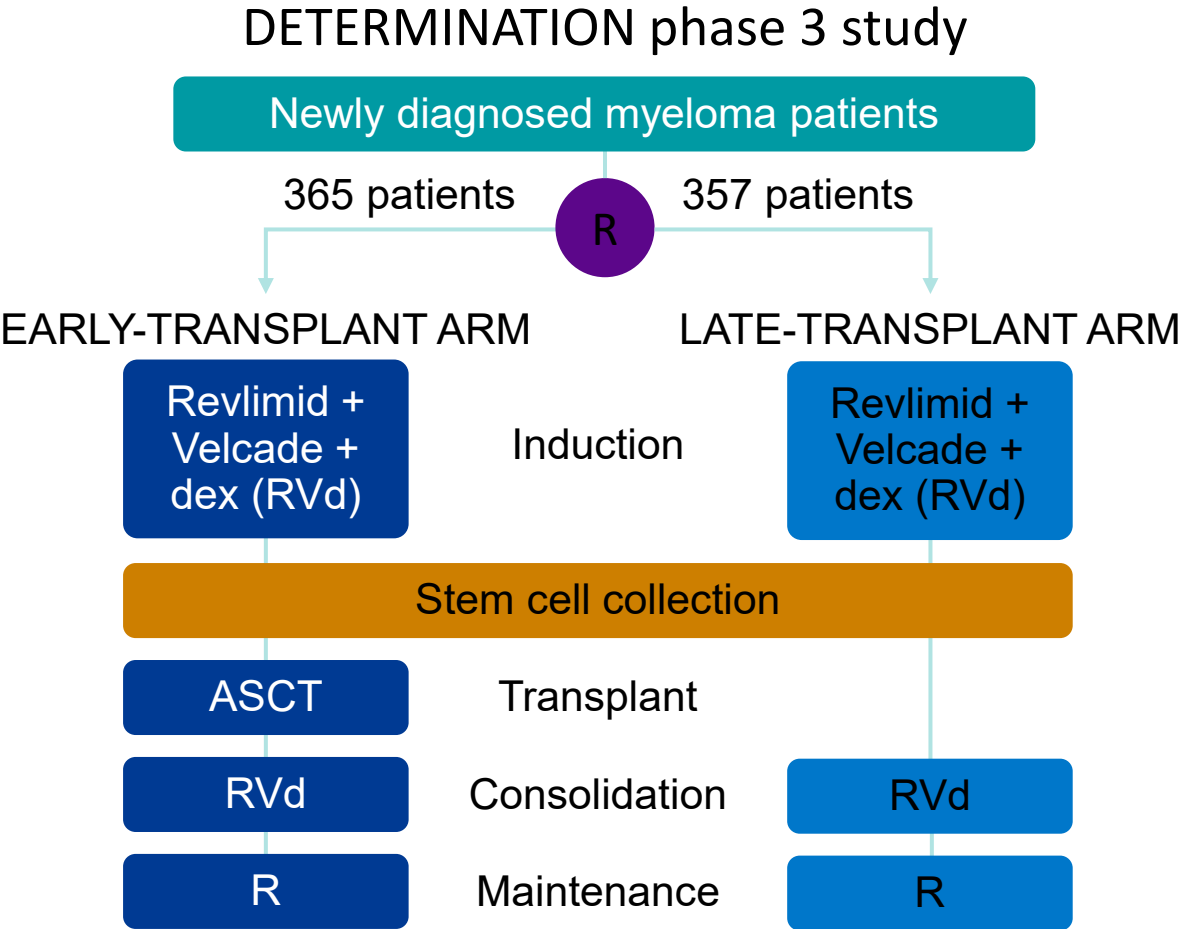
The treatment landscape for MM has expanded significantly, targeting different pathways and mechanisms



# Autologous Stem Cell Transplantation



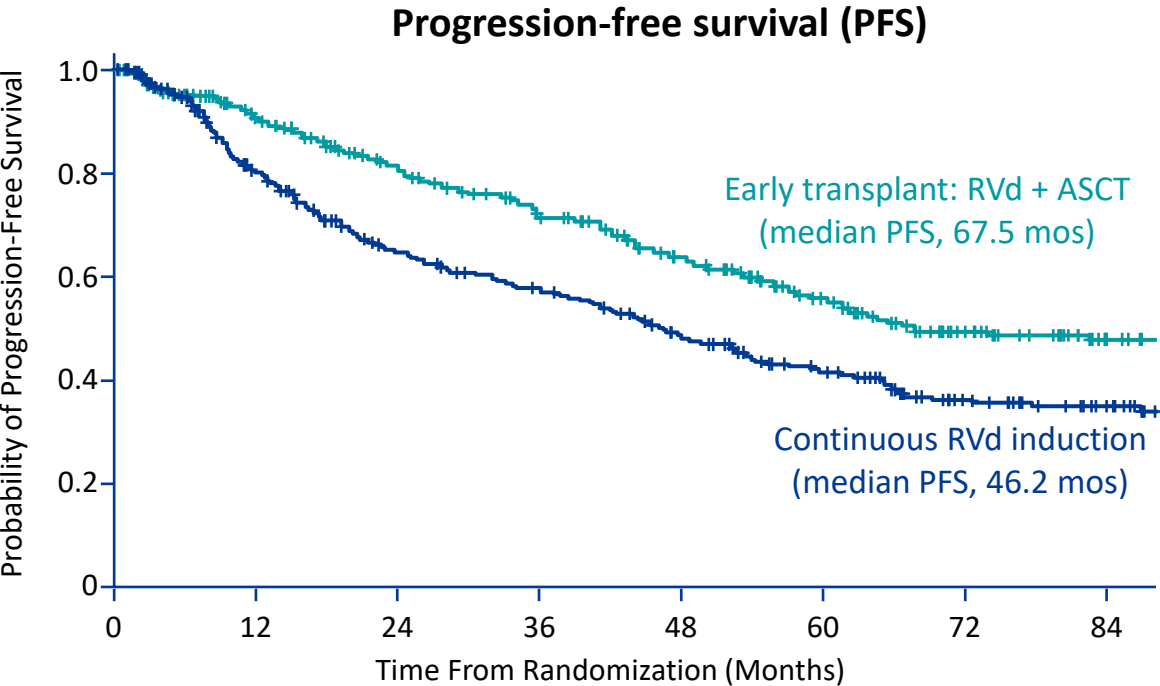
# Is transplant still required in newly diagnosed myeloma?



*Q: Should I get a transplant after induction OR wait until relapse?*

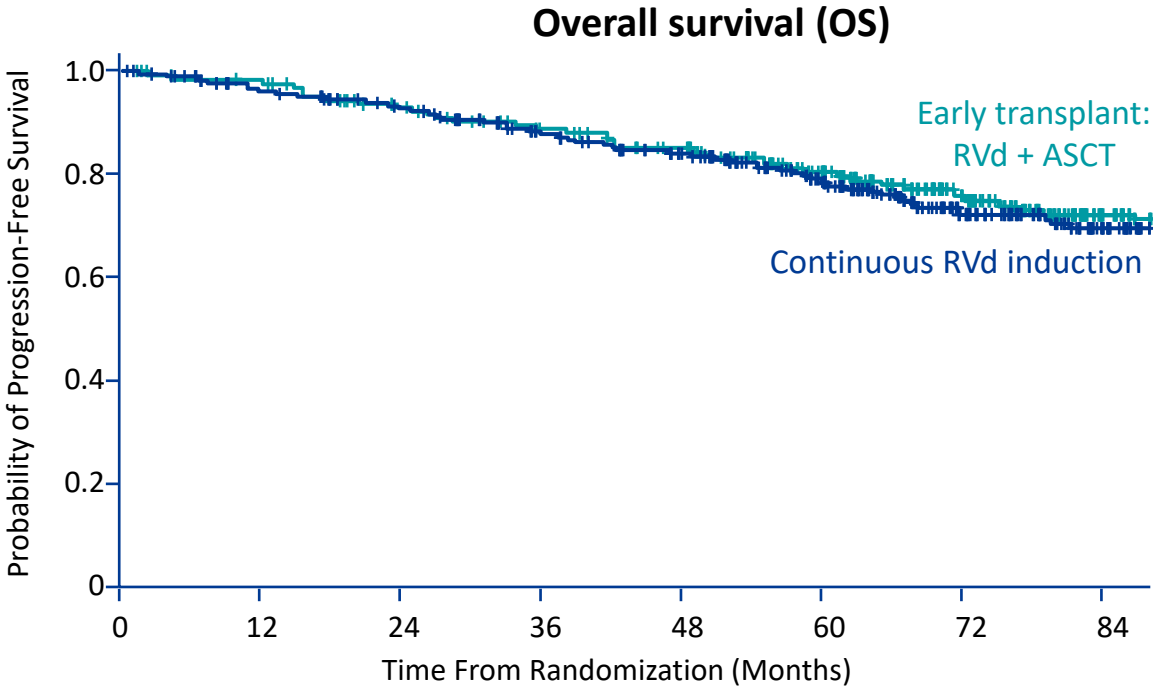


# Phase 3 Study of ASCT for NDMM: Survival Analysis



PFS for early transplant: approximately 5.5 years  
PFS for continuous induction: approximately 4 years

*Transplant extended time to progression by 20 months*



Length of overall survival: no difference.



# Early vs Late Transplant

## *Pros and Cons*



### Pros

#### **Early ASCT**

- Deeper and more durable response
- Youngest/healthiest you are going to be
- Allows for fewer cycles of induction treatment

#### **Late ASCT**

- PFS may be shorter, but currently appears OS is the same
- Less side effects without high-dose chemotherapy
- Conserve quality of life in the early part of disease journey



### Cons

#### **Early ASCT**

- No proven impact on overall survival
- 20% of patients still relapse within 2 years
- More side effects including a small risk of serious life-threatening complications and late toxicities
- 3 months to full clinical recovery

#### **Late ASCT**

- Need more cycles of induction
- May need next treatment sooner, including (late) transplant
- Not all patients relapsing are able to undergo salvage ASCT

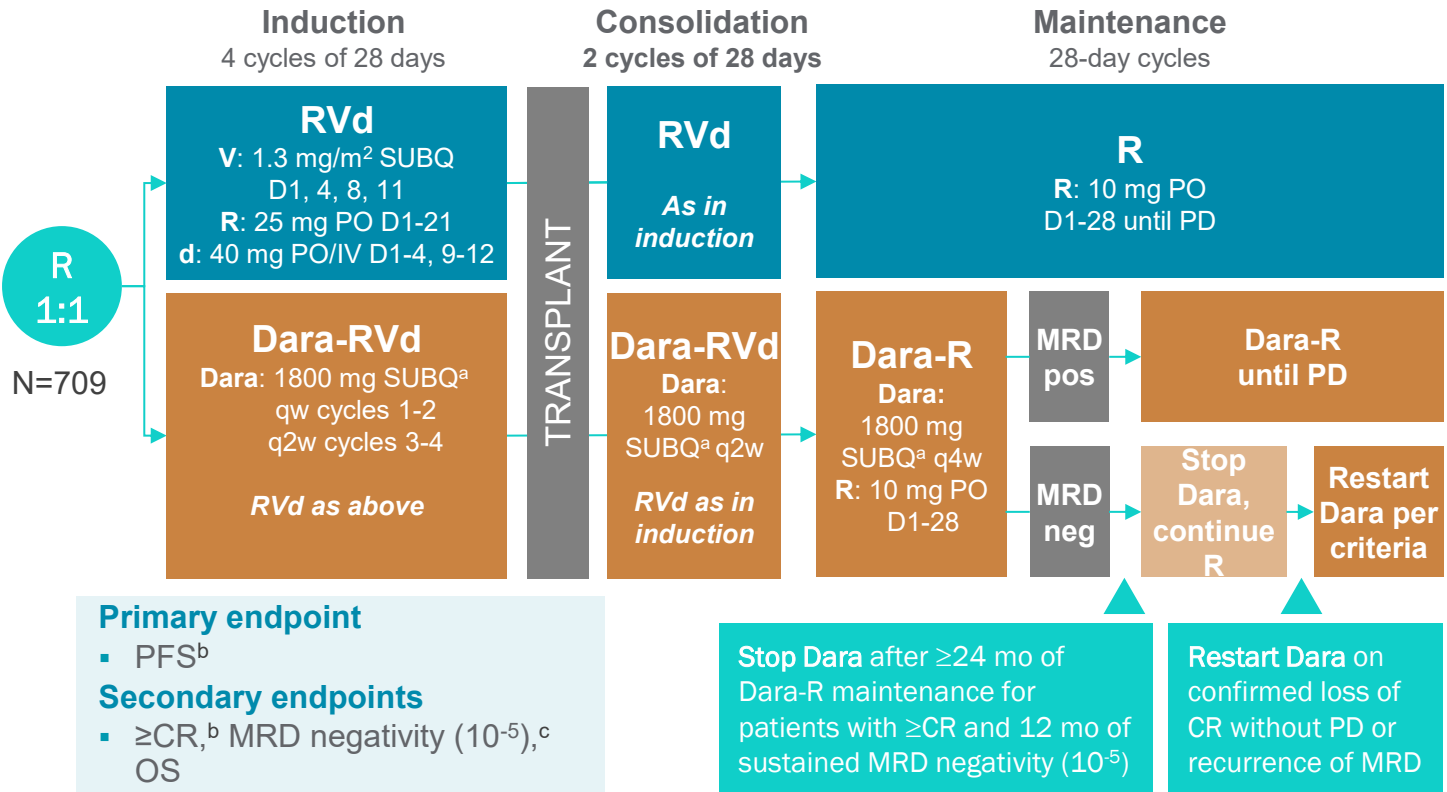


# PERSEUS: Dara-RVd to Dara-R vs RVd to R in Transplant-Eligible NDMM

## Study Design and Patients

## Key Eligibility Criteria

- Transplant-eligible NDMM; aged 18-70 years; ECOG PS  $\leq 2$

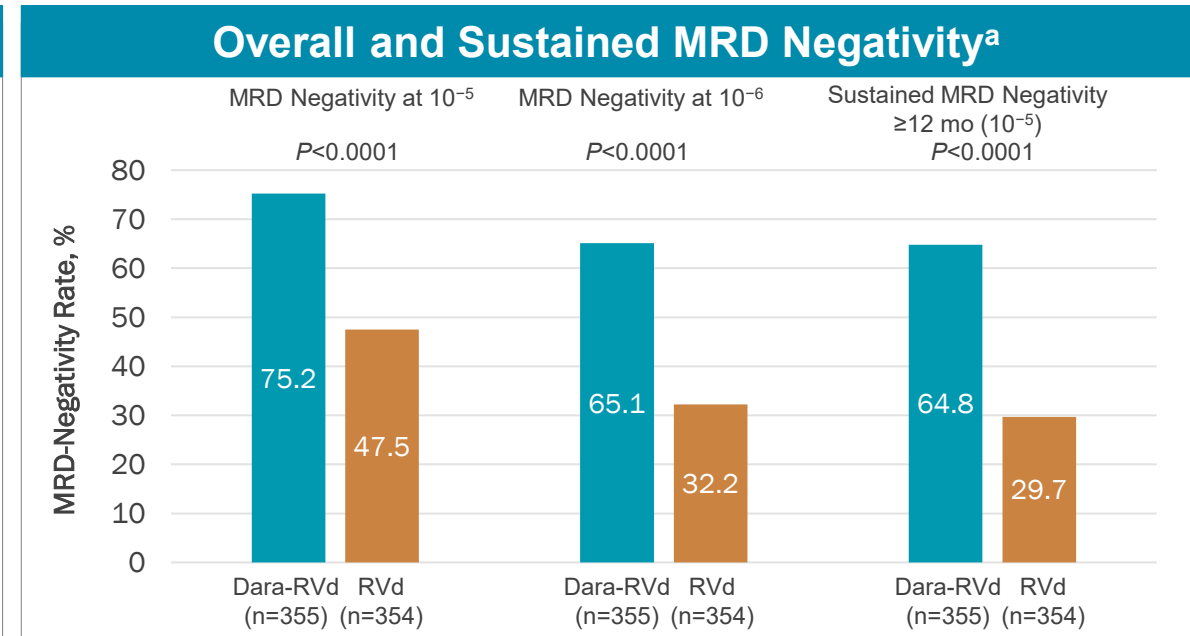
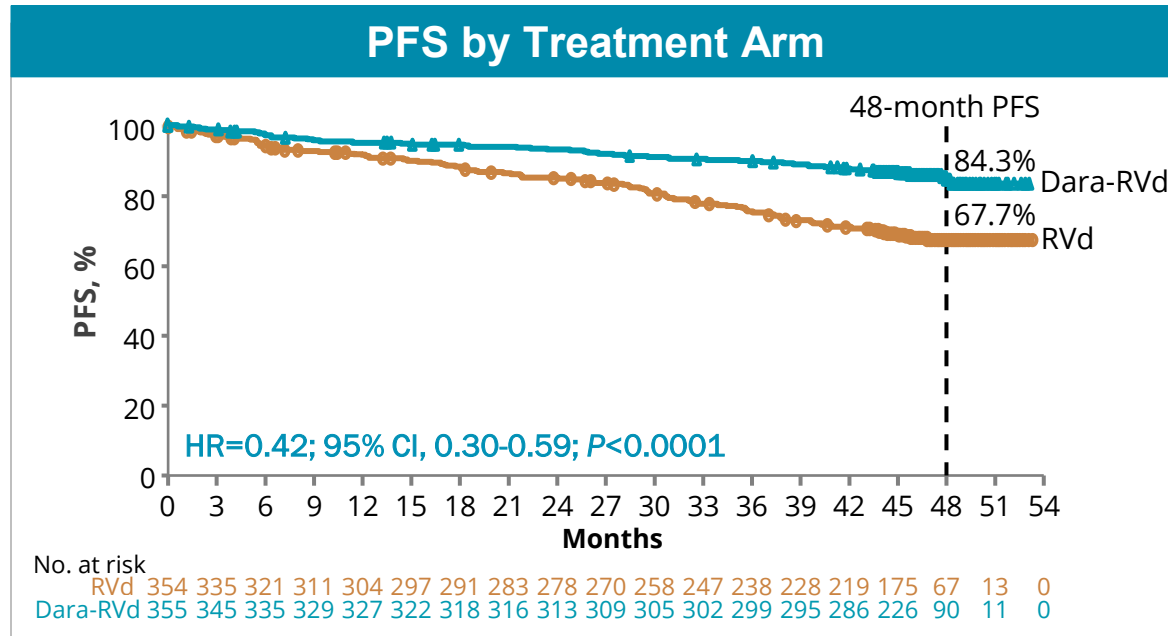


| Patient Characteristics              |          | Dara-RVd<br>(n=355) | RVd<br>(n=354) |
|--------------------------------------|----------|---------------------|----------------|
| Median age (range), years            |          | 61 (32-70)          | 59 (31-70)     |
| ECOG PS, <sup>d</sup> n (%)          | 0        | 221 (62.3)          | 230 (65.0)     |
|                                      | 1        | 114 (32.1)          | 108 (30.5)     |
|                                      | 2        | 19 (5.4)            | 16 (4.5)       |
|                                      | 3        | 1 (0.3)             | 0              |
| ISS stage, <sup>e</sup> n (%)        | I        | 186 (52.4)          | 178 (50.4)     |
|                                      | II       | 114 (32.1)          | 125 (35.4)     |
|                                      | III      | 55 (15.5)           | 50 (14.2)      |
| Cytogenetic risk, <sup>f</sup> n (%) | Standard | 264 (74.4)          | 266 (75.1)     |
|                                      | High     | 76 (21.4)           | 78 (22.0)      |
| EMD, n (%)                           | 0        | 340 (95.8)          | 338 (95.5)     |
|                                      | 1        | 15 (4.2)            | 16 (4.5)       |



# PERSEUS: Dara-RVd to Dara-R vs RVd to R in Transplant-Eligible NDMM

## Efficacy and Safety



- There was a 58% reduction in the risk of progression or death in patients receiving Dara-RVd vs RVd
- OS data were immature but there was a trend toward beneficial treatment effect with Dara-RVd with an estimated HR of 0.73

|                             | TEAE, n (%)           | Dara-RVd (n=351) |              | RVd (n=347) |              |
|-----------------------------|-----------------------|------------------|--------------|-------------|--------------|
|                             |                       | Any Grade        | Grade 3 or 4 | Any Grade   | Grade 3 or 4 |
| Hematologic AEs             | Neutropenia           | 243 (69.2)       | 218 (62.1)   | 204 (58.8)  | 177 (51.0)   |
|                             | Thrombocytopenia      | 170 (48.4)       | 102 (29.1)   | 119 (34.3)  | 60 (17.3)    |
|                             | Anemia                | 78 (22.2)        | 21 (6.0)     | 72 (20.7)   | 22 (6.3)     |
| Specific nonhematologic AEs | Peripheral neuropathy | 188 (53.6)       | 15 (4.3)     | 179 (51.6)  | 14 (4.0)     |
|                             | Infections            | 305 (86.9)       | 124 (35.3)   | 266 (76.7)  | 95 (27.4)    |
|                             | COVID-19              | 123 (35.0)       | 12 (3.4)     | 83 (23.9)   | 4 (1.2)      |
|                             | URTI                  | 111 (31.6)       | 2 (0.6)      | 87 (25.1)   | 6 (1.7)      |



# Summary of Data in Transplant-Eligible NDMM

|                                        | PERSEUS <sup>1</sup>           | GMMG-HD7 <sup>2</sup>        | GRIFFIN <sup>3,4</sup>         | MASTER <sup>5</sup>            | GMMG-CONCEPT <sup>6</sup>                      | IsKia <sup>7</sup>       |
|----------------------------------------|--------------------------------|------------------------------|--------------------------------|--------------------------------|------------------------------------------------|--------------------------|
| Induction<br>Maintenance               | Dara-RVd vs RVd<br>Dara-R vs R | Isa-RVd vs RVd<br>Isa-R vs R | Dara-RVd vs RVd<br>Dara-R vs R | Dara-KRd<br>R/MRD surveillance | Isa-KRd<br>Isa-KR                              | Isa-KRd vs KRd<br>R      |
| Total N                                | 355 vs 354                     | 331 vs 329                   | 104 vs 103                     | 123                            | 99<br>(transplant eligible, high-risk disease) | 151 vs 151               |
| Median follow-up                       | 47.5 mo                        | NA                           | 49.6 mo                        | 42.2 mo                        | 44 mo                                          | 21 mo                    |
| ≥VGPR <sup>a</sup><br>≥CR <sup>a</sup> | NA<br>88% vs 70%               | 83% vs 69%<br>44% vs 34%     | 90% vs 73%<br>52% vs 42%       | NA<br>72%                      | 91%<br>73%                                     | 94% vs 94%<br>74% vs 72% |
| MRD-neg 10 <sup>-5</sup> <sup>a</sup>  | 75% vs 48%                     | 66% vs 48%                   | 50% vs 20%                     | 81%                            | 68%                                            | 77% vs 67%               |
| PFS <sup>a</sup>                       | 4 year:<br>84% vs 68%          | NA                           | 4 year:<br>87% vs 70%          | NA                             | 3 year: 69%                                    | 1 year:<br>95% vs 95%    |

No direct comparisons can be made without head-to-head studies.

<sup>a</sup> Post-consolidation in transplant-eligible patients.

1. Sonneveld P, et al. ASH 2023. Abstract LBA-1. 2. Raab MS, et al. EHA 2024. Abstract S202. 3. Voorhees PM, et al. *Lancet Haematol.* 2023;10(10):e825-e837. 4. Sborov DW, et al. IMS 2022. Abstract OAB-057. 5. Costa LJ, et al. *Lancet Haematol.* 2023;10(11):e890-e901. 6. Leyboldt LB, et al. *J Clin Oncol.* 2024;42(1):26-37. 7. Gay F, et al. ASH 2023. Abstract 4.

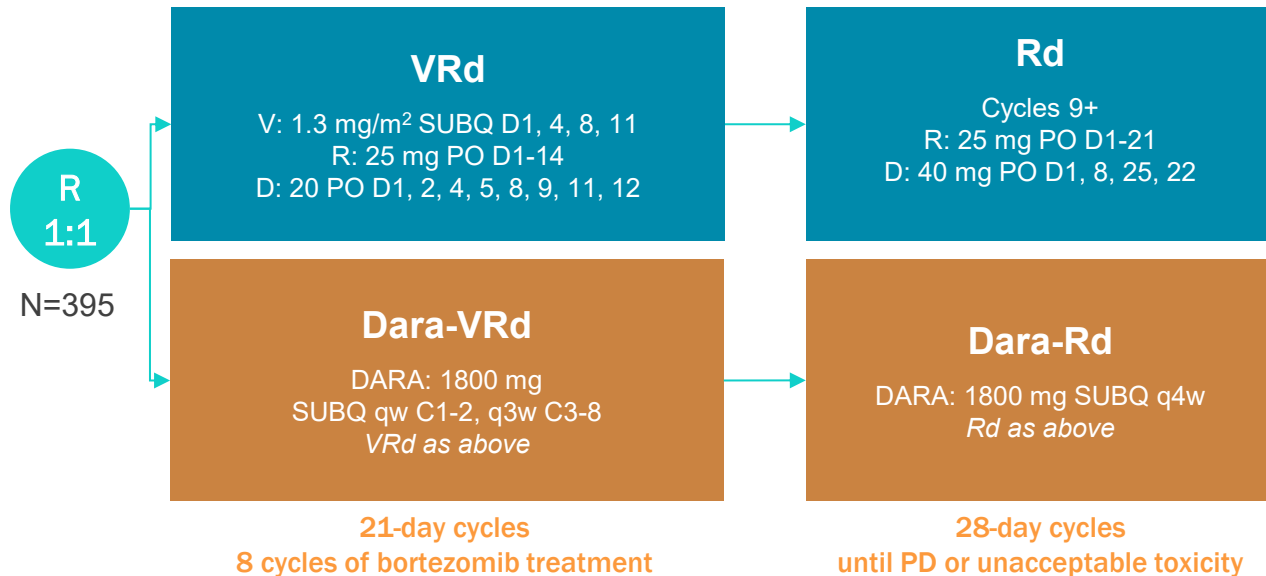


# CEPHEUS: Dara-VRd vs VRd in Transplant-Ineligible/-Deferred NDMM

## Study Design and Patients

### Key Eligibility Criteria

- Transplant-ineligible or transplant-deferred, aged  $\geq 18$  years
- ECOG PS score of 0-2, frailty score of 0-1



### Primary endpoint

- Overall MRD ( $\geq$ CR) negativity

### Secondary endpoints

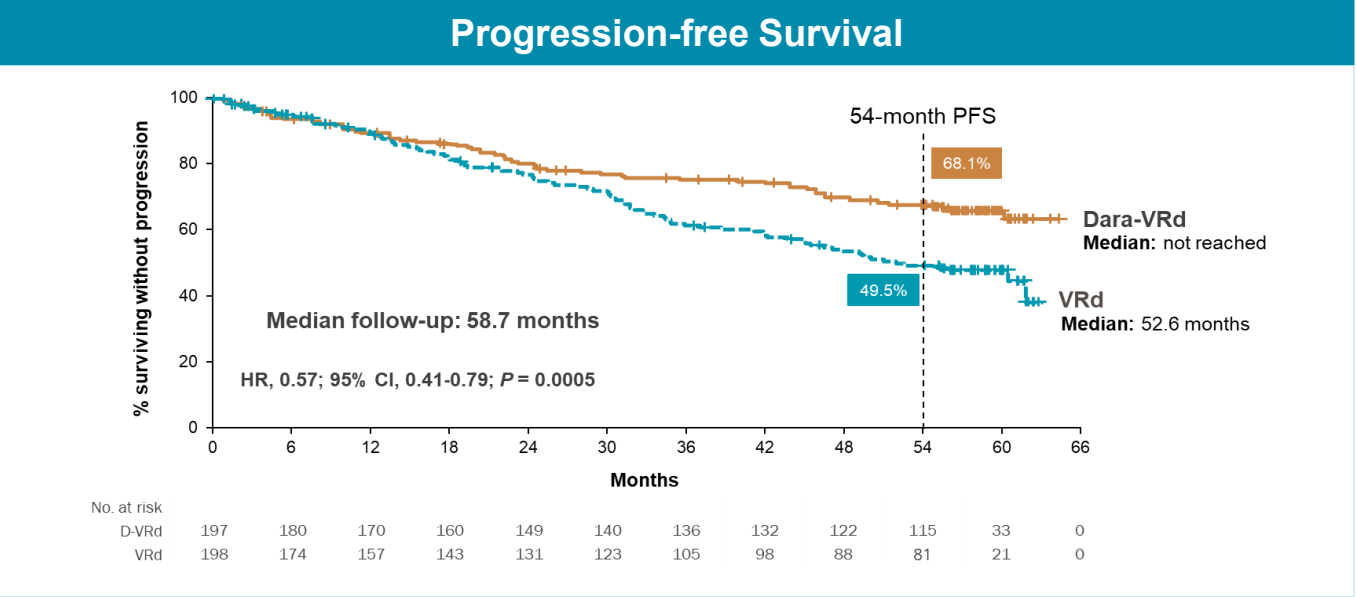
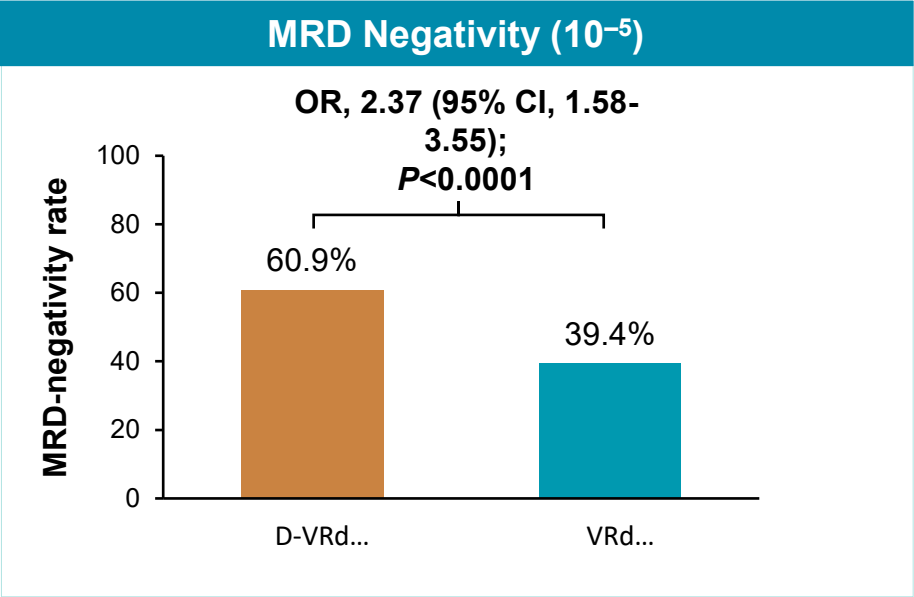
- PFS, sustained MRD ( $\geq$ CR) negativity ( $\geq 12$  months),  $\geq$ CR rate, OS

| Patient Characteristics (ITT)                |                   | D-VRd (n=197) | VRd (n=198)  |
|----------------------------------------------|-------------------|---------------|--------------|
| Median age (range), years                    |                   | 70.0 (42-79)  | 70.0 (31-80) |
| Aged <65 years, n (%)                        |                   | 36 (18.3)     | 35 (17.7)    |
| Aged $\geq 70$ years, n (%)                  |                   | 109 (55.3)    | 110 (55.6)   |
| ECOG PS, n (%)                               | 0                 | 71 (36.0)     | 84 (42.4)    |
|                                              | 1                 | 103 (52.3)    | 100 (50.5)   |
|                                              | 2                 | 23 (11.7)     | 14 (7.1)     |
| Frailty score, n (%) <sup>a</sup>            | 0                 | 124 (62.9)    | 132 (66.7)   |
|                                              | 1                 | 73 (37.1)     | 66 (33.3)    |
| ISS disease stage, n (%)                     | I                 | 68 (34.5)     | 68 (34.5)    |
|                                              | II                | 73 (37.1)     | 75 (37.9)    |
|                                              | III               | 56 (28.4)     | 55 (27.8)    |
| Cytogenetic risk profile, n (%) <sup>b</sup> | Standard risk     | 149 (75.6)    | 149 (75.3)   |
|                                              | High risk         | 25 (12.7)     | 27 (13.6)    |
|                                              | Intermediate risk | 23 (11.7)     | 22 (11.1)    |
| Transplant ineligible, n (%)                 |                   | 144 (73.1)    | 145 (73.2)   |
| Transplant deferred, n (%)                   |                   | 53 (26.9)     | 53 (26.8)    |



# CEPHEUS: Dara-VRd vs VRd in Transplant-Ineligible/-Deferred NDMM

## Efficacy and Safety



| TEAEs, n (%)                |                       | Dara-VRd (n=197) | VRd (n=195) |
|-----------------------------|-----------------------|------------------|-------------|
| Grade 5 AEs <sup>a</sup>    |                       | 21 (10.7)        | 15 (7.7)    |
| Hematologic AEs             | Neutropenia           | 110 (55.8)       | 76 (39.0)   |
|                             | Thrombocytopenia      | 92 (46.7)        | 66 (33.8)   |
|                             | Anemia                | 73 (37.1)        | 62 (31.8)   |
| Specific nonhematologic AEs | Peripheral neuropathy | 110 (55.8)       | 119 (61.0)  |
|                             | Infections            | 181 (91.9)       | 167 (85.6)  |
|                             | COVID-19              | 75 (38.1)        | 48 (24.6)   |
|                             | SPMs                  | 15 (7.6)         | 18 (9.2)    |

Daratumumab significantly increased overall MRD-negativity rate and overall  $\geq$ CR rate by approximately 20%

There was a 43% reduction in the risk of progression or death in patients receiving Dara-VRd vs VRd

|                                                     | Dara-VRd (n=197) | VRd (n=195) | OR (95% CI); $P$ value      |
|-----------------------------------------------------|------------------|-------------|-----------------------------|
| Overall MRD negativity ( $10^{-5}$ )                | 60.9             | 39.4        | 2.37 (1.58-3.55); $<0.0001$ |
| Sustained MRD negativity ( $10^{-5}$ ) $\geq 12$ mo | 48.7             | 26.3        | 2.63 (1.73-4.00); $<0.0001$ |
| $\geq$ CR rate                                      | 81.2             | 61.6        | 2.73 (1.71-4.34); $<0.0001$ |



# Summary of Data in Transplant-Ineligible/-Deferred NDMM

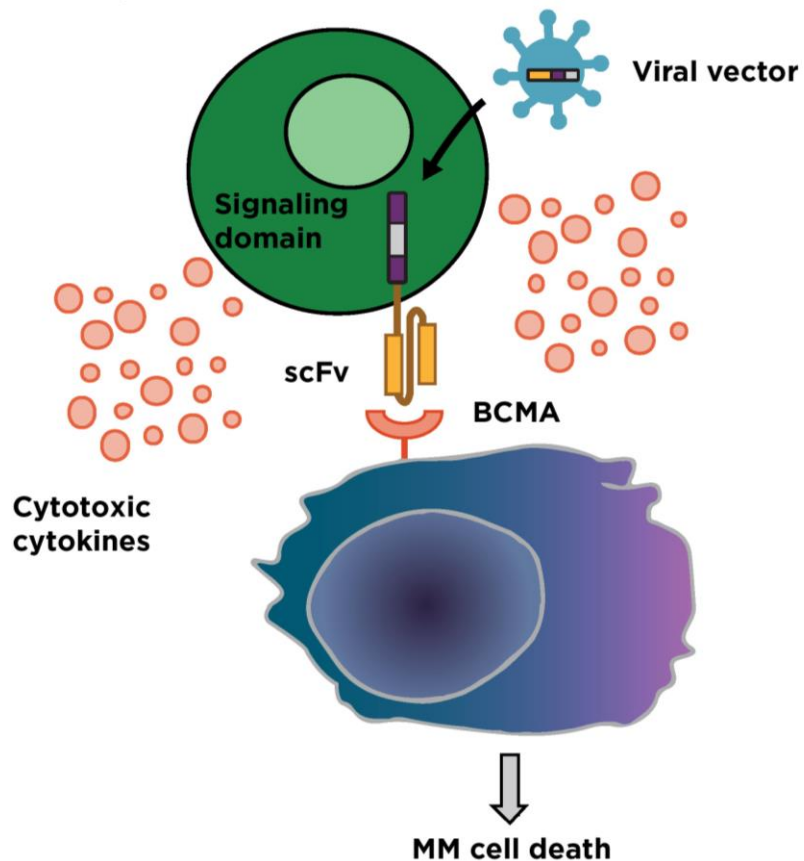
|                  |                                          | SWOG S0777 <sup>1</sup>                                                |                                | MAIA <sup>2,4</sup>                            |                                              | IMROZ <sup>5,6</sup>                          |                                 | CEPHEUS <sup>7</sup>                                      |                   | BENEFIT <sup>8-10</sup>                               |                           |
|------------------|------------------------------------------|------------------------------------------------------------------------|--------------------------------|------------------------------------------------|----------------------------------------------|-----------------------------------------------|---------------------------------|-----------------------------------------------------------|-------------------|-------------------------------------------------------|---------------------------|
|                  |                                          | VRd (n=235)                                                            | Rd (n=225)                     | DRd (n=368)                                    | Rd (n=369)                                   | Isa-VRd (n=285)                               | VRd (n=190)                     | D-VRd (n=197)                                             | VRd (n=198)       | Isa-VRd (n=135)                                       | Isa-Rd (n=135)            |
| Population       |                                          | Patients ≥18 y <sup>a</sup><br>(includes transplant-deferred patients) |                                | Inclusive of frail & older<br>(>80 y) patients |                                              | Patients 18-80 y<br>(excludes patients >80 y) |                                 | Patients ≥18 y<br>(includes transplant-deferred patients) |                   | Nonfrail patients 65-79 y<br>(excludes frail & ≥80 y) |                           |
| Median follow-up |                                          | 84 mo                                                                  |                                | 89.3 mo                                        |                                              | 59.7 mo                                       |                                 | 58.7 mo                                                   |                   | 23.5 mo                                               |                           |
| EFFICACY         | ≥CR rate                                 | 24.2%                                                                  | 12.1%                          | 51.1% <sup>b</sup>                             | 30.1% <sup>b</sup>                           | 74.7%                                         | 64.1%                           | 81.2%                                                     | 61.6%             | 58%                                                   | 31%                       |
|                  | ≥CR, MRD-neg<br>(10 <sup>-5</sup> ) rate | N/A                                                                    | N/A                            | 32.1% <sup>b</sup>                             | 11.1% <sup>b</sup>                           | 58.1%                                         | 43.6%                           | 60.9%                                                     | 39.4%             | 53%                                                   | 26%                       |
|                  | PFS                                      | 41 mo                                                                  | 29 mo                          | 60-mo: 52.1%<br>Median: 61.9 mo <sup>b</sup>   | 60-mo: 29.6%<br>Median: 34.4 mo <sup>b</sup> | 60-mo: 63.2%<br>Median: NR                    | 60-mo: 45.2%<br>Median: 54.3 mo | 54-mo: 68.1%                                              | 54-mo: 49.5%      | 24-mo: 85.2%<br>Median: NR                            | 24-mo: 80%<br>Median: NR  |
|                  | OS                                       | NR                                                                     | 69 mo                          | 60-mo: ~67%<br>Median: 90.3 mo                 | 60-mo: ~54%<br>Median: 64.1 mo               | 60-mo: 72.3%                                  | 60-mo: 66.3%                    | NR                                                        | NR                | 24-mo: 91.1%                                          | 24-mo: 91.5%              |
| SAFETY           | Grade 5 AEs                              | <3%                                                                    | <2%                            | 6.9%                                           | 6.3%                                         | 11.0%                                         | 5.5%                            | 10.7% <sup>c</sup>                                        | 7.7% <sup>c</sup> | Not reported                                          | Not reported              |
|                  | Serious TEAEs                            | N/A                                                                    | N/A                            | 62.9%                                          | 62.7%                                        | 70.7%                                         | 67.4%                           | Not reported                                              | Not reported      | 34%                                                   | 35%                       |
|                  | Discontinuation<br>due to TRAEs          | N/A                                                                    | N/A                            | 7.1%                                           | 25.8%                                        | 22.8%                                         | 26.0%                           | Not reported                                              | Not reported      | Not reported                                          | Not reported              |
|                  | Infections                               | 19% gr 3/4                                                             | 14% gr 3/4                     | 42.6% gr 3/4                                   | 29.6% gr 3/4                                 | 44.9% gr ≥3                                   | 38.1% gr ≥3                     | 40.1% gr 3/4                                              | 31.8% gr 3/4      | 35% grade ≥2 <sup>d</sup>                             | 40% grade ≥2 <sup>d</sup> |
|                  | Peripheral neuropathy                    | Gr ≥3 neurologic<br>AEs: 34.6%                                         | Gr ≥3 neurologic<br>AEs: 11.3% | 2.5% gr 3/4                                    | 0.5% gr 3/4                                  | 7.2% gr ≥3                                    | 6.1% gr ≥3                      | 8.1% gr 3/4                                               | 8.2% gr 3/4       | 27% grade ≥2                                          | 10% grade ≥2              |



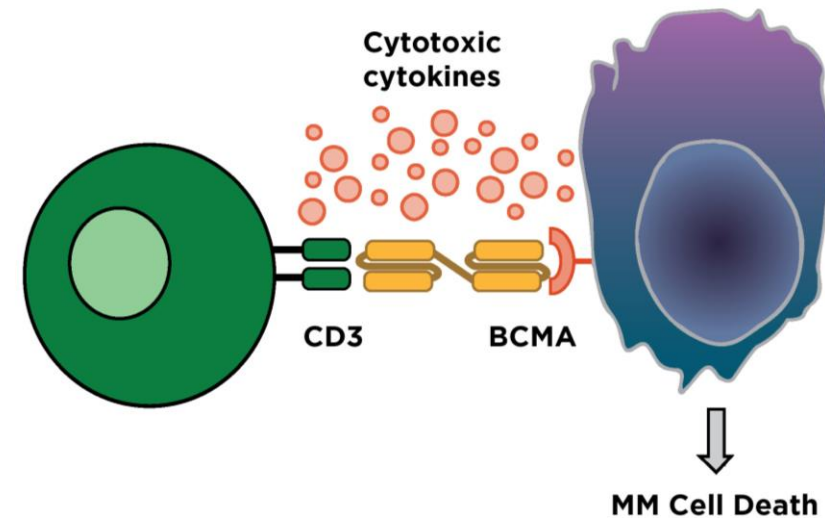
1. Durie BGM, et al. *Blood Cancer J.* 2020;10(5):53. 2. Facon T, et al. EHA 2024. Abstract P968. 3. Kumar S, et al. ASH 2022. Poster 4559. 4. Facon T, et al. *N Engl J Med.* 2019;380(22):2104-2115. 5. Facon T, et al. *N Engl J Med.* June 3, 2024. 6. Facon T, et al. ASCO 2024. Abstract 7500. 7. Usmani SZ et al. IMS, 2024. Abstract OA63. 8. Leleu X, et al. *Nat Med.* 2024. 9. Leleu XP, et al. ASCO 2024. Abstract 7501. 10. Leleu XP, et al. EHA 2024. Abstract S203.

# T-cell Redirecting Therapies in Multiple Myeloma

## CAR T-Cell Therapy



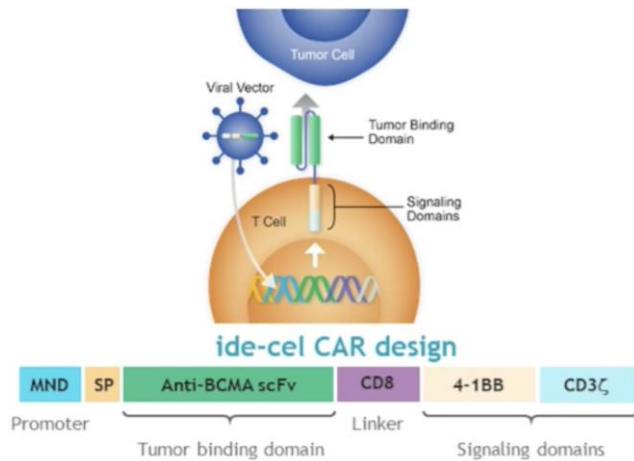
## Bispecific Antibodies



# Current Approved Anti-BCMA CAR T-Cell Therapy

## Idecabtagene-Vicleucel (ide-cel, Abecma)

- Autologous CAR T-cell
- Anti-BCMA scFv
- 4-1BB costimulatory domain
- CD3 $\zeta$  intracellular signaling domain

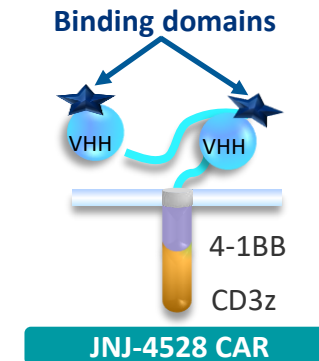


### FDA Label

- 2 or more prior lines of therapy
- Previously treated with IMiD, PI, and anti-CD38 monoclonal antibody

## Ciltacabtagene Autoleucel (cilta-cel, Carvykti)

- Autologous CAR T-cell
- **2 BCMA-targeting sites (increased avidity)**
- 4-1BB signaling domain
- CD3 $\zeta$  intracellular signaling domain



### FDA Label

- 1 or more prior lines of therapy and lenalidomide refractory
- Previously treated with IMiD, PI



# Current Approved Bispecific Antibodies

## **BCMA**

**Teclistamab**

**Elranatamab**

**Linvoseltamab**

## **GPRC5D**

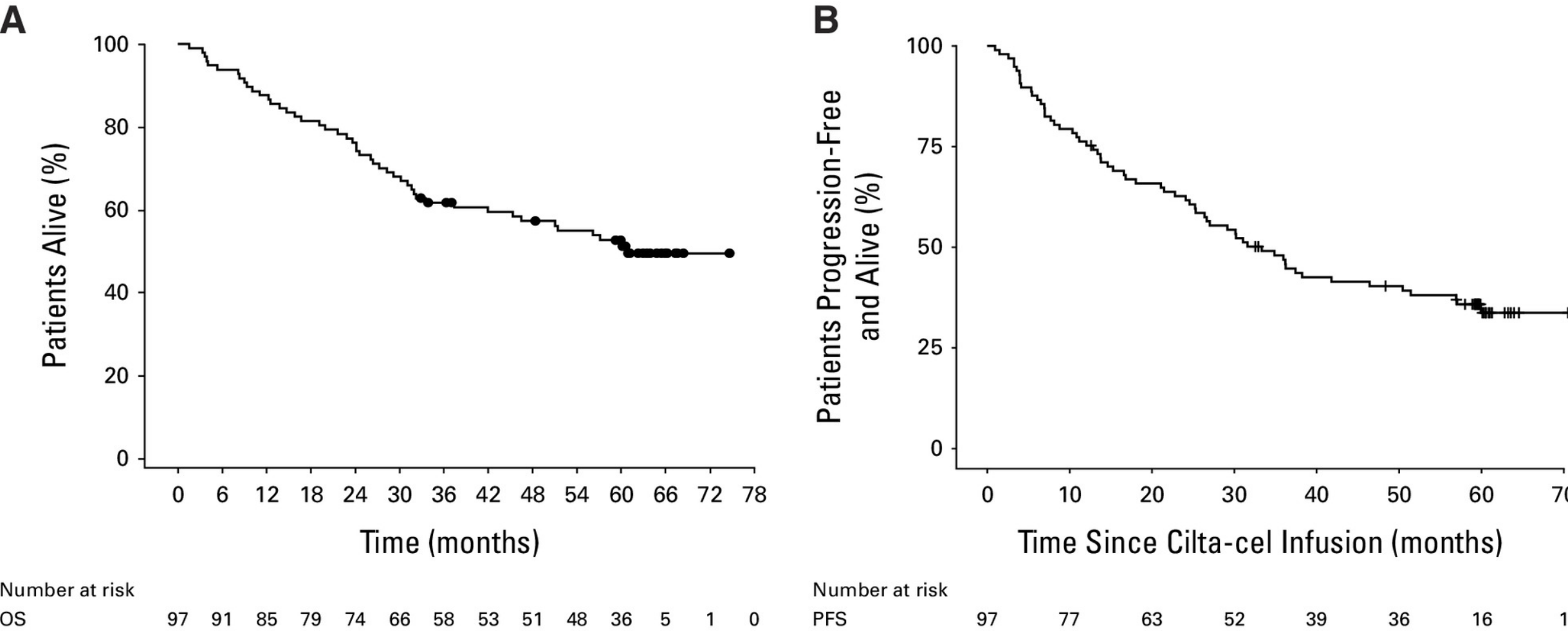
**Talquetamab**

### **FDA Label**

- 4 or more prior lines of therapy
  - Previously treated with IMiD, PI, and anti-CD38 monoclonal antibody
- 1 prior line of therapy (teclistamab and daratumumab)

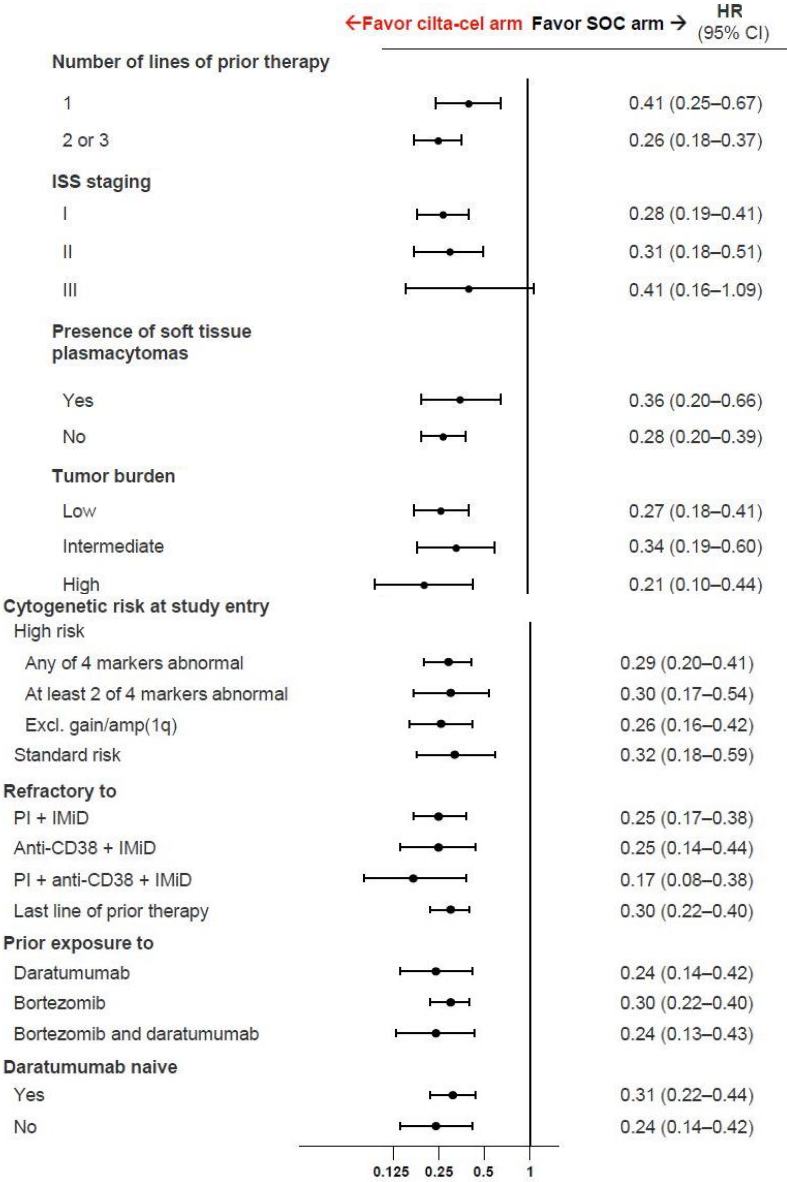
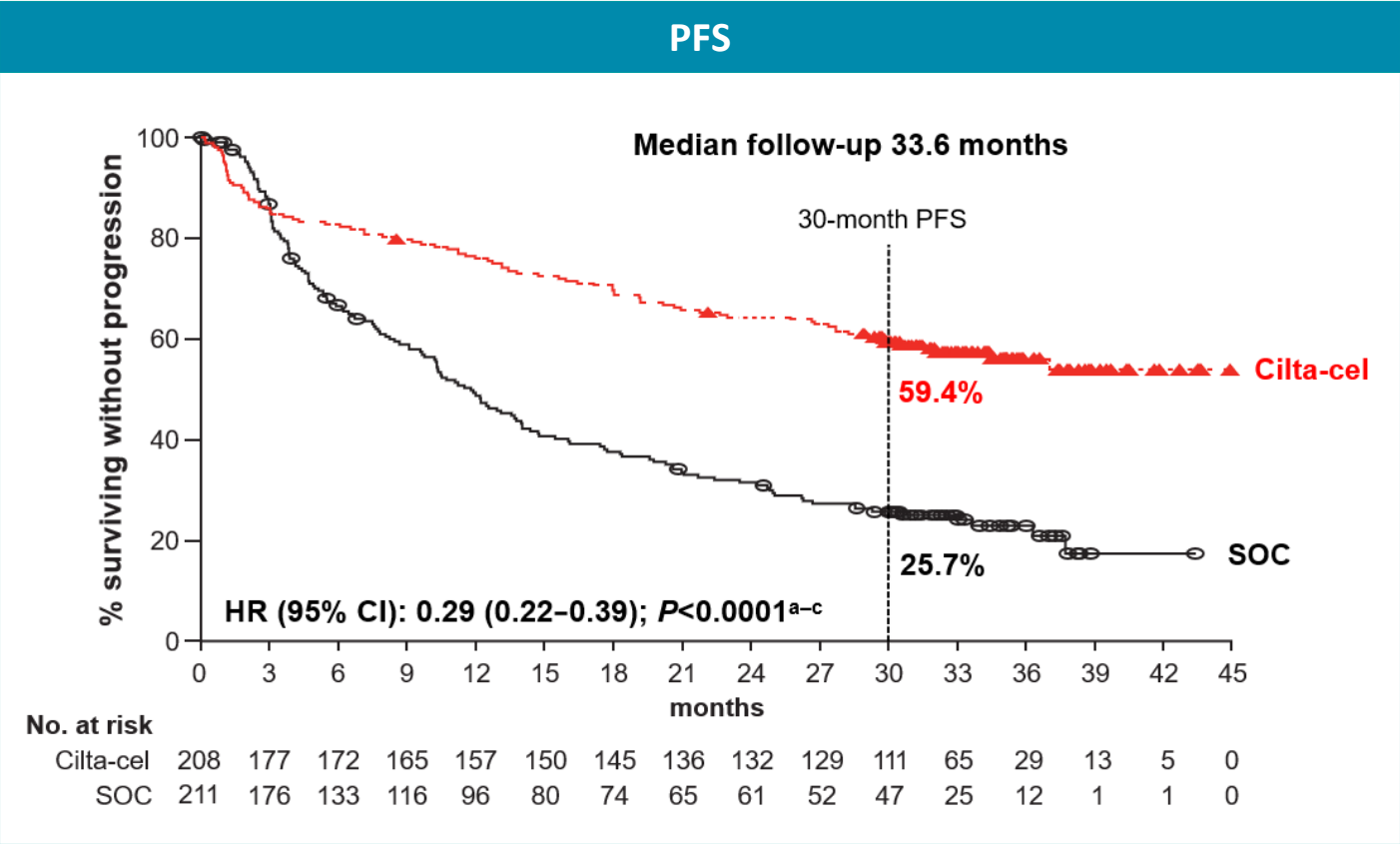


# CARTITUDE-1: Long-Term Survival Outcomes (≥5 Year)



# CARTITUDE-4: Cilta-Cel vs SOC in Len-Refractory RRMM

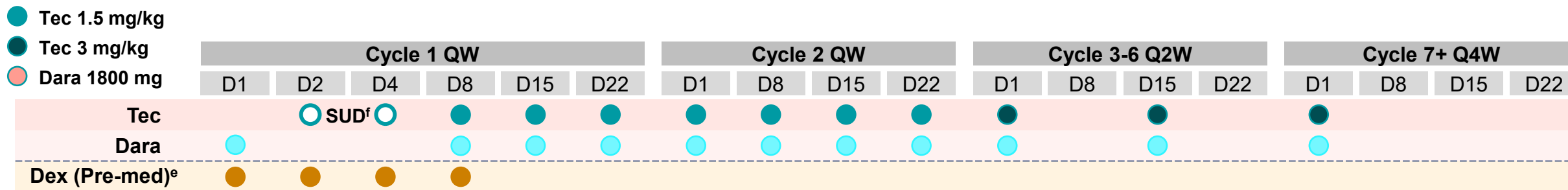
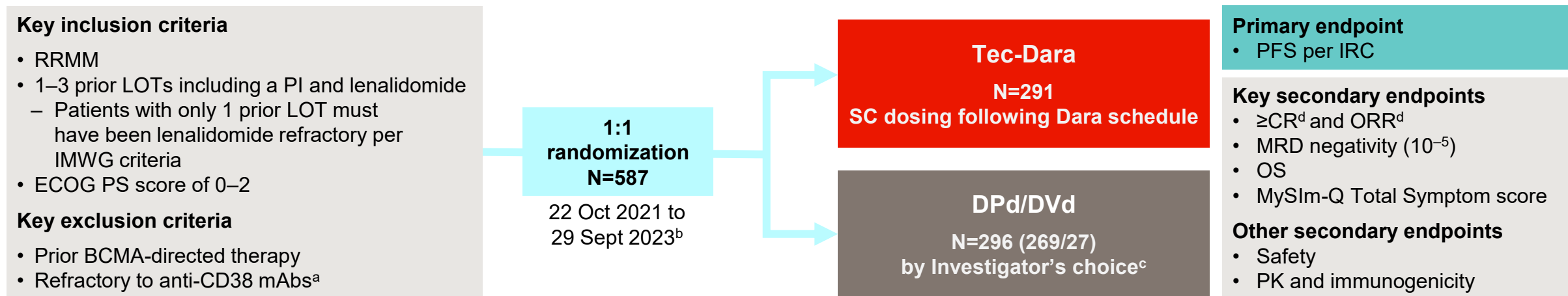
## PFS (ITT)



# Bispecific Antibodies in Late Relapse: Summary

| Bispecific Antibody       | Teclistamab <sup>1-3</sup>                                                   | Elranatamab <sup>4</sup>                                        | Talquetamab                                                                                    |                                                                                                                  |            |
|---------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------|
| Pivotal Study             | MajesTEC-1                                                                   | MagnetisMM-3<br>(BCMA-naïve cohort)                             | MonumentAL-1                                                                                   |                                                                                                                  |            |
| Target                    | BCMA                                                                         | BCMA                                                            | GPC5D                                                                                          |                                                                                                                  |            |
| Dosing & Frequency        | Step-up dosing D 1 and 4<br>(0.06 mg/kg and 0.3 mg/kg<br>SC)→1.5 mg/kg SC QW | Step-up dosing D 1 and 4<br>(12 mg and 32 mg SC→<br>76 mg SC QW | TCR Naive<br>Step-up dosing on D 1<br>and 4 (0.01 mg/kg and<br>0.06 mg/kg)→<br>0.4 mg/kg SC QW | TCR Naïve<br>Step-up dosing on Ds 1, 4,<br>and 7 (0.01 mg/kg, 0.06<br>mg/kg and 0.04 mg/kg)→<br>0.8 mg/kg SC Q2W | Prior TCR  |
| Patients, n               | 165                                                                          | 123                                                             | 143                                                                                            | 154                                                                                                              | 78         |
| Prior therapy             | BCMA-therapy naïve                                                           | BCMA-therapy naïve                                              | TCR naïve or pretreated cohorts                                                                |                                                                                                                  |            |
| Prior LOT, n              | 5 (2-14)                                                                     | 5 (2-22)                                                        | 6 (2-17)                                                                                       |                                                                                                                  |            |
| High-risk cytogenetics, % | 26                                                                           | 25                                                              | 29-31                                                                                          |                                                                                                                  |            |
| Median f/u, mo            | 30.4                                                                         | 28.4                                                            | 18.8                                                                                           | 12.7                                                                                                             | 14.8       |
| Overall response / ≥CR, % | 63 / 46                                                                      | 61 / 37                                                         | 74 / 33                                                                                        | 70 / 40                                                                                                          | 67 / 42    |
| mDOR, mo                  | 24                                                                           | NR                                                              | 9.5                                                                                            | 17.5                                                                                                             | N/A        |
| PFS, mo                   | 11                                                                           | 17                                                              | 7.5                                                                                            | 11.2                                                                                                             | 7.7        |
| OS                        | Median: 22 mo<br>30-mo: 42%                                                  | Median: 25 mo<br>15-mo: 56%                                     | Median: NR<br>24-mo: 61%                                                                       | Median: NR<br>24-mo: 67%                                                                                         | 24-mo: 57% |

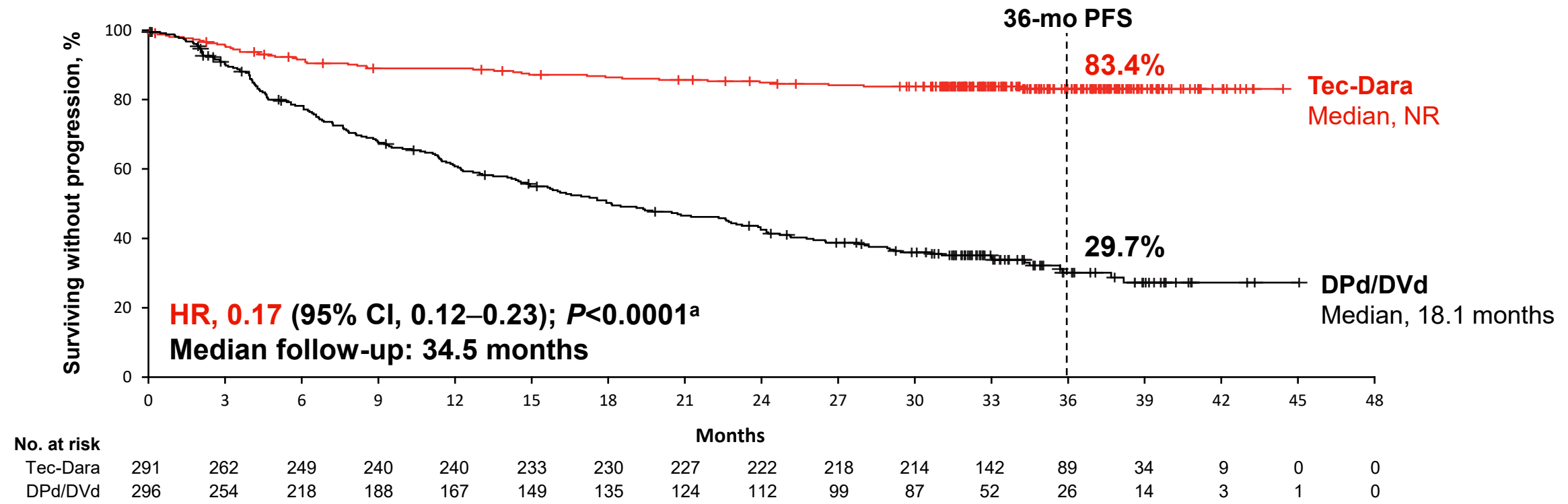
# MajesTEC-3: Phase 3 Study Design



**SC dosing aligned with Dara schedule, with monthly dosing after 6 cycles;  
steroid sparing after Cycle 1 Day 8**



# MajesTEC-3: PFS (Primary Endpoint)



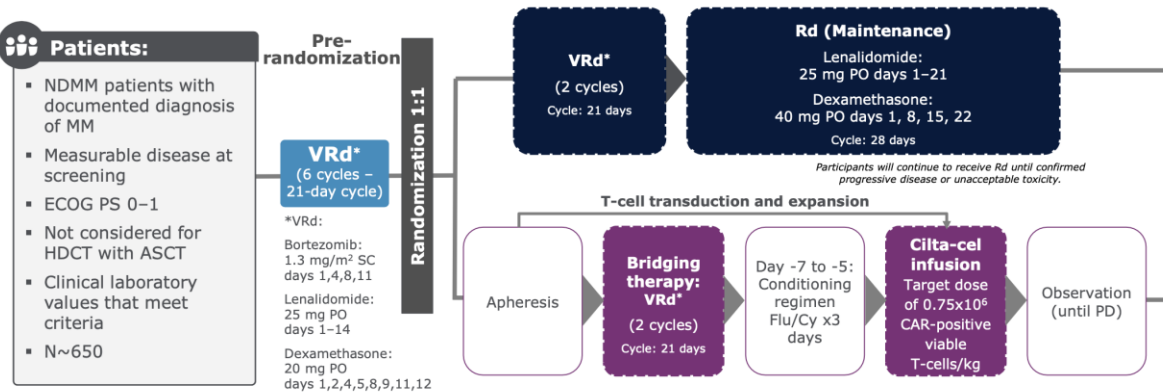
Tec-Dara significantly improved PFS, with a plateauing curve after ~6 months and >90% of patients progression-free at 6 months sustaining such a benefit at 3 years



# Cilta-Cel CAR T cells in Newly Diagnosed Multiple Myeloma

## Cilta-cel: CARTITUDE-5 (MMY3004) study design

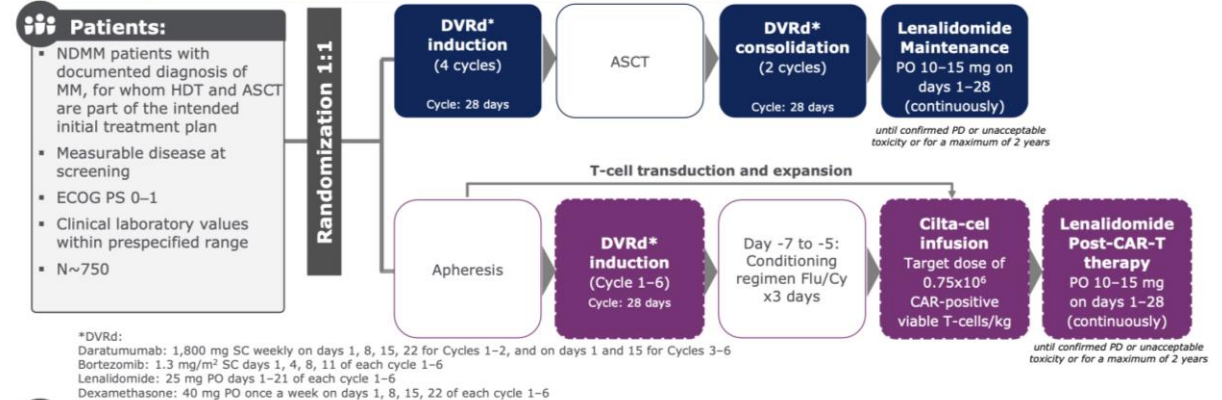
### Phase 3, Randomized, Open-Label Study



| Primary Outcome:                                      | Key Secondary Outcomes:                                                                                          |                                                                                                    |                                                                                      |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>PFS</li> </ul> | <ul style="list-style-type: none"> <li>Sustained MRD-negative CR</li> <li>MRD-negative CR at 9 months</li> </ul> | <ul style="list-style-type: none"> <li>Overall MRD-negative CR</li> <li>OS</li> <li>≥CR</li> </ul> | <ul style="list-style-type: none"> <li>TTNT</li> <li>PFS2</li> <li>Safety</li> </ul> |

## Cilta-cel: CARTITUDE-6 (MMY3005) study design

### Phase 3, Randomized, Open-Label Study

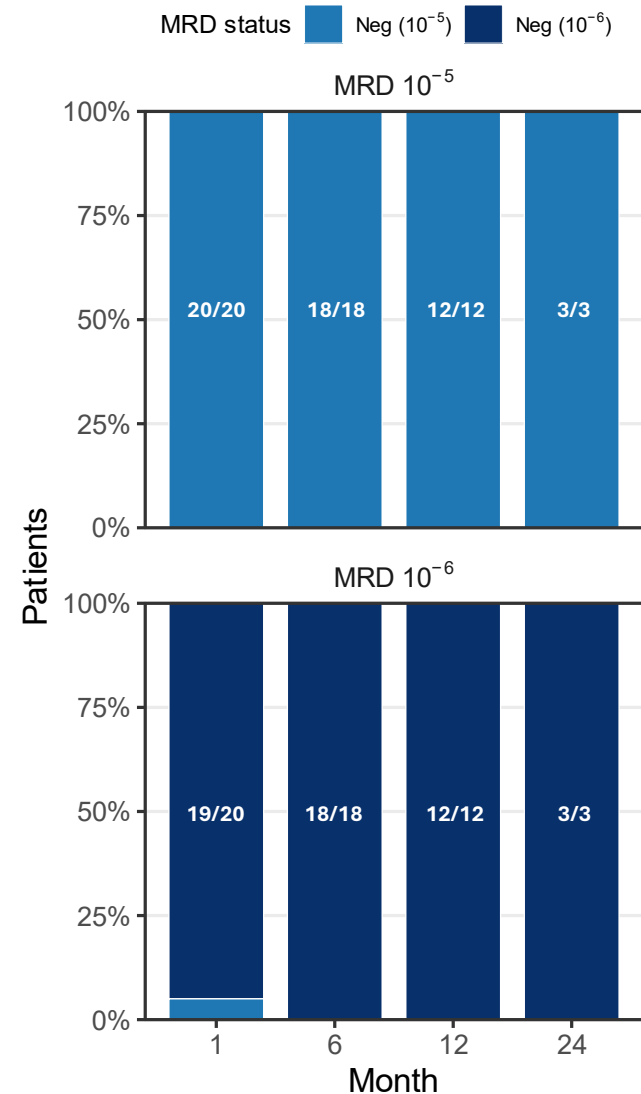


| Primary Outcomes:                                                                        | Key Secondary Outcomes:                                                                                                               |                                                                                                                                   |
|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>PFS</li> <li>Sustained MRD-negative CR</li> </ul> | <ul style="list-style-type: none"> <li>Overall response</li> <li>CR or better status</li> <li>MRD-negative CR</li> <li>AEs</li> </ul> | <ul style="list-style-type: none"> <li>Time to subsequent antimyeloma therapy</li> <li>PFS2</li> <li>OS</li> <li>HRQoL</li> </ul> |



# Ciltacabtagene Autoleucel in Patients with High-Risk Smoldering Myeloma: Results from the CAR-PRISM Trial

- At a median follow-up of 15.3 months, **all patients achieved MRD negativity at a sensitivity threshold of  $10^{-6}$  by NGS (100% MRD negativity rate).**
- The median time to MRD negativity was 1 month.
- All patients had MRD negativity at  $10^{-5}$  at month 1 and at  $10^{-6}$  at month 2 post-infusion.
- MRD negativity  $10^{-6}$  was **sustained** in subsequent assessments (months 3, 6, 12, and 24) through the data cutoff.



## Question 1

A 65-year-old male has an elevated total protein on routine laboratory evaluation. His CBC, renal function and electrolytes are normal, and he is asymptomatic. A serum protein electrophoresis and IFE identify an IgG kappa monoclonal gammopathy with an M spike of 3.5 gm/dl. He is referred to a hematologist. A bone marrow biopsy and aspirate demonstrate a population of kappa restricted plasma cells constituting 20% of the marrow cellularity. The serum free light chain ratio (kappa:lambda) is 5. A skeletal survey demonstrates no evidence of lytic bone lesions. This process is best classified as:

- A) Monoclonal gammopathy of undetermined significance (MGUS)
- B) Smoldering multiple myeloma (SMM)
- C) Multiple myeloma
- D) Amyloidosis
-  E) Waldenstrom macroglobulinemia

## Question 1

A 65-year-old male has an elevated total protein on routine laboratory evaluation. His CBC, renal function and electrolytes are normal, and he is asymptomatic. A serum protein electrophoresis and IFE identify an IgG kappa monoclonal gammopathy with an M spike of 3.5 gm/dl. He is referred to a hematologist. A bone marrow biopsy and aspirate demonstrate a population of kappa restricted plasma cells constituting 20% of the marrow cellularity. The serum free light chain ratio (kappa:lambda) is 5. A skeletal survey demonstrates no evidence of lytic bone lesions. This process is best classified as:

A) Monoclonal gammopathy of undetermined significance (MGUS)

**B) Smoldering multiple myeloma (SMM)**

C) Multiple myeloma

D) Amyloidosis

E) Waldenstrom's macroglobulinemia

- This patient has an M spike of greater than 3 gm/dl and has greater than 10% plasma cells on bone marrow biopsy but does not have any end organ damage or myeloma defining events. This is consistent with smoldering multiple myeloma.
- MGUS would require an M spike of less than 3 gm/dl and less than 10% plasma cells on bone marrow examination.
- Multiple myeloma would require a plasma cell disorder and at least one of the following: 1 or more myeloma-defining events;  $\geq 1$  CRAB feature
- Waldenstrom macroglobulinemia is associated with elevated IgM, not IgG, and lymphoplasmacytic lymphoma.
- The patient has no end organ damage or biopsy evidence to suggest amyloidosis.



## Question 2

What is the true about management of multiple myeloma?

- A) Bispecific antibodies involve apheresis and manufacturing of T cells prior to administration
- B) A single infusion of CAR T-cells with ciltacabtagene autemcelt (Cilta-cel) can lead to long term durable responses beyond 5 years in one-third of patients with relapsed multiple myeloma
- C) Teclistamab and daratumumab is approved for patients with AL amyloidosis
- D) Autologous stem cell transplant improves overall survival in myeloma in the current era



## Question 2

What is the true about management of multiple myeloma?

- A) Bispecific antibodies involve apheresis and manufacturing of T cells prior to administration
- B) A single infusion of CAR T cells with cilta cel can lead to long term durable responses beyond 5 years in one-third of patients with relapsed and refractory multiple myeloma**
- C) Teclistamab and daratumumab are only approved for patients with AL amyloidosis
- D) Autologous stem cell transplant improves overall survival in the current era

**In the CARTITUDE-1 trial, single infusion of cilta cel lead to durable response beyond 5 year in 1/3 of patients**



# MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

- Significant advances in management of newly diagnosed multiple myeloma with marked improvement in progression-free and overall survival
- Quadruplet-based induction therapy is the standard of care in both transplant-eligible and non-eligible patients
- Role of stem cell transplantation continues to evolve and is now more individualized depending on depth of response and underlying risk of disease
- MRD-adaptive therapy will continue to drive treatment decisions in the future
- T cell immunotherapies show tremendous promise in earlier lines and has the potential to change practice in the future





# Thank You



**Dana-Farber**  
Cancer Institute

# REFERENCES

Embedded in presentation

