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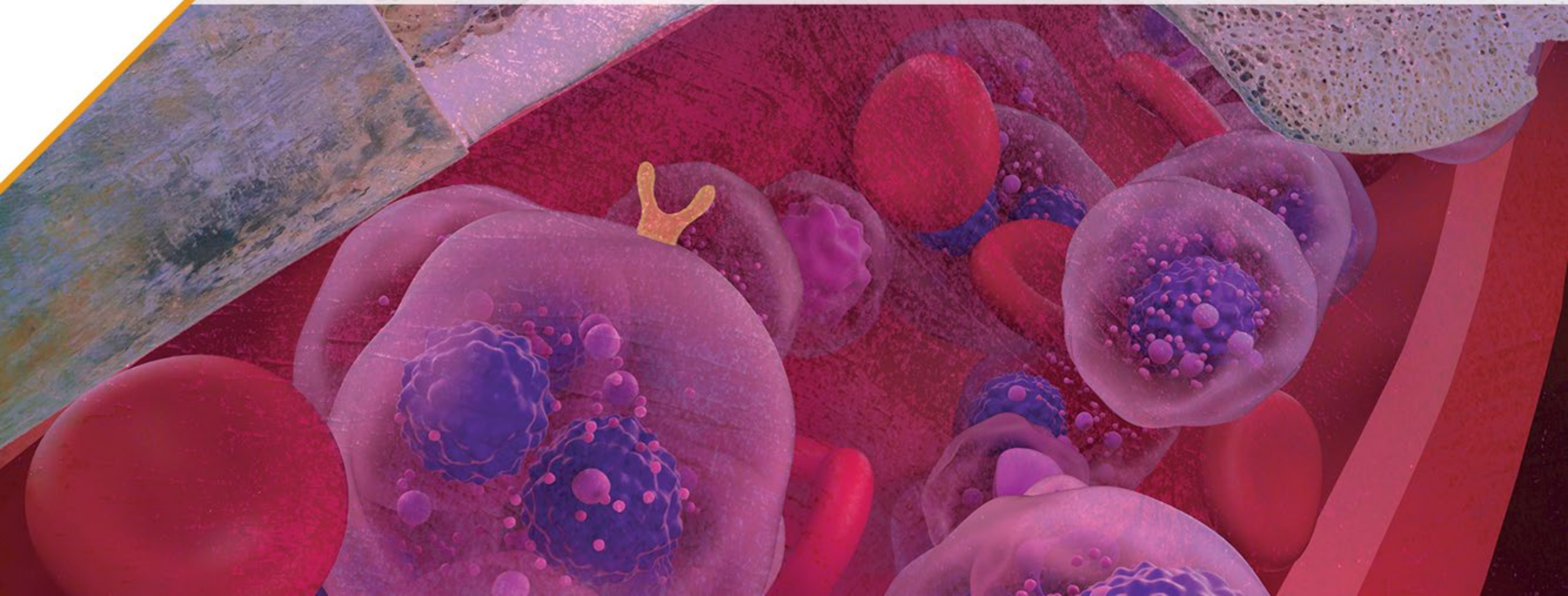
Redefining Treatment at First Relapse In RRMM:

Exploring BCMA-Targeted Therapies



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Learning Objectives

Upon completion of this activity, participants should be better able to:

1. Identify the ongoing unmet need in patients with multiple myeloma (MM) who relapse after primary therapy
2. Analyze the evidence- and guideline-based treatment options with BCMA-directed therapies for patients with MM who relapse after primary therapy
3. Develop patient selection and sequencing strategies with BCMA-directed therapies for patients with MM who relapse after primary therapy
4. Incorporate interprofessional approaches to optimizing safety with BCMA-directed therapies for patients with MM who relapse after primary therapy

Management of Early Relapse in MM

Sagar Lonial, MD
Professor and Chair

Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

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General Principles

- Duration of initial response defines biology
- Triplet (two active classes + dexamethasone) preferred over doublet
  - **At least one drug from a non-refractory class**
- Consider PS, age, and comorbidities when selecting drug/doses
- Take into account prior toxicities/residual toxicities
- Treat to maximum response and maintain on one drug until progression or tolerability

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PS, performance status.

Definition of R/R MM

Relapsed/refractory multiple myeloma

1. Meets IMWG criteria for PD
   a) R/R MM: progression on therapy in patients who obtain ≥ minor response or progress within 60 days of most recent therapy
   b) Primary refractory MM: progression on therapy without having achieved at least minor response
   c) Relapsed MM: meets IMWG criteria for PD but does not fit definition of R/R or primary refractory MM

IMWG Criteria for PD

≥25% increase from nadir in:

- Serum or urine M-protein (absolute increase ≥0.5 g/dL and ≥200 mg/24 hrs, respectively), or
- Difference between involved and uninvolved FLC levels (absolute increase > 100 mg/L), or
- Bone marrow plasma cells (absolute increase ≥10%), or
- New lesions (≥50% increase in SPD of >1 lesion or longest diameter of previous lesion >1 cm in short axis), or
- Circulating plasma cells (≥50% increase [minimum 200 cells/μL] if only measure of disease)

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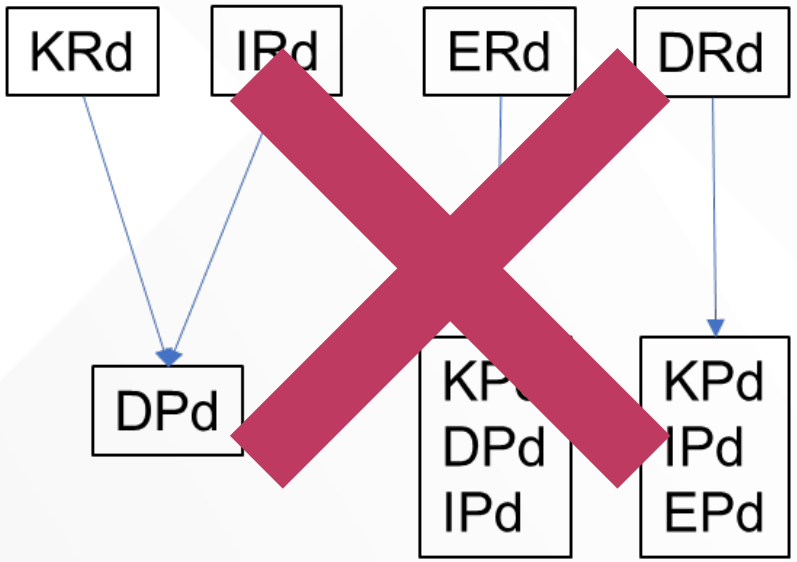
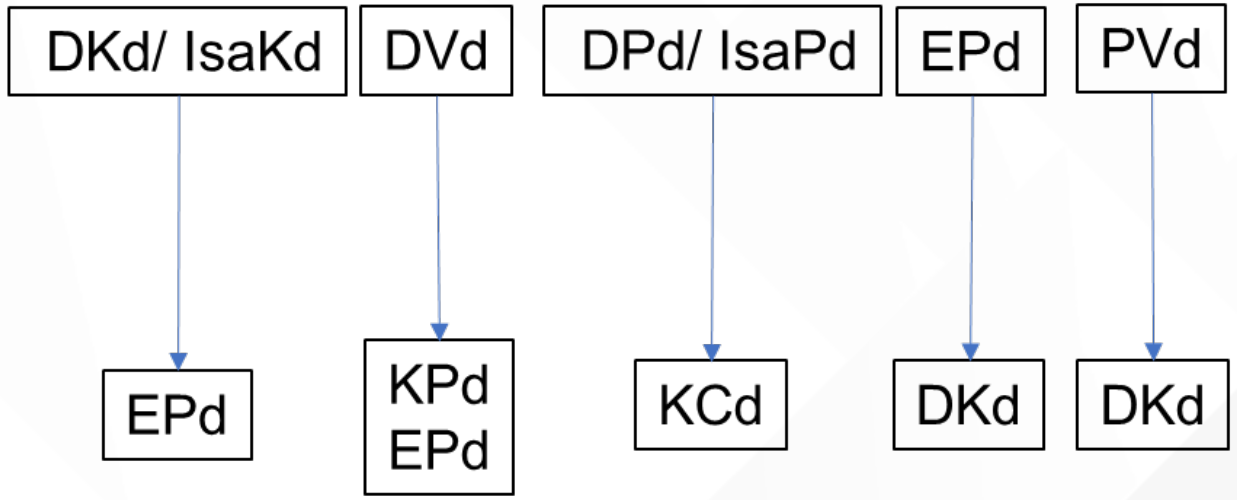
IMWG, International Myeloma Working Group; MM, multiple myeloma; PD, progressive disease; R/R, relapsed/refractory; SPD, sum of products of the two longest perpendicular diameters.
Kumar S, et al. *Lancet Oncol.* 2016;17(8):e328-e346.

Approach to First Relapse – and Later

Not refractory to Len at 1st relapse



Refractory to Len at 1st relapse

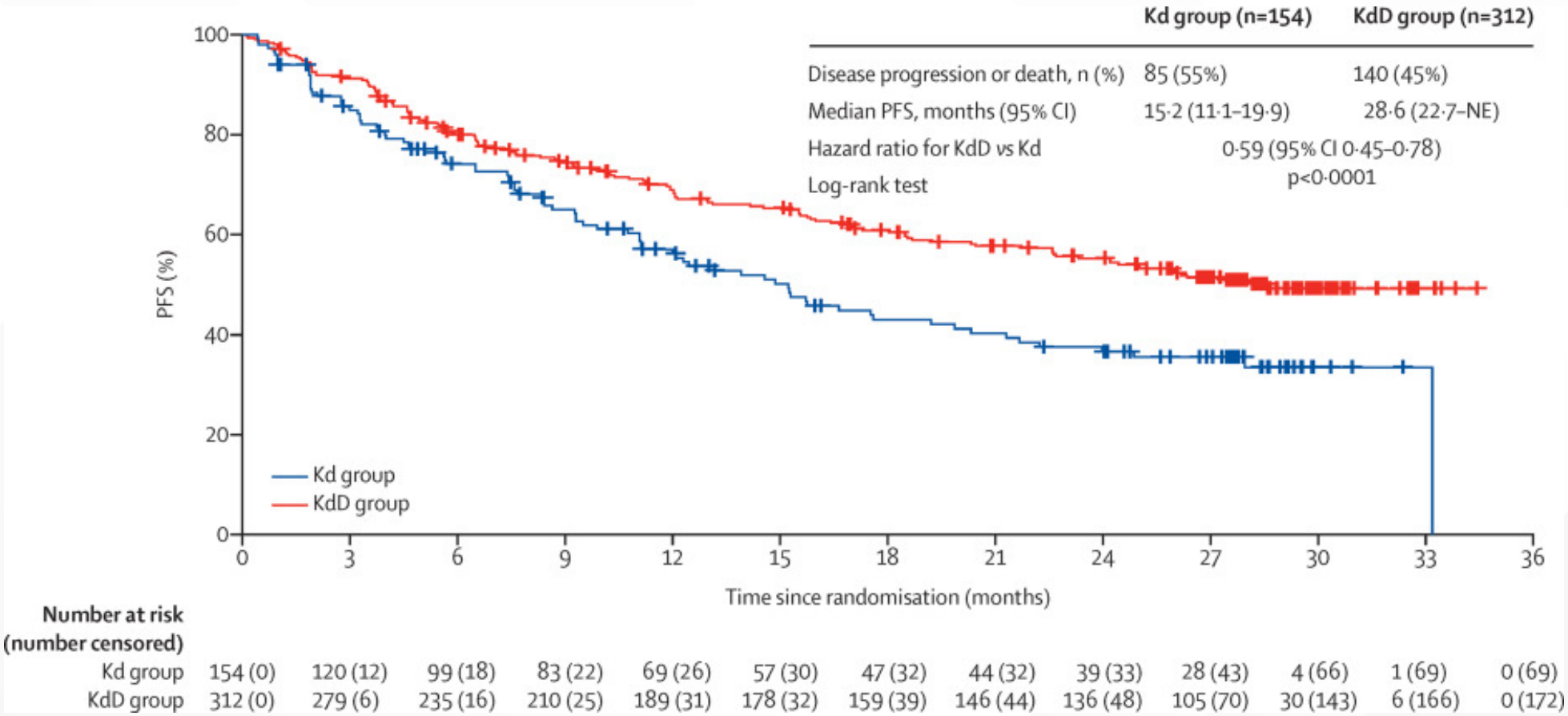


Clinical trials OR repeat combinations of agents most remotely used

Overall: while triplets are preferred, lower dose triplets or doublets can be used in frail and older patients

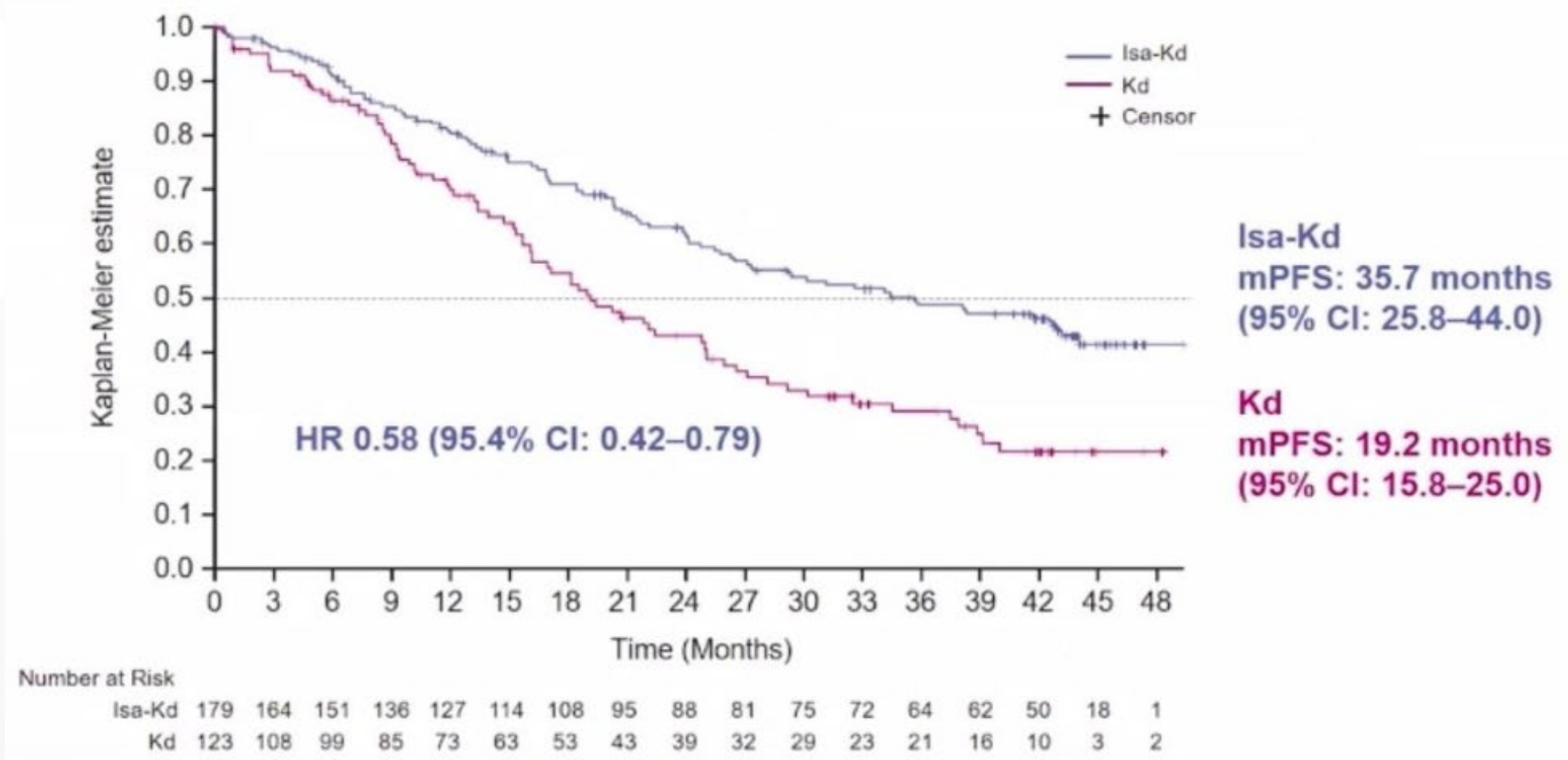
DKd, daratumumab, carfilzomib, dexamethasone; DPd, daratumumab, pomalidomide, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; EPd, elotuzumab, pomalidomide, and dexamethasone; ERd, elotuzumab, lenalidomide, dexamethasone; IPd, ixazomib, pomalidomide, dexamethasone; IRd, ixazomib, lenalidomide, dexamethasone; IsaKd, isatuximab, carfilzomib, dexamethasone; IsaPd, isatuximab, pomalidomide, dexamethasone; KCd, carfilzomib, cyclophosphamide, dexamethasone; KPd, carfilzomib, pomalidomide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; Len, lenalidomide; PVd, pomalidomide, bortezomib, dexamethasone.

CANDOR: Dara-Kd Improved PFS vs Kd



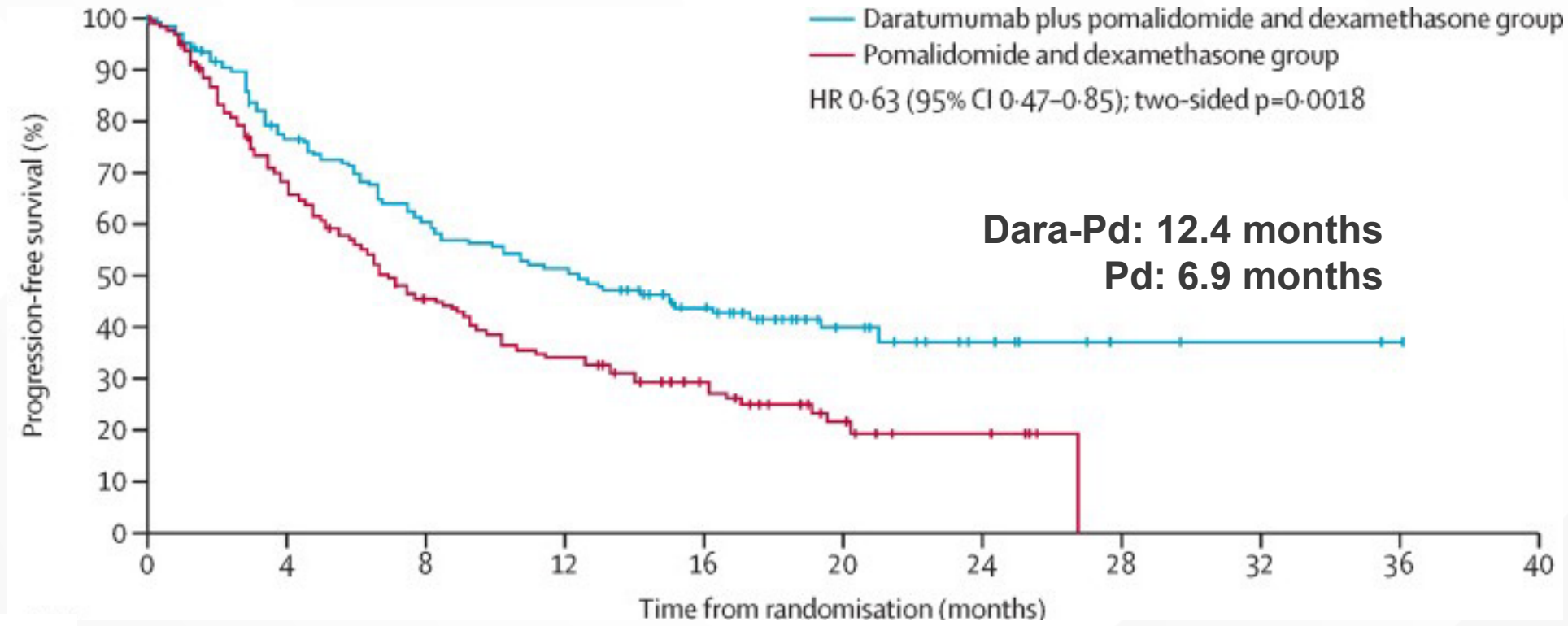
Dara-Kd/KdD, daratumumab, carfilzomib, dexamethasone; Kd, carfilzomib, dexamethasone; NE, not established; PFS, progression-free survival.
Usmani SZ, et al. *Lancet Oncol.* 2022;23(1):65-76.

IKEMA: Isa-Kd Improved PFS vs Kd



IsaKd, isatuximab, carfilzomib, dexamethasone; Kd, carfilzomib, dexamethasone; mPFS, median progression-free survival; PFS, progression-free survival.
Moreau P, et al. COMy 2022. Abstract VP5-2022.

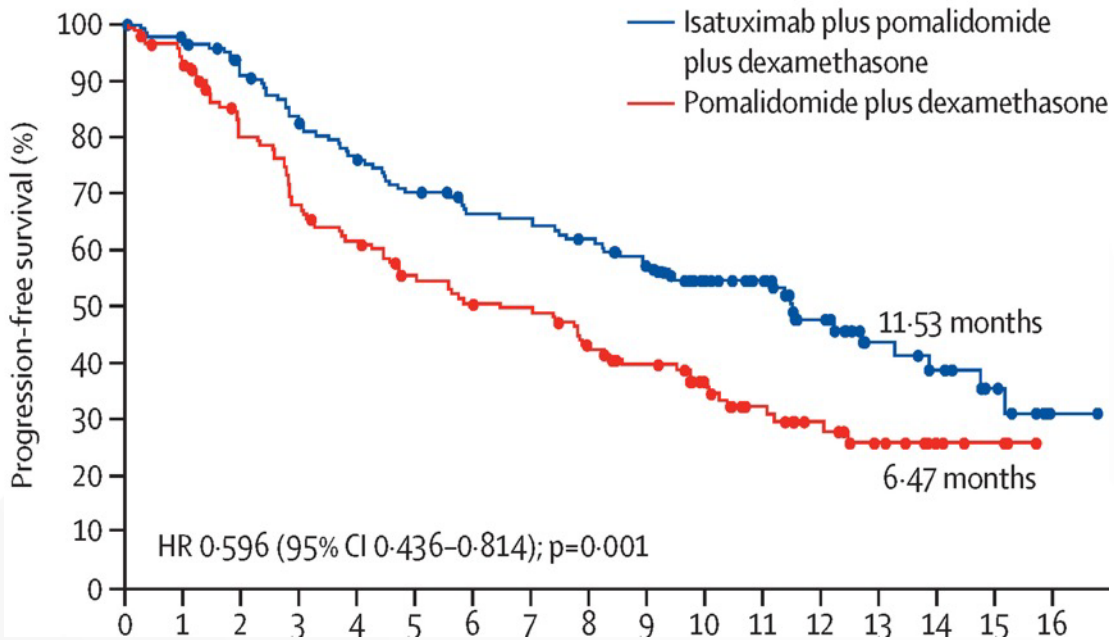
APOLLO: Dara-Pd Improved PFS vs Pd

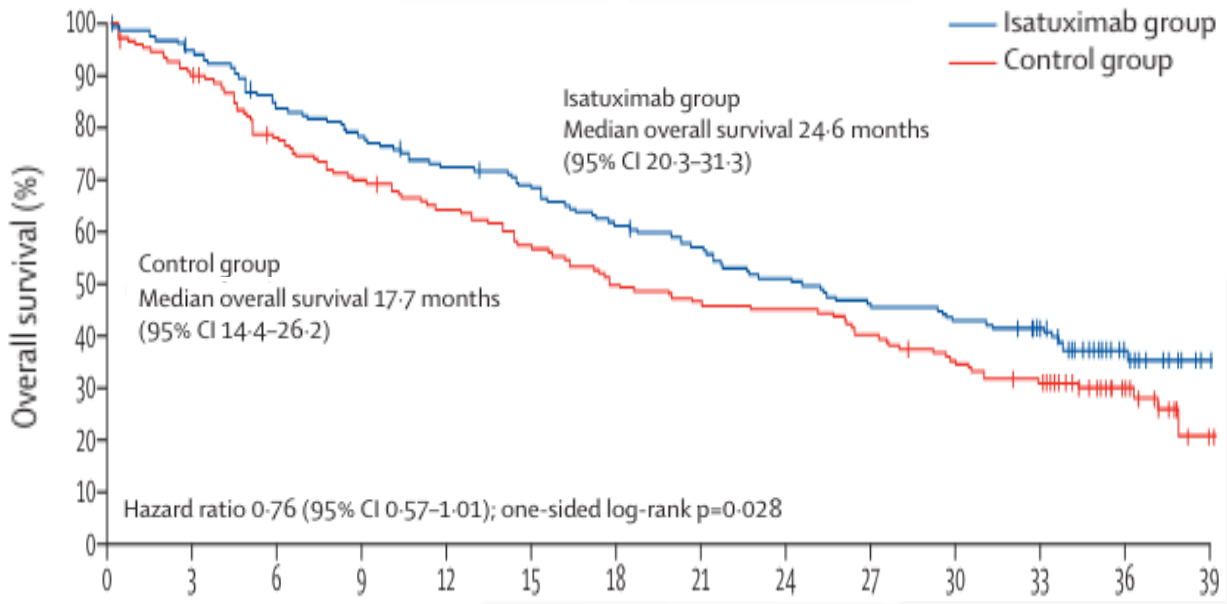


Median PFS among patients refractory to lenalidomide was 9.9 months for Dara-Pd and 6.5 months for Pd

Dara-Pd, daratumumab, pomalidomide, dexamethasone; Pd, pomalidomide, dexamethasone; PFS, progression-free survival.
Dimopoulos MA, et al. *Lancet Oncol.* 2021;22(6):801-812.

ICARIA-MM: Isa-Pd Improved PFS vs Pd





IsaPd, isatuximab, pomalidomide, dexamethasone; Pd, pomalidomide, dexamethasone; PFS, progression-free survival.
Attal M, et al. *Lancet.* 2019;394(10214):2096-2107. Richardson PG, et al. *Lancet Oncol.* 2022;23(3):416-427.

Minimal Residual Disease (MRD) Status in MM

- Lack of uniformity in MRD testing, timing of MRD assessments, use of MRD status–based treatment thresholds, and types of interventions have hindered application of trial findings to clinical practice
- MRD assessment was incorporated into IMWG uniform response criteria for MM in 2016 after multiple prospective clinical trials established the power of next-generation flow cytometry and NGS as effective techniques to measure depth of remission
  - **IMWG defines MRD negativity as the absence of clonal plasma cells on bone marrow aspirate with a minimum test sensitivity to detect 1 in 10^5 nucleated cells (10^{-5} threshold)**
- MRD negativity is associated with prolonged PFS and OS in newly diagnosed and R/R settings
  - MRD status is a surrogate for PFS and OS
- Available data suggest that highly sensitive MRD tests may be used in a risk-adapted approach to define patients with MM at imminent risk of relapse, those needing novel therapy approaches to deepen remission status, and defining treatment-free periods
- In recent clinical trials, MRD has become a key endpoint, reflecting its growing importance in evaluating treatment efficacy

In 2024, the FDA's Oncologic Drugs Advisory Committee concluded that considering the comprehensive available data, there is sufficient support for utilizing MRD as an endpoint for accelerated approval of new treatments targeting patients with MM

IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

ASCO Daily News. https://dailynews.ascopubs.org/do/minimal-residual-disease-status-multiple-myeloma-can-its-use-reveal-path-cure. Bertamini L, et al. *Curr Hematol Malig Rep*. 2021;16(2):162-171. OncLive.com. https://www.onclive.com/view/fda-s-odac-recognizes-mrd-as-an-accepted-end-point-for-accelerated-approval-in-multiple-myeloma. Meeting of the Oncologic Drugs Advisory Committee (ODAC). https://www.youtube.com/watch?v=pooME9gMaL0. Oncologic Drugs Advisory Committee (ODAC) Meeting. https://www.fda.gov/media/177652/download. Kumar S, et al. *Lancet Oncol*. 2016;17(8):e328-e346. Munshi NC, et al. *Blood Adv*. 2020;4(23):5988-5999. Costa LJ, et al. *Leukemia*. 2021;35(1):18-30.

Common Minimal Residual Disease Assessment Techniques

Technique	Source of specimen	Method	Level of detection	Reference	Limitation
MFC	Bone marrow aspirate	Uses multiple surface and cytoplasmic markers (colors) to identify phenotypically aberrant clonal plasma cells	Depends on the number of markers tested	Rawstron et al[1]	Cannot be done on stored sample
(ASO)-qPCR	Bone marrow aspirate	Identify clonal MM plasma cell-specific *IGH* gene rearrangements	10^{-5}	Bakkus et al[2]	Requires patient-specific primers
NGF	Bone marrow aspirate	Standardized MFC with automate readouts	$> 10^{-5}$	Flores-Montero et al[3]	Cannot be done on stored sample
NGS	Bone marrow aspirate	DNA is amplified using primers designed for IGH-VDJH, IGH-DJH, or IGK and sequenced to determine the presence and quantity of clonal DNA sequence	$> 10^{-5}$	Ladetto et al[4]	Dominant sequence might not be identified in <10% of cases
LC MALDI-TOF or mass-fix mass spectrometry	Serum	M-protein detection by scanning the overall mass distribution of denatured intact immunoglobulin LCs	< 0.01 g/dL	Mills et al[5]	Variable resolution can affect level of detection
Clonotypic mass spectrometry	Serum	Ig trypsin digestion and detection of peptides specific to the M-protein antigen-binding region, also called the complementarity-determining region	0.001 g/L	Bergen et al[6]	Identifying unique clonotypic peptide depends on sequencing and might be difficult in some cases
BloodFlow	Peripheral blood	Immunomagnetic enrichment of circulating plasma cells followed by NGF	10^{-8}	Notarfranchi et al[7]	Requires 50 mL peripheral blood sample

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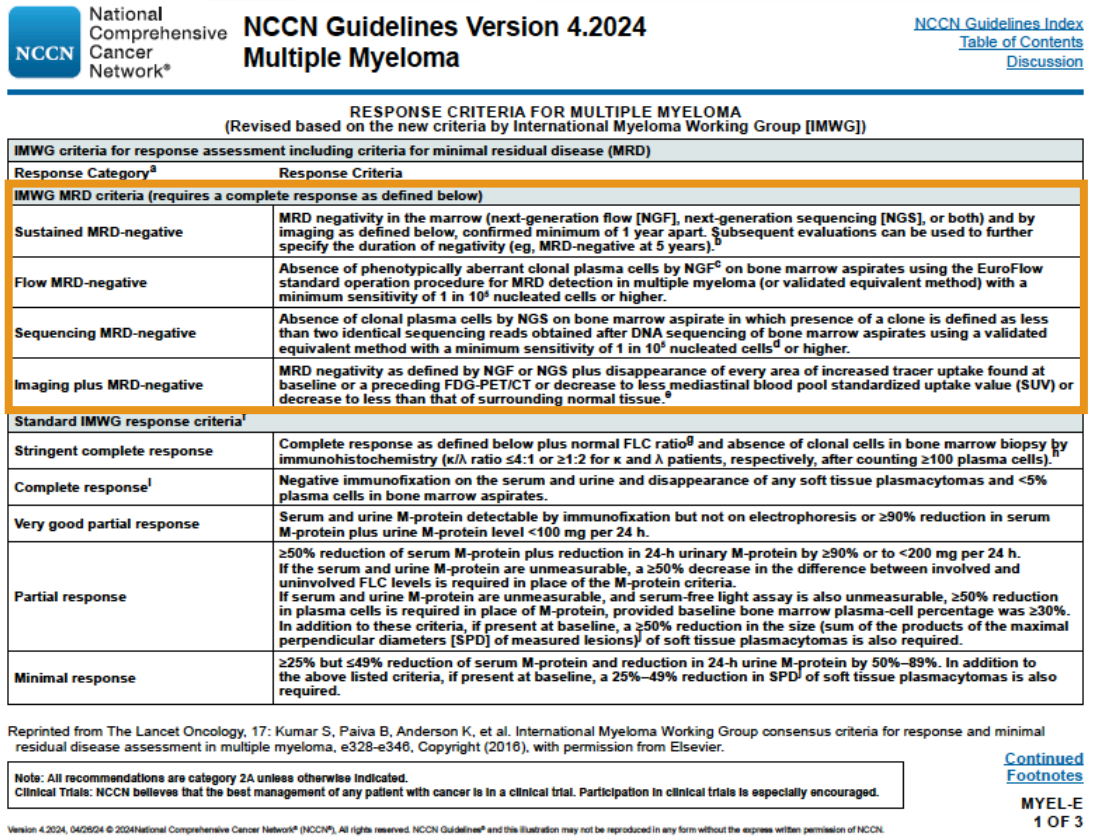
(ASO)-qPCR, allele-specific oligonucleotide quantitative polymerase chain reaction; LC MALDI-TOF, light chain matrix-assisted laser desorption/ionization-time-of-flight; MFC, multiparametric flow cytometry; MM, multiple myeloma; NGF, next-generation flow cytometry; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival.

ASCO Daily News. https://dailynews.ascopubs.org/do/minimal-residual-disease-status-multiple-myeloma-can-its-use-reveal-path-cure. Bertamini L, et al. *Curr Hematol Malig Rep*. 2021;16(2):162-171.
1. Rawstron AC, et al. *J Clin Oncol*. 2013;31(20):2540-2547. 2. Bakkus MH, et al. *Br J Haematol*. 2004;126(5):665-674. 3. Flores-Montero J, et al. *Leukemia*. 2017;31(10):2094-2103. 4. Ladetto M, et al. *Biol Blood Marrow Transplant*. 2000;6(3):241-253. 5. Mills JR, et al. *Clin Chem*. 2016;62(10):1334-1344. 6. Bergen HR III, et al. *Clin Chem*. 2016;62(1):243-251. 7. Notarfranchi L, et al. *Blood*. 2022;140(suppl 1):2095-2097.

Assessing Response After Primary Therapy: NCCN Guidelines and IMWG Consensus Criteria



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NCCN Guidelines Version 4.2024
Multiple Myeloma

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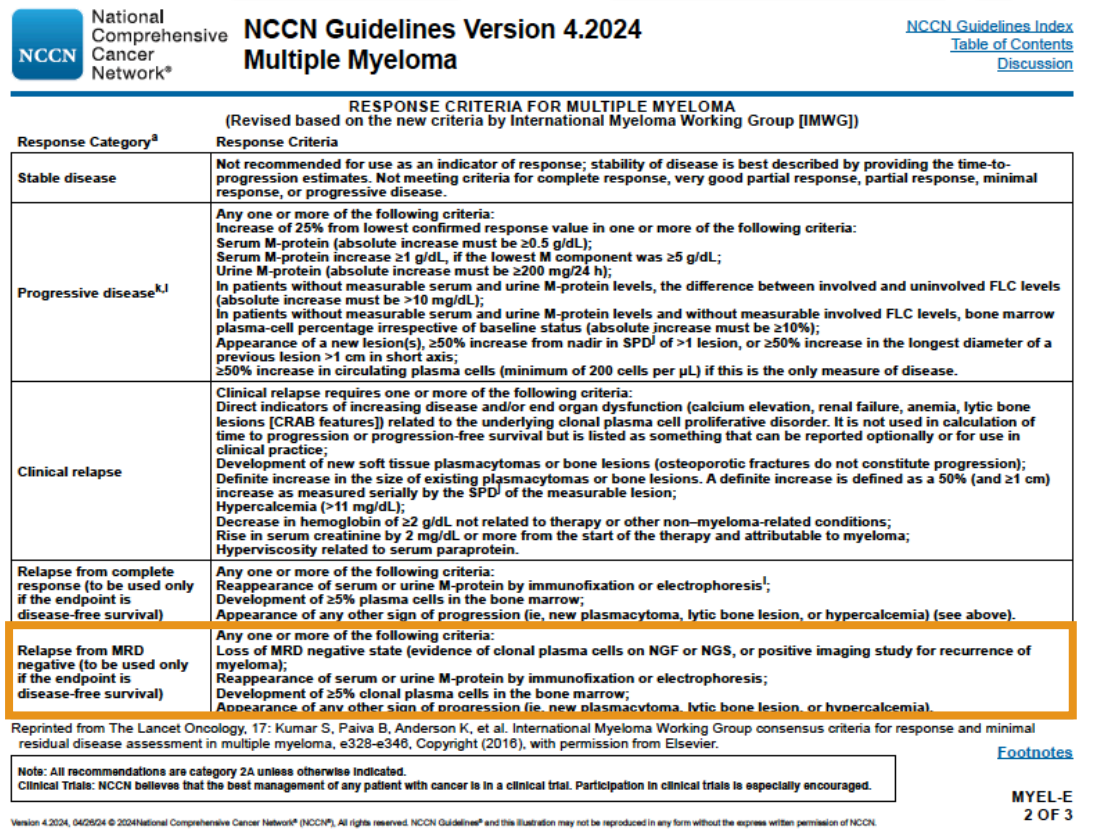
RESPONSE CRITERIA FOR MULTIPLE MYELOMA
(Revised based on the new criteria by International Myeloma Working Group [IMWG])

IMWG criteria for response assessment including criteria for minimal residual disease (MRD)	
Response Category[a]	**Response Criteria**
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).[b]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[c] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10^5 nucleated cells[d] or higher.
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding FDG-PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue.[e]
Standard IMWG response criteria[f]	
Stringent complete response	Complete response as defined below plus normal FLC ratio[g] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).[h]
Complete response[i]	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h.
Partial response	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)[j] of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a 25%–49% reduction in SPD[j] of soft tissue plasmacytomas is also required.

Reprinted from The Lancet Oncology, 17: Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328-e346, Copyright (2016), with permission from Elsevier.

Continued
Footnotes

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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RESPONSE CRITERIA FOR MULTIPLE MYELOMA
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Response Category[a]	Response Criteria
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive disease[k,l]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD[j] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[j] of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non–myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein.
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis[i]; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia) (see above).
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).

Reprinted from The Lancet Oncology, 17: Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328-e346, Copyright (2016), with permission from Elsevier.

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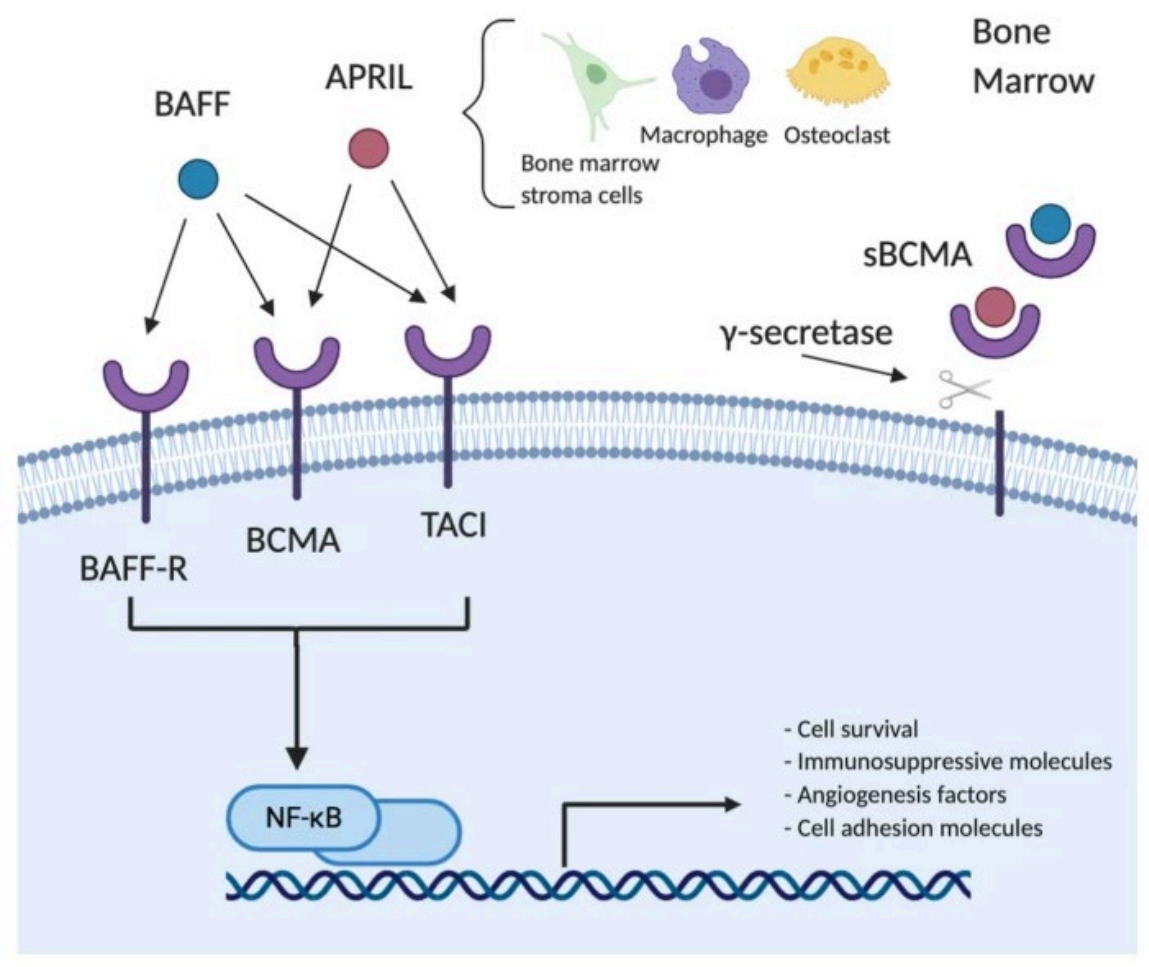
IMWG, International Myeloma Working Group; MRD, minimal residual disease; NCCN, National Comprehensive Cancer Network.

NCCN Guidelines. Multiple Myeloma (Version 4.2024). NCCN.org. Kumar S, et al. *Lancet Oncol*. 2016;17(8):e328-e346.

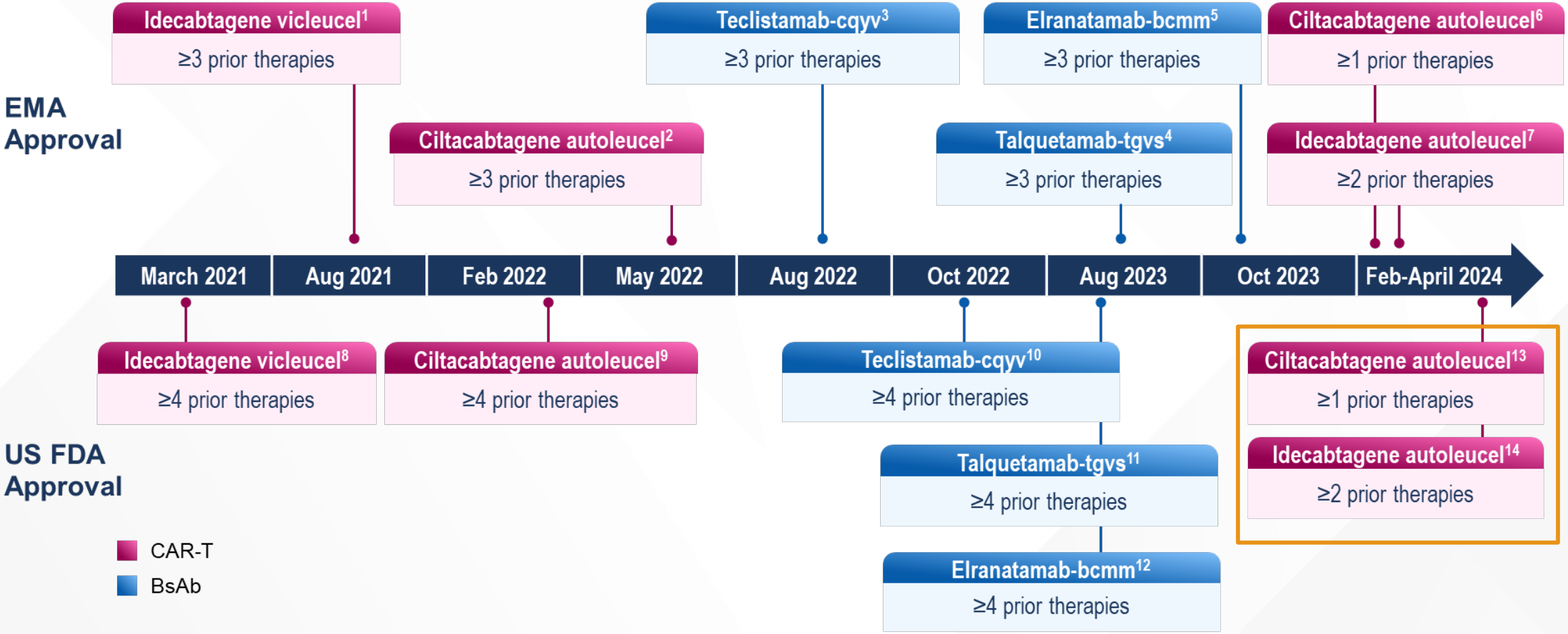
BCMA Signaling Pathway



APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; BCMA, B cell maturation antigen; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

Yu B, et al. *J Hematol Oncol.* 2020;13(1):125.

Recent Immunotherapy Advancements in R/R MM



BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; EMA, European Medicines Agency; FDA, Food and Drug Administration; MM, multiple myeloma; R/R, relapsed/refractory.

1. Abecma. Summary of product characteristics. Bristol-Myers Squibb; 2024. 2. Carvykti. Summary of product characteristics. Janssen; 2023. 3. Tecvayli. Summary of product characteristics. Janssen; 2024. 4. Talvey. Summary of product characteristics. Janssen; 2024. 5. Elrexfio. Summary of product characteristics. Pfizer; 2024. 6. Carvykti. Summary of product characteristics. Janssen; 2024. 7. Abecma. Summary of product characteristics. Bristol-Myers Squibb; 2024. 8. Abecma. Prescribing information. Bristol-Myers Squibb; 2024. 9. Carvykti. Prescribing information. Janssen; 2023. 10. Tecvayli. Prescribing information. Janssen; 2023. 11. Talvey. Prescribing information. Janssen; 2023. 12. Elrexfio. Prescribing information. Pfizer; 2023. 13. Carvykti. Prescribing information. Janssen; 2024. 14. Abecma. Prescribing information. Bristol-Myers Squibb; 2024.

KarMMa-3: Study Design (NCT03651128)

KarMMa-3

Key inclusion criteria

- 2-4 previous regimens (including an IMiD agent, PI, and daratumumab)
- Refractory to the last regimen

Stratification factors

- Age (<65 vs ≥65 years)
- Number of previous regimens (2 vs 3 or 4)
- High-risk cytogenetics (yes vs no/unknown)

R 2:1

PFS analysis[a]

Leukapheresis

LDC

Ide-cel
n = 254

Optional bridging therapy ≤1 cycle,[b] min 14 days of washout

Single ide-cel infusion 150 to 450 x 10^6 CAR+ T cells
n = 225

PFS follow-up; 3-month safety follow-up

Survival follow-up

Standard regimens (DPd, DVd, IRd, Kd, or EPd)
n = 132

Standard regimens Continuous treatment until PD, unacceptable toxicity, or consent withdrawal
n = 126

Ide-cel crossover therapy allowed after confirmed PD

Objectives

Endpoints

Primary endpoints

- PFS by IRC

Key secondary endpoints

- ORR, OS

Other secondary endpoints

- CRR, DOR, MRD negative CR, PFS2
- Safety

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[a]Time from randomization to the first occurrence of disease progression or death from any cause according to IMWG criteria. [b]Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as bridging.
CR, complete response; CRR, complete response rate; DOR, duration of response; DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; EPd, elotuzumab, pomalidomide, dexamethasone; IMiD, immunomodulatory drugs; IRC, Independent Response Committee; IRd, ixazomib, lenalidomide, dexamethasone; Kd, carfilzomib, dexamethasone; LDC, lymphodepleting chemotherapy; min, minimum; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS2, progression-free survival on next line of therapy; PI, proteasome inhibitor; R, randomization.
Rodríguez-Otero P, et al. ASH 2023. Abstract 1028. ClinicalTrials.gov identifier: NCT03651128.

KarMMa-3: Baseline Characteristics

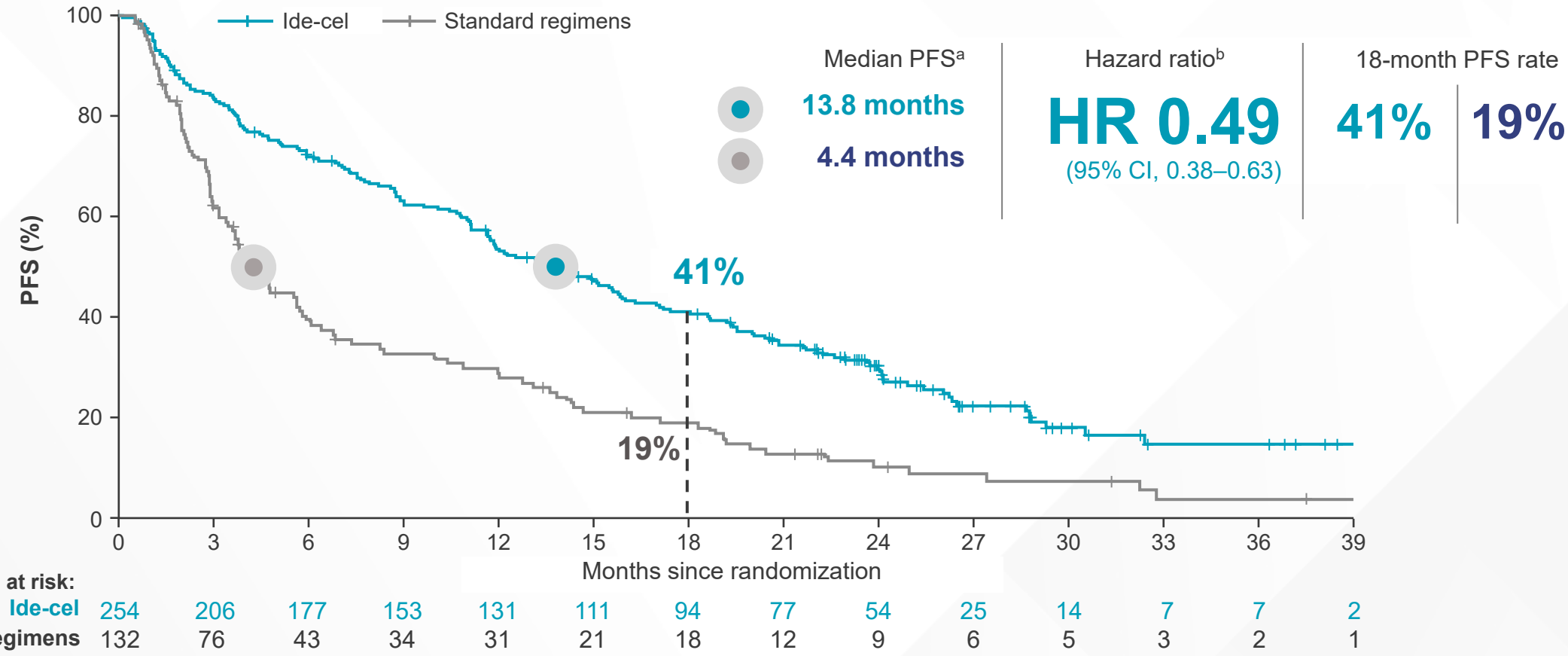
Characteristic	Ide-cel (n = 254)	Standard regimens (n = 132)
Median (range) age, years	63 (30–81)	63 (42–83)
Median (range) time from diagnosis to screening, years	4.1 (0.6–21.8)	4.0 (0.7–17.7)
Previous autologous HSCT	214 (84)	114 (86)
R-ISS disease stage		
I	50 (20)	26 (20)
II	150 (59)	82 (62)
III	31 (12)	14 (11)
EMP	61 (24)	32 (24)
High tumor burden[a]	71 (28)	34 (26)
High-risk cytogenetics[b]	166 (65)	82 (62)
del(17p)	66 (26)	42 (32)
t(4;14)	43 (17)	18 (14)
t(14;16)	8 (3)	4 (3)
1q gain/amplification	124 (49)	51 (39)
Ultra-high–risk cytogenetics[c]	67 (26)	29 (22)
Median (range) time to progression on last prior antimyeloma therapy, months	7.1 (0.7–67.7)	6.9 (0.4–66.0)
Daratumumab refractory	242 (95)	123 (93)
Triple-class–refractory[d]	164 (65)	89 (67)

Baseline characteristics were generally balanced between treatment arms

Overall, 66% of patients had triple-class refractory RRMM and 95% were daratumumab refractory, indicating a difficult-to-treat patient population

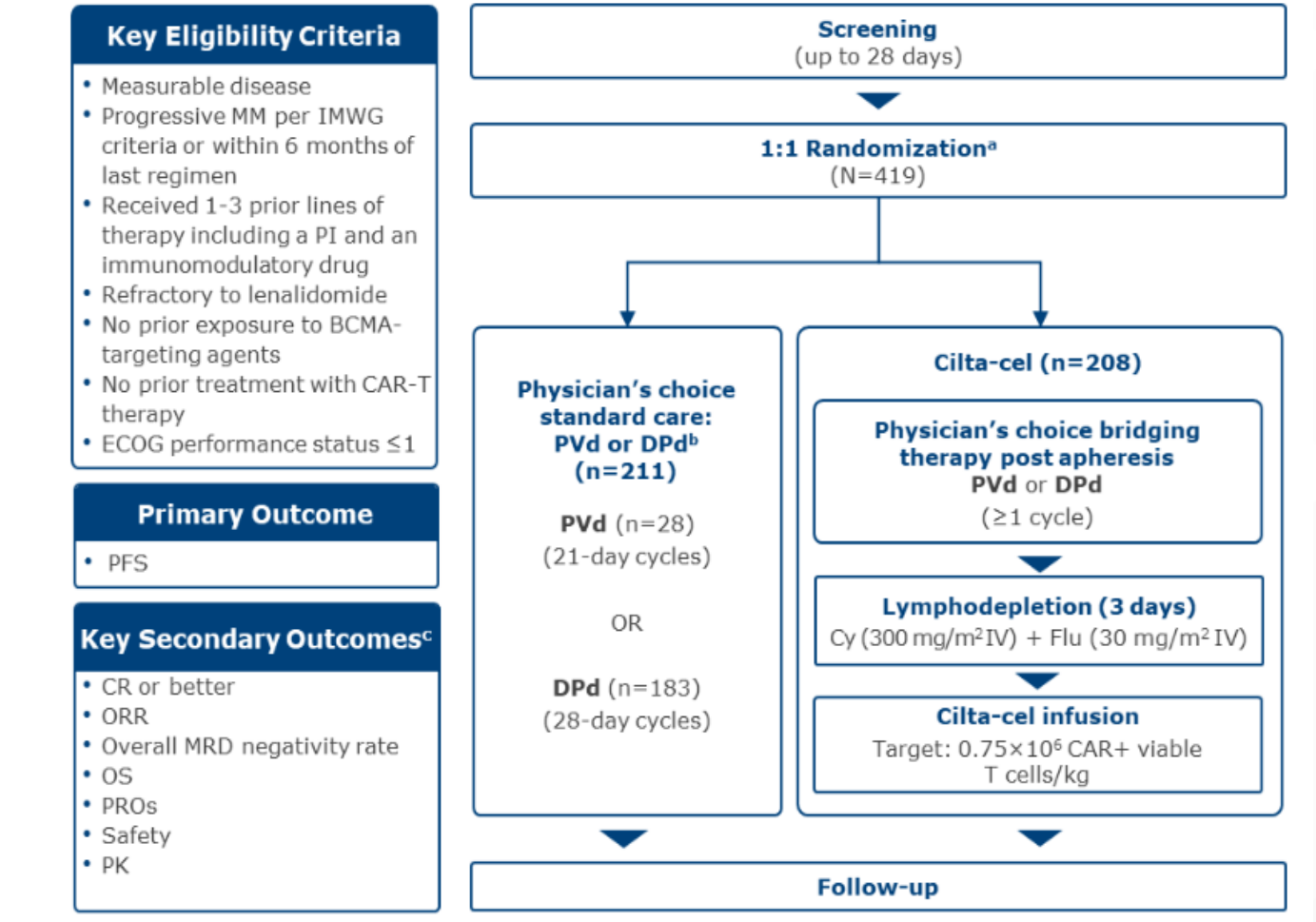
Data are n (%) unless otherwise stated. [a]≥ 50% CD138+ plasma cells in bone marrow. [b]Included del(17p), t(4;14), t(14;16), or 1q gain/amplification. [c]≥ 2 of del (17p), t(4;14), t(14;16), t(14;20), or 1q gain/amplification. [d]Refractory to ≥1 each of an IMiD agent, a PI, and an anti-CD38 antibody.
EMP, extramedullary plasmacytoma; HSCT, hematopoietic stem cell transplantation; R-ISS, revised International Staging System.
Adapted from Rodríguez-Otero P, et al. *N Engl J Med.* 2023;388:1002-1014.
Rodríguez-Otero P, et al. ASH 2023. Abstract 1028.

KarMMa-3: Significant Benefit With Ide-cel at Final PFS Analysis (ITT Population)



PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion. PFS based on IMWG criteria per IRC.
[a]Based on Kaplan–Meier approach. [b]Stratified HR based on univariate Cox proportional hazard model. CI is two-sided.
IMWG, International Myeloma Working Group; ITT, intent-to-treat; PFS, progression-free survival.
Rodríguez-Otero P, et al. ASH 2023. Abstract 1028.

CARTITUDE-4: Study Design



BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; cilta-cel; ciltacabtagene autoleucel; CR, complete response; DPd, daratumumab, pomalidomide, dexamethasone; ECOG, Eastern Cooperative Oncology Group; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome Inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, dexamethasone.

San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

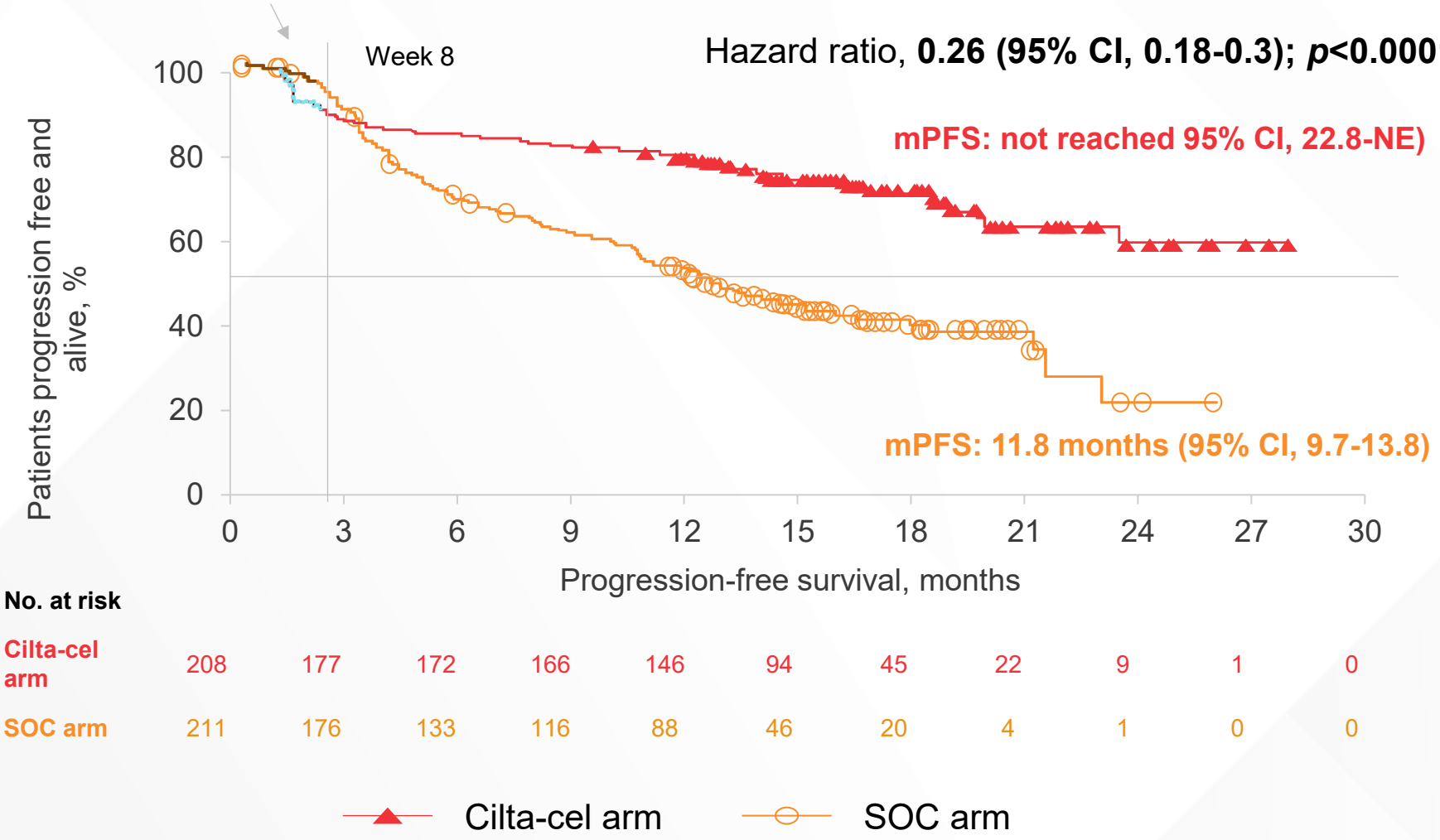
CARTITUDE-4: Prior Therapies at Baseline

Treatment, n (%)	Cilta-cel (n=208)	Standard of Care (n=211)
Prior Lines of Therapy		
Lenalidomide	208 (100.0)	211 (100.0)
Pomalidomide	8 (3.8)	10 (4.7)
Prior Anti-CD38 Antibody	**53 (25.5)**	**55 (26.1)**
Daratumumab	51 (24.5)	54 (25.6)
Isatuximab	2 (1.0)	2 (0.9)
Prior Proteasome Inhibitors	**208 (100.0)**	**211 (100.0)**
Bortezomib	203 (97.0)	205 (97.2)
Carfilzomib	77 (37.0)	66 (31.3)
Ixazomib	21 (10.1)	21 (10.0)
Triple-Class Exposed	**53 (25.5)**	**55 (26.1)**
Penta-Drug Exposed	**14 (6.7)**	**10 (4.7)**
Refractory Status		
Lenalidomide	208 (100.0)	211 (100.0)
Bortezomib	55 (26.4)	48 (22.7)
Carfilzomib	51 (24.5)	45 (21.3)
Any Anti-CD38 Antibody	50 (24.0)	46 (21.8)
Daratumumab	48 (23.1)	45 (21.3)
Ixazomib	15 (7.2)	17 (8.1)
Pomalidomide	8 (3.8)	9 (4.3)
Triple-Class Refractory	30 (14.4)	33 (15.6)
Penta-Drug Refractory	1 (1.0)	1 (0.5)

Treatment, n (%)	Cilta-cel (n=208)	Standard of Care (n=211)
Prior Lines of Therapy		
1	68 (32.7)	68 (32.2)
2	83 (39.9)	87 (41.2)
3	57(27.4)	50 (20.5)
Prior Immunomodulatory Drugs	208 (100.0)	211 (100.0)

San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

CARTITUDE-4: Primary Endpoint – PFS



Cilta-cel vs SOC

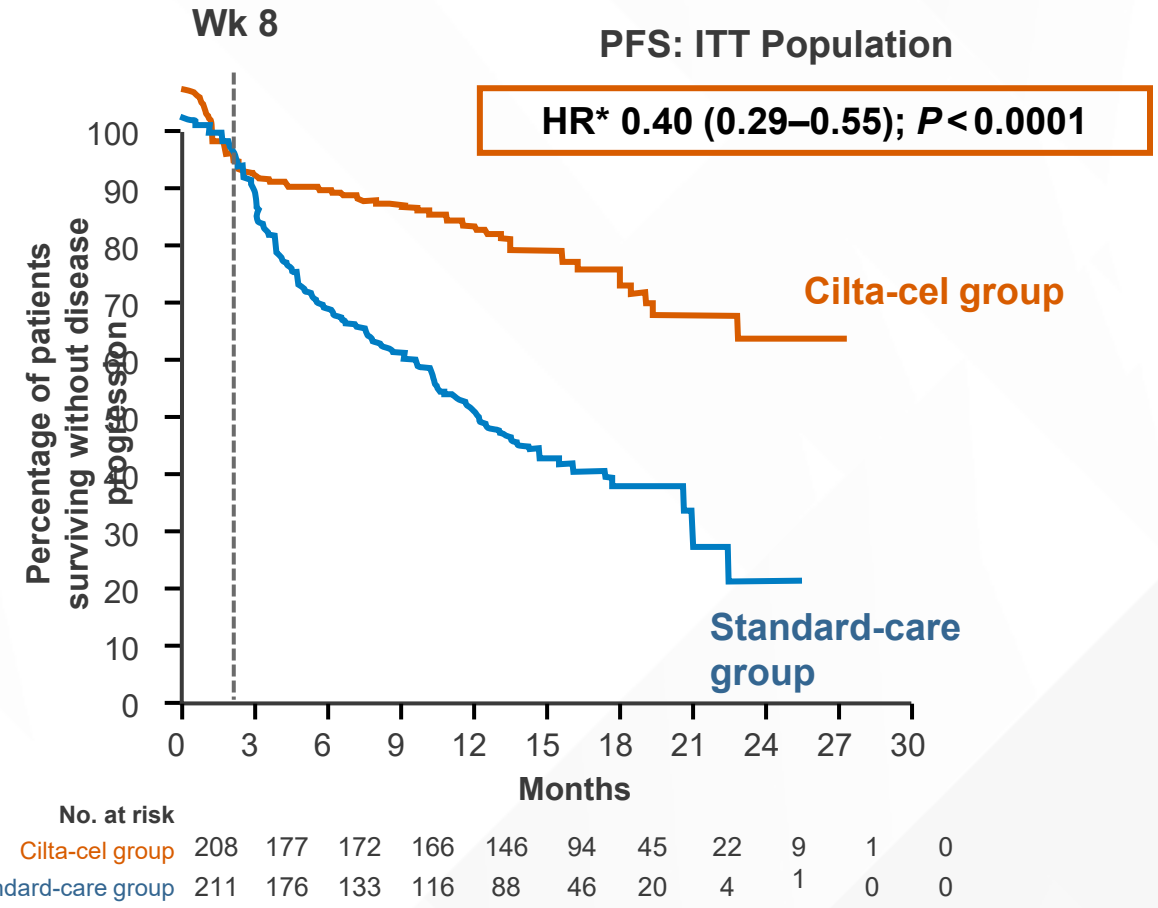
- 12-month PFS rate: 76% vs 49%
- SOC performed as expected

cilta-cel, ciltacabtagene autoleucel; mPFS, median progression-free survival; PFS, progression-free survival; SOC, standard of care.

Dhakal B, et al. *J Clin Oncol.* 2023;41(17 suppl):LBA106. San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

CARTITUDE-4: Phase 3 Cilta-Cel vs SOC (DPd or PVd)

Median follow-up 15.9 months	Cilta-cel (n=208)	SOC (n=211)
Median lines of therapy	2 (1–3)	2 (1–3)
Extramedullary disease	21%	17%
HR cytogenetics	59%	63%
Triple-class refractory	25.5%	26.1%
Penta-exposed	6.7%	4.7%
ORR	ITT: 84.6% As-tx: 99.4%	67.3%
MRD-neg (10^{-5})	ITT: 61% As-tx: 72%	16%
12-month DOR	84.7	63.0%



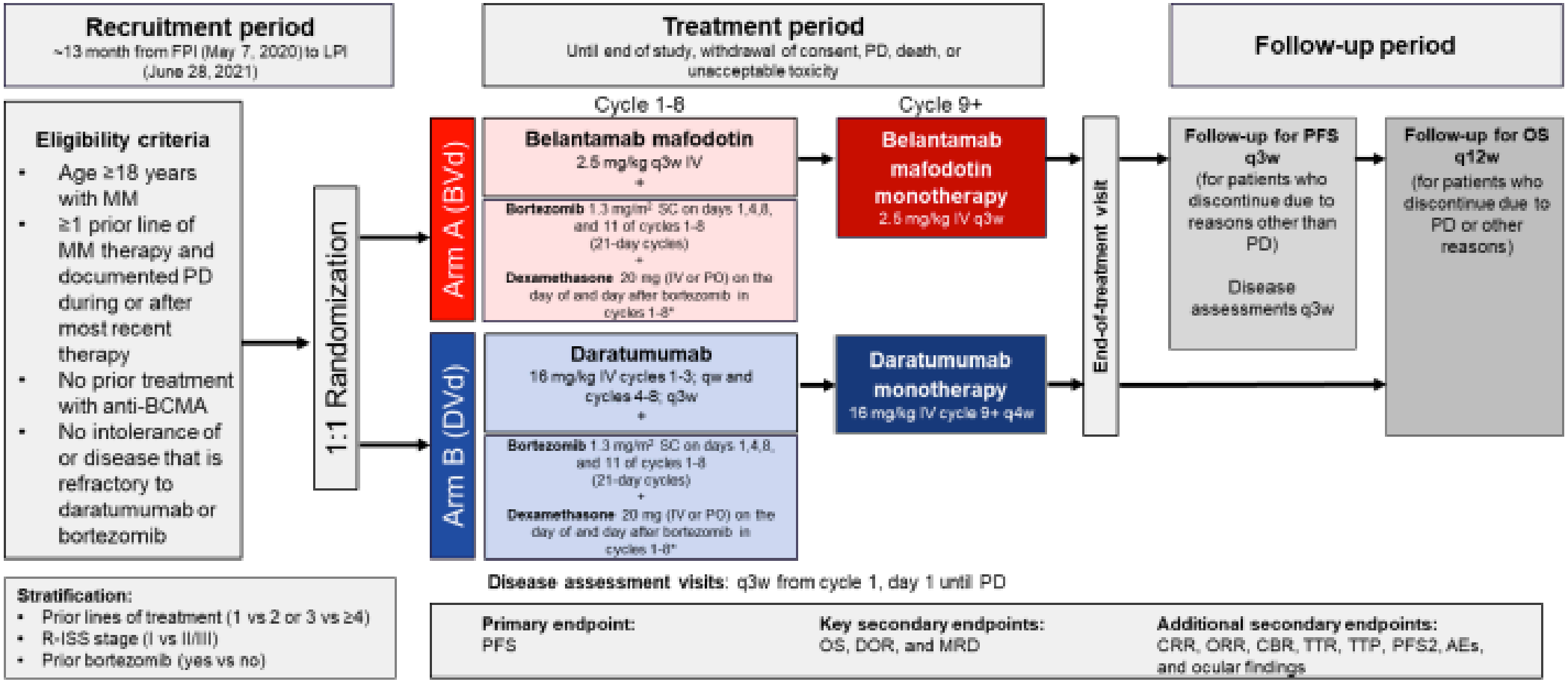
Cilta-cel was associated with superior PFS in the ITT population; patients in cilta-cel arm received DVd or VPd bridging, but had higher number of early progressions vs SOC

*unweighted

cilta-cel, ciltacabtagene autoleucel; DOR, duration of response; DPd, daratumumab, pomalidomide, dexamethasone; ITT, intent-to-treat; MRD, minimal residual disease; ORR, objective response rate; PFS, progression-free survival; PVd, pomalidomide, bortezomib, dexamethasone; SOC, standard of care.

San-Miguel J, et al. *N Engl J Med.* 2023;389(4):335-347.

DREAMM-7 Trial Design



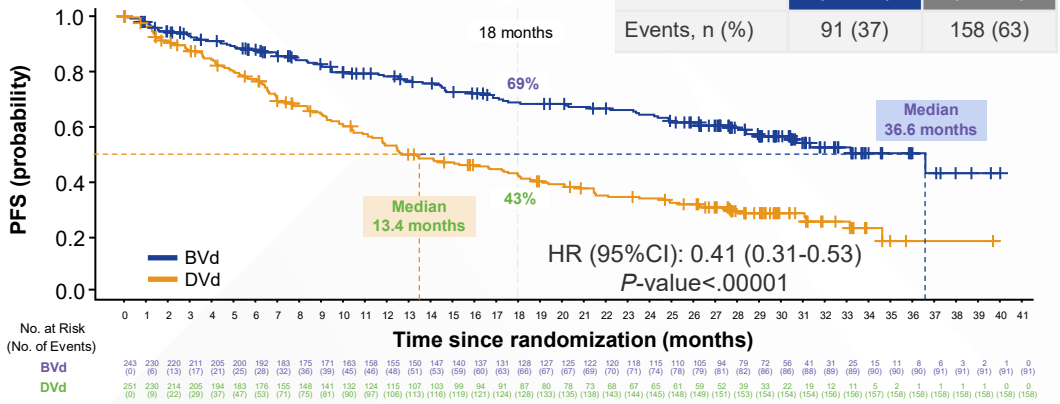
*Reduce starting dose of dexamethasone to 10 mg for patients aged >75 years with a body mass index of <18.5 kg/m^2, previous unacceptable side effects associated with glucocorticoid therapy, or inability to tolerate the starting dose.
AE, adverse event; BCME, B-cell maturation antigen; BVd, belantamab mafodotin, bortezomib, dexamethasone; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; DVd, daratumumab, bortezomib dexamethasone; FPI, first patient in; IV, intravenous; LPI, last patient in; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, time from randomization to progression on next-line treatment or death from any cause; PO, oral; q3w, every 3 weeks; q4w, every 4 weeks; q12w, every 12 weeks; qw, every week; R-ISS, Revised International Staging System; SC, subcutaneous; TTP, time to progression; TTR, time to response.
ClinicalTrials.gov identifier: NCT04246047.

DREAMM-7: BVd Demonstrated a Statistically Significant PFS Benefit Versus DVd in 2L+ RRMM

DREAMM-7: phase III, open-label, randomized study of **BVd** versus **DVd** in **2L+ RRMM**

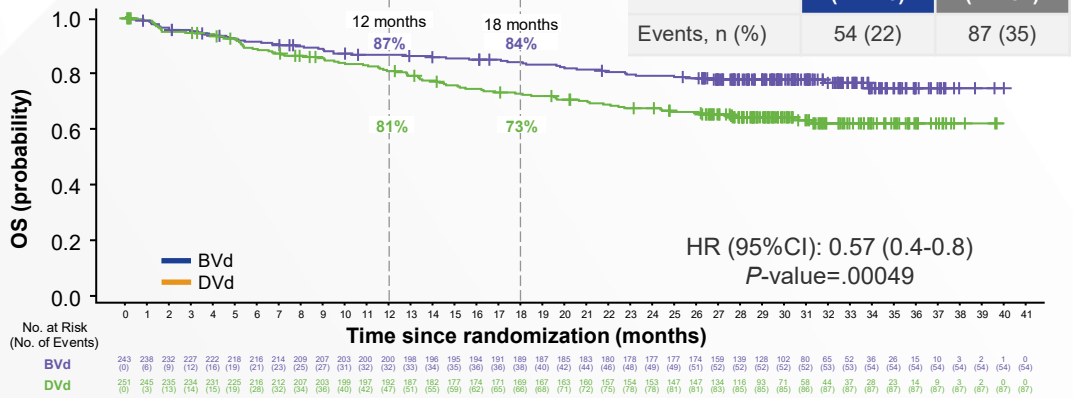
Progression-free survival

PFS*	BVd (n=243)	DVd (n=251)
Events, n (%)	91 (37)	158 (63)

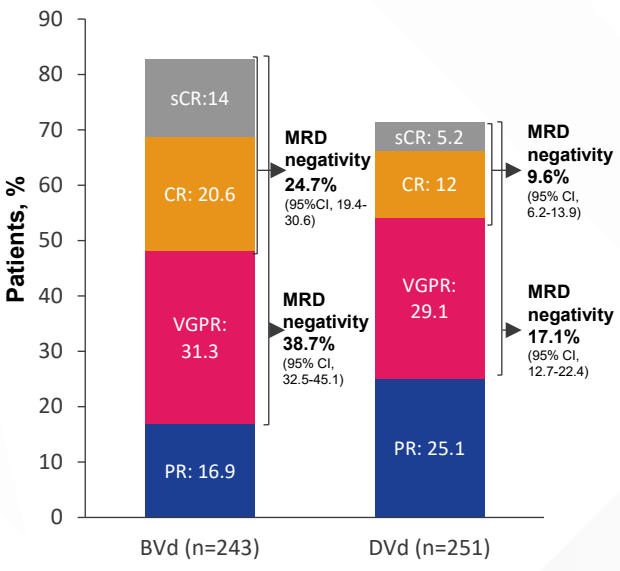


Overall survival

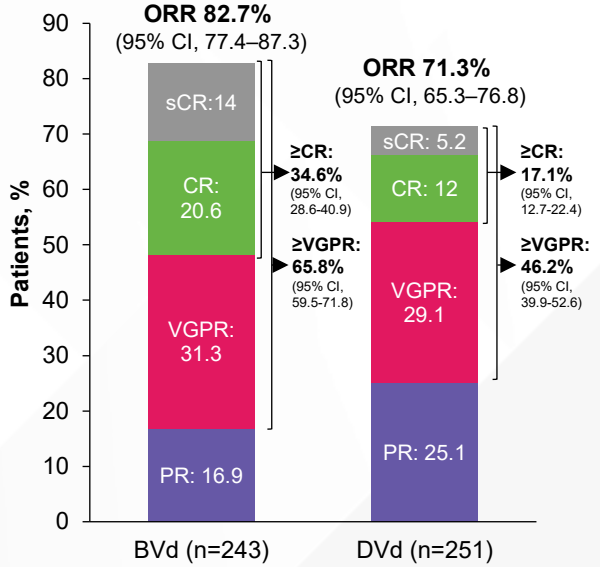
OS*	BVd (n=243)	DVd (n=251)
Events, n (%)	54 (22)	87 (35)



MRD negativity



Overall response rate



The **PFS benefit** of **BVd** versus DVd was also seen in patients who were **exposed/refractory** to **lenalidomide** and in those with **high-risk cytogenetic** features. BVd also demonstrated a **greater rate of MRD negativity** (38.7% versus 17.1%‖) and an **early trend for OS benefit¶** compared with DVd

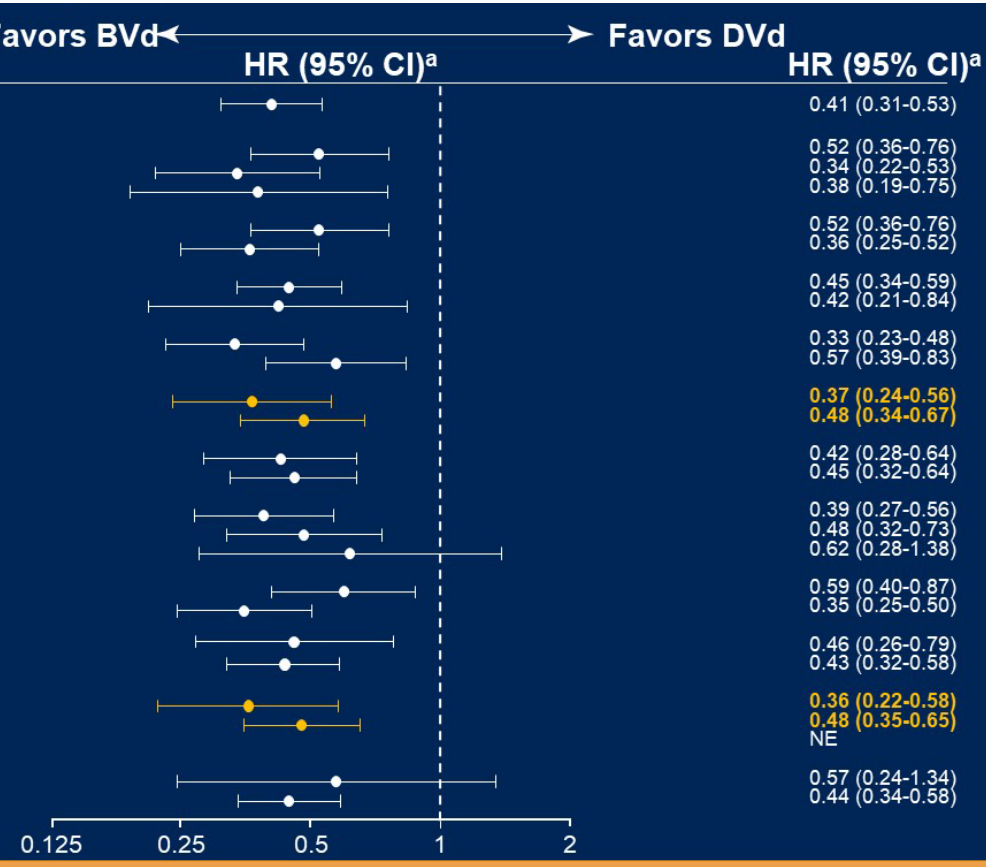
Median follow-up: 28.2 months. *Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as four unique patients in this output. †CIs estimated using the Brookmeyer-Crowley method. ‡HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS at screening (I vs II/III), with a covariate of treatment. §*P*-value from one-sided stratified log-rank test. ‖In patients who achieved ≥VGPR. ¶Additional OS follow-up ongoing.

2L, second line; BVd, belantamab mafodotin, bortezomib, dexamethasone; CI, confidence interval; CR, complete response; DVd, daratumumab, bortezomib, dexamethasone; HR, hazard ratio; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

Mateos MV, et al. ASCO Plenary Series 2024. Abstract 439572.

DREAMM-7: Prespecified Subgroup Analysis of IRC-Assessed PFS

Categories	BVd n/N	DVd n/N	HR (95% CI)[a]	HR (95% CI)[a]
All Subjects (Stratified)[b]	91/243	158/251		0.41 (0.31-0.53)
Number of Prior LOT (1 vs 2 or 3 vs ≥4)				
1	46/125	76/125		0.52 (0.36-0.76)
2 or 3	30/88	62/99		0.34 (0.22-0.53)
≥4	15/30	20/27		0.38 (0.19-0.75)
Number of Prior LOT (1 vs >1)				
1	46/125	76/125		0.52 (0.36-0.76)
>1	45/118	82/126		0.36 (0.25-0.52)
Prior Bortezomib				
Yes	79/210	132/211		0.45 (0.34-0.59)
No	12/33	26/40		0.42 (0.21-0.84)
Prior Lenalidomide				
Yes	44/127	88/130		0.33 (0.23-0.48)
No	47/116	70/121		0.57 (0.39-0.83)
Refractory to Lenalidomide				
Yes	**33/79**	**64/87**		**0.37 (0.24-0.56)**
No	**58/164**	**94/164**		**0.48 (0.34-0.67)**
Revised ISS Staging at Screening				
I	37/102	64/103		0.42 (0.28-0.64)
II/III	53/139	94/146		0.45 (0.32-0.64)
Age				
<65 years	42/121	84/126		0.39 (0.27-0.56)
65-<75 years	37/85	61/95		0.48 (0.32-0.73)
≥75 years	12/37	13/30		0.62 (0.28-1.38)
Gender				
Female	48/115	59/107		0.59 (0.40-0.87)
Male	43/128	99/144		0.35 (0.25-0.50)
Time to Relapse After Completion of 1L Treatment				
≤12 months	23/49	31/50		0.46 (0.26-0.79)
>12 months	68/194	127/201		0.43 (0.32-0.58)
Cytogenetics Risk				
High Risk[c]	**26/67**	**48/69**		**0.36 (0.22-0.58)**
Standard Risk[d]	**65/175**	**106/175**		**0.48 (0.35-0.65)**
Missing or Not Evaluable	0/1	4/7		NE
Extramedullary Disease at Baseline				
Yes	8/13	18/25		0.57 (0.24-1.34)
No	83/230	140/226		0.44 (0.34-0.58)



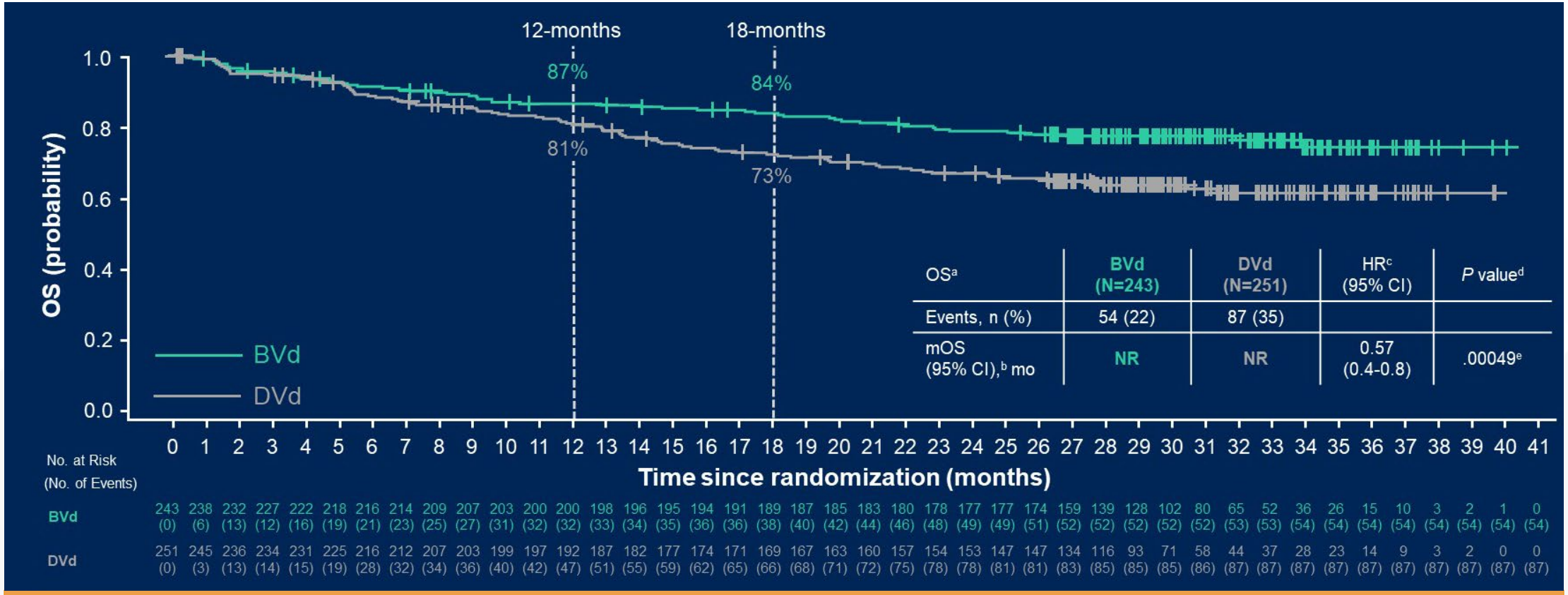
PFS benefit consistently favored BVd vs DVd across prespecified subgroups, including patients with lenalidomide refractory or high-risk cytogenetic MM

[a]HRs for subgroups were only plotted if number of the events was ≥20 in total across both treatments. HRs for subgroups were estimated using Cox proportional hazards model, without adjustment for stratification variables. [b]Stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs II/III) according to IVRS strata, with a covariate of treatment. [c]A patient was considered as high risk if the subject had any of the following cytogenetics: t(14,16), t(14,16) or del(17p13). [d]A patient was considered standard risk if the subject has negative results for all high-risk abnormalities: t(4,14), t(14,16) or del(17p13).

BVd, belantamab mafodotin, bortezomib, dexamethasone; CI, confidence interval; DVd, daratumumab, bortezomib, dexamethasone; HR, hazard ratio; IVRS, interactive voice response system; LOT, line of therapy; NE, not evaluable; PFS, progression-free survival.

Mateos MV, et al. ASCO Plenary Series 2024. Abstract 439572.

DREAMM-7: Early OS Trend Favoring BVd vs DVd



OS[a]	BVd (N=243)	DVd (N=251)	HR[c] (95% CI)	*P* value[d]
Events, n (%)	54 (22)	87 (35)		
mOS (95% CI),[b] mo	NR	NR	0.57 (0.4-0.8)	.00049[e]

OS showed an early, strong, and clinically8 meaningful trend favoring the BVd arm; additional OS follow-up is ongoing

[a]Two patients in the ITT population were randomized, not treated, re-screened, and re-randomized. They are counted as 4 unique patients in this output. [b]CIs were estimated using the Brookmeyer Crowley method. [c]HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior theray (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS at screening (I vs II/III), with a covariate of treatment. [d]*P* value from 1-sided stratified log-rank test. [e]Has not yet reached criteria for statistical significance ($P \leq .00037$) at this interim analysis. Follow-up for OS is ongoing.
BVd, belantamab mafodotin, bortezomib, dexamethasone; CI, confidence interval; DVd, daratumumab, bortezomib, dexamethasone; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; NR, not reached.
Mateos MV, et al. ASCO Plenary Series 2024. Abstract 439572.

AXIS Medical Education

DREAMM-8: Study Design

Recruitment period
October 2020 to December 2022

Treatment period
Until PD, death, unacceptable toxicity, end of study, or withdrawal of consent

Eligibility criteria

- Adults with MM
- ≥1 prior line of MM therapy including LEN
- Documented PD during or after their most recent therapy
- No prior treatment with anti-BCMA or pomalidomide; not refractory/intolerant to bortezomib

N=302

1:1 randomization

BPd (Q4W)

Belantamab mafodotin
2.5 mg/kg IV (cycle 1) then 1.9 mg/kg IV Q4W from cycle 2 onward
+
Pomalidomide 4 mg orally on days 1-21 (28-day cycles)
+
Dexamethasone 40 mg[a] on days 1, 8, 15, and 22

PVd (Q3W)

Bortezomib
1.3 mg/m^2 SC on days 1, 4, 8, and 11 of cycles 1-8 then days 1 and 8 (21-day cycles)
+
Pomalidomide 4 mg orally on days 1-14 (21-day cycles)
+
Dexamethasone 20 mg[a] on the day of and day after bortezomib

End-of-treatment visit

Primary endpoint:
PFS (IRC assessed per IMWG)

Key secondary endpoints:
OS, MRD negativity, DOR

Additional secondary endpoints include:
ORR, CRR, ≥VGPR,TTBR, TTR, TTP, PFS2, AEs, ocular findings, HRQOL, and PROs

Stratification[b]:
- Prior lines of treatment (1 vs 2 or 3 vs ≥4)
- Prior bortezomib (yes vs no)
- Prior anti-CD38 therapy (yes vs no)

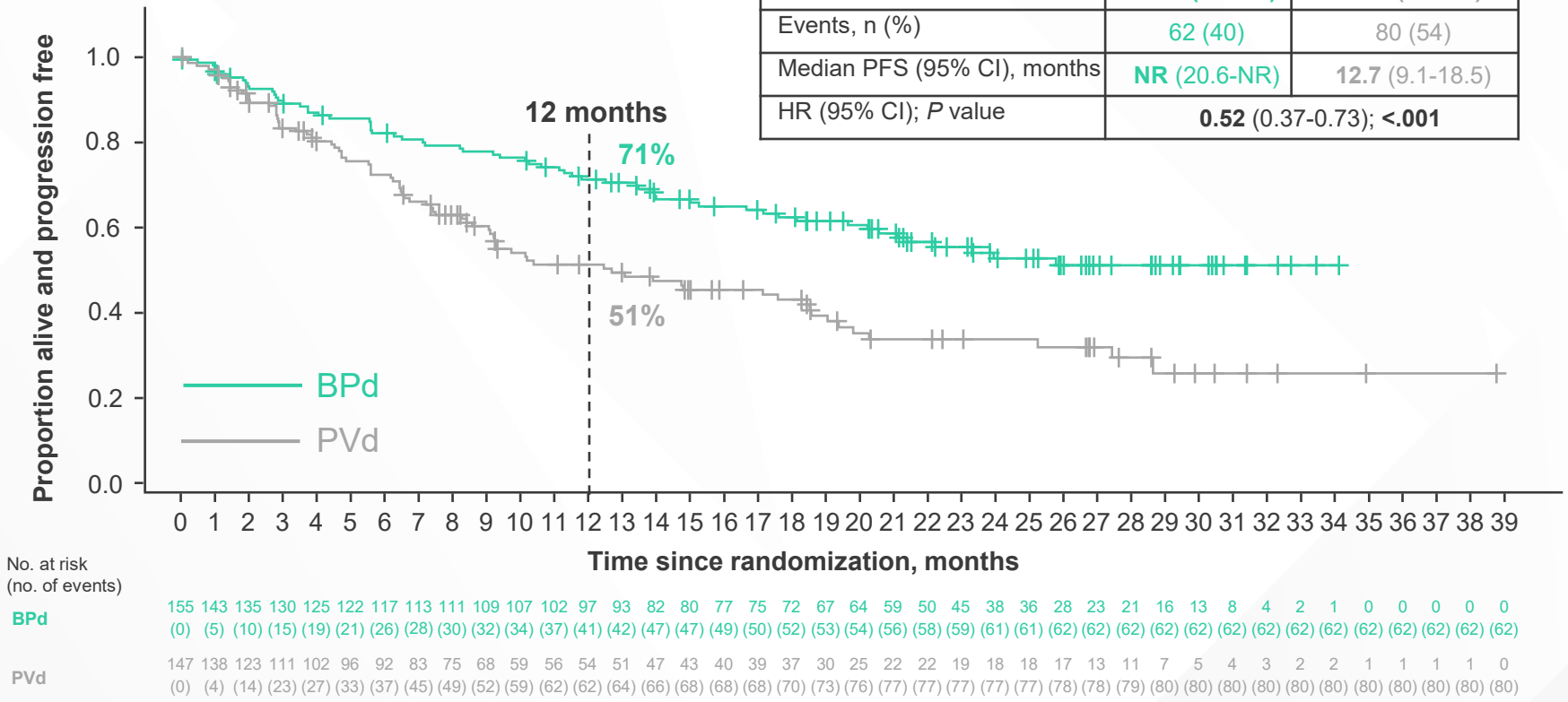
[a]Patients aged >75 years, with comorbidities, or intolerant to 40 mg dose in Arm A or 20 mg dose in Arm B could have dose level reduced to half per investigator discretion. [b]Some patients were stratified by ISS status (I vs II/III); the protocol was amended on 20 April 2021 to replace this randomization factor with prior anti-CD38 treatment (yes vs no).

AE, adverse event; BCMA, B-cell maturation antigen; BPd, belamaf, pomalidomide, and dexamethasone; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; HRQOL, health-related quality of life; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; IV, intravenous; LEN, lenalidomide; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival on subsequent line of therapy; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous; TTBR, time to best response; TTP, time to progression; TTR, time to response; VGPR, very good partial response.

Trudel S, et al. *J Clin Oncol.* 2024;42(17 suppl):LBA105.

BPd Led to a Significant PFS Benefit vs PVd

PFS	BPd (N=155)	PVd (N=147)
Events, n (%)	62 (40)	80 (54)
Median PFS (95% CI), months	**NR** (20.6-NR)	**12.7** (9.1-18.5)
HR (95% CI); *P* value	**0.52** (0.37-0.73); **<.001**	

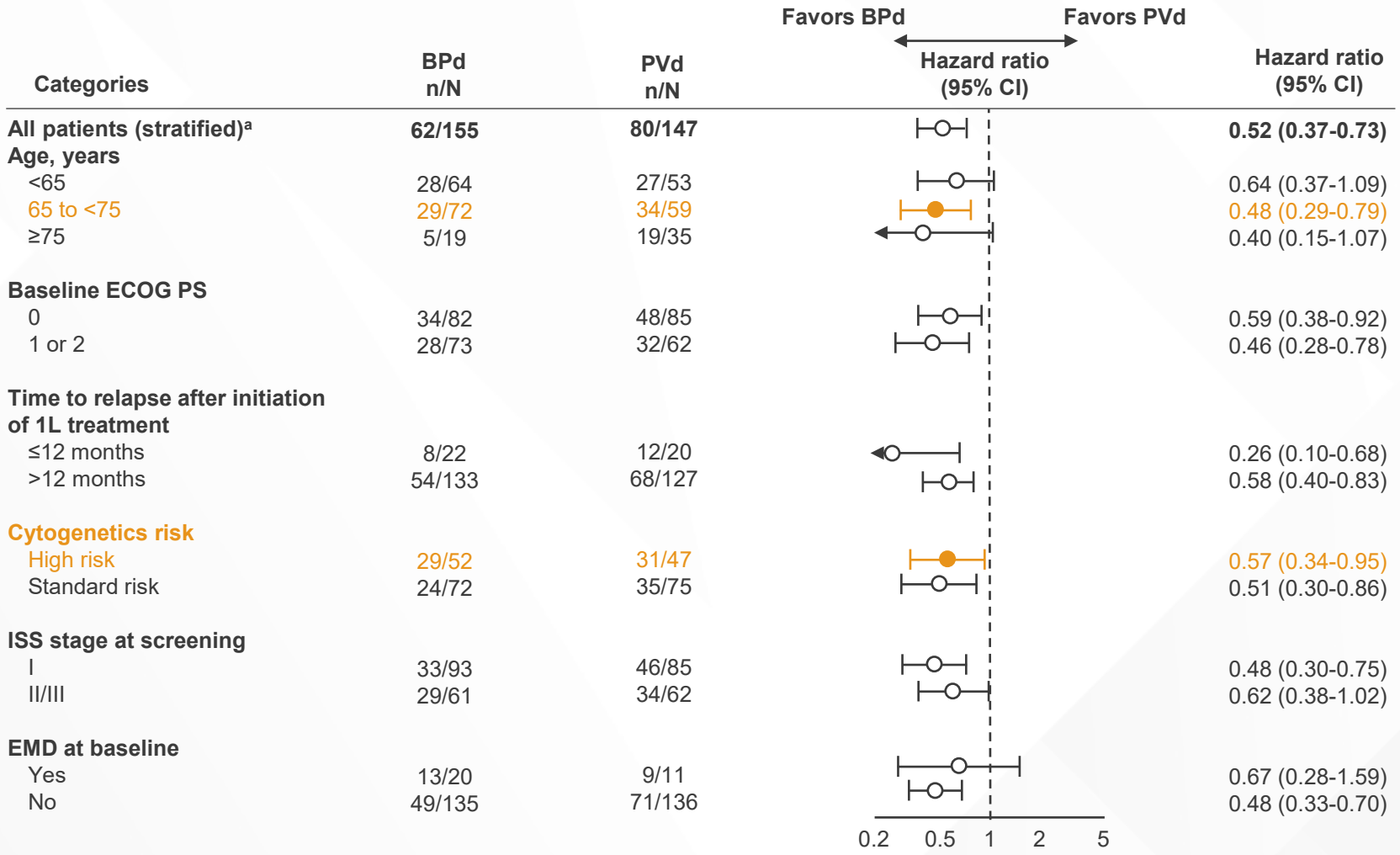


BPd led to a statistically significant and clinically meaningful reduction in risk of disease progression or death vs PVd (HR, 0.52; 95% CI, 0.37-0.73; *P*<.001)

Median follow-up, 21.8 months (range, 0.03-39.23 months). The treatment effect (HR and corresponding 95% CIs) was estimated using the stratified Cox proportional hazards model, and the *P* value was produced based on the 1-sided stratified log-rank test. Stratified analyses were adjusted for number of prior lines of therapy and prior bortezomib use.
BPd, belamaf, pomalidomide, and dexamethasone; HR, hazard ratio; NR, not reported; PFS, progression-free survival; PVd, pomalidomide, bortezomib, dexamethasone.
Trudel S, et al. *J Clin Oncol.* 2024;42(17 suppl):LBA105.

AXIS Medical Education

PFS Benefit Was Seen Consistently Across All Prespecified Subgroups



Categories	BPd n/N	PVd n/N	Hazard ratio (95% CI)
All patients (stratified)[a]	**62/155**	**80/147**	**0.52 (0.37-0.73)**
Age, years			
<65	28/64	27/53	0.64 (0.37-1.09)
65 to <75	29/72	34/59	0.48 (0.29-0.79)
≥75	5/19	19/35	0.40 (0.15-1.07)
Baseline ECOG PS			
0	34/82	48/85	0.59 (0.38-0.92)
1 or 2	28/73	32/62	0.46 (0.28-0.78)
Time to relapse after initiation of 1L treatment			
≤12 months	8/22	12/20	0.26 (0.10-0.68)
>12 months	54/133	68/127	0.58 (0.40-0.83)
Cytogenetics risk			
High risk	29/52	31/47	0.57 (0.34-0.95)
Standard risk	24/72	35/75	0.51 (0.30-0.86)
ISS stage at screening			
I	33/93	46/85	0.48 (0.30-0.75)
II/III	29/61	34/62	0.62 (0.38-1.02)
EMD at baseline			
Yes	13/20	9/11	0.67 (0.28-1.59)
No	49/135	71/136	0.48 (0.33-0.70)

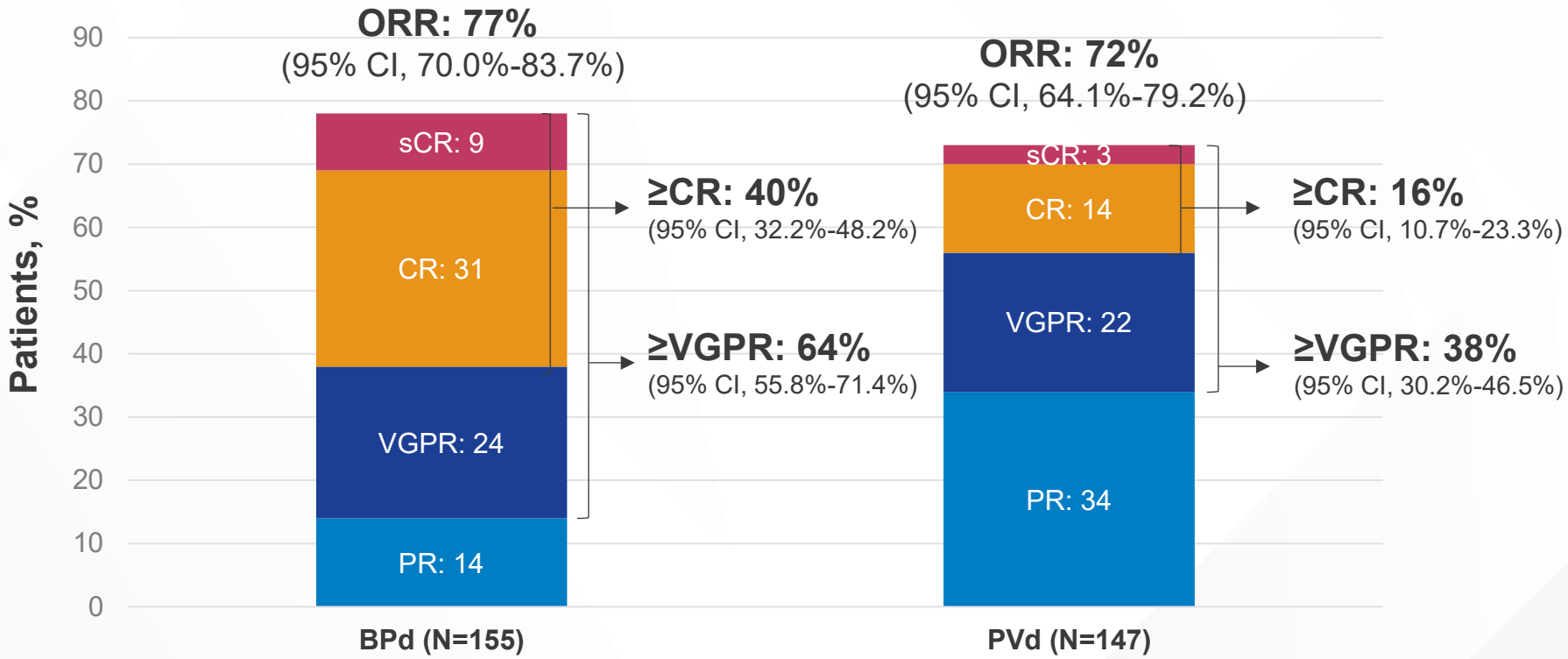
HRs for subgroups were only plotted if the number of events was ≥20 in total across both treatments and were estimated using Cox proportional hazards models, without adjustments for stratification variables. A patient was considered high risk if they had any of the following cytogenetics: t(4;14), t(14;16), or del(17p13) and considered standard risk if they had negative results for all high-risk cytogenetics listed above.

[a]HR for all patients was stratified by the number of lines of prior therapy (1 vs 2/3 vs ≥4) and prior bortezomib (yes or no) according to interactive voice response system strata with a covariate of treatment.

1L, first line; BPd, belamaf, pomalidomide, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; HR, hazard ratio; ISS, International Staging System; LOT, line of therapy; PFS, progression-free survival; PVd, pomalidomide, bortezomib, dexamethasone.

Trudel S, et al. *J Clin Oncol.* 2024;42(17 suppl):LBA105.

Deeper Responses With BPd vs PVd



The CR or better rate in the BPd arm was more than double that reported in the PVd arm

CIs were based on the exact method. All percents are based on the ITT population.
BPd, belamaf, pomalidomide, dexamethasone; CR, complete response; ITT, intent to treat; ORR, objective response rate; PR, partial response; PVd, pomalidomide, bortezomib, dexamethasone; sCR, stringent complete response; VGPR, very good partial response.
Trudel S, et al. *J Clin Oncol.* 2024;42(17 suppl):LBA105.

Depth of Response by MRD

Response	DREAMM-7		DREAMM-8	
	BVd (N=243)	DVd (N=251)	BPd (N=155)	PVd (N=147)
MRD-Negative status*				
Patients with CR or better, %	25	10	24	5
Patients with VGPR or better, %	39	17	32	5
MRD-negative status sustain for ≥12 months*				
Patients with CR or better, %	10	2	8	1

*MRD-negative status determined on the basis of next-generation sequencing with a sensitivity of 10^{-5}.
BPd, belamaf, pomalidomide, dexamethasone; CR, complete response; MRD, minimal residual disease; PVd, pomalidomide, bortezomib, dexamethasone; VGPR, very good partial response.

Real-World Considerations, Such as Access to Care and Monitoring Requirements, are Vital in Selecting Treatment[1-11]

	ADCs	CAR-T cell therapies (autologous)	Bispecific antibodies	CELMoDs
Treatment availability	**Little to no wait** time is required prior to administration[1]	Cell manufacturing takes **~4 weeks**[3]	**Little to no wait** time is required prior to administration; limited **resource utilization**[3]	**Little to no wait** time is required prior to administration[11]
Administration setting	**Outpatient** (no hospitalization required)[1]	Usually administered in **specialized medical center** and/or **hospitals**[4-7]	Usually administered in **specialized medical centers** and/or **hospitals**; outpatient administration approaches are being explored[8-10]	**Outpatient** (no hospitalization required)[11]
Post-administration monitoring	Regular visits with an **ophthalmologist (Q3W)**[2]	Post treatment monitoring for CRS/neurotoxicity requires patients to remain **within proximity to an administration center for ≥4 weeks** following administration[4-7]	Must remain **within proximity to a healthcare facility for 48 hours** after step-up dosing[8,9]	--*

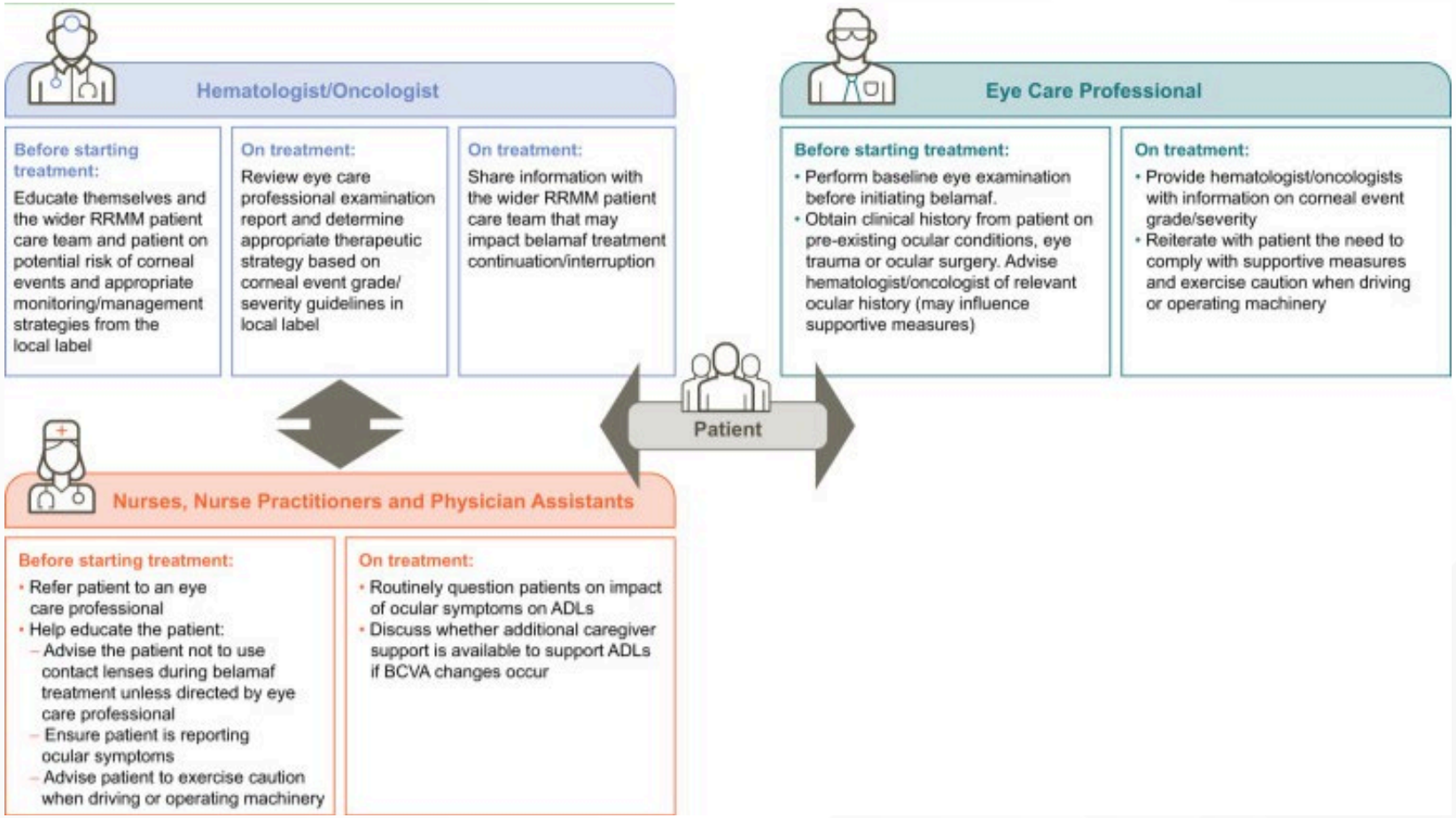
*Specific monitoring requirements are currently unknown.

ADC, antibody-drug conjugate; CAR-T, chimeric antigen receptor t-cell; CELMoD, cereblon E3 ligase modulator; CRS, cytokine release syndrome; Q3W, every three weeks.

1. Herrera AF, Molina A. *Clin Lymphoma Myeloma Leuk*. 2018;18(7):452-468. 2. Morè S, et al. *Cancers (Basel)*. 2023;15(11):2948. 3. Barilà G, et al. *Pharmaceuticals (Basel)*. 2021;14(1):40. 4. Abecma. Prescribing Information. Bristol Myers Squibb; 2021. 5. Abecma. Summary of Product Characteristics. Bristol Myers Squibb; 2021. 6. Carvykti. Prescribing Information. Janssen Biotech, Inc.; 2022. 7. Carvykti. Summary of Product Characteristics. Janssen-Cilag International NV; 2022. 8. Tecvayli. Prescribing Information. Janssen Biotech, Inc.; 2022. 9. Tecvayli. Summary of Product Characteristics. Janssen-Cilag International NV; 2022. 10. Varshavsky-Yanovsky AN, et al. *Hemasphere*. 2023;7(Suppl):e605007f. 11. Hartley-Brown MA, et al. *Cancers (Basel)*. 2024;16(6):1166.

Multidisciplinary Approach to Managing Corneal Events With Belamaf: Healthcare Professional Roles

RRMM Patient Care Team



ADL, activity of daily living; BCVA, best-corrected visual acuity; RRMM, relapsed/refractory multiple myeloma.
Lonial S, et al. *Blood Cancer J.* 2021;11(5):103.

Conclusion

- “Early relapse” is the new “newly diagnosed” in terms of outcomes
- Benefit from phase 3 trials of standard agents may be less in an era of quads
- Transplant remains a standard as part of induction, so less use in relapse
- Timing of CAR-T remains an unanswered question, but clearly better than many standard treatments in early relapse
- How to consider ADC vs TCE vs CAR-T in early relapse are ongoing questions

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ADC, antibody-drug conjugate; CAR-T, chimeric antigen receptor T cell; TCE, T-cell engager.

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Redefining Treatment at First Relapse In RRMM:

Exploring BCMA-Targeted Therapies