Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2024 San Diego

Multiples Myelom

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Comprehensive
Cancer Center
Tübingen - Stuttgart

Universitätsklinikum
Tübingen

Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition: -

2. Beratungs- bzw. Gutachtertätigkeit: *Janssen-Cilag*

3. Besitz von Geschäftsanteilen, Aktien oder Fonds: -

4. Patent, Urheberrecht, Verkaufslizenz: -

5. Honorare : *Janssen-Cilag, GSK, AMGEN, Sanofi, Takeda, Pfizer, Oncopeptides*

6. Finanzierung wissenschaftlicher Untersuchungen: -

7. Andere finanzielle Beziehungen: -

8. Immaterielle Interessenkonflikte: -

Multiples Myelom - ASH 2024

Bispezifische Antikörper

CAR-T
BCMA **GPRC5D**

Multiples Myelom

BCMA-ADC

CELMoD

Trispezifische Antikörper
(BCMA/CD38/CD3)
……..

Agenda

SMM	Aquila
NDMM	MajesTEC-5
RRMM	DREAMM-7
	CC-92480-MM-002

SMM - Aquila

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

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Aquila

PETHEMA Score (2007)

Risk factor	Score
≥95% aberrant PC within BM PC compartment (aberrant phenotypes outlined in *Blood* 2007 publication[28])	1
Presence of immunoparesis (defined as uninvolved qIg level below the LLN)	1

Risk category (score)	Median TTP
0	NR
1	73 mo
2	23 mo

Mayo 20/20/2 Score (2018)

Risk factor	Score
BM PC >20%	1
M-protein >2 g/dL	1
FLC ratio *(involved to uninvolved FLC)* >20	1

Risk category (score)	Progression risk (%)	
	2 year	5 year
Low (0)	10	23
Intermediate (1)	26	47
High (≥2)	47	82

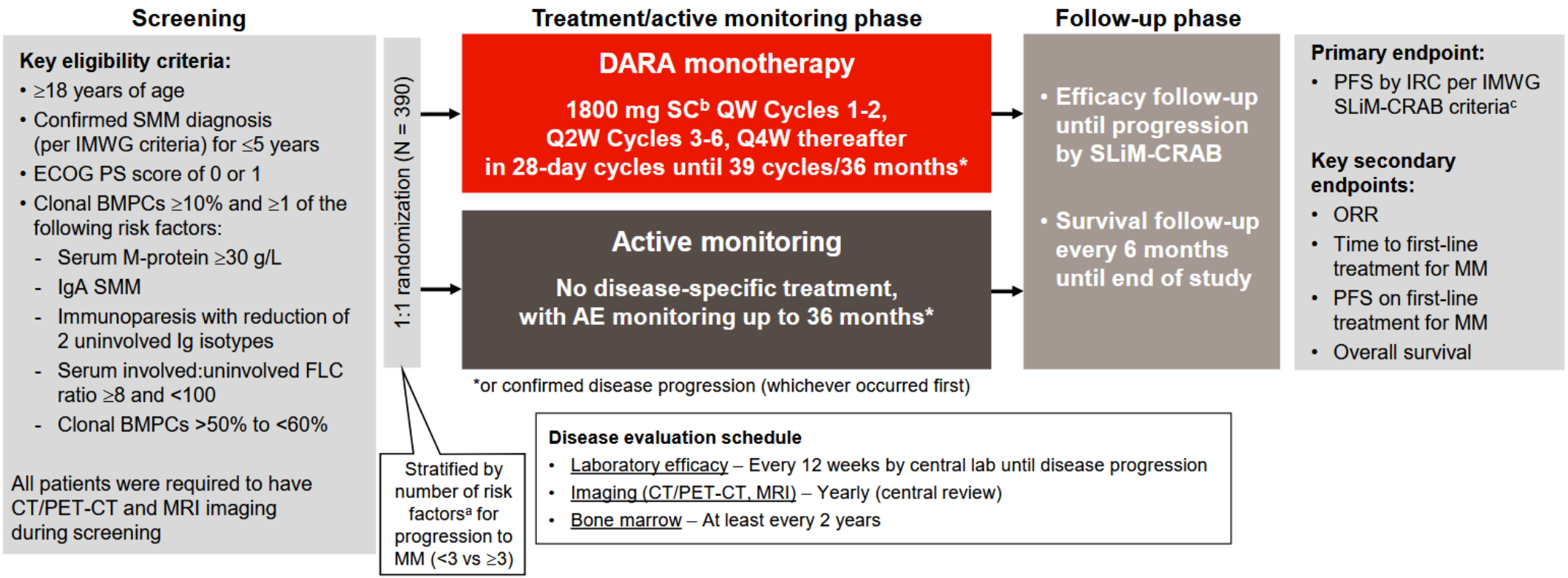
IMWG Score (2020)

Risk factor	Score
FLC ratio *(involved to uninvolved FLC)*	
0-10	0
>10-25	2
>25-40	3
>40	5
M-protein (g/dL)	
0-1.5	0
>1.5-3	3
>3	4
BM PC (%)	
0-15	0
>15-20	2
>20-30	3
>30-40	5
>40	6
FISH abnormality (t(4;14), t(14;16), +1q, del(13q), monosomy 13)	2

Risk category (score)	Progression risk (%)	
	2 year	5 year*
Low (0-4)	4	20
Low-intermediate (5-8)	26	55
Intermediate (9-12)	51	70
High (>12)	73	85

Aquila – Study design

AQUILA enrollment period: December 2017 and May 2019, at 124 sites in 23 countries



IMWG, International Myeloma Working Group; ECOG PS, Eastern Cooperative Oncology Group performance status; BMPC, bone marrow plasma cell; FLC, free light chain; CT, computed tomography; MRI, magnetic resonance imaging; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; AE, adverse event; IRC, independent review committee; ORR, overall response rate. [a]Risk factors included involved:uninvolved FLC ratio ≥8 (yes vs no), serum M-protein ≥30 g/L (yes vs no), IgA SMM (yes vs no), immunoparesis (reduction of 2 uninvolved immunoglobulins vs other), or clonal BMPCs (>50% to <60% vs ≤50%). [b]DARA SC (1800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc.]). [c]PFS was defined as duration from randomization to initial documented progression to active MM or death due to any cause, whichever occurred first.

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Presented by M A Dimopoulos at the 66th American Society of Hematology (ASH) Annual Meeting; December 7-10, 2024; San Diego, California

Aquila – Baseline Demographics

Characteristic	DARA (n = 194)	Active monitoring (n = 196)
Age		
Median (range), years	63.0 (31-86)	64.5 (36-83)
18 to <65 years, n (%)	106 (54.6)	98 (50.0)
65 to <75 years, n (%)	67 (34.5)	74 (37.8)
≥75 years, n (%)	21 (10.8)	24 (12.2)
Sex, n (%)		
Female	99 (51.0)	103 (52.6)
Male	95 (49.0)	93 (47.4)
ECOG PS score, n (%)		
0	165 (85.1)	160 (81.6)
1	29 (14.9)	36 (18.4)
Median time from diagnosis of SMM to randomization (range), years	0.80 (0-4.7)	0.67 (0-5.0)
Median BMPCs (range), %	20.0 (8.0-59.5)	20.0 (10.0-55.0)

Characteristic	DARA (n = 194)	Active monitoring (n = 196)
Type of SMM, n (%)		
IgG	127 (65.5)	138 (70.4)
IgA	55 (28.4)	42 (21.4)
Other	12 (6.2)	16 (8.2)
AQUILA risk factors for progression to MM, n (%)[a]		
<3	154 (79.4)	156 (79.6)
≥3	40 (20.6)	40 (20.4)
Cytogenetic risk profile[b]	n = 167	n = 170
≥1 of del(17p), t(4;14), and/or t(14;16), n (%)	29 (17.4)	22 (12.9)
Mayo 2018 risk criteria, n (%)[c]		
Low	45 (23.2)	34 (17.3)
Intermediate	77 (39.7)	76 (38.8)
High	72 (37.1)	86 (43.9)

Baseline characteristics were generally balanced between groups

[a]Risk factors: serum M-protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, serum involved:uninvolved FLC ratio ≥8 and <100, or clonal BMPCs >50% to <60% with measurable disease. [b]Cytogenetic risk was assessed by fluorescence in situ hybridization. [c]Mayo 2018 risk criteria: serum M-protein >2 g/L, involved:uninvolved FLC ratio >20, and clonal BMPCs >20%. Patients with 0 factors = low risk, 1 factor = intermediate risk, ≥2 factors = high risk (Lakshman A, et al. *Blood Cancer J*. 2018:8(6):59).

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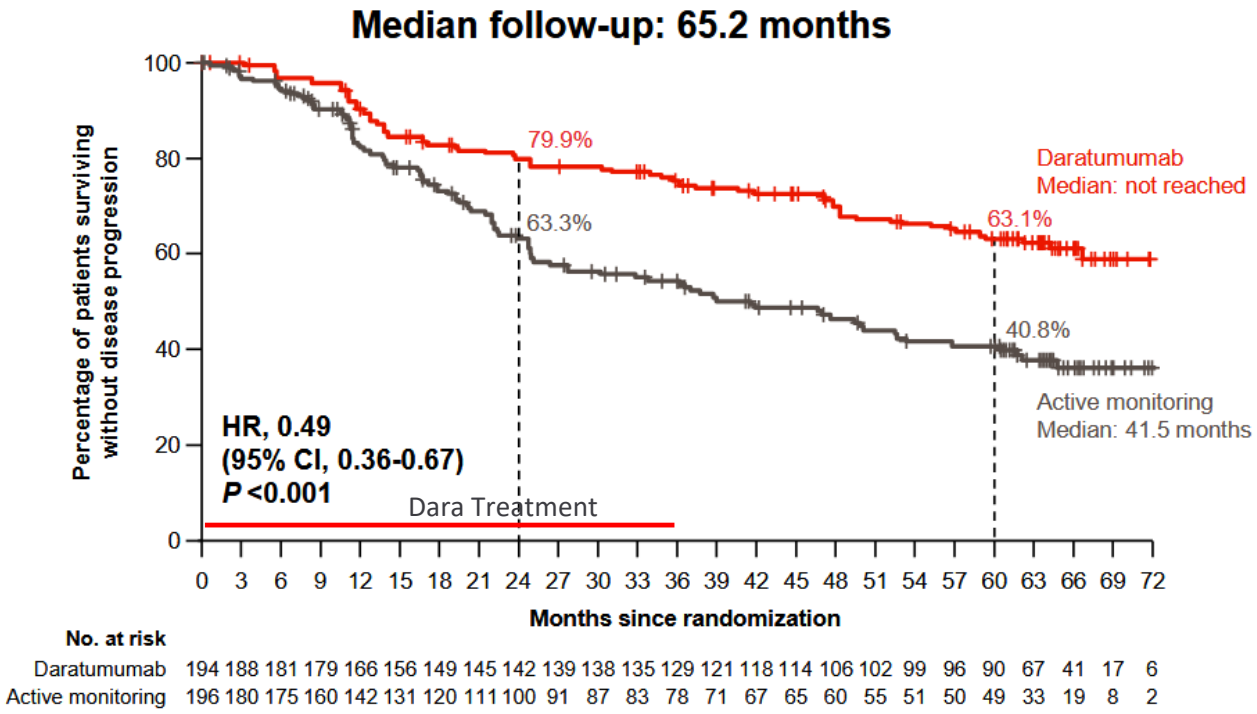
Aquila – Progression to MM



	DARA (n = 194)	Active monitoring (n = 196)
PFS event, n (%)	67 (34.5)	99 (50.5)
Death without disease progression	5 (7.5)	5 (5.1)
Disease progression[a,b]	62 (92.5)	94 (94.9)
CRAB criteria[c]	12 (19.4)	34 (36.2)
Calcium elevation	0	2 (2.1)
Renal insufficiency[d]	0	0
Anemia	2 (3.2)	14 (14.9)
Bone disease	10 (16.1)	18 (19.1)
SLiM criteria[c]	50 (80.6)	65 (69.1)
Clonal BMPCs	5 (8.1)	16 (17.0)
Serum FLC	33 (53.2)	33 (35.1)
Focal lesion by MRI	12 (19.4)	16 (17.0)

DARA significantly reduced the risk of progression to MM or death by 51% versus active monitoring

HR, hazard ratio; CI, confidence interval. [a]A patient may show disease progression based on ≥1 criterion. [b]Percentages based on the number of patients with a PFS event in each group. [c]Percentages based on the number of patients with progressive disease in each group. [d]Some patients met the CRAB criteria for renal insufficiency, but the investigator attributed this to a cause other than disease progression to MM.

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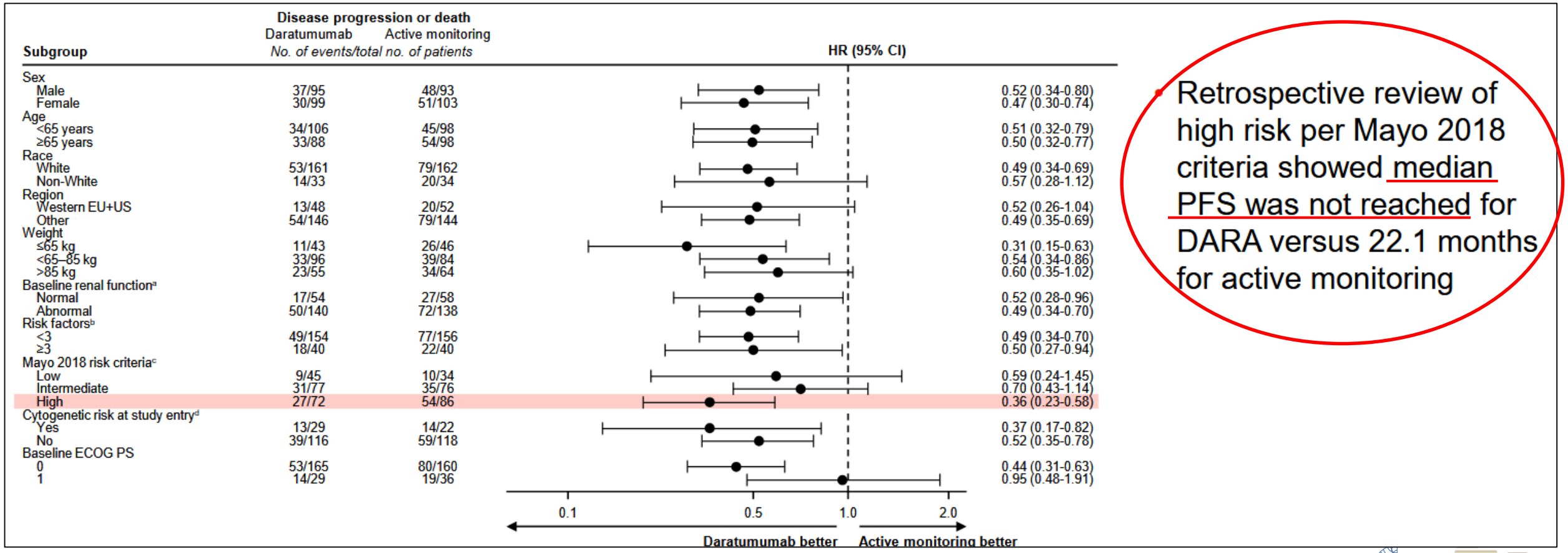
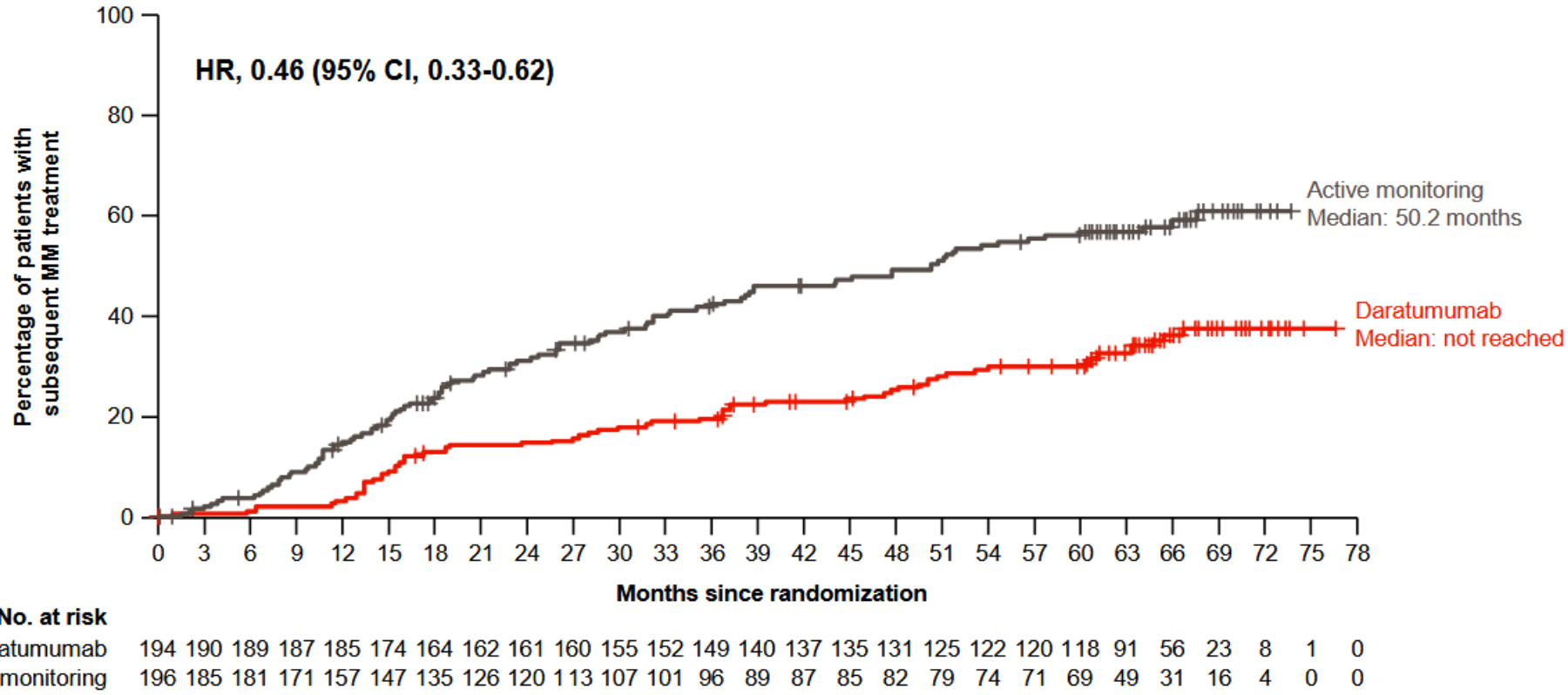
Aquila – Progression to MM (Subgroup analysis)



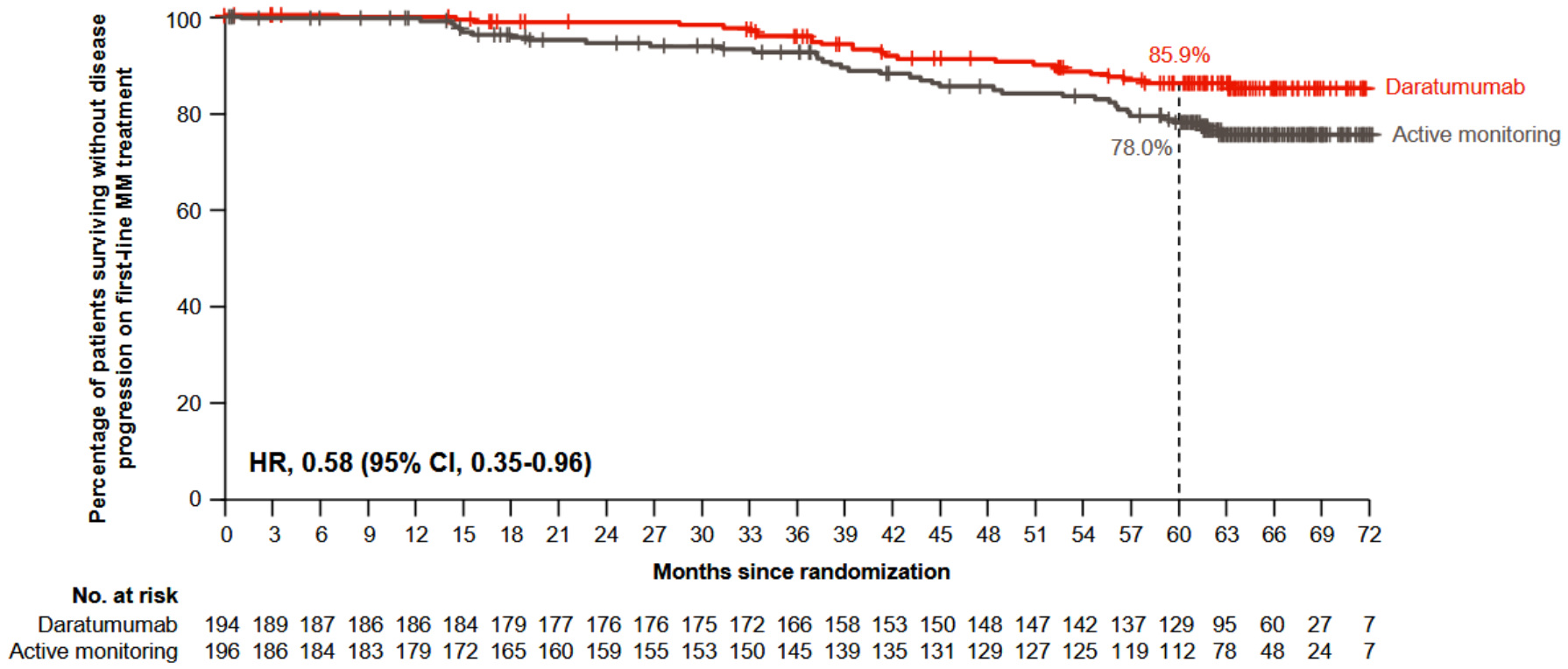
- Retrospective review of high risk per Mayo 2018 criteria showed median PFS was not reached for DARA versus 22.1 months for active monitoring

Aquila – time to First-line Treatment for MM



- First-line treatment for MM was initiated by 33.2% (64/193) in the DARA group and 53.6% (105/196) in the active monitoring group

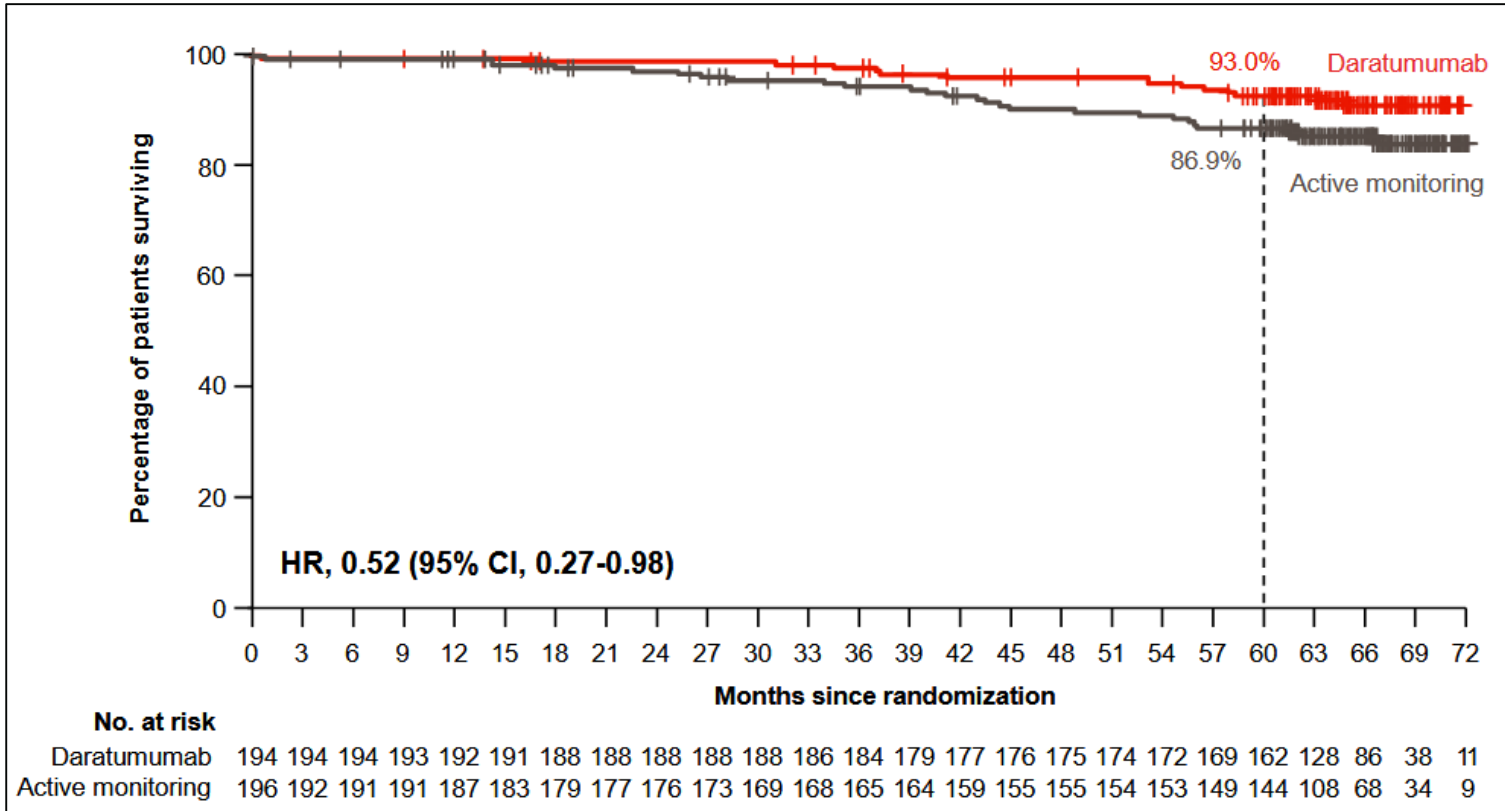
Aquila – PFS on First-line treatment for MM (PFS2)



- VRd was the most common first-line treatment for MM (DARA, 9.8%; active monitoring, 14.8%)
- 25.0% (16/64) in the DARA group and 33.3% (35/105) in the active monitoring group received anti-CD38 regimens

DARA improved PFS on first-line treatment for MM versus active monitoring and does not appear to impair later treatment for MM

Aquila – Overall Survival



	DARA (n = 194)	Active monitoring (n = 196)
Deaths, n (%)	15 (7.7)	26 (13.3)
Primary cause, n		
Disease progression	3	9
AE	2	4
Other*	10	13

*Deaths due to an event occurring after the AE reporting window (ie, events that happened after patient started subsequent therapy or >30 days after last dose) or deaths with unknown reason.

Early intervention with fixed duration DARA extended overall survival versus active monitoring

Aquila - Conclusions

- In this large phase 3 study in a well-defined population with high-risk SMM, DARA SC monotherapy for 36 months demonstrated a statistically significant PFS benefit versus active monitoring (HR, 0.49 [95% CI, 0.36-0.67])
  - The greatest PFS benefit with DARA was observed among patients with high-risk SMM retrospectively identified by Mayo 2018 criteria (HR, 0.36 [95% CI, 0.23-0.58])
- DARA prolonged PFS on first-line treatment for MM (HR, 0.58 [95% CI, 0.35-0.96])
- DARA demonstrated a favorable safety profile, with a low rate of treatment discontinuation due to TEAEs
- There was no detriment to patients' health-related quality of life, with a trend toward improvement with DARA
- DARA extended overall survival (HR, 0.52 [95% CI, 0.27-0.98])

AQUILA strongly favored early intervention with DARA monotherapy in patients with high-risk SMM, representing an opportunity to delay or avoid end-organ damage and progression to MM and to extend overall survival

NDMM (TE)

DaraVRD-Induktion – HD Mel + ASZT – DaraVRD-Konsolidierung – Dara+Lena-Erhaltung
(PERSEUS)

<u>CarT-Zell Therapie/Bispezifische Antikörper in Firstline:</u>

*DaraVRD-Induktion – **HD Mel + ASZT vs CAR-T-Zell-Therapie** (Cartitude-6)*

*(Quadrupel-Induktion – HD-Mel + ASZT) – **Erhaltung Tec/Lena vs Tec vs Lena** (MajesTEC-4)*

***TecD(V)R-Induktion** – HD-Mel + ASZT + **TecD-Erhaltung** (**MajesTEC-5**)*

GMMG-HD10/DSMM-XX (MajesTEC-5)

Phase 2 Study of Teclistamab-based Induction Regimens in Patients With Transplant-eligible Newly Diagnosed Multiple Myeloma: Results From the GMMG-HD10/DSMM-XX (MajesTEC-5) Trial*

*ClinicalTrials.gov Identifier: NCT05695508; sponsored by the University of Heidelberg Medical Center and is in collaboration with Janssen Research & Development, LLC

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GMMG-HD10/DSMM-XX (MajesTEC-5) - Introduction

- Teclistamab (Tec), a first-in-class BCMA × CD3 BsAb with weight-based dosing, is approved in TCE RRMM and is being evaluated as monotherapy in early-line RRMM and in daratumumab (Dara)-based combinations in early-line RRMM and NDMM[1-7]
- Dara-based triplet and quadruplet therapies (DRd, DVRd) have extended survival in NDMM[8-10]
  - MRD negativity (10^{-5}) of 57.5% post-consolidation with DVRd in TE NDMM in the PERSEUS study[11]
- Rationale for Tec-DR or Tec-DVR in transplant-eligible NDMM:
  - Target treatment-naive T cells for potential early eradication of all myeloma subclones to further improve rates of MRD-negativity and long-term outcomes
  - Potentially further augment T-cell cytotoxic activity and enhance efficacy by combining Tec with Dara and Len[12,13]
  - Improve patient outcomes with a steroid-sparing regimen
- MajesTEC-5 is the first study to evaluate the efficacy and safety of Tec-DR[a] and Tec-DVR[a] induction in patients with TE NDMM; here, we present initial outcomes from 3 induction cohorts in our phase 2 study

[a]Dexamethasone was also administered in C1 and C2.
BCMA, B-cell maturation antigen; BsAb, bispecific antibody; C, Cycle; D, daratumumab; d, dexamethasone; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; R, lenalidomide; RRMM, relapsed/refractory multiple myeloma; TCE, triple-class–exposed; TE, transplant-eligible; Tec, teclistamab; V, bortezomib.

1. TECVAYLI® (teclistamab). Summary of product characteristics. Janssen Biologics BV; 2024. 2. TECVAYLI® (teclistamab-cqyv) injection [package insert]. Janssen Biotech, Inc.; 2024. 3. Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505. 4. Garfall AL, et al. *J Clin Oncol*. 2024;42(16 suppl). Abstract 7540. 5. Touzeau C, et al. *J Clin Oncol*. 2024;42(16 suppl). Abstract 7506. 6. Searle E, et al. *Blood*. 2022;140(suppl 1):394-396. 7. Rodriguez-Otero P, et al. *Blood*. 2021;138(suppl 1):1647. 8. Facon T, et al. *Lancet Oncol*. 2021;22(11):1582-1596. 9. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313. 10. Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115. 11. Rodriguez-Otero P, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA. Abstract 7502. 12. Frerichs KA, et al. *Clin Cancer Res*. 2020:26(9):2203-2215.13. Cho SF, et al. *Blood Adv*. 2020;4(17):4195-4207.

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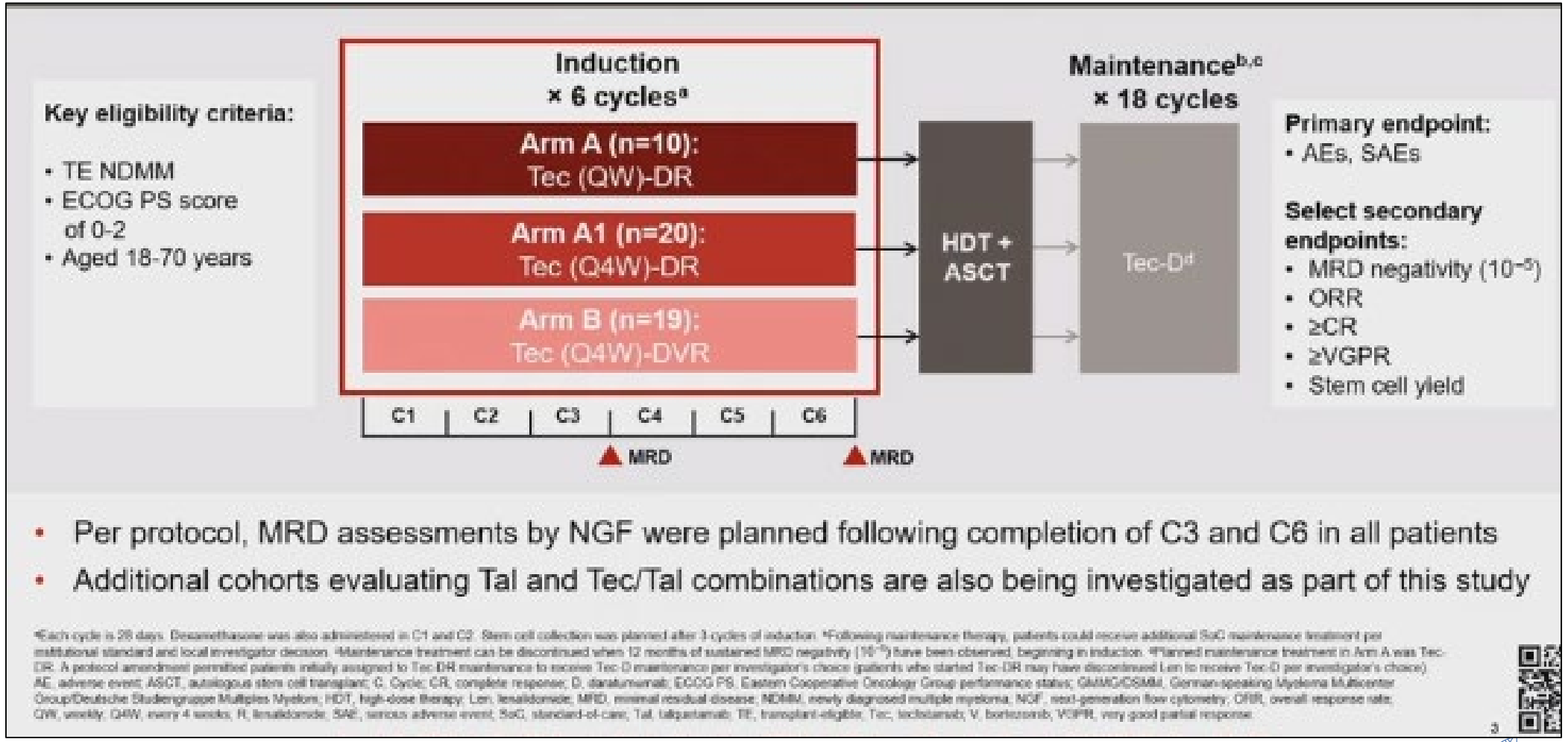
MajesTEC-5 – Study design



- Per protocol, MRD assessments by NGF were planned following completion of C3 and C6 in all patients
- Additional cohorts evaluating Tal and Tec/Tal combinations are also being investigated as part of this study

[a]Each cycle is 28 days. Dexamethasone was also administered in C1 and C2. Stem cell collection was planned after 3 cycles of induction. [b]Following maintenance therapy, patients could receive additional SoC maintenance treatment per institutional standard and local investigator decision. [c]Maintenance treatment can be discontinued when 12 months of sustained MRD negativity (10^{-5}) have been observed, beginning in induction. [d]Planned maintenance treatment in Arm A was Tec-DR. A protocol amendment permitted patients initially assigned to Tec-DR maintenance to receive Tec-D maintenance per investigator's choice (patients who started Tec-DR may have discontinued Len to receive Tec-D per investigator's choice).
AE, adverse event; ASCT, autologous stem cell transplant; C, Cycle; CR, complete response; D, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; HDT, high-dose therapy; Len, lenalidomide; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGF, next-generation flow cytometry; ORR, overall response rate; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; SAE, serious adverse event; SoC, standard-of-care; Tal, talquetamab; TE, transplant-eligible; Tec, teclistamab; V, bortezomib; VGPR, very good partial response.

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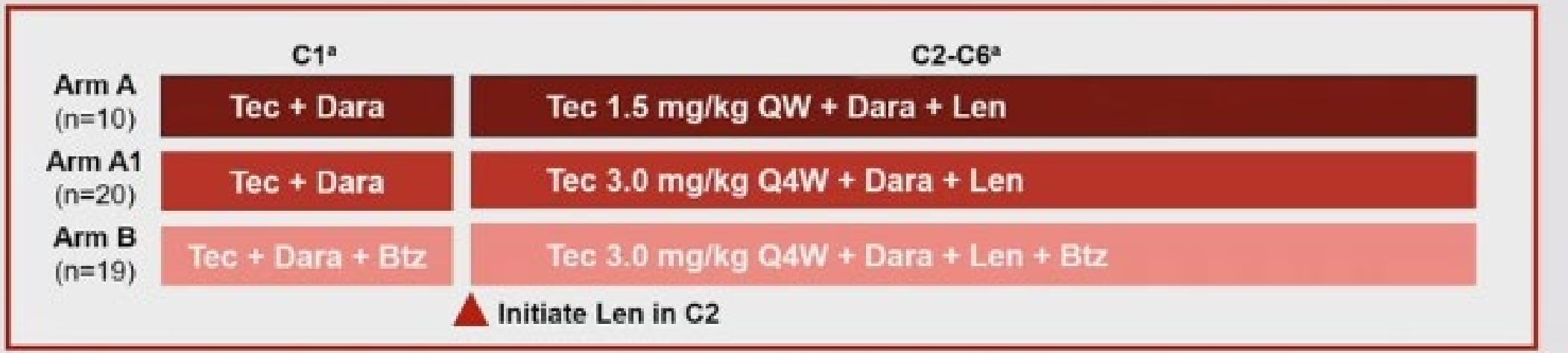
MajesTEC-5 - Dosing schedule



- **Tec in C1:** Tec step up[a] + 1.5 mg/kg on Days 8 and 15[b]
- **Dara:** 1800 mg SC per label (QW for C1 and C2; Q2W for C3-C6)
- **Btz:** 1.3 mg/m^2 SC QW
- **Len:** 25 mg PO daily starting in C2 (Days 1-21)
- **Dex:** 20 mg (PO or IV) in C1 and C2[c]

[a]Patients received step-up doses of 0.05 and 0.3 mg/kg on Day 2 and 4. [b]Patients in Arm A received an additional dose of Tec 1.5 mg/kg on Day 22 [c]Days 1-2, 8-9, 15-16, and 22-23
Btz, bortezomib; C, Cycle; Dara, daratumumab; Dex, dexamethasone; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; IV, intravenously; Len, lenalidomide; PO, orally; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneously; Tec, teclistamab

MajesTEC-5 – Hematologic adverse events

TEAEs, n (%)[a]	Arm A: Tec (QW)-DR (n=10)		Arm A1: Tec (Q4W)-DR (n=20)		Arm B: Tec (Q4W)-DVR (n=19)		Total (N=49)	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Hematologic								
Neutropenia	4 (40)	3 (30)	13 (65)	13 (65)	14 (73.7)	12 (63.2)	31 (63.3)	28 (57.1)
Lymphopenia	8 (80)	7 (70)	7 (35)	7 (35)	7 (36.8)	7 (36.8)	22 (44.9)	21 (42.9)
Thrombocytopenia	3 (30)	1 (10)	7 (35)	2 (10)	7 (36.8)	1 (5.3)	17 (34.7)	4 (8.2)
Anemia	5 (50)	0	6 (30)	4 (20)	5 (26.3)	0	16 (32.7)	4 (8.2)
Leukopenia	5 (50)	2 (20)	3 (15)	2 (10)	6 (31.6)	5 (26.3)	14 (28.6)	9 (18.4)

- The most common hematologic TEAE was neutropenia
- Weekly bortezomib did not increase the frequency of thrombocytopenia

Data cutoff: September 30, 2024. [a]TEAEs reported in ≥25% of patients in any arm. AEs are graded according to the NCI-CTCAE Version 5.0.
AE, adverse event; D, daratumumab; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; TrAE, treatment-emergent adverse event; Tec, teclistamab; V, bortezomib.

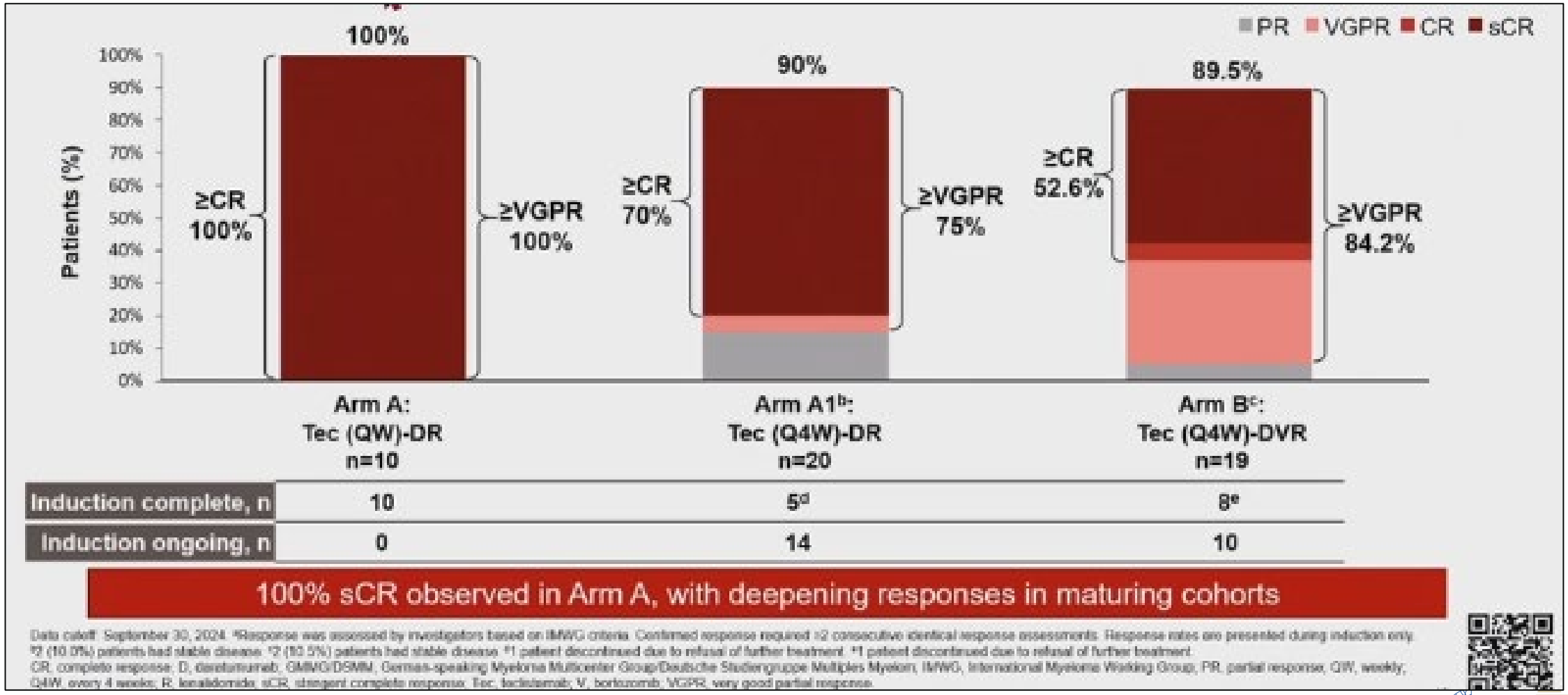
MajesTEC-5 – Infections

TEAE, n (%)[a]	Arm A: Tec (QW)-DR (n=10)		Arm A1: Tec (Q4W)-DR (n=20)		Arm B: Tec (Q4W)-DVR (n=19)		Total (N=49)	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Any infection	10 (100)	4 (40)	18 (90)	9 (45)	11 (57.9)	4 (21.1)	39 (79.6)	17 (34.7)
Infections[b]								
URTI	6 (60)	0	8 (40)	1 (5)	6 (31.6)	0	20 (40.8)	1 (2)
COVID-19	2 (20)	0	4 (20)	1 (5)	3 (15.8)	3 (15.8)	9 (18.4)	4 (8.2)
Nasopharyngitis	3 (30)	0	2 (10)	0	2 (10.5)	0	7 (14.3)	0
Bronchitis	2 (20)	0	0	0	0	0	2 (4.1)	0
Infection (NOS)	0	0	1 (5)	1 (5)	2 (10.5)	1 (5.3)	3 (6.1)	2 (4.1)
Pneumonia	1 (10)	1 (10)	1 (5)	0	2 (10.5)	2 (10.5)	4 (8.2)	3 (6.1)

- 17 (34.7%) patients had grade 3/4 infections
  - URTI and COVID-19 were the most common all grade
  - No discontinuations due to infection
  - No grade 5 infections
- Hypogammaglobulinemia[c] was reported in 45 (91.8%) patients
  - 44 (89.8%) received ≥1 dose of IVIg[d]
- Infection prophylaxis, including Ig replacement, was strongly recommended[e]

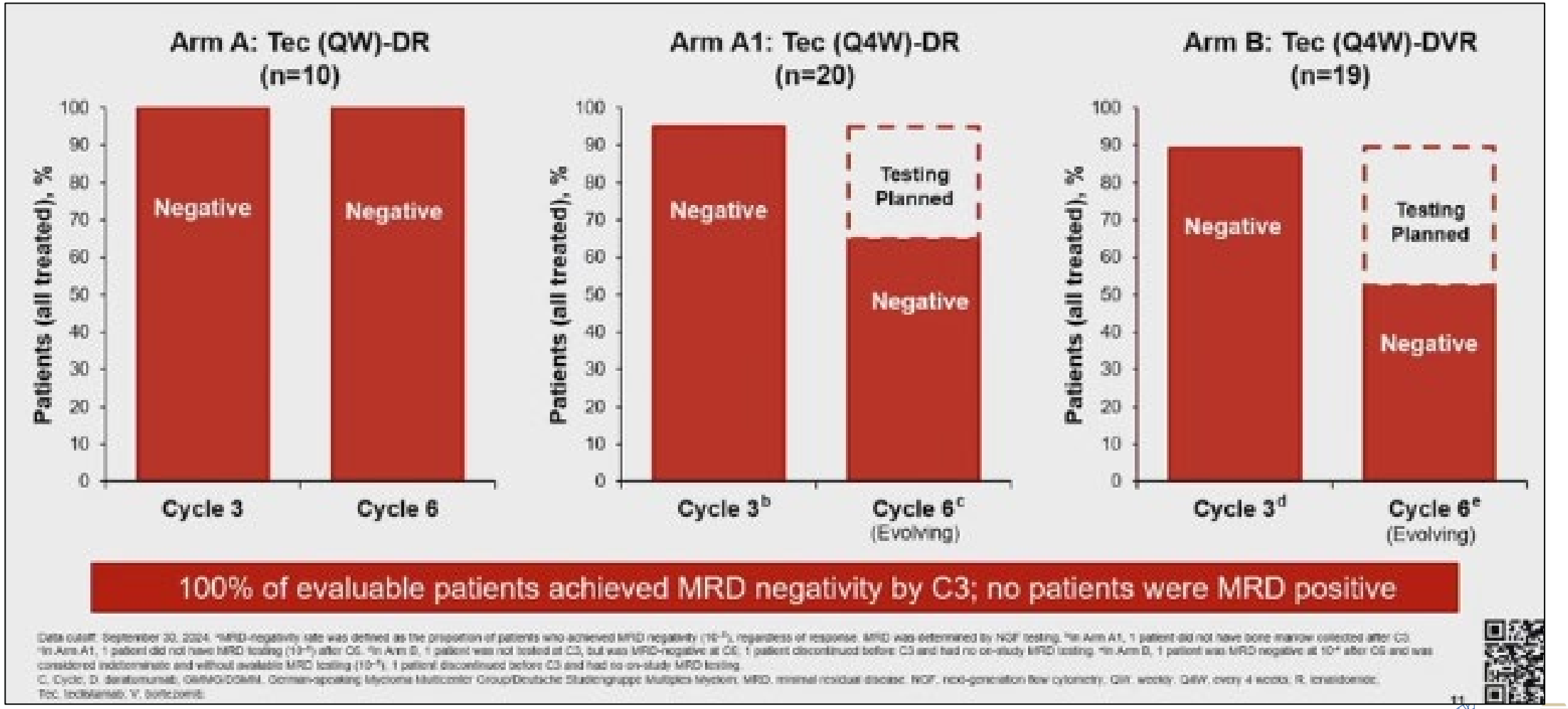
Data cutoff: September 30, 2024. [a]AEs are graded according to the NCI-CTCAE Version 5.0. [b]Infections reported in >10% of patients in any arm. [c]Includes patients with ≥1 TEAE of hypogammaglobulinemia or post-baseline IgG value <400 mg/dL. [d]Includes patients who started IVIg prior to Tec. [e]Prophylaxis for *Pneumocystis jirovecii* pneumonia and herpes zoster reactivation was also recommended, as well as routine antibiotic prophylaxis.
D, daratumumab; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; Ig, immunoglobulin; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NOS, not otherwise specified; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; TEAE, treatment-emergent adverse event; Tec, teclistamab; URTI, upper respiratory tract infection; V, bortezomib.

MajesTEC-5 – Response rates



Data cutoff: September 30, 2024. [a]Response was assessed by investigators based on IMWG criteria. Confirmed response required ≥2 consecutive identical response assessments. Response rates are presented during induction only. [b]2 (10.0%) patients had stable disease. [c]2 (10.5%) patients had stable disease. [d]1 patient discontinued due to refusal of further treatment. [e]1 patient discontinued due to refusal of further treatment.
CR, complete response; D, daratumumab; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; IMWG, International Myeloma Working Group; PR, partial response; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; sCR, stringent complete response; Tec, tecletamab; V, bortezomib; VGPR, very good partial response.

MajesTEC-5 – MRD-Negativity (10^{-5})



MajesTEC-5 - Conclusions

- Tec-DR[a] and Tec-DVR[a] induction was feasible, with very high and early clinical efficacy in patients with TE NDMM
- MRD negativity (10^{-5}) was achieved in 100% of MRD-evaluable patients after C3 and maintained in evaluable patients through C6
- No TEAE-related discontinuations and no new safety signals compared with individual regimen components
- Infections were common, 34.7% of patients had grade 3/4 infections, and no grade 5 events were reported
  - Infection prophylaxis, including Ig replacement, was adopted
- Stem cell mobilization was feasible with Tec-D(V)R[a]

Teclistamab in combination with daratumumab-based standard of care in patients with transplant-eligible NDMM demonstrates promising efficacy with unprecedented early MRD-negativity rates

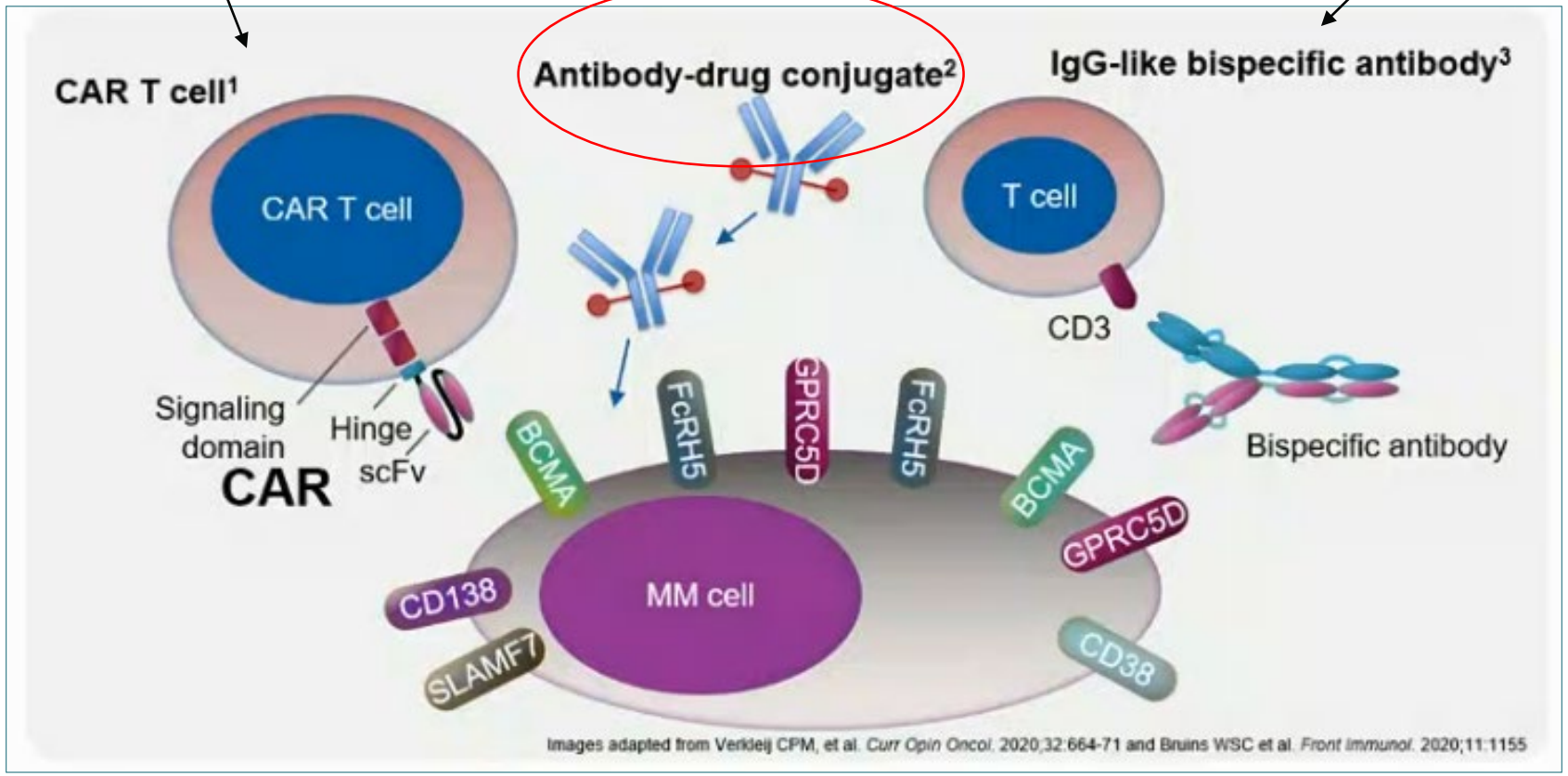
[a]Dexamethasone was also administered in C1 and C2.
C, Cycle; D, daratumumab; d, dexamethasone; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; Ig, immunoglobulin; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; R, lenalidomide; TE, transplant-eligible; Tec, teclistamab; TEAE, treatment-emergent adverse event; V, bortezomib

RRMM

2nd Line

?

4th Line



RRMM – DREAMM-7

Belantamab Mafodotin, Bortezomib, and Dexamethasone vs Daratumumab, Bortezomib, and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Overall Survival Analysis and Updated Efficacy Outcomes of the Phase 3 DREAMM-7 Trial

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NX-DE-BLM-PPT-240039, Dec 24

DREAMM-7 - Introduction

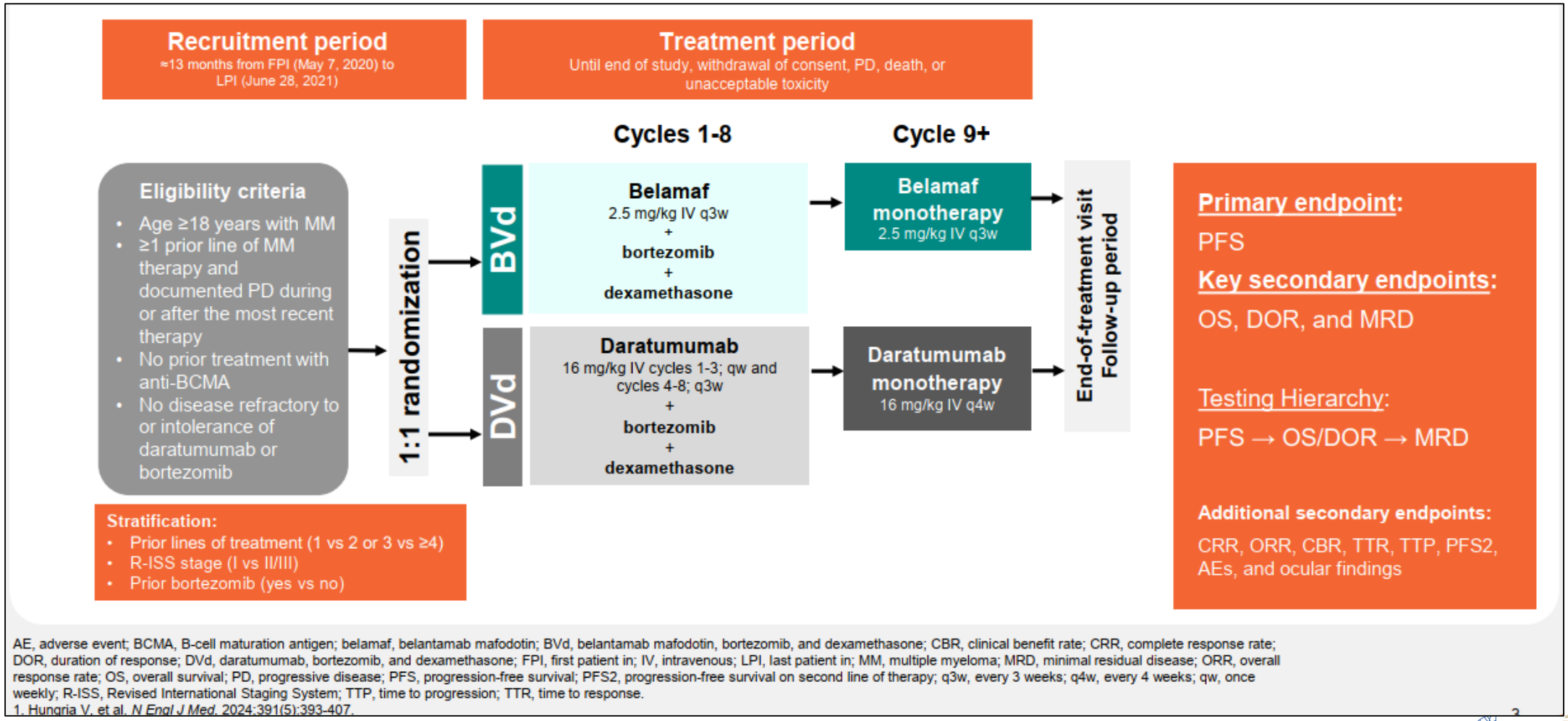
- Patients with multiple myeloma (MM) often have disease that becomes refractory to first-line triplet or quadruplet regimens and experience relapse; therefore, efficacious second-line combinations that incorporate new therapy classes are needed[1,2]
- The DREAMM-7 trial (NCT04246047) evaluated the anti–B-cell maturation antigen monoclonal antibody-drug conjugate belantamab mafodotin (belamaf) in combination with bortezomib and dexamethasone (BVd) vs daratumumab, bortezomib, and dexamethasone (DVd) in patients with relapsed or refractory MM (RRMM) who received ≥1 prior line of therapy[3]
- At a median follow-up of 28.2 months (range, 0.1-40.0 months), the primary endpoint was met, with a median progression-free survival (PFS; 95% CI) of 36.6 months (28.4 months-not reached) with BVd and 13.4 months (11.1-17.5 months) with DVd (hazard ratio [HR], 0.41; 95% CI, 0.31-0.53; *P*<.00001)[3,4]
- Although median overall survival (OS) was not reached in either arm in this primary analysis, a strong trend in favor of BVd vs DVd was observed, with an HR of 0.57 (95% CI, 0.40-0.80)[3,4]

We report updated efficacy and safety, including prespecified OS analysis, at a median follow-up of 39.4 months[a]

[a] Data cutoff: October 7, 2024.

1. Gill SK, et al. *Blood Cancer J*. 2022;12(9):138. 2. Raje N, et al. *Blood Cancer J*. 2023;13(1):41. 3. Hungria V, et al. *N Engl J Med*. 2024;391(5):393-407. 4. Mateos MV, et al. ASCO Plenary Series 2024. Abstract 439572.

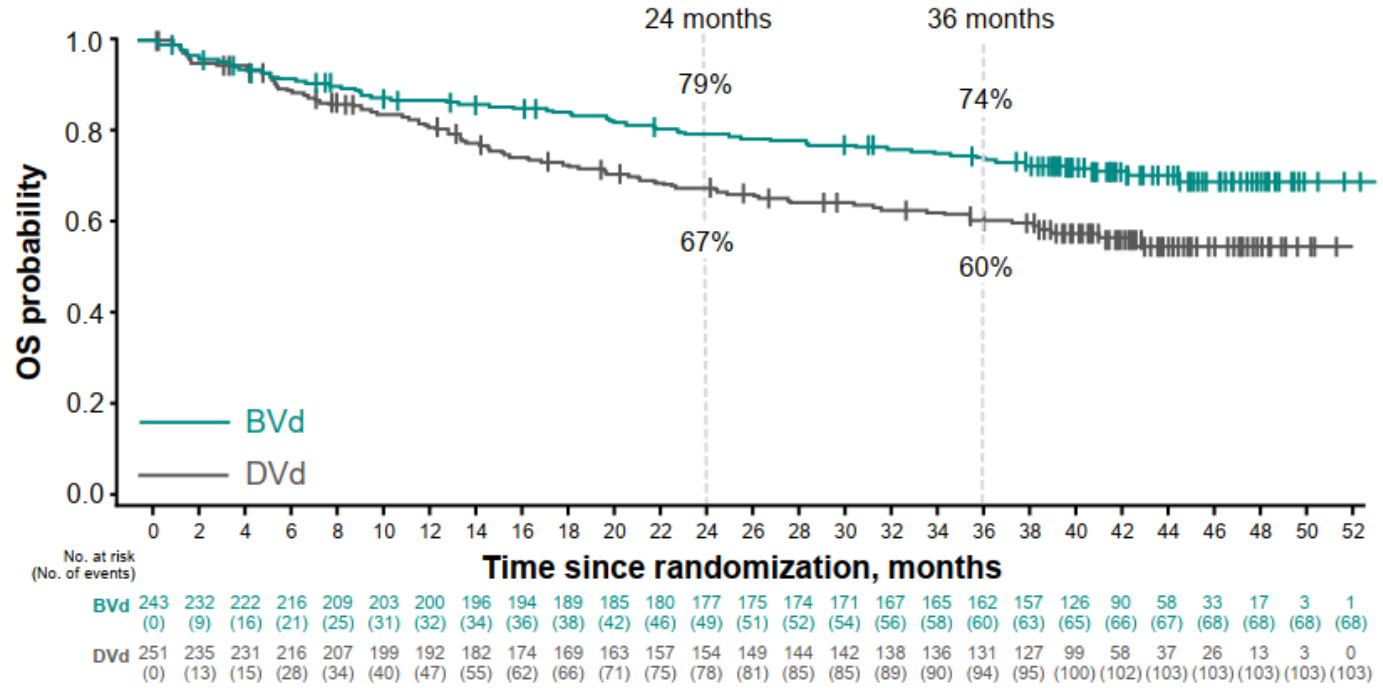
DREAMM-7 – Study design



AE, adverse event; BCMA, B-cell maturation antigen; belamaf, belantamab mafodotin; BVd, belantamab mafodotin, bortezomib, and dexamethasone; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; DVd, daratumumab, bortezomib, and 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, progression-free survival on second line of therapy; q3w, every 3 weeks; q4w, every 4 weeks; qw, once weekly; R-ISS, Revised International Staging System; TTP, time to progression; TTR, time to response.

1. Hungria V, et al. *N Engl J Med*. 2024;391(5):393-407.

DREAMM-7 – Overall survival



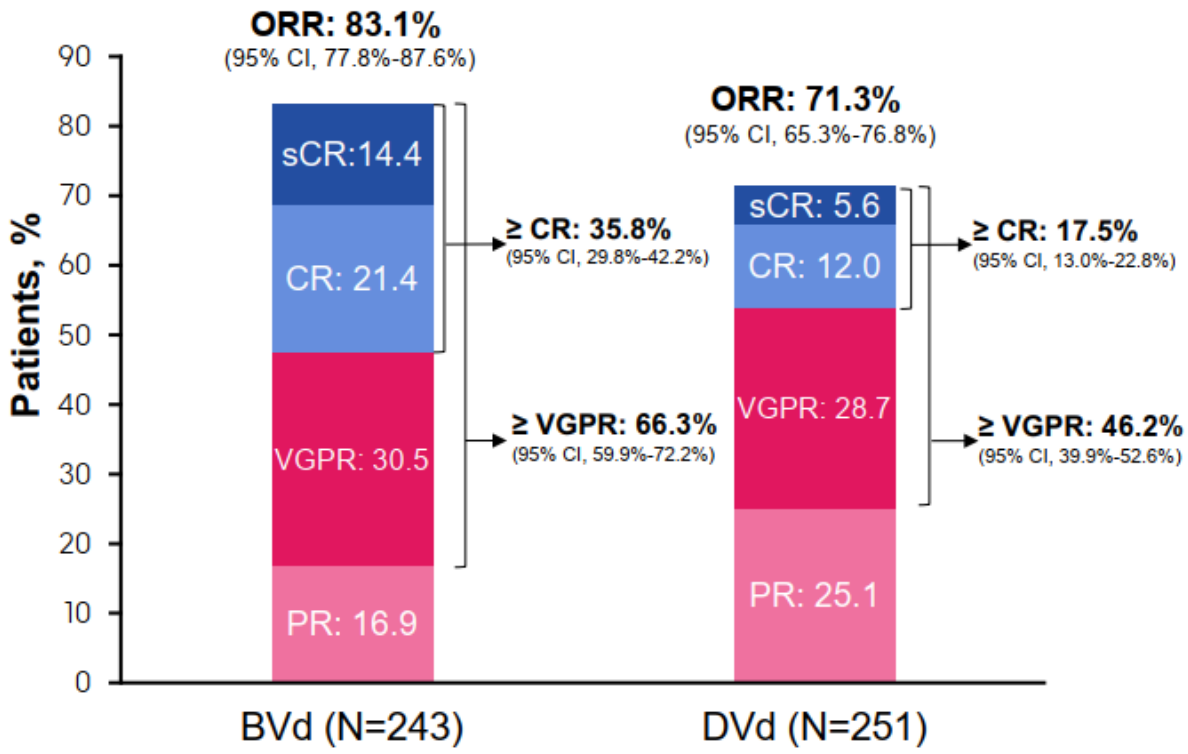
OS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	68 (28)	103 (41)
OS, median (95% CI), months[b]	**NR (NR, NR)**	**NR (41.0, NR)**
HR (95% CI)[c]	**0.58 (0.43-0.79)**	
P value[d]	**.00023**	
24-month survival, % (95% CI)	79 (73-84)	67 (61-73)
36-month survival, % (95% CI)	74 (68-79)	60 (54-66)

Median OS was not reached.
Predicted median OS based on modeling is 84 months with BVd and 51 months with DVd.[e]

BVd, belantamab mafodotin, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; HR, hazard ratio; ITT, intention to treat; NR, not reached; OS, overall survival; R-ISS, Revised International Staging System.
[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. 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 therapy (1 vs 2 or 3 vs ≥4), prior bortezomib (no vs yes), and R-ISS stage at screening (I vs II or III), with a covariate of treatment. [d] *P* value is from a 1-sided stratified log-rank test. At 171 actual events (48.2% OS information fraction), OS was declared significant if the *P* value was <.00112. [e] Post hoc analysis was performed with simulation using an exponential distribution to predict median OS values in each arm using the observed data at this interim analysis 2, with a 39.4-month median follow-up, to extrapolate time to death in ongoing censored patients. Predicted median OS values are subject to change as data mature.

6

DREAMM-7 – Response rates/MRD Negativity



Responses (95% CI), %	BVd (N=243)	DVd (N=251)
≥ CR and MRD negativity (sensitivity of 10^{-5})[b]	25.1 (19.8-31.0)	10.4 (6.9-14.8)
≥ VGPR and MRD negativity (sensitivity of 10^{-5})[b]	38.7 (32.5-45.1)	17.9 (13.4-23.2)

- MRD negativity from the primary analysis can now be considered statistically significant[1,c]
  - ≥ CR and MRD negativity: 24.7% vs 9.6%, *P*<.00001
  - ≥ VGPR and MRD negativity: 38.7% vs 17.1%, *P*<.00001

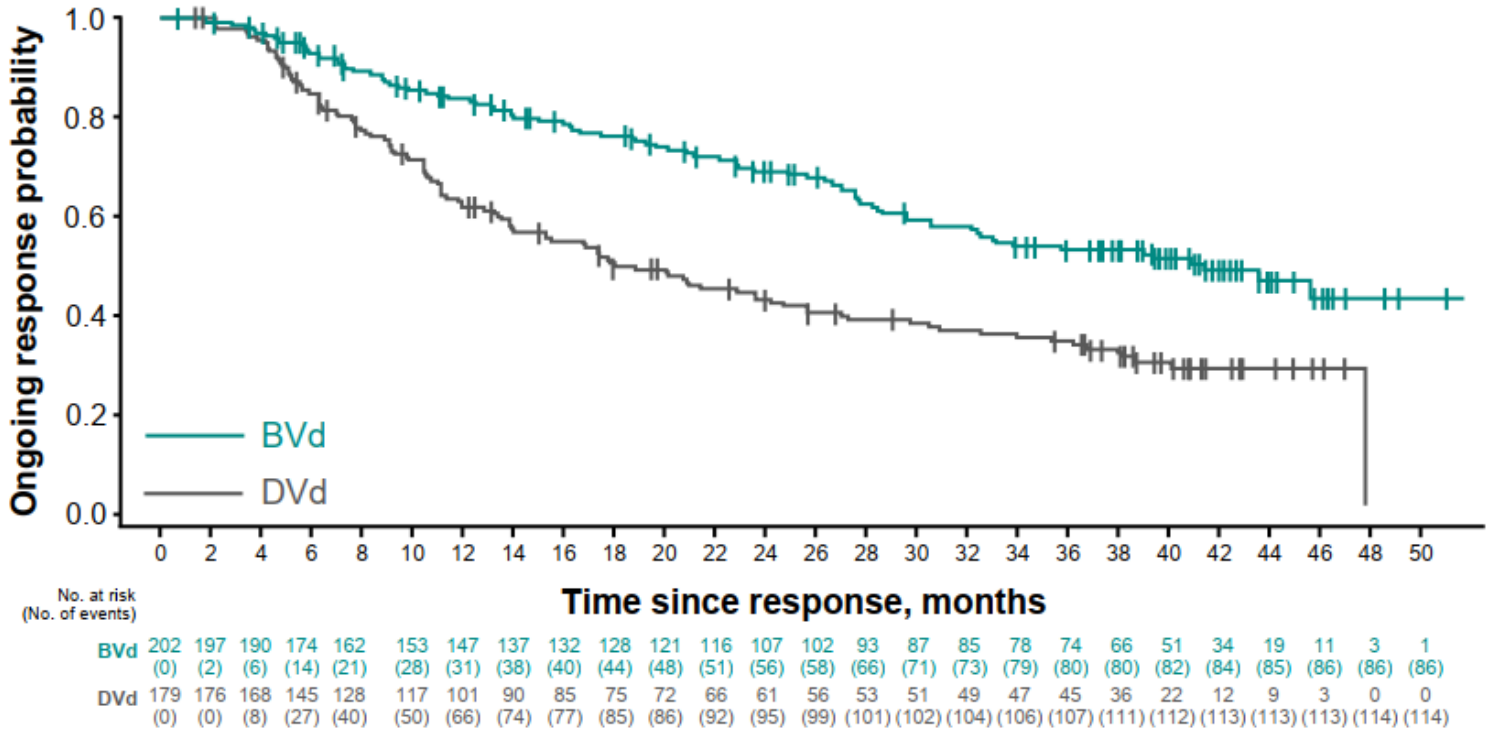
BVd, belantamab mafodotin, bortezomib, and dexamethasone; CR, complete response; DVd, daratumumab, bortezomib, and dexamethasone; ITT, intention to treat; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

[a] CIs were based on the exact method. Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] MRD-negativity rate is defined as the percentage of patients who were MRD negative by NGS based on a sensitivity of 10^{-5}. [c] Since OS is significant in this analysis, the MRD-negativity results from the primary analysis can now be considered statistically significant due to testing hierarchy.

1. Hungria V, et al. *N Engl J Med*. 2024;391(5):393-407.

10

DREAMM-7 – Duration of response



DOR[a]	BVd (N=243)	DVd (N=251)
Responders, n	202	179
Events, n (%)	86 (43)	114 (64)
Ongoing response, n (%)	79 (39)	39 (22)
DOR, median (95% CI), months[b]	**40.8 (30.5, NR)**	**17.8 (13.8-23.6)**

Median DOR with BVd was more than double that with DVd.

BVd, belantamab mafodotin, bortezomib, and dexamethasone; DOR, duration of response; DVd, daratumumab, bortezomib, and dexamethasone; ITT, intention to treat; NR, not reached.
[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs estimated using the Brookmeyer-Crowley method.

DREAMM-7 – Adverse events

n (%)	BVd (N=242)		DVd (N=246)	
Blood and lymphatic system disorders	All grades	Grade ≥3	All grades	Grade ≥3
Thrombocytopenia[b]	169 (70)	135 (56)	122 (50)	87 (35)
Anemia[c]	48 (20)	21 (9)	65 (26)	25 (10)
Neutropenia[d]	45 (19)	34 (14)	44 (18)	24 (10)
Infections and infestations	176 (73)	80 (33)	167 (68)	49 (20)
Pneumonia	48 (20)	30 (12)	23 (9)	10 (4)

Exposure-adjusted rate (per 100 person-years)[e]	BVd (N=242)		DVd (N=246)	
Blood and lymphatic system disorders	All grades	Grade ≥3	All grades	Grade ≥3
Thrombocytopenia	42.01	33.56	35.58	25.37
Neutropenia	11.19	8.45	12.83	7.00
Infections and infestations	43.75	19.89	48.71	14.29
Pneumonia	11.93	7.46	6.71	2.92

In the BVd and DVd arms, exposure-adjusted rates of infections per 100 person-years[e] were 43.75 and 48.71 (all grades) and 19.89 and 14.29 (grade ≥3), respectively.

DREAMM-7 – ocular events

Reprinted from Shi C, et al. *J Vis*. 2020;20(8):29. Copyright © 2020 The Authors.

BVd	Bilateral worsening of BCVA in patients with normal baseline 20/25 or better	
	20/50 or worse[a]	20/200 or worse[a]
Patients, n/N (%)	84/242 (35)	5/242 (2)
Time to onset of first event, median (range), days	79 (16-1320)	105 (47-304)
Time to resolution of first event to baseline, median (range), days[b]	64 (8-908)	87 (22-194)
Time to improvement of first event, median (range), days[c]	22 (6-257)	19 (8-26)
First event resolved, n/N (%)[b]	78/84 (93)	4/5 (80)
First event improved, n/N (%)[c]	81/84 (96)	5/5 (100)
Follow-up ended with event ongoing, n/N (%)	2/84 (2)	0

- Blurred vision was the most frequent ocular adverse reaction in the BVd arm, with 68% and 24% of patients experiencing all grades and grade 3/4 events, respectively[d]
- Discontinuation due to any ocular events was 10%

DREAMM-7 - Conclusions

- BVd demonstrated a statistically significant and clinically meaningful improvement in OS compared with DVd in patients with RRMM after ≥1 prior line of therapy (HR, 0.58; 95% CI, 0.43-0.79; *P*=.00023)
  - OS benefit with BVd was early and sustained
  - Although median OS was not reached, predicted median OS using modeling is 84 months with BVd and 51 months with DVd[a]
  - Minimal residual disease (MRD)–negativity rates in favor of BVd from the primary analysis can now be considered statistically significant[b]
- Treatment benefits with BVd were also maintained after subsequent antimyeloma therapy, with an HR (95% CI) for PFS2 of 0.59 (0.45-0.77)
- BVd maintained durable and deep responses and continued to result in double the ≥ CR rates, MRD-negativity rates, and median duration of response (DOR) compared with DVd, with extended follow-up
- The safety profile was consistent with the previous analysis and known profiles of the individual agents
  - Ocular events were generally resolved, were manageable with dose modifications, and led to low treatment discontinuation rates

- **DREAMM-7 demonstrated statistically significant PFS, OS, DOR, and MRD-negativity benefits with BVd compared with DVd**

RRMM – CC-92480-MM-002

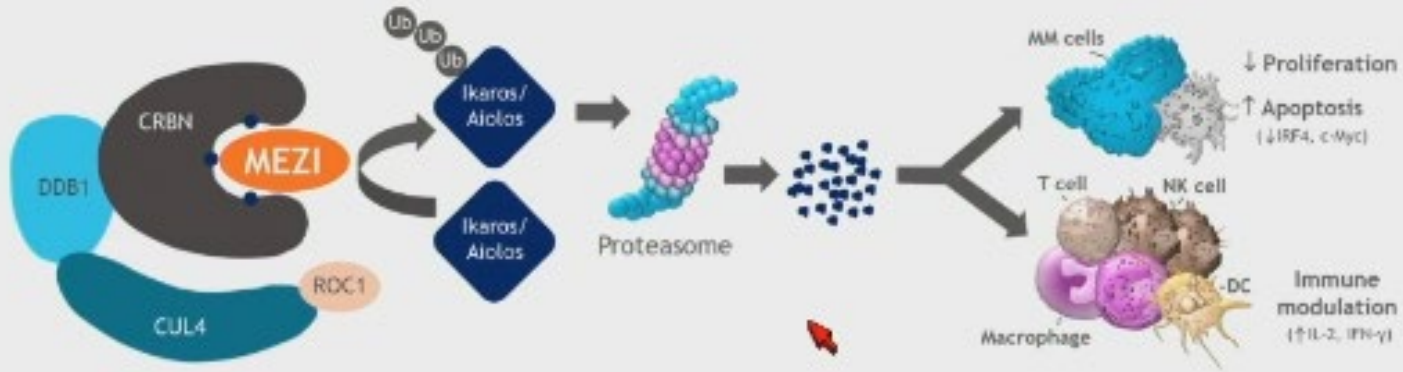
Mezigdomide plus dexamethasone and bortezomib or carfilzomib in patients with relapsed/refractory multiple myeloma: updated results from the CC-92480-MM-002 trial

Irwindeep Sandhu,[1] Paul G. Richardson,[2] Albert Oriol,[3] Darrell White,[4] Richard LeBlanc,[5] Noopur Raje,[6] Enrique M. Ocio,[7] Aurore Perrot,[8] Thierry Facon,[9] Cesar Rodriguez,[10] Ralph Wäsch,[11] Meletios A. Dimopoulos,[12] Tracy T. Chow,[13] Allison Gaudy,[13] Jing Gong,[13] Zehua Zhou,[13] Tiziana Civardi,[14] Joseph T. Hadala,[13] Yue Zhu,[15] Jessica Katz,[13] Marc S. Raab[16]

[1]University of Alberta, Edmonton, AB, Canada; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Catalan Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Spain; [4]Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [5]Hôpital Maisonneuve-Rosemont, Université de Montréal, Montreal, QC, Canada; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Hospital Universitario Marqués de Valdecilla (IDIVAL), Universidad de Cantabria, Santander, Spain; [8]Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France; [9]Centre Hospitalier Universitaire (CHU) Lille, Service des Maladies du Sang, University of Lille, Lille, France; [10]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [11]Department of Medicine, University of Freiburg Medical Center, Freiburg, Germany; [12]National and Kapodistrian University of Athens, Athens, Greece; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [15]Bristol Myers Squibb, Princeton, NJ, USA, at the time the study was conducted; [16]Heidelberg Myeloma Center, Department of Medicine V, Heidelberg University Hospital, Heidelberg, Germany

CC-92480-MM-002

- MEZI is a novel, oral CELMoD™ agent that is a potent inducer of Ikaros and Aiolos degradation, resulting in immune-modulatory effects and enhanced tumoricidal activity in myeloma cells[1-3]
- In patients with triple-class RRMM, MEZI + DEX had a manageable safety profile and a promising ORR of 41%[4]
- In preclinical studies, MEZI has shown marked synergy in combination with other antimyeloma therapies, including DEX, PIs, and anti-CD38 mAbs[5]
- This study reports updated results with longer follow-up from the phase 1/2 CC-92480-MM-002 trial (NCT03989414)[6-8] from the MEZI + DEX + BORT (MeziVd) and MEZI + DEX + CFZ (MeziKd) dose-escalation cohorts (A and C) and the MeziVd dose-expansion cohort (D)

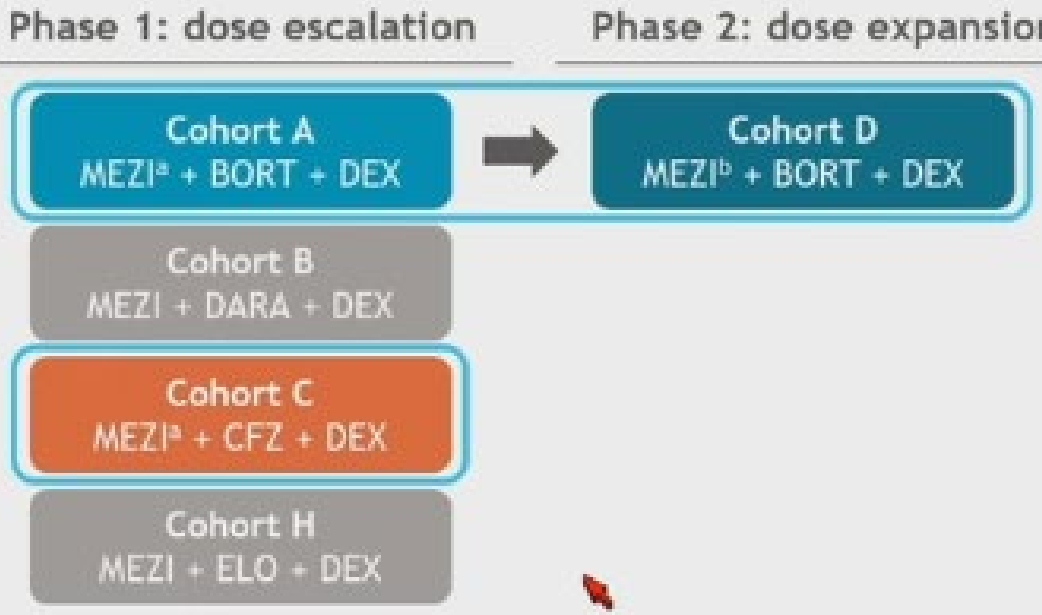


BORT, bortezomib; CD, cluster of differentiation; CFZ, carfilzomib; c-Myc, cellular Myc; CRBN, cereblon; CUL4, cullin 4; DC, dendritic cell; DDB1, DNA damage-binding protein 1; DEX, dexamethasone; IFN, interferon; IL, interleukin; IRF4, interferon regulatory factor 4; mAb, monoclonal antibody; MEZI, mezigdomide; MM, multiple myeloma; NK, natural killer; ORR, overall response rate; PI, proteasome inhibitor; RDC1, regulator of cullins-1; RRMM, relapsed/refractory multiple myeloma; Ub, ubiquitin.

1. Hansen JD, et al. *J Med Chem* 2020;63:6648-6676. 2. Lu G, et al. *Science* 2014;343:305-309. 3. John LB, Ward AC. *Mol Immunol* 2011;48:1272-1278. 4. Richardson PG, et al. *N Engl J Med* 2023;389:1009-1022. 5. Wang L, et al. *Blood* 2019;134(suppl 1). Abstract 1815. 6. ClinicalTrials.gov. NCT03989414. 7. Richardson PG, et al. *Blood* 2021;138(suppl 1). Abstract 2731. 8. Oriol A, et al. Oral presentation at the International Myeloma Society (IMS) Annual Meeting; September 27-30; 2023; Athens, Greece. Abstract OA-49.

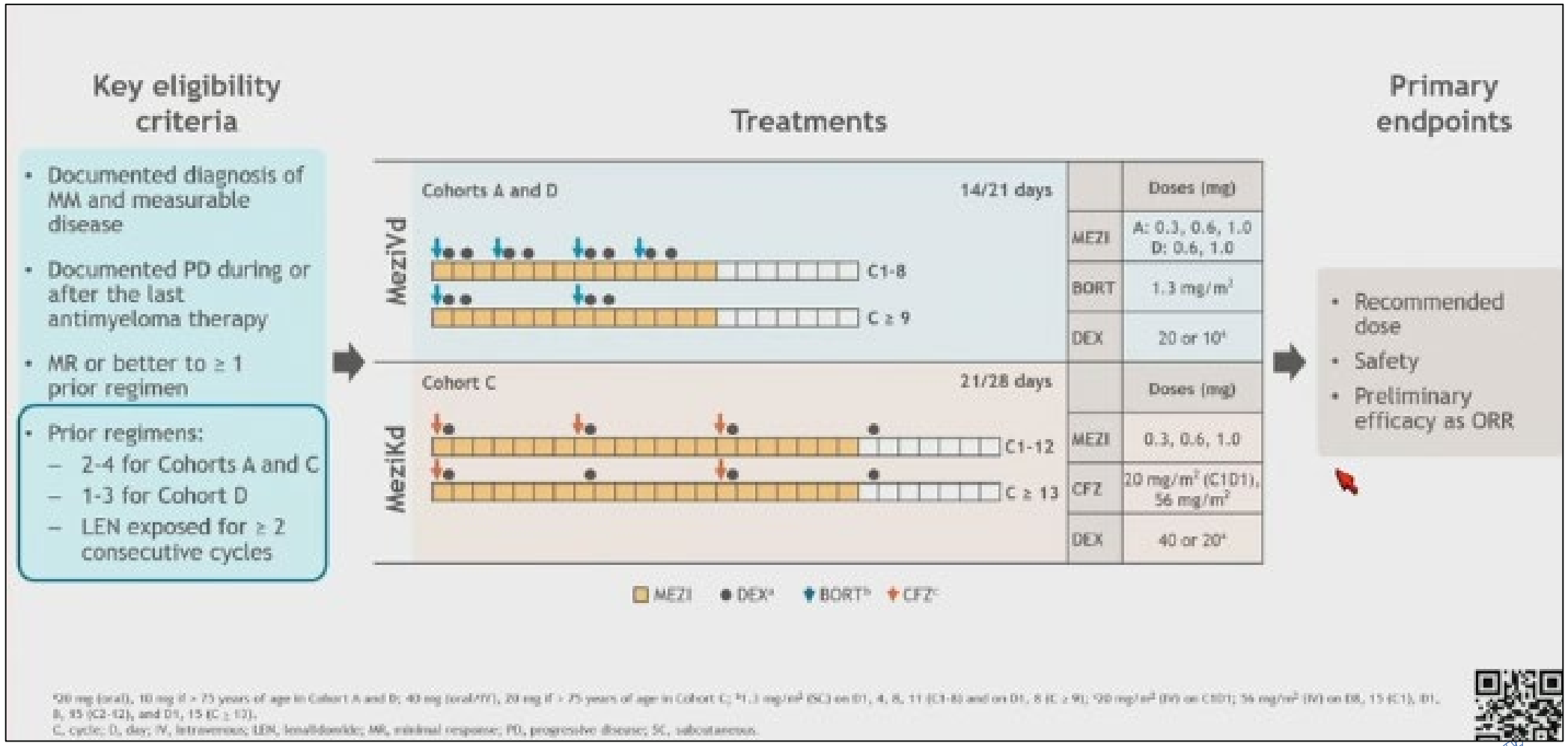
CC-92480-MM-002 – Study design

Open-label, multicenter, phase 1/2 dose-finding and dose-expansion clinical trial evaluating MEZI + DEX in combination with different treatments in patients with MM[1,2]



[illegible], 0.4, or 1.0 mg; [b]0.6 and 1.0 mg.
DARA, daratumumab; ELO, elotuzumab.
1. ClinicalTrials.gov: NCT03989414; 2. EudraCT number: 2018-004767-31.

CC-92480-MM-002 – Cohorts A, D, C



CC-92480-MM-002 – Baseline characteristics

Characteristic[a]	Cohort A (MeziVd) (N = 28)	Cohort D (MeziVd) (N = 49)	Cohort C (MeziKd) (N = 27)
Age, median (range), years	65.5 (46-86)	64.0 (43-83)	68.0 (41-76)
Sex, n (%)			
Female	16 (57.1)	16 (32.7)	18 (66.7)
Time since initial diagnosis, median (range), years	4.8 (1.9-17.1)	4.2 (0.9-20.5)	5.4 (0.7-15.7)
ECOG PS score, n (%)			
0	11 (39.3)	22 (44.9)	10 (37.0)
1	15 (53.6)	25 (51.0)	15 (55.6)
2	2 (7.1)	2 (4.1)	2 (7.4)
ISS stage at study entry, n (%)			
I	20 (71.4)	34 (69.4)	21 (77.8)
II	6 (21.4)	9 (18.4)	3 (11.1)
III	2 (7.1)	6 (12.2)	3 (11.1)
Presence of plasmacytomas,[b] n (%)	5 (17.9)	6 (12.2)	3 (11.1)
High-risk cytogenetics,[c] n (%)	12 (42.9)[d]	26 (53.1)[e]	16 (59.3)[f]

Approximately half of all patients had high-risk cytogenetics

CC-92480-MM-002 – prior therapies

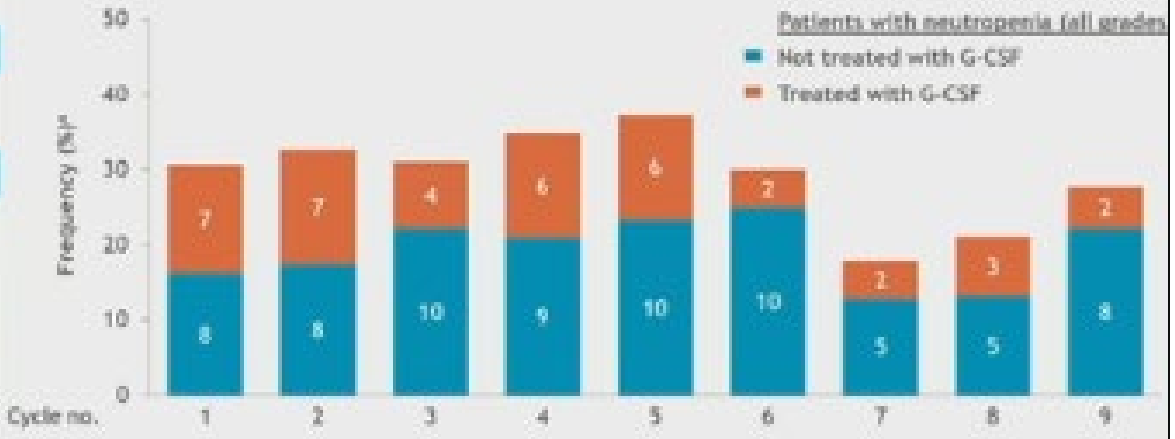
Treatment characteristic[a]	Cohort A (MeziVd) (N = 28)	Cohort D (MeziVd) (N = 49)	Cohort C (MeziKd) (N = 27)
Prior therapies, median (range), n	3 (2-4)	1 (1-3)	2 (2-4)
Stem cell transplantation, n (%)	17 (60.7)	35 (71.4)	19 (70.4)
PI, n (%)	27 (96.4)	44 (89.8)	27 (100.0)
BORT, n (%)	23 (82.1)	36 (73.5)	27 (100.0)
CFZ, n (%)	10 (35.7)	13 (26.5)	2 (7.4)
IMiD® agent, n (%)	28 (100.0)	49 (100.0)	27 (100.0)
Anti-CD38 mAb, n (%)	14 (50.0)	19 (38.8)	22 (81.5)
IMiD agent refractory, n (%)	24 (85.7)	31 (63.3)	24 (88.9)
LEN refractory, n (%)	23 (82.1)	31 (63.3)	21 (77.8)
POM refractory, n (%)	13 (46.4)	0	12 (44.4)
PI refractory, n (%)	14 (50.0)	8 (16.3)	14 (51.9)
IXA refractory, n (%)	6 (21.4)	2 (4.1)	2 (7.4)
BORT refractory, n (%)	3 (10.7)	1 (2.0)	13 (48.1)
CFZ refractory, n (%)	7 (25.0)	5 (10.2)	0
Anti-CD38 mAb refractory, n (%)	14 (50.0)	17 (34.7)	20 (74.1)
Triple-class refractory,[b] n (%)	9 (32.1)	1 (2.0)	10 (37.0)

Patients in Cohorts A and C were heavily pretreated, and all patients were exposed to IMiD agents

CC-92480-MM-002 – Cohort D (MeziVd) - Adverse events

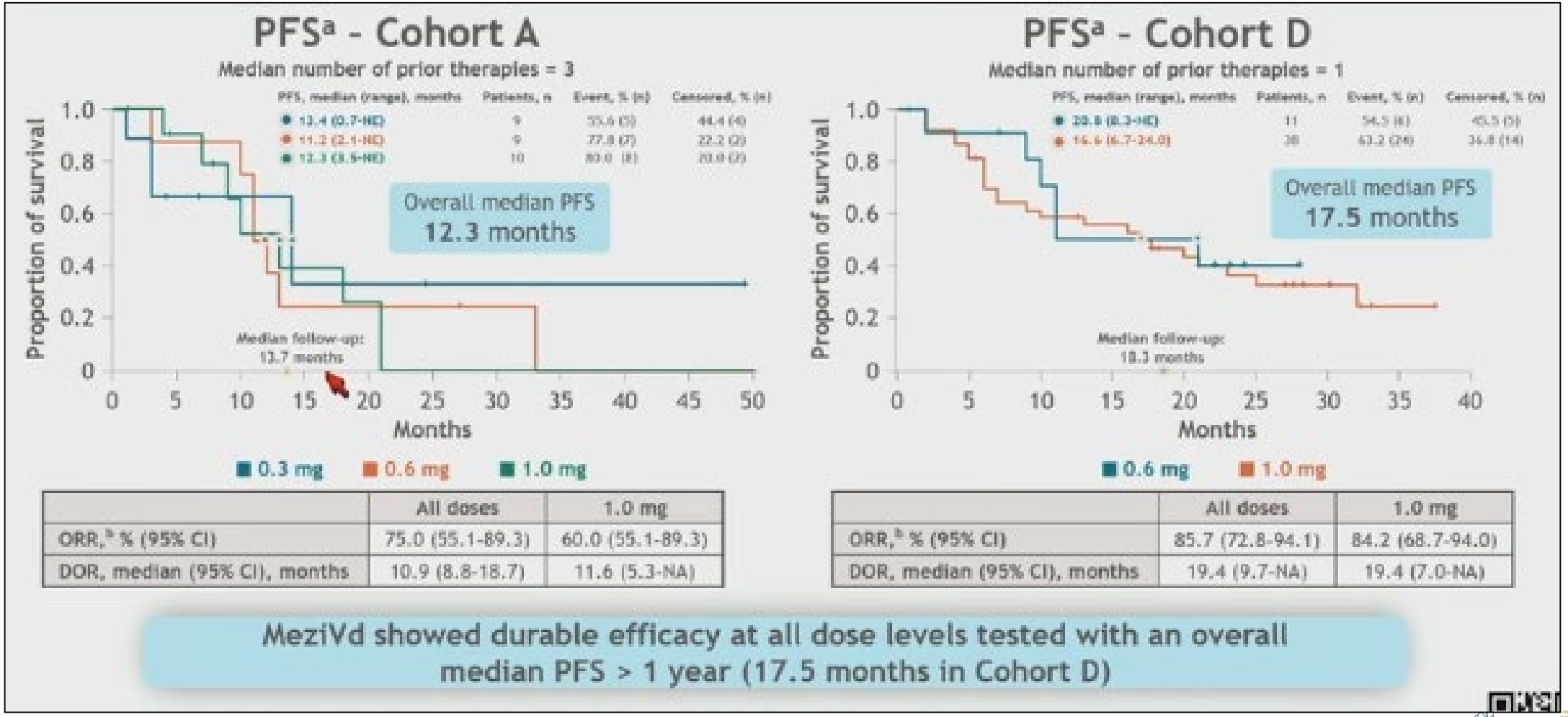
Most common[a,b] grade 3/4 TEAEs and events of interest, n (%)	Cohort D (MeziVd) (N = 49)[f]	
	0.6 mg (n = 11)	1.0 mg (n = 38)
Hematologic TEAEs		
Neutropenia	8 (72.7)	23 (60.5)
Thrombocytopenia	2 (18.2)	11 (28.9)
Anemia	0	3 (7.9)
Infections	2 (18.2)	14 (36.8)
COVID-19[c]	1 (9.1)	3 (7.9)
Pneumonia[d]	1 (9.1)	9 (23.7)
Patients with neutropenia and concurrent[e] infection, n (%)		
Any neutropenia + grade 3/4 infection	1 (9.1)	3 (7.9)
Grade 3/4 neutropenia + any infection	4 (36.4)	12 (31.6)

Occurrence of neutropenia by cycle[a]



Neutropenia was managed with G-CSF treatment and fewer than 10% of patients with any neutropenia had grade 3/4 infections

CC-92480-MM-002 – PFS (Cohort A and D (MeziVd))

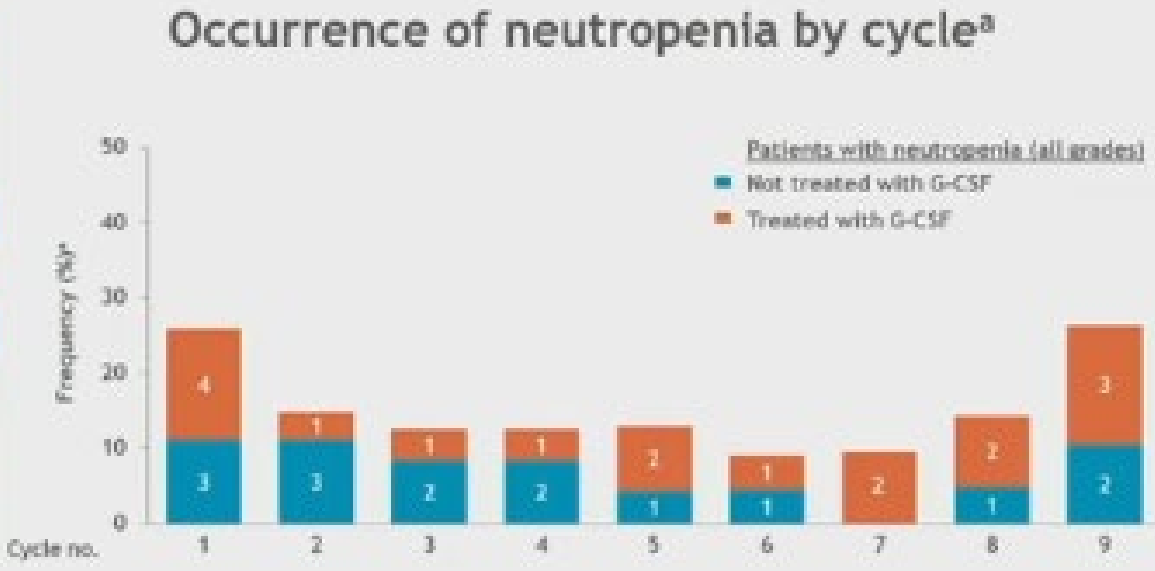


	All doses	1.0 mg
ORR,[b] % (95% CI)	75.0 (55.1-89.3)	60.0 (55.1-89.3)
DOR, median (95% CI), months	10.9 (8.8-18.7)	11.6 (5.3-NA)

	All doses	1.0 mg
ORR,[b] % (95% CI)	85.7 (72.8-94.1)	84.2 (68.7-94.0)
DOR, median (95% CI), months	19.4 (9.7-NA)	19.4 (7.0-NA)

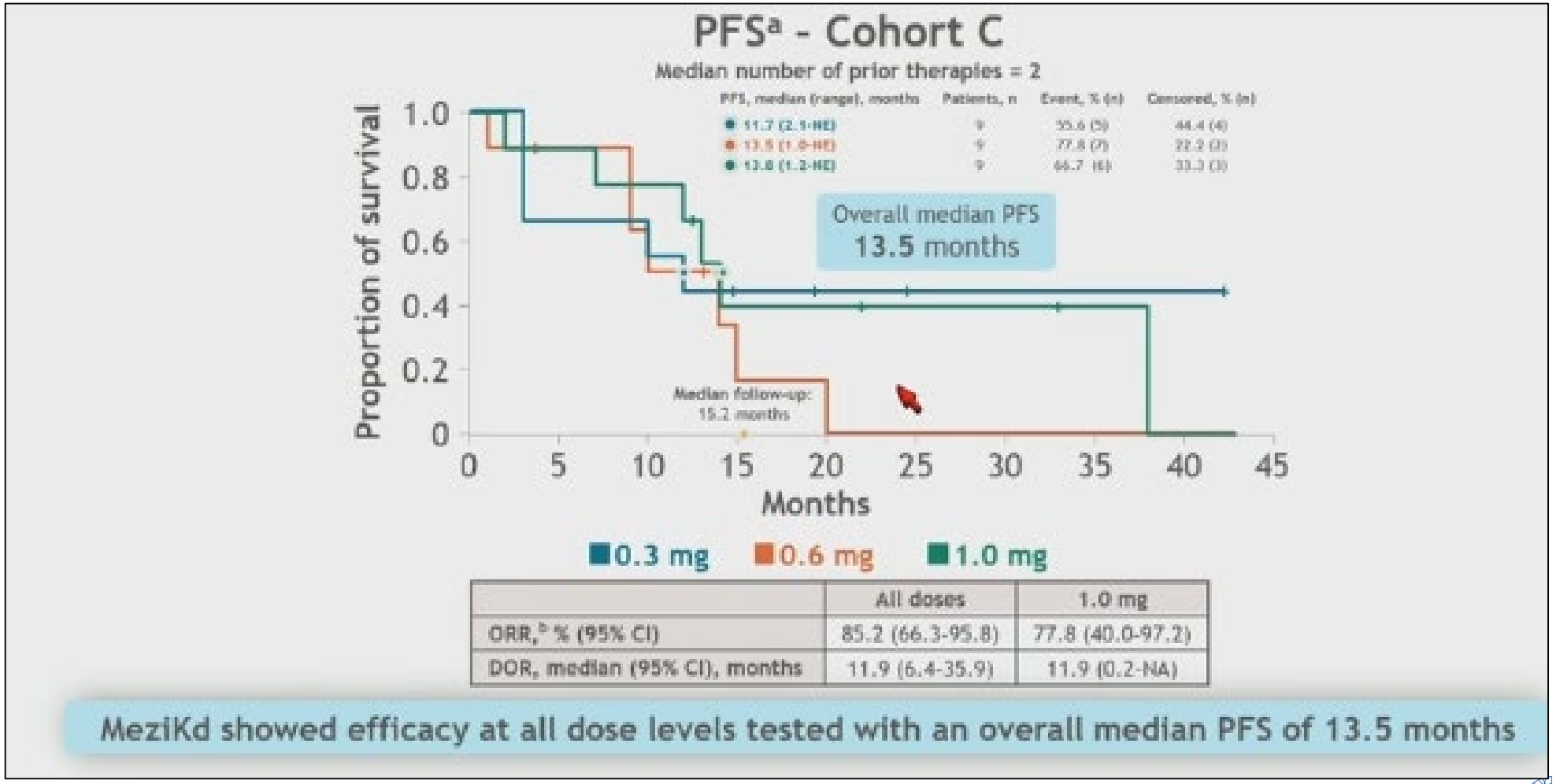
CC-92480-MM-002 - Cohort C (MeziKd) - Adverse events

Most common[a,b] grade 3/4 TEAEs and events of interest, n (%)	Cohort C (MeziKd) (N = 27)[f]	
	0.3 + 0.6 mg (n = 18)[g]	1.0 mg (n = 9)
Hematologic TEAEs		
Neutropenia	6 (33.3)	6 (66.7)
Thrombocytopenia	1 (5.6)	3 (33.3)
Anemia	2 (11.1)	2 (22.2)
Infections	6 (33.3)	3 (33.3)
COVID-19[e]	4 (22.2)	1 (11.1)
Pneumonia[d]	0	1 (11.1)
Patients with neutropenia and concurrent[a] infection, n (%)		
Any neutropenia + grade 3/4 infection	0	1 (11.1)
Grade 3/4 neutropenia + any infection	0	2 (22.2)



Neutropenia was managed with G-CSF treatment and was associated with few grade 3/4 infections

CC-92480-MM-002 – PFS (Cohort C (MeziKd))



	All doses	1.0 mg
ORR,[b] % (95% CI)	85.2 (66.3-95.8)	77.8 (40.0-97.2)
DOR, median (95% CI), months	11.9 (6.4-35.9)	11.9 (0.2-NA)

MeziKd showed efficacy at all dose levels tested with an overall median PFS of 13.5 months

CC-92480-MM-002 - Conclusions

- MEZI is a novel, oral CELMoD agent that induces rapid, potent, and deep degradation of Ikaros and Aiolos, resulting in enhanced cytotoxic effects in myeloma cells and direct T-cell and NK-cell immune-stimulatory activities[1]
- Proteasome inhibition does not abrogate the substrate degradation induced by MEZI
- MEZI demonstrated dose-dependent linear pharmacokinetics, with no difference in exposure between Cohorts A, D, or C[2]
- MeziVd and MeziKd in RRMM confirmed promising efficacy at all dose levels tested, including at the 1.0-mg dose, in patients with RRMM previously exposed to IMiD agents, PI, and anti-CD38 mAbs
  - Responses were deep and durable (ORR Cohort A: 75.0%; Cohort D: 85.7%; Cohort C: 85.2%), with median PFS of ≥ 1 year in all cohorts (Cohort A: 12.3 months; Cohort D: 17.5 months; Cohort C: 13.5 months)
  - PFS was longer in the MeziVd dose-expansion cohort (Cohort D) with 1 median prior line of therapy than in the dose-escalation cohort (Cohort A) with 3 median prior lines of therapy
- Among all cohorts, MEZI demonstrated a manageable safety profile with no cumulative toxicity
  - Neutropenia was the most common grade 3/4 TEAE, occurred infrequently with grade 3/4 infections, and was manageable with G-CSF and dose interruption/reduction
  - Non-hematologic grade 3/4 TEAEs were uncommon

These results support the investigation of MEZI in the phase 3 trials SUCCESSOR-1[a] (MeziVd vs PVd) and SUCCESSOR-2[b] (MeziKd vs Kd) in RRMM

Zusammenfassung

- Daratumumab Monotherapie beim high-risk Smoldering Myelom
- CAR-T-Zell Therapie und bispezifische Antikörper in der Erstlinientherapie/Erhaltung
- „Comeback“ Belantamab Mafodotin als Kombinationstherapie beim RRMM
- Mezigdomide (CELMoD) als Kombinationstherapie bei RRMM

Vielen Dank für Ihre Aufmerksamkeit

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