Phase 3 Randomized Study of Teclistamab Plus Daratumumab Versus Investigator's Choice of Daratumumab and Dexamethasone With Either Pomalidomide or Bortezomib (DPd/DVd) in Patients With Relapsed Refractory Multiple Myeloma (RRMM): Results of MajesTEC-3

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https://www.congresshub.com/ASH2025/Oncology/Teclistamab/Mateos-LBA

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MajesTEC-3: Background

- Front-line MM therapy has dramatically improved; however, new, more effective treatments are needed for patients whose disease progresses[1-3]
- Community-ready combination regimens with outpatient administration on a convenient schedule have the potential to deliver improved outcomes for patients regardless of treatment setting
- Teclistamab (Tec), a combinable BCMA-targeting BsAb redirecting T-cells, provides patients with deep, durable responses in RRMM with improved efficacy and safety in earlier lines of therapy (MajesTEC-1)[4-6]
- Daratumumab (Dara), a foundational anti-CD38 targeting mAb used in ~725K patients worldwide,[7,8] has consistently improved OS in NDMM and RRMM[9-13]
- MajesTEC-3 is a phase 3 randomized study, exploring a fully immunotherapy-based regimen of Tec-Dara versus Dara–based SOC regimens in 1-3 prior LOTs

We present results from the initial pre-planned analysis of MajesTEC-3; the first bispecific phase 3 study to report results

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; LOTs, lines of therapy; mAb, monoclonal antibody; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; OS, overall survival; RRMM, relapsed or refractory multiple myeloma; SOC, standard of care.

1. Fonseca R, et al. *BMC Cancer.* 2020;20:1087. 2. Yong K, et al. *Br J Haematol.* 2016;175:252-264. 3. Bhatt P, et al. *Curr Oncol.* 2023;30:2322-2347. 4. Moreau P, et al. *N Engl J Med.* 2022;387:495-505. 5. Costa LJ, et al. Presented at: HEMO; October 23-26, 2024; São Paulo, Brazil. Poster 912. 6. Garfall AL, et al. Presented at: ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA. Poster 7540. 7. DARZALEX® (daratumumab) [package insert]. Janssen Biotech, Inc.; 2025. 8. Johnson & Johnson, data on file. 9. Facon T, et al. *Leukemia.* 2025;39:942-950. 10. Palumbo A, et al. *N Engl J Med.* 2016;375:754-766. 11. Dimopoulos MA, et al. *Lancet Haematol.* 2023;10:e813-824. 12. Usmani SZ, et al. *Blood Adv.* 2023;7:3739-3748. 13. Voorhees PM, et al. *Lancet Haematol.* 2023;10:e825-837.

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MajesTEC-3: Tec + Dara Synergistic[1] Immunotherapy Combination

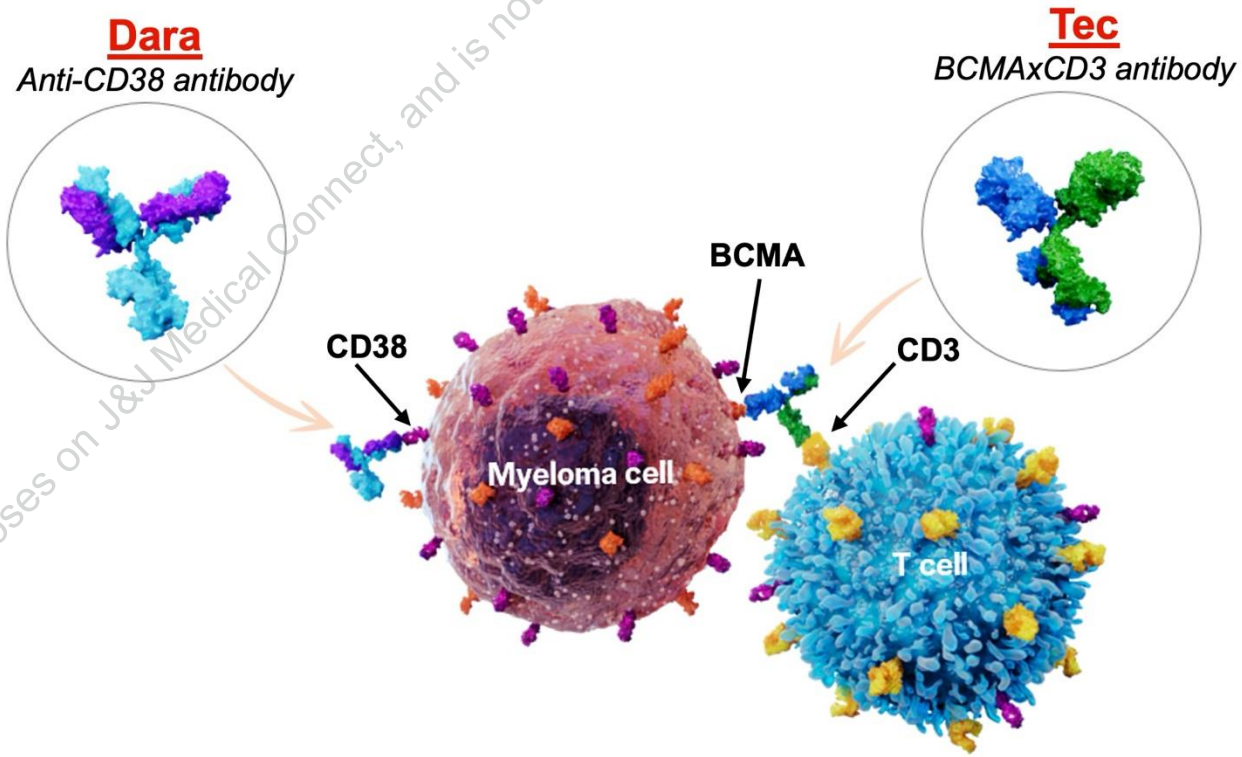
Dara PRIMES
the microenvironment by clearing immunosuppressive CD38+ T_{regs} and B_{regs}, in addition to Dara's direct on-tumor effects[2]

+

Tec + Dara ACTIVATE
CD8+ T cells for sustained immune enhancement

+

Tec REDIRECTS
activated CD8+ T cells to effectively kill myeloma cells



Dara primes and enables the optimal Tec-Dara immune-mediated killing of myeloma cells[1,3]

Breg, regulatory B cell; Treg, regulatory T cell.

1. Vishwamitra D, et al. Presented at: ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, USA. Oral 594. 2. van de Donk NWCJ, et al. *Front Immunol.* 2018;9:2134. 3. Frerichs KA, et al. *Clin Cancer Res.* 2020;26:2203-2215.

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MajesTEC-3: Phase 3 Study Design

Key inclusion criteria

- RRMM
- 1-3 prior LOTs including a PI and lenalidomide
  - Patients with only 1 prior LOT must have been lenalidomide refractory per IMWG criteria
- ECOG PS score of 0-2

Key exclusion criteria

- Prior BCMA-directed therapy
- Refractory to anti-CD38 mAbs[a]

1:1 randomization N=587

22 Oct 2021 to 29 Sept 2023[b]

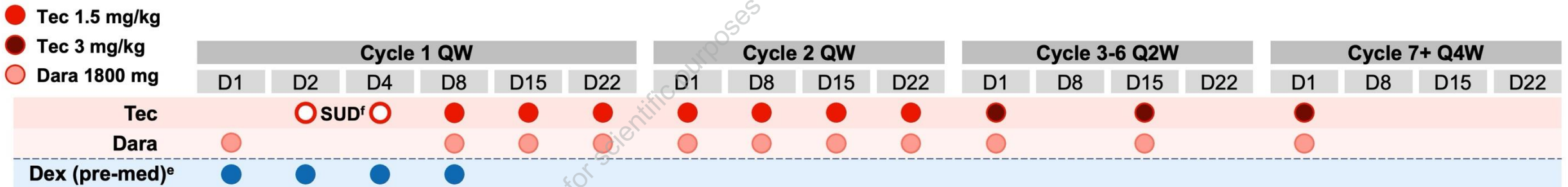
Tec-Dara
N=291
SC dosing following Dara schedule

DPd/DVd
N=296 (91% DPd)
by investigator's choice[c]

Primary endpoint
- PFS per IRC

Key secondary endpoints
- ≥CR[d] and ORR[d]
- MRD negativity (10^{-5})
- OS
- MySIm-Q Total Symptom score

Other secondary endpoints
- Safety
- PK and immunogenicity



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

[a]Prior exposure to anti-CD38 mAbs was permitted. [b]During the COVID-19 pandemic. [c]DPd/DVd were administered per the approved schedules. [d]Response and disease progression were assessed by a blinded IRC per IMWG criteria. [e]Dexamethasone, acetaminophen, and diphenhydramine pre-medication was required for the first 2 weeks; subsequent dexamethasone was not required thereafter. [f]Patients received SUD of 0.06 mg/kg and 0.3 mg/kg on Days 2 and 4, respectively.

CR, complete response; D, day; Dex, dexamethasone; DPd, daratumumab, pomalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; MySIm-Q, Multiple Myeloma Symptom and Impact Questionnaire; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; pre-med, pre-medication; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; SUD, step-up dosing.

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MajesTEC-3: Baseline Demographic and Disease Characteristics

Characteristic	Tec-Dara (n=291)	DPd/DVd (n=296)
Age		
Median (range), years	64 (36–88)	63 (25–84)
≥75 years, n (%)	31 (10.7)	25 (8.4)
Sex, n (%)		
Male	156 (53.6)	169 (57.1)
Female	135 (46.4)	127 (42.9)
Race, n (%)		
White	190 (65.3)	194 (65.5)
Asian	68 (23.4)	63 (21.3)
Black or African American	13 (4.5)	20 (6.8)
Other[a]	20 (6.9)	19 (6.4)

Characteristic	Tec-Dara (n=291)	DPd/DVd (n=296)
Baseline ECOG PS score, n (%)		
0	167 (57.4)	160 (54.1)
1	108 (37.1)	127 (42.9)
2	16 (5.5)	9 (3.0)
ISS stage, n (%)		
I	182 (62.5)	185 (62.5)
II	85 (29.2)	88 (29.7)
III	24 (8.2)	23 (7.8)
BMPCs ≥60%,[b] n/N (%)	28/286 (9.8)	24/293 (8.2)
Presence of soft-tissue plasmacytomas, n (%)	41 (14.1)	41 (13.9)
Extramedullary plasmacytomas[c]	14 (4.8)	17 (5.7)
Paraskeletal plasmacytomas	32 (11.0)	31 (10.5)
High-risk cytogenetics,[d] n/N (%)	104/285 (36.5)	104/294 (35.4)

Baseline demographics were well balanced and reflective of patients seen in real-world practice

[a]"Other" includes Native Hawaiian or Pacific Islander (Tec-Dara, n=1 [0.3%]; DPd/DVd, n=0; total, n=1 [0.2%]), American Indian or Alaska Native (Tec-Dara, n=0; DPd/DVd, n=1 [0.3%]; total, n=1 [0.2%]), not reported (Tec-Dara, n=14 [4.8%]; DPd/DVd, n=16 [5.4%]; total, n=30 [5.1%]), and unknown (Tec-Dara, n=5 [1.7%]; DPd/DVd, n=2 [0.7%]; total, n=7 [1.2%]). [b]Maximum value from bone marrow biopsy or bone marrow aspirate was selected if both results were available. [c]From metastatic or hematogenous spread involving only soft tissues. [d]Presence of ≥1 of del(17p), t(4;14), or t(14;16).
BMPC, bone marrow plasma cell; ISS, International Staging System.
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MajesTEC-3: Prior Lines of Therapy

Characteristic	Tec-Dara (n=291)	DPd/DVd (n=296)
Prior LOTs, n (%)		
Median (range), n	2 (1–3)	2 (1–3)
1 prior LOT	108 (37.1)	114 (38.5)
2 prior LOTs	134 (46.0)	134 (45.3)
3 prior LOTs	49 (16.8)	48 (16.2)
Prior transplantation, n (%)	210 (72.2)	226 (76.4)

- 5% of patients were Dara exposed
- In real-world data sets, 70% of patients in 2L are Dara naïve or exposed[1]

Characteristic	Tec-Dara (n=291)	DPd/DVd (n=296)
Prior therapy exposure, n (%)		
PI	290 (99.7)	296 (100)
IMiD	291 (100)	296 (100)
Anti-CD38	15 (5.2)	16 (5.4)
Refractory status, n (%)		
To last prior LOT	250 (85.9)	251 (84.8)
Any PI	117 (40.2)	104 (35.1)
Any IMiD	247 (84.9)	253 (85.5)
Lenalidomide	240 (82.5)	251 (84.8)
Double (PI and IMiD)	99 (34.0)	88 (29.7)

Median of 2 prior LOTs and >85% of patients were refractory to an IMiD

2L, second-line; IMiD, immunomodulatory drug.
1. Johnson & Johnson, data on file.
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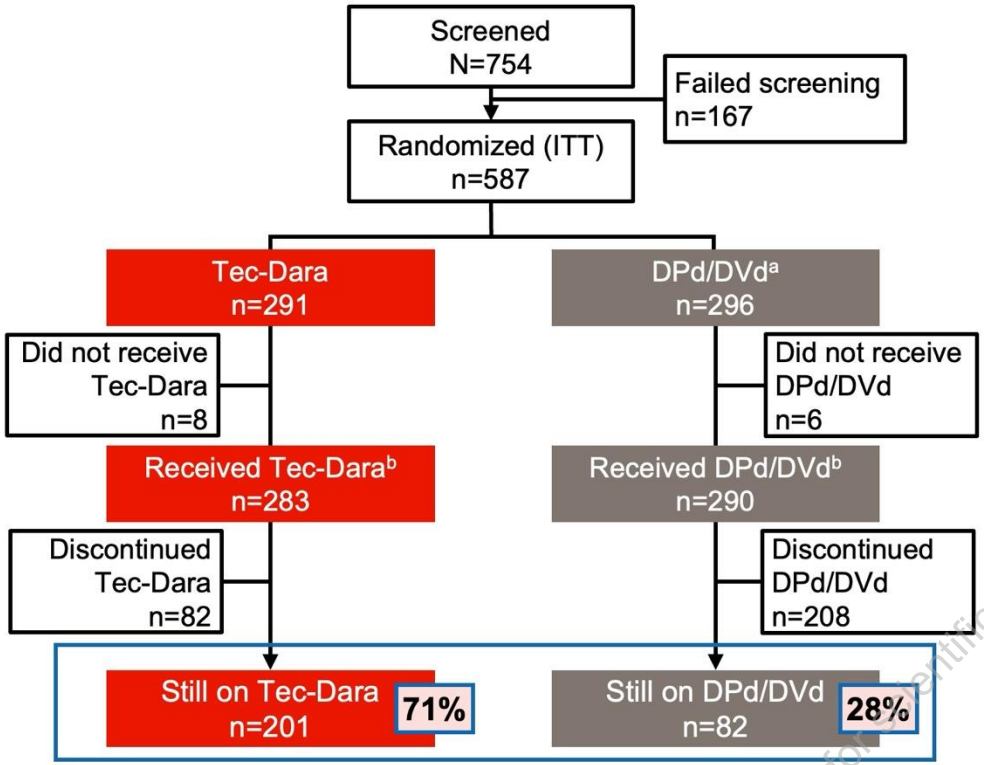
MajesTEC-3: Patient Disposition and Exposure



Median follow-up: 34.5 months

	Tec-Dara (n=291)	DPd/DVd (n=296)
Number of patients treated, n (%)	283 (97.3)	290 (98.0)
Still on study treatment,[c] n (%)	201 (71.0)	82 (28.3)
Discontinued study treatment,[c] n (%)	82 (29.0)	208 (71.7)
Reason for discontinuation,[c,d] n (%)		
AE	13 (4.6)	16 (5.5)
Death	20 (7.1)	13 (4.5)
Physician decision	11 (3.9)	5 (1.7)
PD	21 (7.4)	168 (57.9)
Patient refused further treatment	13 (4.6)	6 (2.1)
Median treatment duration, months	32.4	16.1
Overall deaths due to PD,[e] n/N (%)	13/283 (4.6)	59/290 (20.3)

- Of the 201 patients remaining on Tec-Dara, >95% remained on both drugs
- Median relative dose intensity across all cycles
  - Tec: 91.7%
  - Dara: 90.0%–97.8% across groups

Low and comparable treatment discontinuations due to AEs with Tec-Dara and DPd/DVd; 71% still on study treatment in the Tec-Dara group

Clinical cutoff: August 1, 2025.
[a]In the DPd/DVd group, 269 patients were randomized to receive DPd and 27 to receive DVd per investigator's choice. [b]Patients in the safety analysis set. [c]Percentages are based on number of patients treated. [d]4 (1.4%) patients in the Tec-Dara group discontinued due to "Other" reasons. [e]Percentage of deaths due to PD is based on the number of patients in the safety analysis set.
AE, adverse event; ITT, intent-to-treat; PD, progressive disease.

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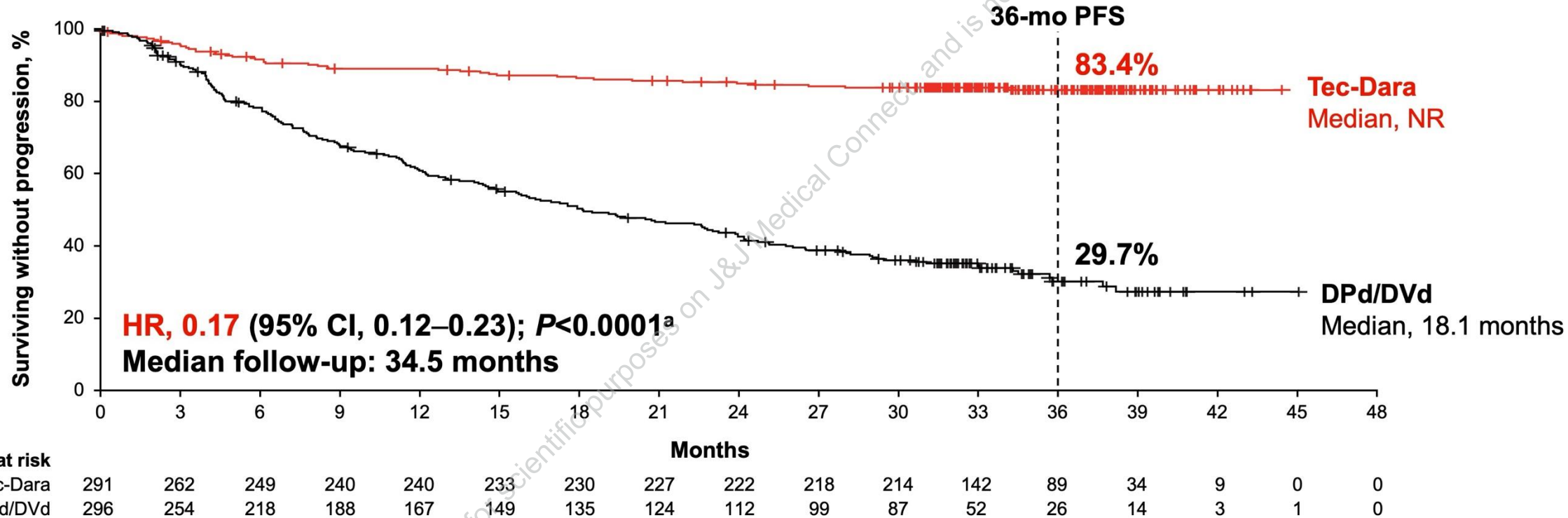
MajesTEC-3: PFS (Primary Endpoint)



No. at risk																	
Tec-Dara	291	262	249	240	240	233	230	227	222	218	214	142	89	34	9	0	0
DPd/DVd	296	254	218	188	167	149	135	124	112	99	87	52	26	14	3	1	0

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

[a]The *P* value crossed the prespecified stopping boundary for superiority for the first interim analysis (*P*=0.0139).
CI, confidence interval; HR, hazard ratio; NR, not reached.
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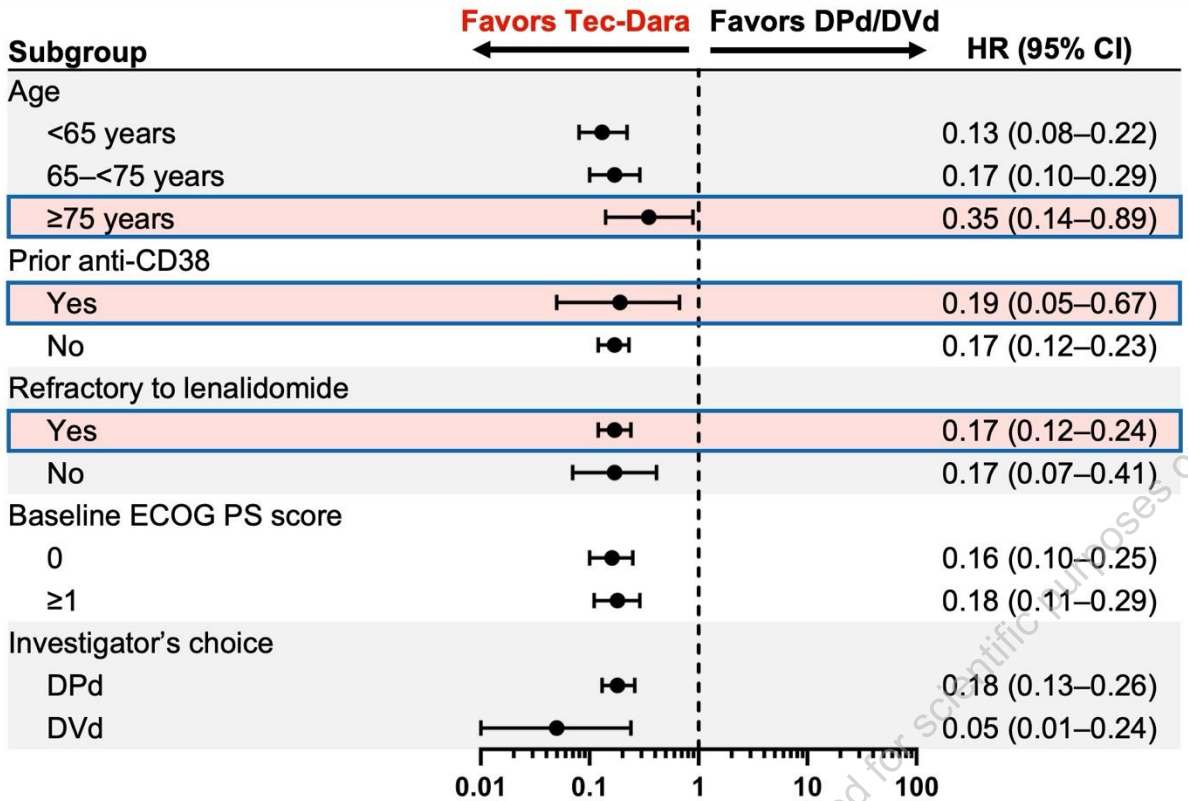
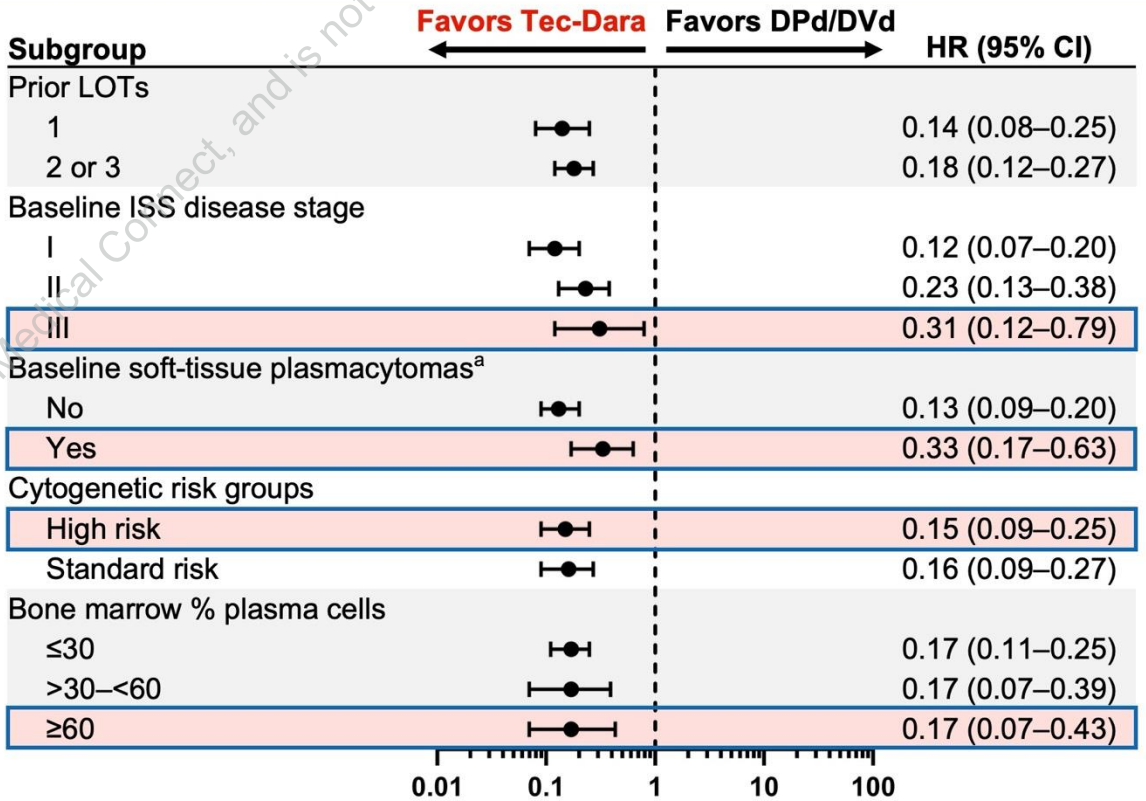
MajesTEC-3: PFS Subgroup Analysis





Superior PFS with Tec-Dara was consistent across all subgroups[b]

[a]Baseline soft-tissue plasmacytomas contain both extramedullary and paraskeletal plasmacytomas. [b]Not all clinically meaningful and prespecified subgroups that were assessed are shown; however, PFS was improved versus DPd/DVd across all subgroups.

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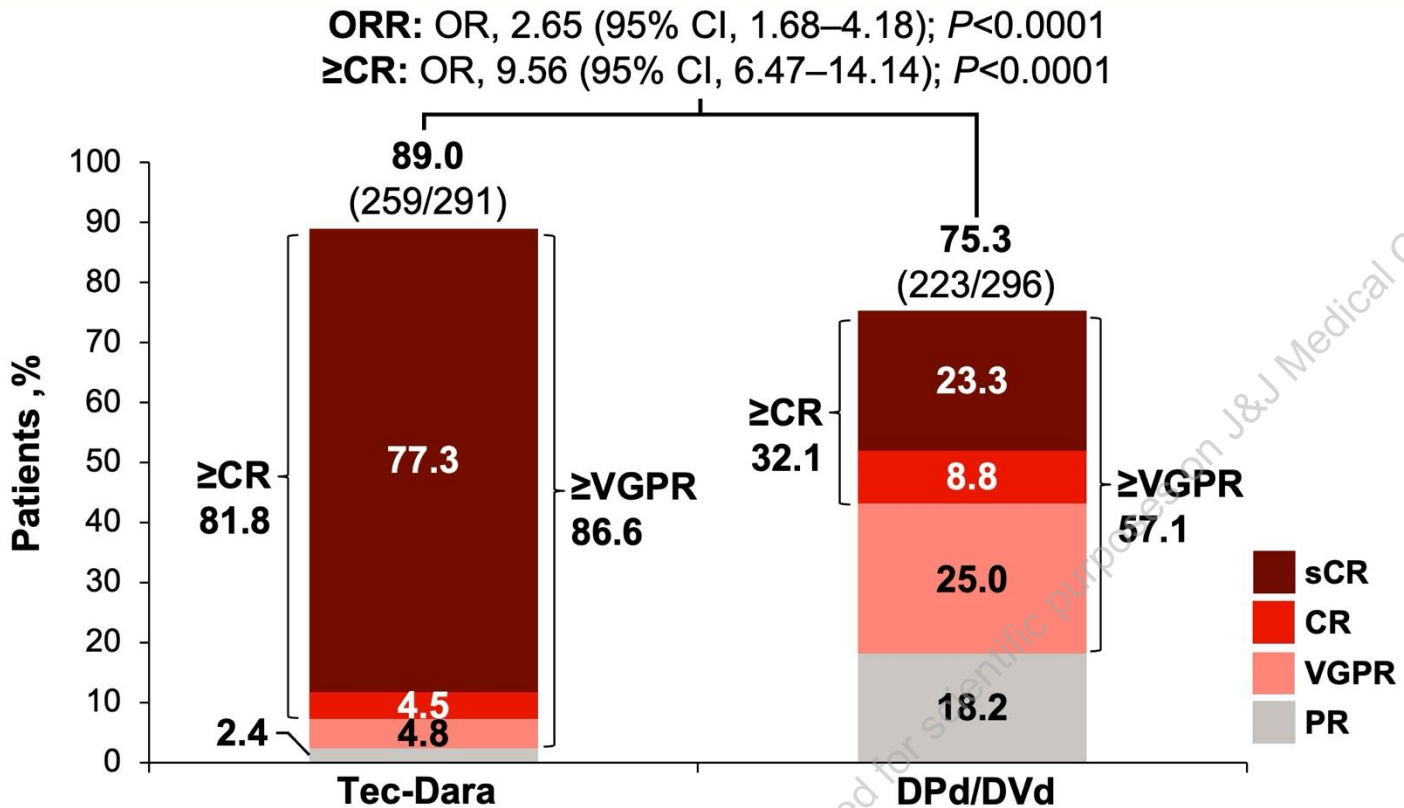
MajesTEC-3: Treatment Response[a] and Response Duration



	Tec-Dara (n=259)	DPd/DVd (n=223)
Median (range) time to first response, months	1.2 (0.9–25.0)	1.2 (0.7–6.3)
Median (range) time to first ≥CR, months	6.9 (1.0–34.5)	6.9 (1.5–18.8)
Median (95% CI) DOR, months	NE (NE–NE)	23.5 (19.8–29.9)
36-month DOR, % (95% CI)	88.5 (83.7–92.0)	36.4 (28.9–43.9)

Tec-Dara demonstrated significantly higher ORR and ≥CR rate versus DPd/DVd

Median follow-up: 34.5 months.
[a]Response and disease progression were assessed by a blinded IRC per IMWG criteria.
DOR, duration of response; NE, not estimable; OR, odds ratio; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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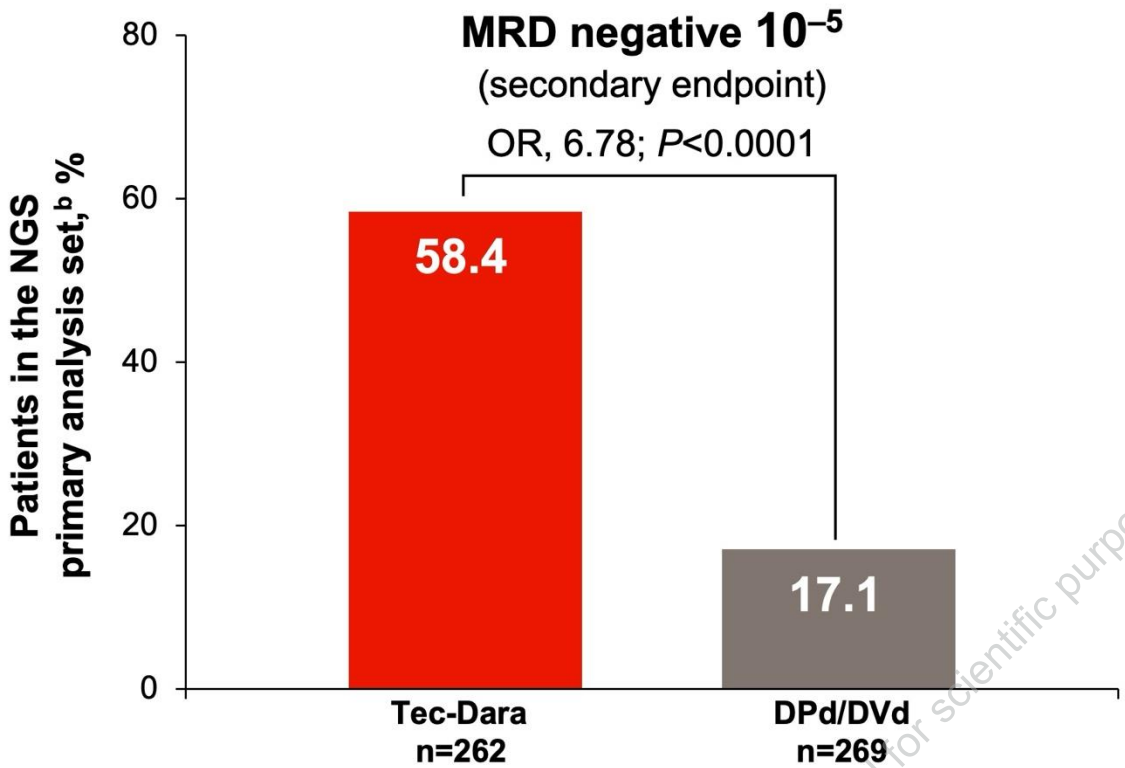
MajesTEC-3: MRD Negativity[a]



	MRD-negative ≥CR (10^{-5})	MRD-negative ≥CR (10^{-6})
Tec-Dara, %		
Primary NGS[b]	57.6	53.8
Evaluable[c]	**89.3**	**87.5**
DPd/DVd, %		
Primary NGS[b]	17.1	10.4
Evaluable[c]	63.0	41.8

~90% MRD-negative ≥CR with Tec-Dara in MRD-evaluable patients

Median follow-up: 34.5 months.

[a]MRD was assessed in the bone marrow by NGS in accordance with IMWG guidelines. [b]The MRD NGS primary analysis set was defined as all randomized patients in the study except those recruited in China (due to China instead utilizing NGF for MRD assessment; Tec-Dara, n=262; DPd/DVd, n=269). [c]The MRD NGS evaluable set was defined as patients who achieved ≥CR, had a successful baseline calibration, and had ≥1 post-baseline MRD sample with a positive or negative result (per NGS) at the indicated threshold (10^{-5}: Tec-Dara, n=168; DPd/DVd, n=73; 10^{-6}: Tec-Dara, n=160; DPd/DVd, n=67).

NGF, next-generation flow cytometry; NGS, next-generation sequencing.

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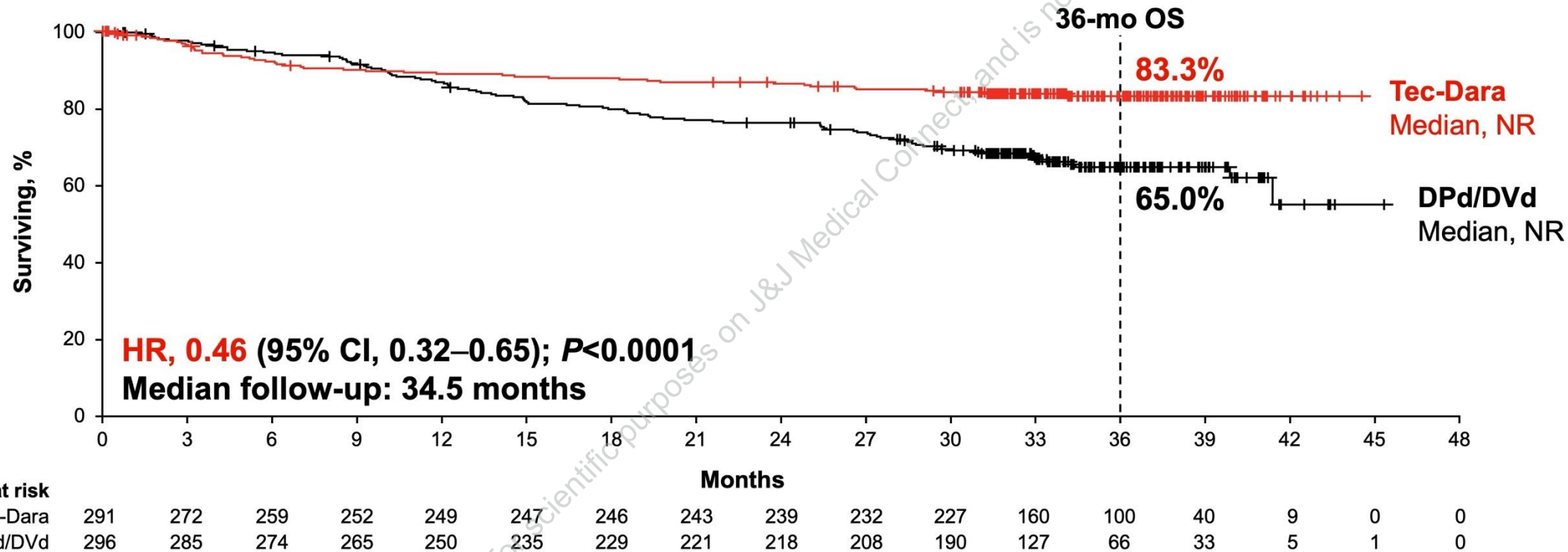
MajesTEC-3: OS



No. at risk																	
Tec-Dara	291	272	259	252	249	247	246	243	239	232	227	160	100	40	9	0	0
DPd/DVd	296	285	274	265	250	235	229	221	218	208	190	127	66	33	5	1	0

Tec-Dara significantly improved OS versus DPd/DVd, with 83% of patients alive at 3 years

Analysis of RMST demonstrated an OS benefit for Tec-Dara versus DPd/DVd (RMST difference, 2.15 months; *P*=0.0088).
RMST, restricted mean survival time.
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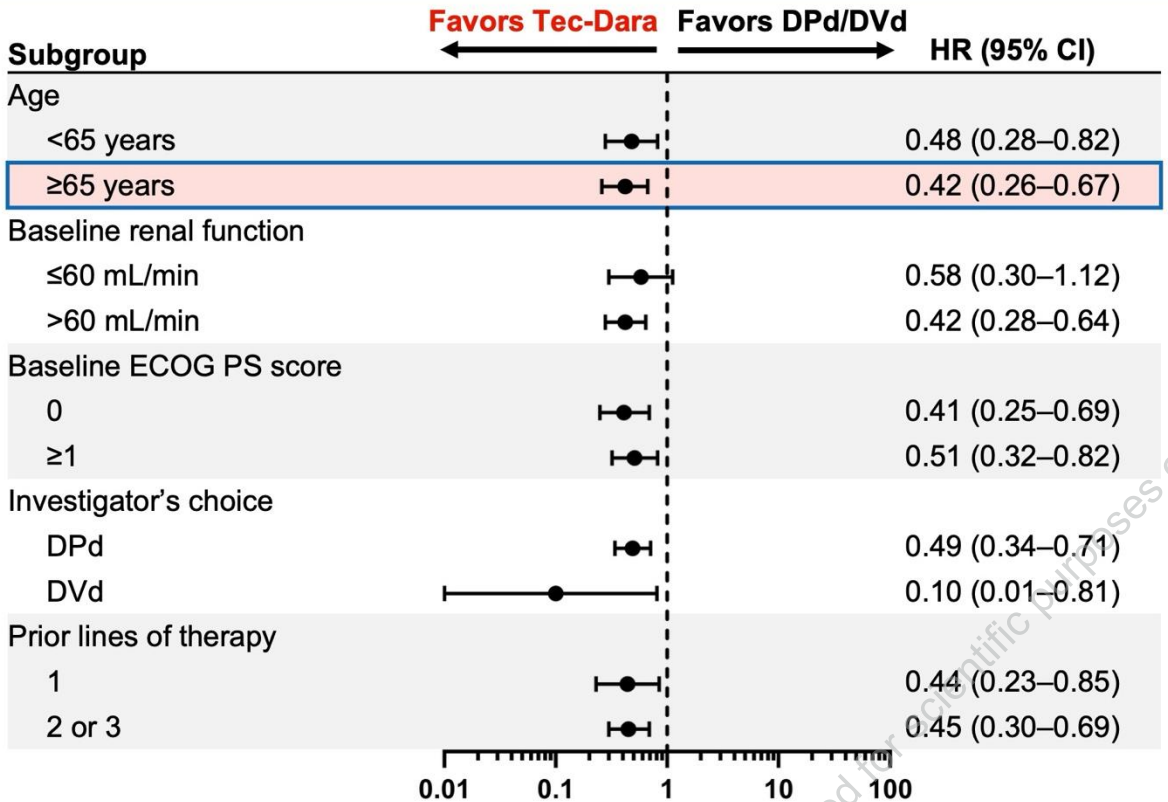
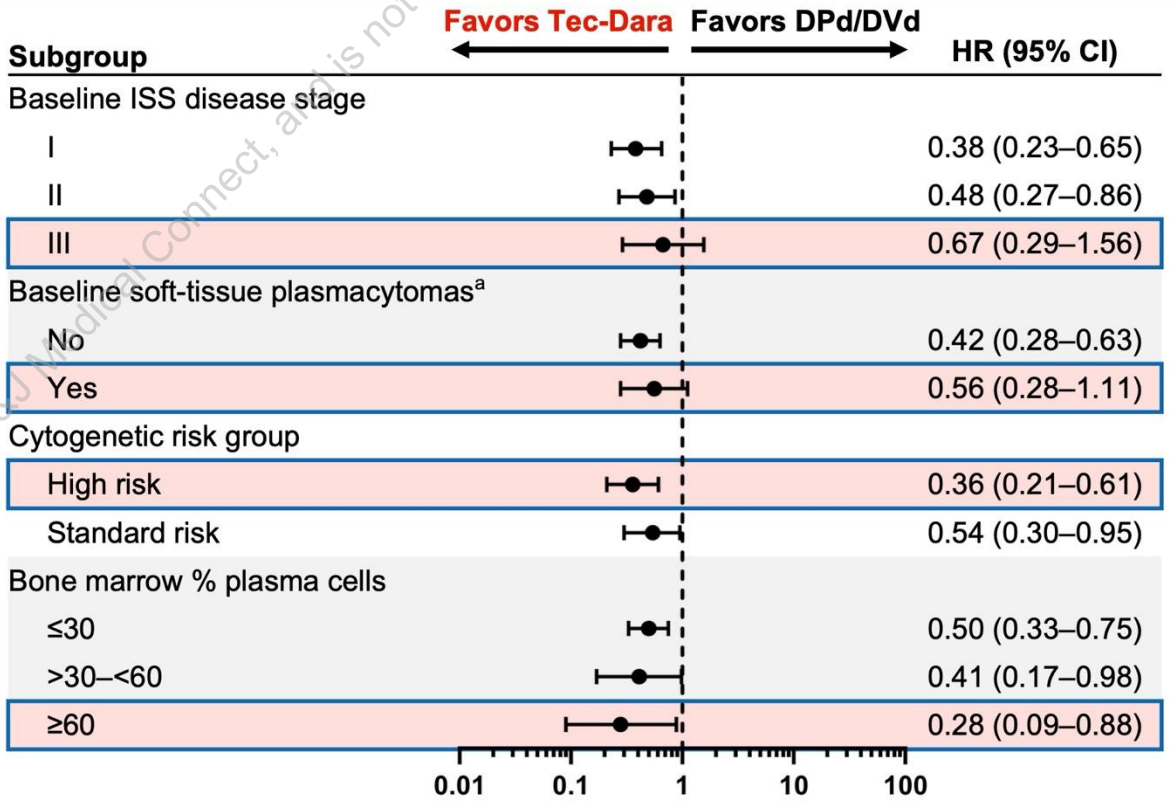
MajesTEC-3: OS Subgroup Analysis





Superior OS with Tec-Dara across prespecified subgroups[b]

[a]Baseline soft-tissue plasmacytomas contain both extramedullary and paraskeletal plasmacytomas. [b]Not all prespecified subgroups that were assessed are shown; however, OS favored Tec-Dara versus DPd/DVd across all subgroups.

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MajesTEC-3: Overall Safety Profile

- Mostly grade 1 CRS (44.2%), with 15.9% grade 2
  - All CRS resolved; no grade 2 after first cycle
  - No grade ≥3 CRS events
  - No prophylactic tocilizumab given per protocol
- 1.1% ICANS[a]; all resolved
- Low rate of TEAEs leading to discontinuation[b] in both Tec-Dara (4.6%) and DPd/DVd (5.5%) groups
- Serious AEs: 70.7% vs 62.4%
- Similar rates of deaths due to TEAEs: 7.1% vs 5.9%

TEAE, n (%)[c]	Tec-Dara (n=283)		DPd/DVd (n=290)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE	283 (100)	269 (95.1)	290 (100)	280 (96.6)
Hematologic				
Neutropenia	222 (78.4)	214 (75.6)	240 (82.8)	228 (78.6)
Anemia	111 (39.2)	58 (20.5)	103 (35.5)	50 (17.2)
Thrombocytopenia	103 (36.4)	55 (19.4)	126 (43.4)	68 (23.4)
Lymphopenia	63 (22.3)	59 (20.8)	50 (17.2)	32 (11.0)
Leukopenia	51 (18.0)	30 (10.6)	61 (21.0)	46 (15.9)
Nonhematologic[d]				
CRS[e]	170 (60.1)	0	-	-
Diarrhea	147 (51.9)	10 (3.5)	89 (30.7)	7 (2.4)
Cough	136 (48.1)	1 (0.4)	66 (22.8)	0
Pyrexia	104 (36.7)	4 (1.4)	55 (19.0)	1 (0.3)

TEAE profile was generally comparable between Tec-Dara and DPd/DVd

[a]In the Tec-Dara group, grade 1, n=2; grade 4, n=1 (led to discontinuation of teclistamab). [b]Patients who discontinued all components of study treatment. [c]Includes the most common TEAEs of any grade occurring in ≥30% of patients in either treatment group and the most common grade 3/4 TEAEs occurring in ≥10% of patients in either treatment group. [d]Hypogammaglobulinemia, COVID-19, COVID-19 pneumonia, URTI, and pneumonia were also reported but are discussed on the following summary of infections slide. [e]CRS is not applicable for the DPd/DVd group.
CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.
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MajesTEC-3: Summary of Infections

- Study started during the COVID-19 pandemic and prior to bispecific treatment guidelines
- Hypogammaglobulinemia[a]: 84.5% with Tec-Dara
- 13 (4.6%) deaths due to infection with Tec-Dara[b]
  - 12 occurred within 6 months of treatment (3 due to COVID-19); 9 of 12 patients did not receive IgRT
  - Protocol was subsequently amended in Feb 2023 to reinforce IgRT supplementation and antimicrobial prophylaxis[c]
    - 87.3% received ≥1 dose of Ig[d]
    - 1 infectious death occurred post amendment

TEAE, n (%)	Tec-Dara (n=283)		DPd/DVd (n=290)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any infection	273 (96.5)	153 (54.1)	244 (84.1)	126 (43.4)
Treatment-emergent infection or infestation[e]				
COVID-19	124 (43.8)	17 (6.0)	97 (33.4)	6 (2.1)
URTI	115 (40.6)	12 (4.2)	88 (30.3)	7 (2.4)
Pneumonia	65 (23.0)	47 (16.6)	53 (18.3)	43 (14.8)
Nasopharyngitis	62 (21.9)	0	57 (19.7)	0
Sinusitis	52 (18.4)	5 (1.8)	17 (5.9)	3 (1.0)
Rhinovirus infection	44 (15.5)	5 (1.8)	10 (3.4)	1 (0.3)
Bronchitis	40 (14.1)	2 (0.7)	31 (10.7)	6 (2.1)
Influenza	38 (13.4)	8 (2.8)	43 (14.8)	10 (3.4)
COVID-19 pneumonia	34 (12.0)	32 (11.3)	12 (4.1)	7 (2.4)
UTI	29 (10.2)	4 (1.4)	27 (9.3)	1 (0.3)

Infections with Tec-Dara require diligent use of established IgRT and prophylaxis protocols

[a]Hypogammaglobulinemia was defined as patients with ≥1 TEAE of hypogammaglobulinemia or a post-baseline IgG value <400 mg/dL. Rate of hypogammaglobulinemia in the DPd/DVd arm was 60.3%. [b]In the DPd/DVd group, 4 patients had a fatal infection, 2 of which occurred after the implementation of protocol amendment #6. [c]Protocol amendment #6 affirmed the importance of medical monitoring of IgG levels and adherence to protocol-specified Ig supplementation guidance. [d]Percentage at clinical cutoff. [e]Most common defined as occurring in ≥10% of patients in either treatment group; shown with percent occurrence of respective grade 3/4 infection.
Ig, immunoglobulin; IgG, immunoglobulin G; IgRT, immunoglobulin replacement therapy; UTI, urinary tract infection.

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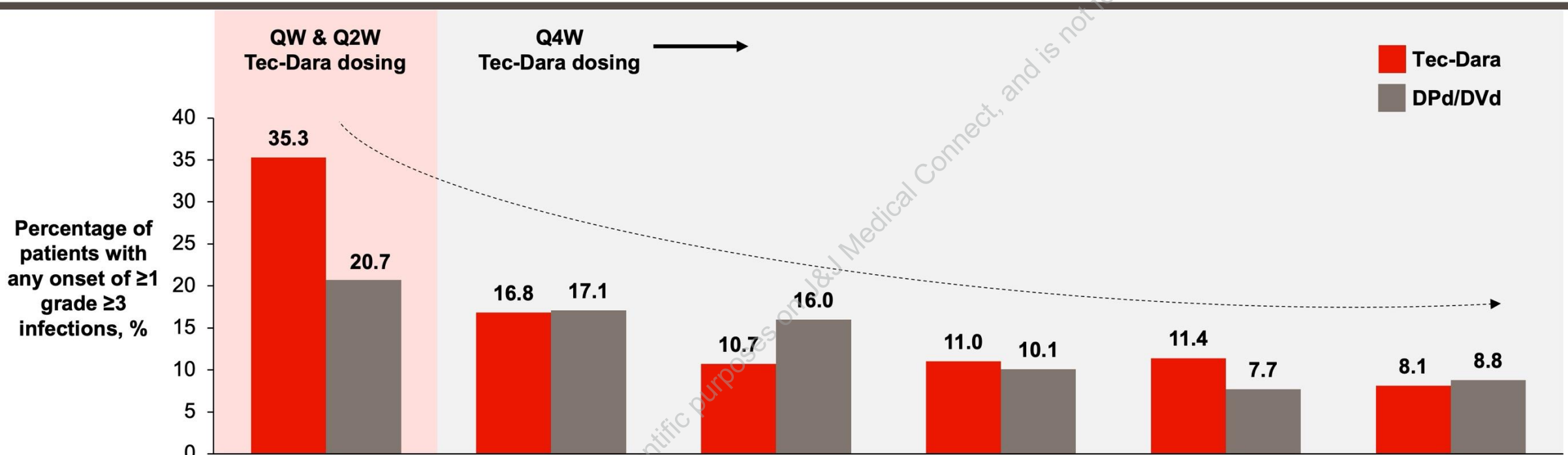
MajesTEC-3: Grade ≥3 Infections Over Time



	≤6 mo	>6–≤12 mo	>12–≤18 mo	>18–≤24 mo	>24–≤30 mo	>30 mo
Tec-Dara (n/N)[a]	100/283	41/244	25/233	24/219	24/210	16/197
DPd/DVd (n/N)[a]	60/290	39/228	28/175	14/138	9/117	8/91

Any onset grade ≥3 infections were comparable across arms after 6 months and decreased over time

[a]Includes patients who are in the TEAE-reporting period for the specific window. Noting that patients are counted only once in a window for any given event, regardless of the number of times they actually experienced the event within the specific time window.

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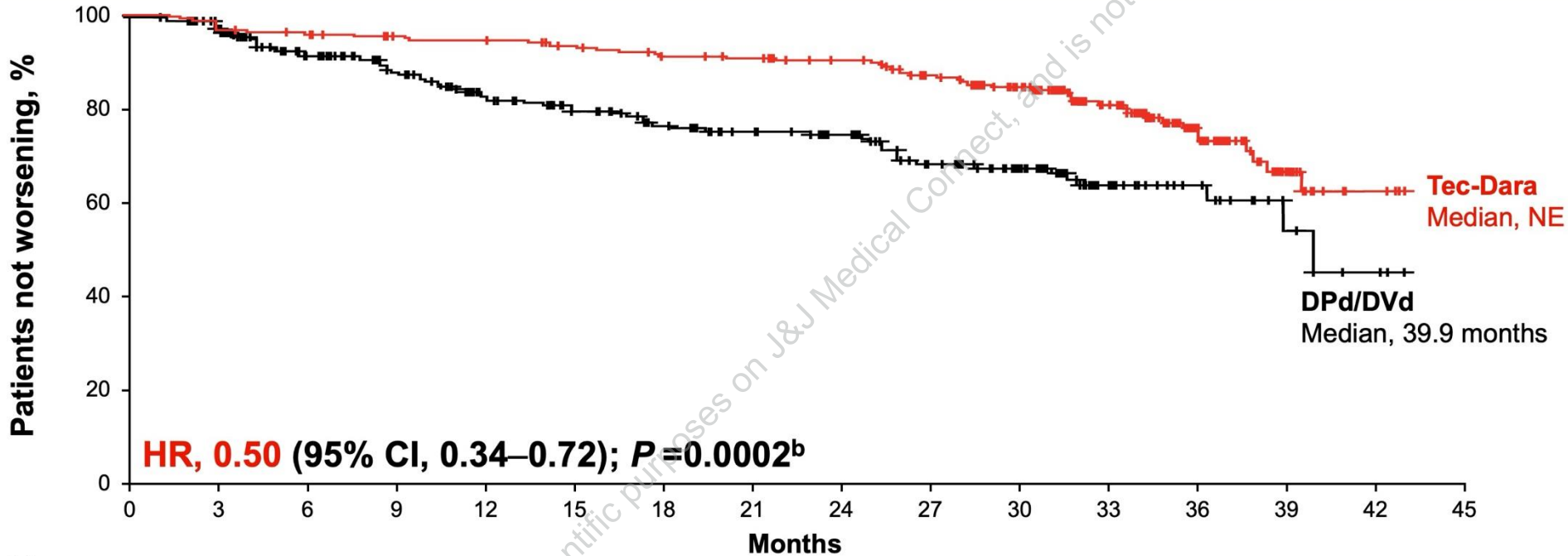
MajesTEC-3: MySIm-Q Total Symptom Score[a]



No. at risk															
Tec-Dara	291	240	232	225	223	216	208	205	197	180	160	101	56	23	5	0
DPd/DVd	296	239	198	173	143	131	117	109	101	83	71	36	21	8	3	0

With Tec-Dara, time to worsening of MM symptoms was significantly longer versus DPd/DVd

Median follow-up: 34.5 months.

[a]The anchor-based worsening minimum importance difference on the MySIm-Q Symptom Scale was the mean change on the MySIm-Q Symptom Scale associated with a 2-point increase on the Patient Global Impression of Severity symptom question between baseline and Cycle 4 Day 1. Worsening was defined as a score greater than or equal to the minimum importance difference threshold without subsequent improvement to a score below this level. [b]*P* value is based on a stratified log-rank test stratified with ISS (I vs II or III) and number of prior LOTs (1 vs 2 or 3), as randomized.

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MajesTEC-3: Conclusions

Synergistic[1] immunotherapy combination of Tec-Dara versus DPd/DVd in 1-3 prior LOTs in RRMM:

- Greatest PFS treatment effect to date (HR, 0.17),[2-6] with plateauing curve after ~6 months suggesting potential for functional cure
  - Benchmark 83.4% PFS rate at 3 years, with clear benefit in patients with high-risk cytogenetics, EMD, ISS stage III, and prior anti-CD38 exposure
- Superior OS (HR, 0.46)
- Grade ≥3 infections were highest in the first 6 months, then declined over time; patients should be supported with infection prophylaxis, monitoring, and established IgRT supplementation protocols
- CRS profile and combinability of Tec with Dara on approved Dara schedule support potential for community adoption

Tec-Dara showed unprecedented efficacy, supporting a new 2L+ SOC with broad potential across academic and community settings

1. Vishwamitra D, et al. Presented at: ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, USA. Oral 594. 2. San-Miguel J, et al. *N Engl J Med*. 2023;389:335-347. 3. Usmani SZ, et al. *Blood Adv*. 2023;7:3737-3748. 4. Hungria V, et al. *N Engl J Med*. 2024;391:393-407. 5. Dimopoulos MA, et al. *N Engl J Med*. 2024;391:408-421. 6. Martin T, et al. *Blood Cancer J*. 2023;13:72.
EMD, extramedullary disease.

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ORIGINAL ARTICLE

Teclistamab plus Daratumumab in Relapsed or Refractory Multiple Myeloma

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https://www.congresshub.com/ASH2025/Oncology/Teclistamab/Mateos-LBA

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