MM-593

Phase 3, Randomized Study of Talquetamab Plus Daratumumab ± Pomalidomide vs Daratumumab Plus Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: MonumenTAL-3

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Key Takeaway

Tal + Dara ± Pom showed substantial efficacy, supporting new 2L+ standard of care with broad potential for use across diverse practice settings

Conclusions

Tal-Dara–based combinations significantly improved PFS (HR: Tal-DP, 0.28; Tal-D, 0.33) with clear benefit across clinically relevant subgroups, including substantial efficacy with Tal-D alone

Safety was consistent with the individual agents, with a favorable infection profile for Tal-D; AEs of interest for Tal infrequently led to treatment discontinuation

Rates of severe neutropenia and severe infections were higher in Pom-containing arms

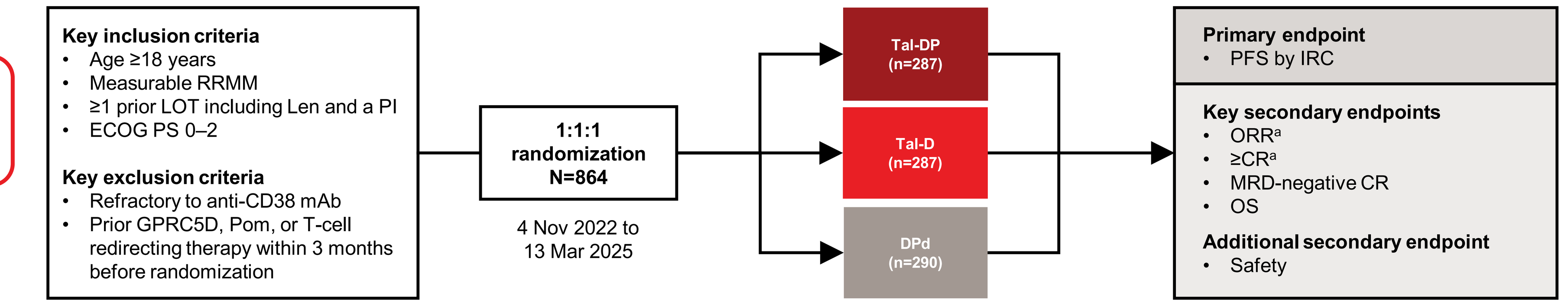
Introduction

- The phase 3 CARTITUDE-4, MajesTEC-3, and MajesTEC-9 studies of ciltacabtagene autoleucel, teclistamab + daratumumab (Tec + Dara), and Tec monotherapy, respectively, support T-cell redirecting (TCR) immunotherapy use as early as second line (2L), when immune function is most preserved[1-3]
- Talquetamab (Tal) is the first and only GPRC5D × CD3 bispecific antibody approved for relapsed/refractory multiple myeloma (RRMM) after ≥3 prior lines of therapy (LOT), with phase 2 data demonstrating deep, durable responses and median overall survival (OS) >3 years[4-8]
- Tal targets myeloma cells while sparing healthy B-cell populations due to limited B-cell expression of GPRC5D,[9-10] leading to an infection profile distinct from BCMA-directed therapies, facilitating combination[9]
- In the phase 1b TRIMM-2 study (RRMM; median 5–6 prior LOT), Tal + Dara + pomalidomide (Pom; Tal-DP) and Tal + Dara (Tal-D) demonstrated robust, durable clinical activity, with high response rates and sustained progression-free survival (PFS)[11,12]

We present results from the preplanned interim analysis of the phase 3 MonumenTAL-3 study investigating Tal-DP and Tal-D vs Dara + Pom + dexamethasone (DPd) in patients with RRMM exposed to ≥1 prior LOT

Methods

Figure 1: MonumenTAL-3 phase 3 study design[13]



Tal was given SC with step-up dosing at 0.01, 0.06, and 0.4 mg/kg, followed by 0.8 mg/kg

Regimen	C1–2[c]	C3–4	C5–6 (Tal Q4W permitted with ≥VGPR at cycle 5–6)	C7+ (Tal Q4W required with ≥PR at cycle 7 and beyond)
Tal-DP[b]	Q2W ● (Tal); QW ● (Dara); ● (Pom)	Q2W ● (Tal); Q2W ● (Dara); ● (Pom)	Q2W ● (Tal); Q2W ● (Dara); ● (Pom)	Q2W ● (Tal); Q4W ● (Dara); ● (Pom)
Tal-D[b]	Q2W ● (Tal); QW ● (Dara)	Q2W ● (Tal); Q2W ● (Dara)	Q2W ● (Tal); Q2W ● (Dara)	Q2W ● (Tal); Q4W ● (Dara)

● Tal: 0.8 mg/kg
● Dara: 1800 mg
● Pom:
• Tal-DP: 2 mg daily (D1–21)[d]
• DPd: 4 mg daily (D1–21)

ClinicalTrials.gov identifier: NCT05455320. [a]Response and disease progression were assessed by a blinded IRC per IMWG criteria. [b]Dexamethasone, acetaminophen, and diphenhydramine premedication was required for the first 2 weeks; subsequent dexamethasone was not required thereafter. [c]Pom is given from cycle 2. [d]Pom dose could be increased to 4 mg at the start of cycle 3 day 1 or after per the investigator's discretion. C, cycle; CR, complete response; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; IRC, independent review committee; Len, lenalidomide; mAb, monoclonal antibody; MRD, measurable residual disease; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneously; VGPR, very good partial response.

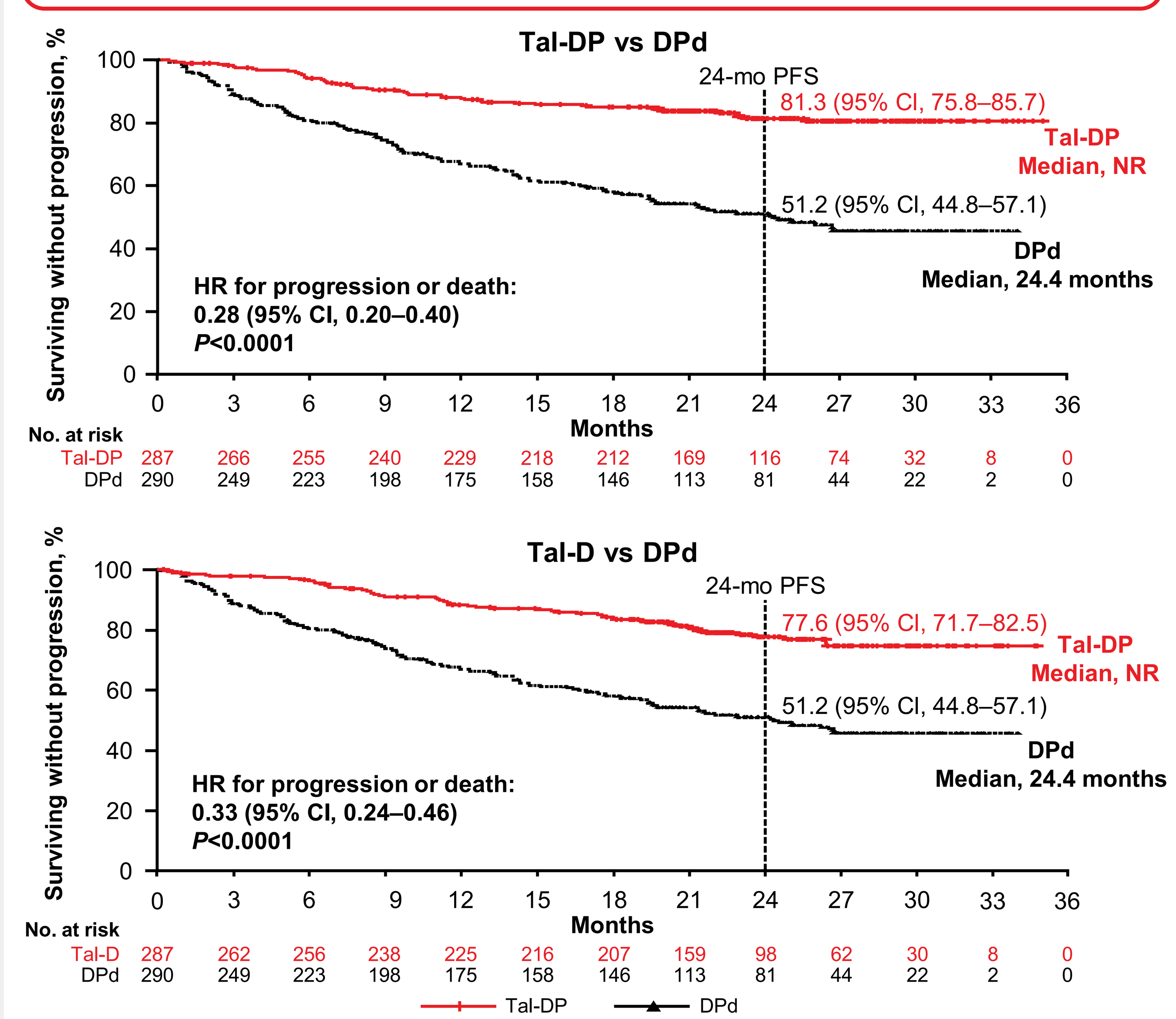
Results

Table 1: Baseline characteristics were balanced and reflective of patients seen in real-world practice. Clinical cut-off was November 3, 2025, with a median follow-up of 24.6 months[13]

Characteristic	Tal-DP (n=287)	Tal-D (n=287)	DPd (n=290)
Age			
Median age (range), years	64 (40–83)	64 (32–88)	63 (30–88)
Sex, n (%)			
Male	169 (58.9)	166 (57.8)	161 (55.5)
ECOG PS, n (%)[a]			
0–1	274 (95.5)	278 (96.9)	276 (95.2)
ISS stage, n (%)[b]			
I–II	258 (89.9)	256 (89.2)	259 (89.3)
III	29 (10.1)	31 (10.8)	31 (10.7)
Soft tissue plasmacytomas ≥1, n (%)	37 (12.9)	51 (17.8)	42 (14.5)
True EMD, n (%)[c]	12 (32.4)	19 (37.3)	17 (40.5)
Paraskeletal, n (%)	31 (83.8)	40 (78.4)	30 (71.4)
High-risk cytogenetics[d]	88 (30.7)	97 (33.8)	82 (28.3)
Prior LOT, n, median (range)	2 (1–8)	2 (1–7)	2(1–8)
Prior exposure, n (%)			
IMiD	287 (100.0)	287 (100.0)	290 (100.0)
PI	287 (100.0)	287 (100.0)	288 (99.3)[e]
Anti-CD38 mAb			
Dara	33 (11.5)	34 (11.8)	33 (11.4)
Isatuximab	0	0	3 (1.0)
Refractory status, n (%)			
Any PI	132 (46.0)	121 (42.2)	118 (40.7)
Any IMiD	253 (88.2)	250 (87.1)	250 (86.2)
Len	244 (85.0)	248 (86.4)	243 (83.8)
To last prior LOT	267 (93.0)	269 (93.7)	271 (93.4)

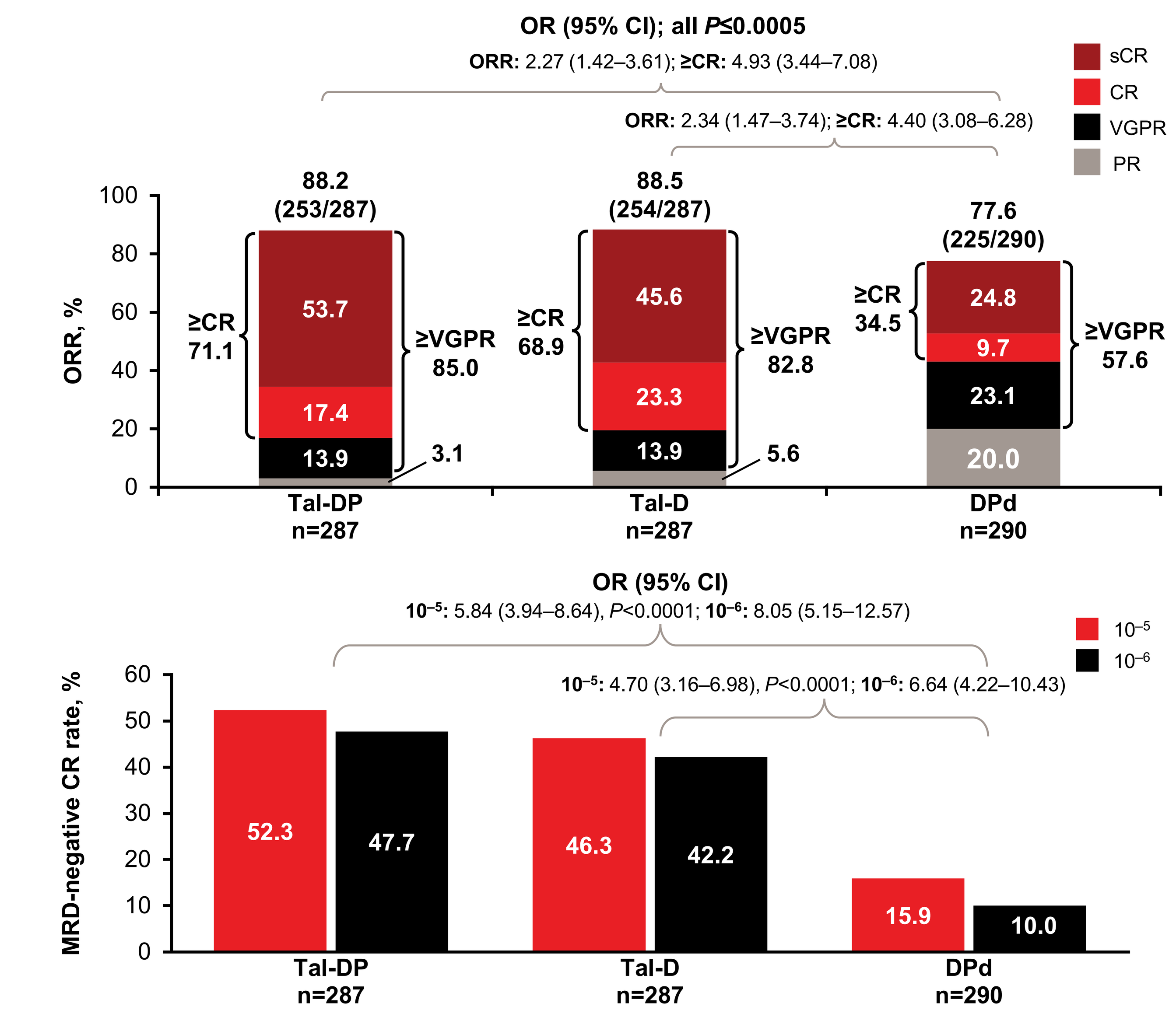
Adapted with permission © *The New England Journal of Medicine* (2026). [a]Scores regarding ECOG PS range from 0–5, with higher scores indicating greater disability. [b]The ISS consists of 3 stages (with a higher stage indicating more advanced disease) and is based on levels of serum β_2-microglobulin and albumin. [c]Plasmacytomas that are not contiguous with bone. Patients could have both true EMD and paraskeletal plasmacytomas. [d]High risk is defined as having t(4;14), t(14;16), or del17p by FISH testing (or karyotype testing if central FISH not available). [e]2 participants were not previously exposed to a PI. One of these patients was reported as a major protocol deviation and the second patient was randomized but not treated due to not meeting laboratory criteria 72 hours prior to the planned dosing. EMD, extramedullary plasmacytoma; FISH, fluorescence in situ hybridization; IMiD, immunomodulatory drug; ISS, International Staging System.

Figure 2: Tal-DP and Tal-D significantly improved PFS vs DPd; improvement was generally consistent across prespecified subgroups (data not shown)[13]



Adapted with permission © *The New England Journal of Medicine* (2026). The O'Brien-Fleming stopping boundary for superiority was crossed for Tal-DP and Tal-D (*P*<0.0001 both arms; Tal-DP boundary, *P*=0.0069; Tal-D boundary, *P*=0.0145). HR, hazard ratio; NR, not reached.

Figure 3: Tal-DP and Tal-D demonstrated significantly higher ORR,[a] ≥CR, and MRD-negative CR[b] (10^{-5}) rates vs DPd[13]



[a]Response and disease progression were assessed by IRC per IMWG criteria. [b]MRD negativity was assessed in bone marrow aspirates with genetic sequencing (clonoSEQ, Adaptive Biotechnologies). MRD-negative CR was defined as the absence of malignant cells at a sensitivity threshold of 10^{-5} or 10^{-6}, achieved within 3 months prior to achieving CR/sCR or at any time after CR/sCR and before progression or subsequent therapy. OR, odds ratio; sCR, stringent complete response.

Table 2 and 3: The safety profiles of Tal-DP and Tal-D were consistent with known effects of each agent.[13] There were low rates of TEAEs leading to treatment discontinuation or death. Rates of grade 3 or 4 infections were numerically lower with Tal-D and comparable for Tal-DP vs DPd

Overall TEAEs, n (%)	Tal-DP (n=276)	Tal-D (n=274)	DPd (n=283)
Any TEAE	276 (100.0)	274 (100.0)	283 (100.0)
Grade 3 or 4 TEAEs	262 (94.9)	205 (74.8)	259 (91.5)
Serious TEAEs	174 (63.0)	144 (52.6)	152 (53.7)
TEAEs leading to treatment discontinuation[a]	29 (10.5)	22 (8.0)	19 (6.7)
TEAEs leading to death	5 (1.8)	11 (4.0)	13 (4.6)
Fatal infections	2 (0.7)	4 (1.5)	5 (1.8)
Hypogammaglobulinemia[b]	224 (81.2)	187 (68.2)	176 (62.2)

	Most common TEAEs,[c] n (%)	Tal-DP (n=276)		Tal-D (n=274)		DPd (n=283)	
		Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic	Neutropenia	232 (84.1)	211 (76.4)	112 (40.9)	80 (29.2)	255 (90.1)	244 (86.2)
	Anemia	136 (49.3)	66 (23.9)	107 (39.1)	41 (15.0)	117 (41.3)	45 (15.9)
	Thrombocytopenia	136 (49.3)	66 (23.9)	93 (33.9)	36 (13.1)	108 (38.2)	39 (13.8)
	Lymphopenia	99 (35.9)	86 (31.2)	82 (29.9)	68 (24.8)	72 (25.4)	50 (17.7)
Non-hematologic	Infections	241 (87.3)	104 (37.7)	231 (84.3)	80 (29.2)	235 (83.0)	120 (42.2)
	Taste changes[d]	201 (72.8)	–	205 (74.8)	–	11 (3.9)	–
	Non-rash skin AE[e]	191 (69.2)	6 (2.2)	177 (64.6)	7 (2.6)	24 (8.5)	0
	CRS	187 (67.8)	2 (0.7)	160 (58.4)	2 (0.7)	–	–
	Nail-related AE[f]	155 (56.2)	1 (0.4)	157 (57.3)	1 (0.4)	1 (0.4)	0
	Pyrexia	127 (46.0)	8 (2.9)	112 (40.9)	3 (1.1)	35 (12.4)	2 (0.7)
	Decreased weight	126 (45.7)	21 (7.6)	105 (38.3)	13 (4.7)	21 (7.4)	1 (0.4)
	Rash AE[g]	105 (38.0)	5 (1.8)	107 (39.1)	7 (2.6)	43 (15.2)	1 (0.4)
	Fatigue	83 (30.1)	14 (5.1)	60 (21.9)	8 (2.9)	69 (24.4)	9 (3.2)

Adapted with permission © *The New England Journal of Medicine* (2026). [a]Discontinuation of all components of study treatment. [b]Defined as AEs of hypogammaglobulinemia or immunoglobulin G <400 mL/dL. [c]>30% of patients in any treatment arm. [d]Taste changes included dysgeusia, ageusia, hypogeusia, and taste disorder. Per the Common Terminology Criteria for Adverse Events, the maximum severity for taste changes is grade 2. [e]Non-rash skin adverse events included skin exfoliation, dry skin, palmar-plantar erythrodysesthesia and pruritus. [f]Nail-related adverse events included nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, and nail ridging. [g]Rash adverse events included rash, maculopapular rash, erythematous rash, and erythema. AE, adverse event; CRS, cytokine release syndrome; TEAE, treatment-emergent adverse event.

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Disclosures

KE is an employee of Johnson & Johnson.

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