Phase 2 Study of Talquetamab, Daratumumab, and Lenalidomide as Induction Therapy in Patients With Transplant Eligible Newly Diagnosed Multiple Myeloma: MajesTEC-5

Leo Rasche[1], Niels Weinhold[2], K Martin Kortüm[1], Christoph Schaefers[3], Stephan Bohl[4], Christine Riedhammer[1], Lilli Podola[2], Uta Bertsch[2], Johannes Waldschmidt[1], Stefanie Huhn[2], Michael Hundemer[2], Gunhild Mechtersheimer[5], Elias K Mai[2], Florian Bassermann[6,7], Mathias Hänel[8], Hans Salwender[9], Christoph Heuck[10], Bas D Koster[11], Elena Ershova[12], Veronique Vreys[12], Josephine Khan[13], Katja Weisel[3], Hartmut Goldschmidt[2], Hermann Einsele[1], Marc S Raab[2]

[1]Department of Internal Medicine II, University Hospital of Würzburg, Würzburg, Germany; [2]Heidelberg Myeloma Center and German-Speaking Myeloma Multicenter Group (GMMG), Department of Medicine V, Heidelberg University Hospital and Medical Faculty Heidelberg, Heidelberg, Germany; [3]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [4]Medical Clinic of Hematology, Oncology and Tumor Immunology, Charité – Universitätsmedizin, Berlin, Germany; [5]Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany; [6]Department of Medicine III, TUM Klinikum, Technische Universität München, München, Germany; [7]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany; [8]Department of Internal Medicine III, Klinikum Chemnitz, Chemnitz, Germany; [9]Asklepios Tumorzentrum Hamburg, AK Altona and AK St Georg, Hamburg, Germany; [10]Johnson & Johnson, Spring House, PA, USA; [11]Johnson & Johnson Biologics Europe, Leiden, Netherlands; [12]Johnson & Johnson, Beerse, Belgium; [13]Johnson & Johnson, High Wycombe, UK

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Disclosure Statement: Leo Rasche, MD, PhD

- **Current employment:** University Hospital of Würzburg, Würzburg, Germany
- **Consultant & Honoraria:** BMS, GSK, Johnson & Johnson, Pfizer, Roche, and Takeda

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GMMG-HD10/DSMM-XX/MajesTEC-5: Background

- Talquetamab (Tal) is the first and only approved GPRC5D-targeting bispecific antibody for patients with RRMM and ≥3 prior LOT[1-3]
- In MonumenTAL-3, Tal + daratumumab (Tal + Dara) ± pomalidomide significantly prolonged PFS vs DPd, establishing this immunotherapy combination as a potential new SOC in 2L+ RRMM[1]
- GPRC5D targeting offers a novel antigen-directed approach that is being explored in NDMM
  - In later lines of relapse, the B-cell sparing mechanism of Tal contributes to low rates of severe infections[4,5]
- Here, we present the first results of Tal-Dara-lenalidomide (Tal-DR) as induction therapy in TE-NDMM in the MajesTEC-5 study

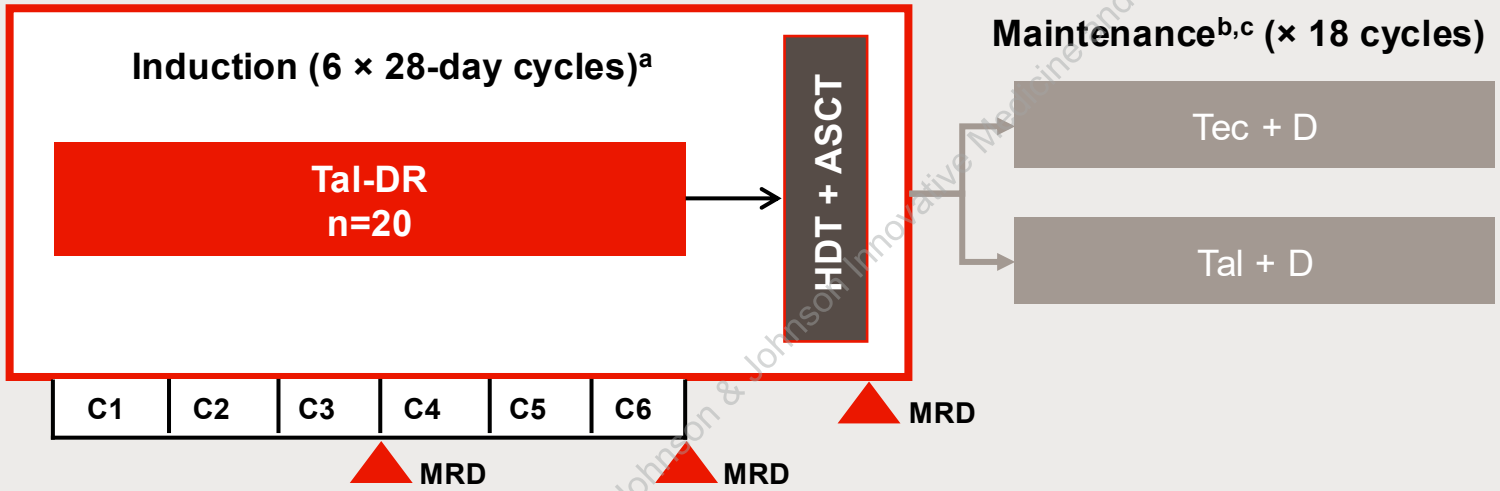
2L+, second line and beyond; BCMA, B-cell maturation antigen; DPd, daratumumab, pomalidomide, and dexamethasone; GMMG, German-speaking Myeloma Multicenter Group; GPRC5D, G protein-coupled receptor class C group 5 member D; LOT, line of therapy; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care; TE-NDMM, transplant-eligible newly diagnosed multiple myeloma.

1. US Food and Drug Administration. TALVEY (talquetamab-tgvs) prescribing information. 2025. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761342s000lbl.pdf. 2. European Commission. TALVEY (talquetamab) summary of product characteristics. 2025. Available at: https://ec.europa.eu/health/documents/community-register/2023/20230821160195/anx_160195_en.pdf. 3. Mina R, et al. *N Engl J Med* 2026;395:671-83. 4. Schinke C, et al. *Blood Adv* 2025;9:5752-62. 5. Rasche L, et al, *Blood* 2026; https://doi.org/10.1182/blood.2025031994.

GMMG-HD10/DSMM-XX/MajesTEC-5: Study Design

Key eligibility criteria:

- TE-NDMM
- Aged 18–70 years
- ECOG PS score 0–2



Primary endpoints:

- AEs, SAEs

Select secondary endpoints:

- MRD negativity (10^{-5} via NGF)
- ORR
- ≥CR
- ≥VGPR
- Stem cell yield

Induction dosing:

Regimen	C1		C2	C3-6
Tal: SC	SUD: 0.01, 0.06, 0.4 mg/kg on Days 2, 4, 8	0.8 mg/kg Day 15	0.8 mg/kg Q4W Day 1	0.8 mg/kg Q4W Day 1
D: 1800 mg SC	QW		QW	Q2W
R: 25 mg PO	–		QD (Days 1–21)	QD (Days 1–21)
d: 20 mg PO or IV	Twice weekly[d]		Twice weekly[d]	–

[a]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]Administered on Days 1–2, 8–9, 15–16, 22–23.
AE, adverse event; ASCT, autologous stem cell transplant; BsAb, bispecific antibody; C, cycle; CR, complete response; D, daratumumab; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; HDT, high-dose therapy; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGF, next-generation flow cytometry; ORR, overall response rate; QD, once daily; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; R, lenalidomide; SAE, serious adverse event; TE, transplant-eligible; Tec, teclistamab; VGPR, very good partial response.

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GMMG-HD10/DSMM-XX/MajesTEC-5: Baseline Demographics and Disease Characteristics

	Tal-DR N=20
Median age, years (range)	57.5 (45-69)
≥65, n (%)	5 (25)
Male, n (%)	15 (75)
Race, n (%)	
White	20 (100)
ECOG PS score, n (%)	
≤1	18 (90)
2	2 (10)
≥60% BMPCs, n (%)	11 (55)
≥1 soft tissue plasmacytoma, n (%)	1 (5)
ISS disease stage, n (%)	
I	9 (45)
II	5 (25)
III	6 (30)
High cytogenetic risk,[a] n (%)	6 (30)

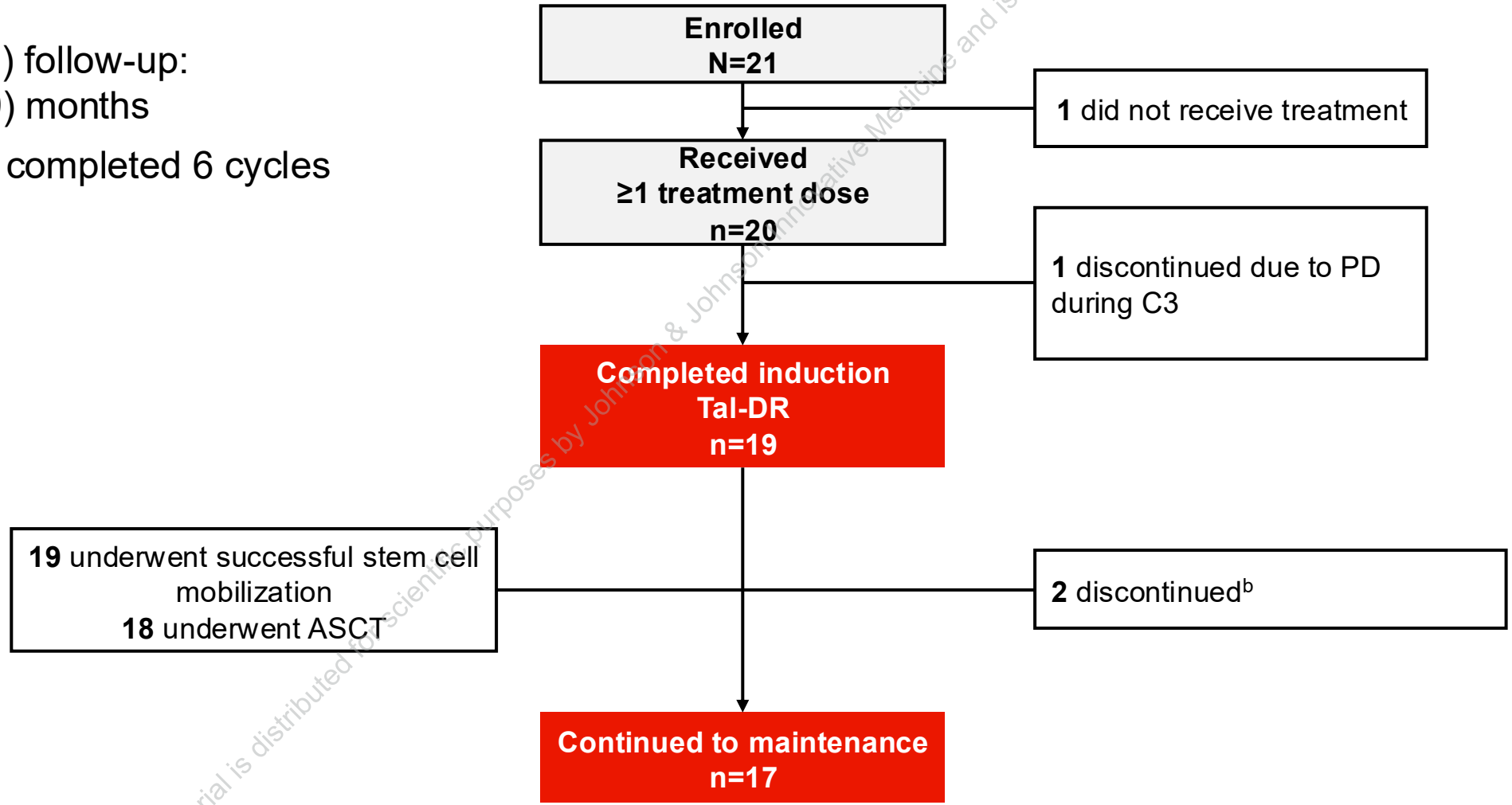
Patients were representative of those with TE-NDMM;[1-3] patients with high-risk disease were well represented

[a]Cytogenetic risk is based on central FISH or local FISH if central FISH is unavailable. High cytogenetic risk is defined as the presence of ≥1 of the following abnormalities: del(17p), t(4;14), or t(14;16). BMPC, bone marrow plasma cell; D, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; ISS, International Staging System; R, lenalidomide.

1. Liu X, et al. *Sci Rep* 2025;15:13595. 2. Abildgaard N, et al. *Eur J Cancer* 2024;201:113921. 3. Martínez-Lopez J, et al. *Future Oncol* 2023;19:2103-21.

GMMG-HD10/DSMM-XX/MajesTEC-5: Disposition

- Median (range) follow-up: 12.5 (3.4–14.9) months
- 19/20 patients completed 6 cycles of induction[a]



[a]1 patient completed only 3 cycles of induction. [b]1 due to an AE after cycle 6 prior to ASCT and 1 due to inadequate response during induction. AE, adverse event; ASCT, autologous stem cell transplant; D, daratumumab; R, lenalidomide; Tal, talquetamab; Tec, teclistamab.

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GMMG-HD10/DSMM-XX/MajesTEC-5: Stem Cell Mobilization and ASCT

- Stem cell collection was done after Induction Cycle 3 according to local SoC
- Recommended yield threshold per protocol: 2.5 × 10^6/kg to 5 × 10^6/kg CD34+ cells
  - 1 patient had a yield below 2.5 × 10^6/kg

	Tal-DR N=20
Underwent stem cell mobilization, n (%)	19 (95)
Stem cell yield (10^6 CD34 cells/kg)	
Median (range)	6.4 (1.4–54.0)
Stem cell transplanted, n (%)	18 (90)
Days to engraftment, median (range)	
Neutrophils (0.5 × 10^9 / L)	14 (3–67)
Platelets (20 × 10^9 / L)	14 (4–57)

Tal-DR enabled successful stem cell mobilization and transplantation in 95% and 90% of patients

ASCT, autologous stem cell transplant; SoC, standard of care; Tal-DR, talquetamab plus daratumumab and lenalidomide.

GMMG-HD10/DSMM-XX/MajesTEC-5: TEAEs

- No ICANS was reported
- CRS all grade 1/2
  - 30% received tocilizumab[a]
  - All resolved with no discontinuations
- 4 patients (20%) discontinued Tal[b] due to a TEAE and remained on other study treatment
- 2 deaths occurred (1 trauma; 1 progressive disease)

TEAE, n (%)		Tal-DR N=20	
		Any Grade	Grade 3/4
	Any AE	20 (100)	13 (65)
Hematologic	Neutropenia	7 (35)	6 (30)
	Leukopenia	8 (40)	6 (30)
	Lymphopenia	5 (25)	5 (25)
	Thrombocytopenia	4 (20)	2 (10)
	Anemia	3 (15)	2 (10)
Non-hematologic[c]	Taste changes[d]	16 (80)	-
	Infections	14 (70)	4 (20)
	CRS	14 (70)	0
	Hypogammaglobulinemia	11 (55)	1 (5)
	Rash AE[e]	11 (55)	2 (10)
	Fatigue	9 (45)	1 (5)
	Decreased weight	8 (40)	3 (15)
	Nausea	7 (35)	0
	Hypokalemia	7 (35)	0

Median follow-up: 12.5 months. Data cutoff: March 2, 2026. [a]2 patients received multiple doses of tocilizumab to treat CRS during the study. 1 patient received tocilizumab as a prophylaxis due to repetitive CRS after each Tal injection. [b]Vertigo G1, n=1; vertigo G3, n=1 (this patient also had diplopia [G1], gait disturbance [G1], tremor [G1], and nausea [G2] leading to discontinuation); eczema [G3] and weight loss [G3], n=1; balance disorder [G2] and aphasia [G2], n=1. [c]AEs shown are those occurring in >30% of patients. [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]Rash adverse events included rash, maculopapular rash, erythematous rash, and erythema. C, cycle; CRS, cytokine release syndrome; G, Grade; ICANS, immune effector cell-associated neurotoxicity syndrome; Tal-DR, talquetamab plus daratumumab and lenalidomide; TEAE, treatment emergent adverse event.

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GMMG-HD10/DSMM-XX/MajesTEC-5: Infections

- Low rates of grade 3/4 infections
- No opportunistic infections
- No treatment discontinuations due to infection
- No fatal infections
- All patients with TE-hypogammaglobulinemia[a] (17 [85%]) received at least 1 dose of IgG replacement

	Tal-DR (N=20)	
	Any Grade	Grade 3/4
Patients with ≥1 TE infections or infestations, n (%)	14 (70)	4 (20)
Patients with opportunistic infections, n (%)	0	0
Most common TE infections and infestations[b], n (%)		
Upper respiratory tract	5 (25)	0
Nasopharyngitis	2 (10)	0
Pneumonia	2 (10)	2 (10)
Urinary tract	2 (10)	1 (5)

Low rates of grade 3/4 infections with no fatal infections

Median follow-up: 12.5 months. Data cutoff: March 2, 2026. [a] Based on AE criteria or post-baseline IgG values <400 mg/dL. [b]AEs shown are those occurring in ≥10% of patients. IgG, Immunoglobulin G; Tal-DR, talquetamab plus daratumumab and lenalidomide; TE, treatment-emergent.

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GMMG-HD10/DSMM-XX/MajesTEC-5: AEs of clinical interest

- Taste changes were common but mostly grade 1[a]
- Rash was predominantly low grade
- Nail events were infrequent
- 3/20 patients had ataxia/balance disorders, events were all grade 1 or 2 and recovered or recovering

Taste, skin, nail, and neurologic AEs were manageable and predominantly low grade

AE, n (%)	Tal-DR N=20
Taste changes[b] (any grade)	16 (80)[a]
Leading to discontinuation of Tal[c]	0
Events recovered or recovering[d]	12/17 (71)
Non-rash skin[e] (any grade)	3 (15)
Grade 3 or 4	0
Leading to discontinuation of Tal[c]	0
Events recovered or recovering[d]	2/3 (67)
Nail related[f] (any grade)	4 (20)
Leading to discontinuation of Tal[c]	0
Events recovered or recovering[d]	2/4 (50)
Rash-related[g] (any grade)	11 (55)
Grade 3[h]	2 (10)
Leading to discontinuation of Tal[c]	1 (5)
Events recovered or recovering[d]	15/16 (94)
Ataxia/balance disorders[i] (any grade)	3 (15)
Grade 3 or 4	0
Leading to discontinuation of Tal[c]	2 (10)
Events recovered or recovering[d]	4/4 (100)
Weight decreased (any grade)	8 (40)
Grade 3[h]	2 (10)
Leading to discontinuation of Tal[c]	1 (3)
Events recovered or recovering[d]	5/9

Median follow-up: 12.5 months. Data cutoff: March 2 2026. [a]Grade 1, n=10 (50%); Grade 2, n=6 (30%). [b]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. [c]Patients could report multiple AEs that lead to discontinuation of Tal. [d]Percent of events resolved is calculated using the total number of events for the respective AE as the denominator. [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, rash maculo-papular, rash erythematous, erythema, rash pruritic and eczema. [h]There were no grade ≥4 events. [i]Ataxia/balance disorders included ataxia, dysarthria, balance disorder, nystagmus, cerebellar ataxia, cerebellar syndrome, dysmetria, and gait disturbance. AE, adverse event; Tal-DR, talquetamab plus daratumumab and lenalidomide.

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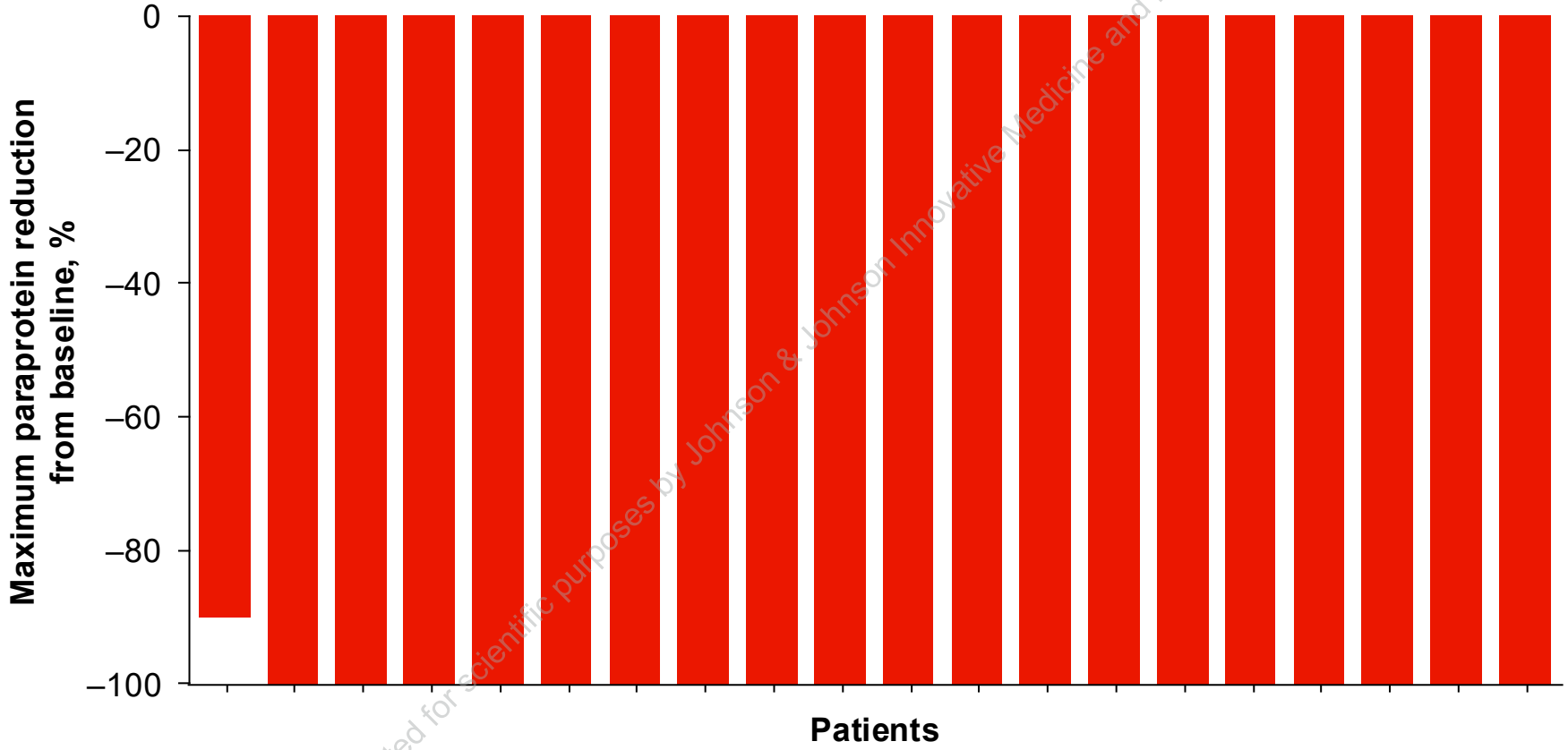
GMMG-HD10/DSMM-XX/MajesTEC-5: Disease Burden



95% of treated patients achieved 100% reduction in paraprotein production by the post-ASCT/pre-maintenance visit

Median follow-up: 12.5 months. Data cutoff: March 2, 2026.

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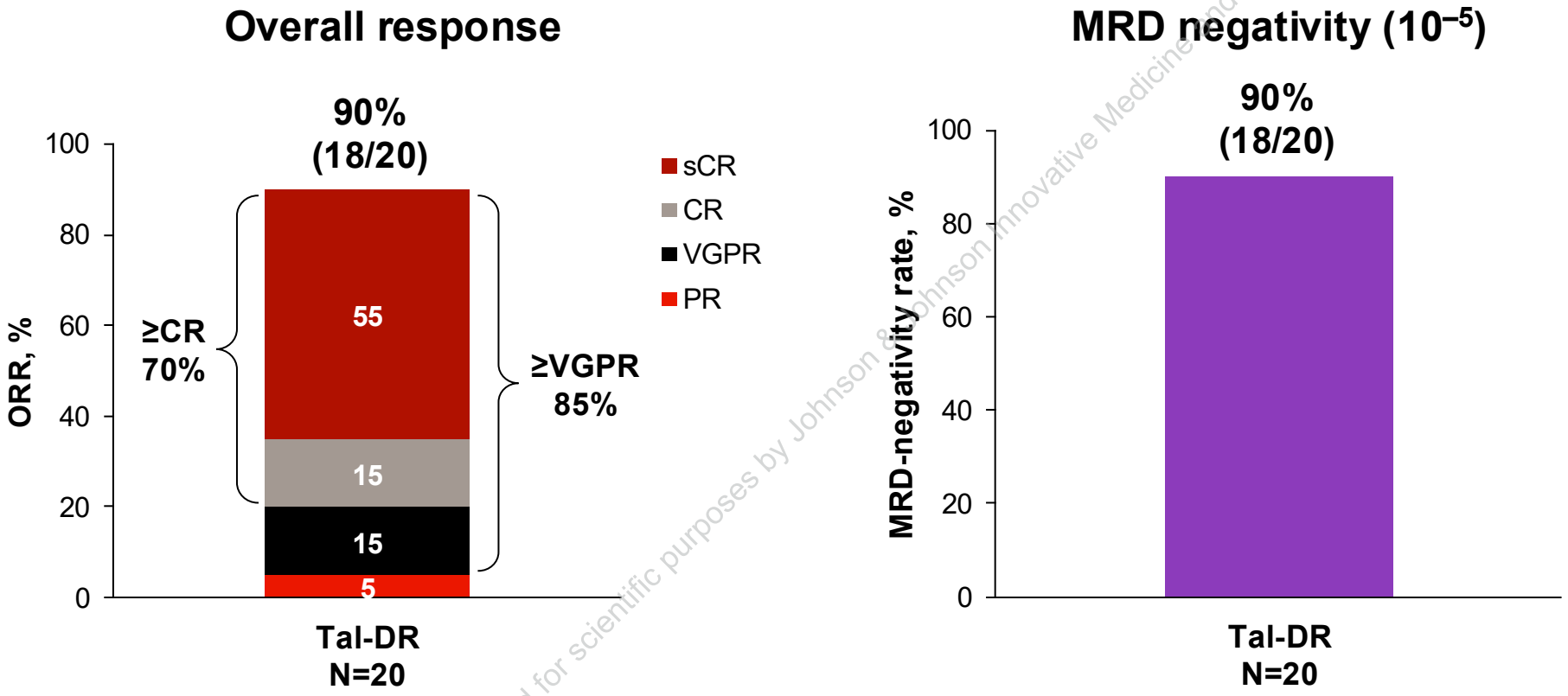
GMMG-HD10/DSMM-XX/MajesTEC-5: Treatment Response[a] and MRD-Negativity Rates



High rate of deep responses with 90% achieving MRD negativity post ASCT/prior to maintenance[b]

Median follow-up: 12.5 months. Data cutoff: March 2, 2026. [a]Response was assessed by computerized algorithm, based on IMWG Criteria. Confirmed response require at least 2 consecutive identical algorithm' response assessments. [b]2 patients remained MRD-positive throughout treatment (1 had progressive disease after C3 and 1 had refractory disease); 2 additional patients became MRD-positive after C6 but converted back to MRD negativity after ASCT. ASCT, autologous stem cell transplant; CR, complete response; MRD, minimal residual disease; PR, partial response; ORR, overall response rate; sCR, stringent complete response; Tal-DR, talquetamab plus daratumumab and lenalidomide; VGPR, very good partial response.

GMMG-HD10/DSMM-XX/MajesTEC-5: Conclusions

- Tal-DR induced deep responses, with MRD negativity prior to maintenance in 90% of patients
- No new safety signals observed; no ICANS reported and CRS limited to grade 1/2
- Infections manageable with established supportive care
  - Few grade 3/4 infections
- Taste, skin, and nail AEs predominantly low grade
- 4/20 patients discontinued Tal due to AEs
- 95% and 90% of patients successfully underwent stem cell mobilization and ASCT, respectively
- The combinations of Tec-DR and Tal-DR are being further explored in the ongoing phase 3 MajesTEC-7 (NCT05552222) study in patients with TIE-NDMM

Tal-DR demonstrated rapid and deep responses, high MRD-negativity rates, and no new safety findings, supporting further evaluation of GPRC5D-directed therapy in TE-NDMM

AE, adverse event; BCMA, B-cell maturation antigen; Tal-DR, talquetamab plus daratumumab and lenalidomide; Tec-DR, teclistamab plus daratumumab and lenalidomide; TE-NDMM, transplant-eligible newly diagnosed multiple myeloma; TIE, transplant ineligible.

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- The patients who are participating in this study and their families
- Staff members at the study sites
- Data and safety monitoring committee
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- Marc S Raab is a co-principal investigator of this study
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DSMM, Deutsche Studiengruppe Multiples Myelom; GMMG, German-speaking Myeloma Multicenter Group.

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