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Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Combination With Daratumumab and Lenalidomide in Patients With Newly Diagnosed Multiple Myeloma: Safety and Efficacy Results From the Phase 1b MonumenTAL-2 Study

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Key Takeaway

This first study combining Tal with Dara and Len in NDMM showed >96% ORRs and a manageable safety profile that continue to support Tal as a versatile combination partner, including in NDMM

Conclusions

- The novel, immune-based combination regimen of Tal-Dara-Len elicited high and rapid responses that were deep in patients with NDMM with 6–13 months of follow-up
- The safety profile was consistent with the individual agents, with no evidence of additive hematologic AEs and no discontinuations due to AEs
- These data support further investigation in the MajesTEC-7 study (NCT05552222; Tal-Dara-Len or teclistamab [Tec]-Dara-Len vs Dara-Len-Dexamethasone in NDMM), given the promising data here and initial results with the Tec (B-cell maturation antigen bispecific antibody) arm[7]

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Poster

Supplementary material

https://www.congresshub.com/ASH2024/Oncology/Talquetamab/Nooka

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Acknowledgments

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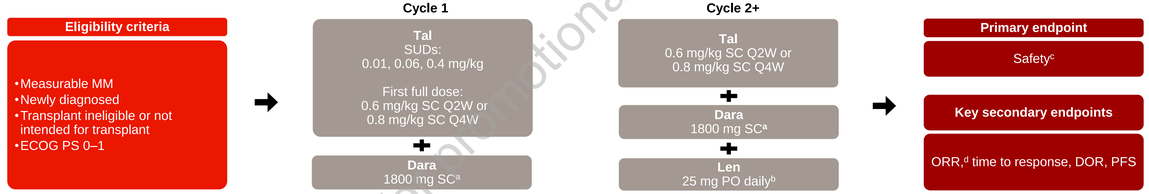
Introduction

- Talquetamab (Tal) is the first approved G protein–coupled receptor class C group 5 member D (GPRC5D)-targeting bispecific antibody for the treatment of patients with relapsed/refractory multiple myeloma (MM)[1-3]
- Daratumumab (Dara), an anti-CD38 monoclonal antibody, is a foundational therapy across all lines of MM therapy with direct on-tumor and immunomodulatory actions[4,5]
- Lenalidomide (Len) is an established immunomodulatory drug that has direct on-tumor apoptotic activity[6]
- Combining Dara and Len with T-cell redirection therapy may potentiate antimyeloma effects
- We report initial efficacy and safety results of the immune-based Tal-Dara-Len regimen in patients with newly diagnosed MM (NDMM) from the MonumenTAL-2 study

Methods

- The design of the Tal-Dara-Len arm of the phase 1b, multi-arm MonumenTAL-2 study (NCT05050097) is shown in **Figure 1**

Figure 1: MonumenTAL-2 (Tal-Dara-Len) study design



[a]Administered QW (on days 1, 8, 15, and 22) during cycles 1 and 2, Q2W during cycles 3–6 (on days 1 and 15), and once (on day 1) during each subsequent 28-day cycle. [b]For 21 days of a 28-day cycle. [c]AEs assessed per CTCAE v5.0, except for CRS and ICANS, which were graded per ASTCT guidelines. [d]Assessed per IMWG 2016 criteria. AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell–associated neurotoxicity syndrome; IMWG, International Myeloma Working Group; ORR, overall response rate; PFS, progression-free survival; PO, by mouth; Q2W, every other week; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; SUD, step-up dose.

Results

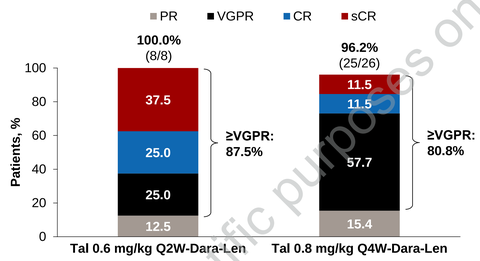
Baseline characteristics

- Patients were mostly White, male, and had an International Staging System stage of I/II with a median age of 68.5 years (Q2W) and 74.0 years (Q4W) (**Supplemental Table**)
- A higher proportion of patients with high-risk cytogenetics and/or extramedullary plasmacytomas were in the Q4W vs Q2W cohort, although numbers are small in the Q2W cohort

Efficacy

- As of September 23, 2024, high response rates with notable depth of response were observed, with a >96% ORR and >80% very good partial response (VGPR) or better across cohorts (**Figure 2**); additional efficacy outcomes are presented in **Table 1**
- Responses deepened over time, with a time to best response of 3.8 months (Q2W) and 1.9 months (Q4W) (**Table 1** and **Figure 3**)

Figure 2: ORR



CR, complete response; PR, partial response; sCR, stringent complete response.

Table 1: Efficacy outcomes

	Tal 0.6 mg/kg Q2W-Dara-Len (n=8)	Tal 0.8 mg/kg Q4W-Dara-Len (n=26)
Median follow-up, months (range)	13.2 (10.0–14.6)	5.8 (1.7[a]–12.0)
Median time to first response, months (range)	1.0 (0.9–2.3)	1.0 (0.9–1.9)
Median time to best response, months (range)	3.8 (1.0–11.6)	1.9 (0.9–9.2)
6-month DOR rate, % (95% CI)	100.0 (100.0–100.0)	100.0 (100.0–100.0)
6-month PFS rate, % (95% CI)	100.0 (100.0–100.0)	95.8 (73.9–99.4)

Median DOR and PFS were not reached in either cohort; data are still maturing.
[a]Denotes patients who died.

Safety

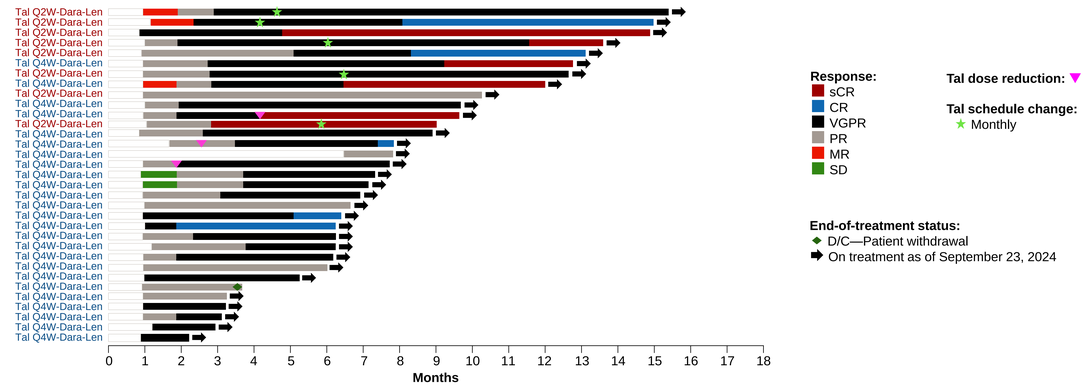
- Most common AEs were taste related, CRS, and skin related (**Table 2**)
- Grade 3/4 AEs occurred in 100% (Q2W) and 77% (Q4W) of patients; most commonly neutropenia, anemia, and rash related
- CRS events were all grade 1/2
- Taste-, skin-, nail-, and rash-related GPRC5D AEs were mainly grade 1/2 with no discontinuations
- Most common infections were COVID-19, rhinovirus, and other upper respiratory tract infections; all infections were mostly grade 1/2
- Hypogammaglobulinemia was reported in 63% (Q2W) and 54% (Q4W) of patients; 50% (Q2W) and 19% (Q4W) received ≥1 dose of intravenous immunoglobulin during treatment
- AEs led to Tal dose reductions in 38% (Q2W) and 23% (Q4W), Tal skipped doses in 75% (Q2W) and 31% (Q4W), and Tal dose delays in 88% (Q2W) and 15% (Q4W) of patients
- No patients discontinued any study treatments due to AEs
- 1 patient had a grade 5 AE in the Q4W cohort (large intestine perforation due to sigmoid mass; not drug related)
- Translational and immune outcomes for this regimen are presented in **Poster 4653**

Table 2: Hematologic and nonhematologic AEs

AEs ≥30%, n (%)	Tal 0.6 mg/kg Q2W-Dara-Len (n=8)		Tal 0.8 mg/kg Q4W-Dara-Len (n=26)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic AEs				
Neutropenia	6 (75.0)	6 (75.0)	12 (46.2)	11 (42.3)
Anemia	5 (62.5)	3 (37.5)	8 (30.8)	3 (11.5)
Thrombocytopenia	4 (50.0)	1 (12.5)	8 (30.8)	2 (7.7)
Nonhematologic AEs				
Taste related[a]	8 (100.0)	0	24 (92.3)	1 (3.8)
CRS	7 (87.5)	0	20 (76.9)	0
Skin related[b]	6 (75.0)	2 (25.0)	20 (76.9)	1 (3.8)
Infections[c]	8 (100.0)	3 (37.5)	13 (50.0)	1 (3.8)
Rash related[d]	5 (62.5)	3 (37.5)	15 (57.7)	3 (11.5)
Diarrhea	7 (87.5)	0	11 (42.3)	1 (3.8)
Nail related[e]	5 (62.5)	0	13 (50.0)	0
Dry mouth	5 (62.5)	0	12 (46.2)	0
Constipation	3 (37.5)	0	13 (50.0)	0
Pyrexia	5 (62.5)	0	10 (38.5)	0
Cough	6 (75.0)	0	8 (30.8)	0
Fatigue	5 (62.5)	1 (12.5)	9 (34.6)	2 (7.7)
Nausea	5 (62.5)	0	9 (34.6)	2 (7.7)
Weight decreased	2 (25.0)	0	11 (42.3)	1 (3.8)

All AEs were treatment emergent. No patients had ICANS in either cohort. [a]Includes dysgeusia, ageusia, taste disorder, and hypogeusia. Per CTCAE v5.0, the maximum grade of dysgeusia is 2. [b]Includes skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome. [c]Grade 3/4 infections included gastroenteritis, influenza, pneumonia, and COVID-19 pneumonia in the Q2W cohort and esophageal candidiasis in the Q4W cohort. [d]Includes rash, maculopapular rash, erythematous rash, and erythema. [e]Includes nail discoloration, nail disorder, nail toxicity, nail dystrophy, nail ridging, onychoclasis, onycholysis, and onychomadesis.

Figure 3: Treatment response in patients who had ≥PR with Tal-Dara-Len



D/C, discontinued; MR, minimal residual; SD, stable disease.

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Multiple Myeloma

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