# Talquetamab + Daratumumab in Patients With Relapsed/Refractory Multiple Myeloma: Updated TRIMM-2 Results

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## INTRODUCTION

- Talquetamab (tal) is a first-in-class bispecific antibody targeting G protein–coupled receptor class C group 5 member D, an antigen uniquely overexpressed on malignant plasma cells[1,2]
  - >70% overall response rate (ORR) was observed in patients with triple-class relapsed/refractory multiple myeloma (RRMM) taking talquetamab[3]
- Daratumumab (dara) is a foundational therapy in RRMM and newly diagnosed multiple myeloma, with direct on-tumor and immunomodulatory actions[4,5]
  - Daratumumab depletion of CD38-expressing regulatory T cells may enhance talquetamab-mediated killing of myeloma cells[1]
- Initial TRIMM-2 (NCT04108195) results showed promising efficacy and increased CD38+/CD8+ T cells and proinflammatory cytokines[6]
- Here, we present updated TRIMM-2 results of the immunotherapy regimen of tal + dara with additional patients and longer follow-up

## METHODS

- TRIMM-2 is an ongoing phase 1b, open-label, multicenter, multicohort study in patients with RRMM (**Figure 1**)
- Key eligibility criteria:
  - Multiple myeloma per International Myeloma Working Group (IMWG) criteria
  - ≥3 prior lines of therapy (LOT), including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double-refractory to PI and IMiD
  - Anti-CD38 monoclonal antibody (mAb) >90 days prior allowed
  - Refractory to anti-CD38 mAb and prior bispecific antibody (BsAb) or chimeric antigen receptor (CAR)-T cell therapy allowed
- Key study objectives:
  - Part 1: Identify the recommended phase 2 dose (RP2D)
  - Part 2: Safety at the selected RP2D(s)
  - Antitumor activity, pharmacokinetics, pharmacodynamics

**FIGURE 1: Tal + dara dosing schedules**

| Dara[a,b] | + | Tal[c,d,e] | | Patients enrolled |
|---|---|---|---|---|
| 1800 mg SC QW (cycles 1–2) Q2W (cycles 3–6) Q4W (cycles ≥7) | | 0.4 mg/kg SC QW | → | n=14 |
| | | 0.8 mg/kg SC Q2W | → | n=51 |

[a]Dara given with 2-week corticosteroid taper (steroid-free administration after first full treatment dose). [b]Dara given first if both administered on same day. [c]2–3 step-up doses before first full dose. [d]Premedication, including glucocorticoid, antihistamine, and antipyretic at step-up and first full dose of tal. [e]Option to transition to tal Q2W or Q4W (tal dose frequency may be reduced after 4 cycles from QW to Q2W if patients achieved a PR and reduced further from Q2W to Q4W after 8 cycles if they achieved a VGPR). Q2W, every other week; Q4W, every 4 weeks; QW, weekly; PR, partial response; SC, subcutaneous; VGPR, very good partial response.

MULTIPLE MYELOMA

## RESULTS

**Study population**

- Median follow-up as of April 6, 2023:
  - Tal 0.4 mg/kg QW + dara, 16.8 mo (range, 1.9–31.0)
  - Tal 0.8 mg/kg Q2W + dara, 15.0 mo (range, 1.0–23.3)

**TABLE 1: Baseline characteristics**

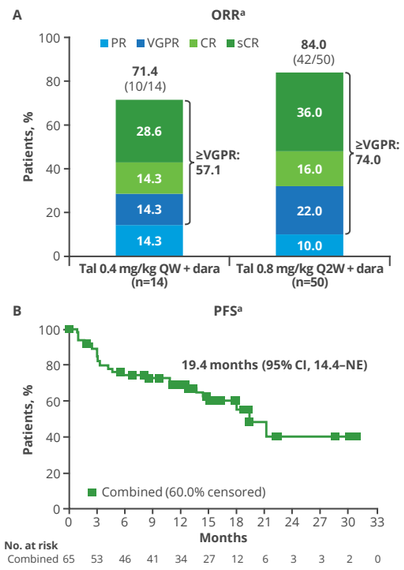
| Characteristic | Tal 0.4 mg/kg QW + dara (n=14) | Tal 0.8 mg/kg Q2W + dara (n=51) |
|---|---|---|
| Age (years), median (range) | 68 (50–77) | 61 (37–81) |
| Male, n (%) | 7 (50.0) | 26 (51.0) |
| Race, n (%) | | |
| White | 9 (64.3) | 46 (90.2) |
| Black/African American | 4 (28.6) | 3 (5.9) |
| Asian | 0 (0) | 1 (2.0) |
| Not reported | 1 (7.1) | 1 (2.0) |
| Extramedullary plasmacytomas ≥1,[a] n (%) | 4 (28.6) | 13 (25.5) |
| High cytogenetic risk,[b] n (%) | 1 (9.1) | 7 (21.2) |
| ISS stage,[c] n (%) | | |
| I | 6 (54.5) | 19 (45.2) |
| II | 4 (36.4) | 16 (38.1) |
| III | 1 (9.1) | 7 (16.7) |
| Time since diagnosis (years), median (range) | 6.4 (3.4–14.7) | 6.7 (1.6–17.4) |
| Prior LOT, n, median (range) | 5.5 (4–16) | 5.0 (2–14) |
| Prior stem cell transplantation, n (%) | 13 (92.9) | 40 (78.4) |
| Exposure status, n (%) | | |
| Anti-CD38 | 11 (78.6) | 46 (90.2) |
| Triple-class[d] | 11 (78.6) | 46 (90.2) |
| Penta-drug[e] | 10 (71.4) | 31 (60.8) |
| BCMA-targeted therapy | 8 (57.1) | 27 (52.9) |
| ADC | 4 (28.6) | 11 (21.6) |
| CAR-T therapy | 2 (14.3) | 9 (17.6) |
| Bispecifics | 5 (35.7) | 8 (15.7) |
| Other BsAb | 0 (0) | 2 (3.9) |
| Refractory status, n (%) | | |
| Anti-CD38[d] | 11 (78.6) | 40 (78.4) |
| Triple-class[d] | 8 (57.1) | 31 (60.8) |
| Penta-drug[e] | 6 (42.9) | 12 (23.5) |
| Any BsAb | 5 (35.7) | 10 (19.6) |
| To last LOT | 11 (78.6) | 38 (74.5) |

[a]Soft tissue plasmacytomas not associated with the bone were included. [b]del(17p), t(4;14), and/or t(14;16); denominator n=11 for tal 0.4 mg/kg QW and n=33 for tal 0.8 mg/kg Q2W. [c]Denominator n=11 for tal 0.4 mg/kg QW and n=42 for tal 0.8 mg/kg Q2W. [d]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [e]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; ISS, International Staging System.

**Efficacy**

- ORRs are shown in **Figure 2A**
  - At 12 months, 80.9% of patients were still in response, and among those who achieved ≥ CR, 93.3% remained in response
  - 65.4% of responders remained on therapy
- Median progression-free survival (PFS) was not reached for tal 0.4 mg/kg QW + dara and was 19.4 months (95% CI, 12.5–NE [not estimable]) for tal 0.8 mg/kg Q2W + dara (**Figure 2B**)
- Median overall survival was not reached for either cohort

**FIGURE 2: Efficacy**




[a]Response was assessed by investigators in response-evaluable patients, based on IMWG criteria. Percentages may not total due to rounding. CR, complete response; sCR, stringent complete response.

**Safety**

- Skin, nail, and oral adverse events (AEs) were common but mostly low grade (**Table 2**)
- AEs led to dose reductions of tal in 16.9% and to discontinuation in 1.5% (1 patient, due to toxic skin eruption)
- Rashes were managed with topical corticosteroids or a short course of oral corticosteroids
- Dysgeusia and dry mouth were managed with mouthwashes, saliva stimulants, or dose modifications
- 76.9% had dysgeusia and 6.2% required tal dose reduction
- Cytokine release syndrome (CRS) was mostly confined to step-up and cycle 1 dosing
  - There were no grade 3/4 CRS or discontinuations due to CRS
- Of the 4.6% of patients who had immune effector cell–associated neurotoxicity syndrome, all were grade 1/2 and resolved in 1–2 days
- Overall infections were 57.1% (tal 0.4 mg/kg QW + dara) and 72.5% (tal 0.8 mg/kg Q2W + dara)
  - Onset of most high-grade infections occurred during the first 6 months (75.0%)
  - Grade 3/4 infections were 21.4% (tal 0.4 mg/kg QW + dara) and 25.5% (tal 0.8 mg/kg Q2W + dara)
  - Most high-grade infections were pneumonia (7.1% for tal 0.4 mg/kg QW + dara and 13.7% for tal 0.8 mg/kg Q2W + dara)
  - 1 death from treatment-related pneumonia (tal 0.8 mg/kg Q2W + dara)
  - 3.1% of patients had low-grade cytomegalovirus reactivation
  - Immunoglobulin G level <500 mg/dL: 35.4% at baseline and 86.2% post baseline; of these, 33.8% received intravenous immunoglobulin
  - No reduction in total CD19 B cells was observed in either tal dose level
- Of the 80.0% of patients with grade 3/4 AEs, most were hematologic (60.0%)
  - Grade 3/4 neutropenia was <30% in both cohorts
  - Cytopenias were generally confined to step-up and cycle 1–2 doses and resolved in most patients

**TABLE 2: Adverse events**

| | Tal 0.4 mg/kg QW + dara (n=14) | | Tal 0.8 mg/kg Q2W + dara (n=51) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| **Nonhematologic AE (≥25% overall), n (%)** | | | | |
| Oral AEs[a] | 12 (85.7) | 0 (0) | 46 (90.2) | 2 (3.9) |
| Skin AEs[b] | 10 (71.4) | 2 (14.3) | 43 (84.3) | 4 (7.8) |
| CRS | 10 (71.4) | 0 (0) | 41 (80.4) | 0 (0) |
| Nail AEs[c] | 8 (57.1) | 0 (0) | 35 (68.6) | 1 (2.0) |
| Fatigue | 11 (78.6) | 0 (0) | 20 (39.2) | 1 (2.0) |
| Pyrexia | 5 (35.7) | 0 (0) | 19 (37.3) | 2 (3.9) |
| Pruritus | 6 (42.9) | 0 (0) | 16 (31.4) | 0 (0) |
| Decreased appetite | 4 (28.6) | 1 (7.1) | 17 (33.3) | 1 (2.0) |
| Dizziness | 6 (42.9) | 0 (0) | 15 (29.4) | 0 (0) |
| Weight decreased | 7(50.0) | 0 (0) | 14 (27.5) | 0 (0) |
| Back pain | 4 (28.6) | 0 (0) | 15 (29.4) | 1 (2.0) |
| Diarrhea | 5 (35.7) | 0 (0) | 13 (25.5) | 1 (2.0) |
| Headache | 3 (21.4) | 0 (0) | 15 (29.4) | 0 (0) |
| Arthralgia | 5 (35.7) | 0 (0) | 12 (23.5) | 0 (0) |
| **Hematologic AE (≥20% overall), n (%)** | | | | |
| Anemia | 9 (64.3) | 5 (35.7) | 25 (49.0) | 13 (25.5) |
| Neutropenia | 6 (42.9) | 4 (28.6) | 20 (39.2) | 14 (27.5) |
| Thrombocytopenia | 6 (42.9) | 4 (28.6) | 19 (37.3) | 10 (19.6) |
| Lymphopenia | 8 (57.1) | 8 (57.1) | 10 (19.6) | 9 (17.6) |

[a]Includes dysgeusia, dry mouth, stomatitis, ageusia, hypogeusia, and taste disorder. [b]Includes skin exfoliation, dry skin, pruritus, rash maculopapular, rash, erythema, and rash erythematous. [c]Includes nail disorder, onychomadesis, nail dystrophy, nail discoloration, nail ridging, onycholysis, nail bed disorder, and onychalgia.

## KEY TAKEAWAY

Tal + dara may be a versatile combination therapy, showing deep and durable responses with promising median PFS in heavily pretreated patients with RRMM, including those refractory to anti-CD38, anti-BCMA, and BsAb therapies

## CONCLUSIONS

Promising responses were observed in subgroups with high unmet need, including anti-CD38–refractory (ORR, 80%) and prior T-cell redirection (ORR, 79%) patients

The safety profile of tal + dara is consistent with monotherapies, with low rates of talquetamab discontinuation due to AEs

Preservation of B cells and low rates of high-grade neutropenia contribute to modest grade 3/4 infection rates

## ACKNOWLEDGMENTS

We thank the patients who participated in the study and their families and caregivers, the physicians and nurses who cared for patients and supported this clinical trial, staff members at the study sites, and staff members involved in data collection and analyses. This study was funded by Janssen Research & Development, LLC. Medical writing support was provided by Eloquent Scientific Solutions and funded by Janssen Scientific Affairs, LLC. This abstract was previously presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA & Virtual, and the European Hematology Association (EHA) 2023 Hybrid Congress; June 8–11, 2023; Frankfurt, Germany.

## DISCLOSURES

**BD** has served in a consulting/advisory role for Arivan Research, Beam Therapeutics, Gamida Cell, Jazz Pharmaceuticals, and Pluristem Therapeutics; is a stockholder in Iovance Biotherapeutics and Syndax; has received honoraria from Adaptive Biotechnologies, Curio Science, MJH Healthcare Holdings, and Wiley; and has received research funding from Angiocrine Bioscience, Janssen Oncology, MEI Pharma, Orca Bio Pfizer, Poseida Therapeutics, Takeda, and WUGEN. **KW** has served as a consultant and received honoraria from Adaptive Biotechnologies, Karyopharm, and Takeda; has received honoraria from Roche; and has received honoraria and served as a member on boards of directors and/or advisory committees for Amgen, BMS, Celgene, GSK, Janssen, OncoPeptides, and Sanofi. **M-VM** has received honoraria from or served on the board of directors or on an advisory committee for AbbVie, Adaptive Biotechnologies, Amgen, BMS/Celgene, GSK, Janssen, Oncopeptides, Pfizer, Regeneron, Roche, Sanofi, Sea-Gen, and Takeda. **HG** has served as a consultant at Amgen, Adaptive Biotechnology, BMS, Celgene, Janssen, and Sanofi; has received honoraria from Amgen, BMS, Celgene, GSK, Janssen, Novartis, and Sanofi; and has received grants or research funding from Amgen, BMS, Celgene, Chugai, Dietmar-Hopp-Foundation, Incyte, Janssen, Johns Hopkins University, Molecular Partners, MSD, MudiPharma, Novartis, Sanofi, and Takeda. **TGM** has served in a consulting/advisory role for GSK and Legend; and received research funding from Amgen, Janssen Oncology, and Sanofi. **DM** has received honoraria from AbbVie, Janssen, and Takeda. **DR** has served in a consulting/advisory role for Amgen, BMS, Janssen, Karyopharm, and Takeda; received honoraria from Amgen, Celgene, GSK, Janssen, Sanofi, and Takeda; and received research funding from BMS, Celgene, Janssen, Mellenium, Merck, Otsuka, and Takeda. **PR-O** has served on advisory boards for Amgen, BMS, GSK, Janssen, Kite Pharma, Oncopeptides, Pfizer, Sanofi, and Takeda; has provided consultancy to AbbVie, BMS, and Roche; and has received honoraria from Amgen, BMS, GSK, Janssen, Regeneron, Sanofi, and Takeda. **MB** has served in a consulting role for Janssen and Sanofi; received research funding from Adaptive Biotechnologies, Amgen, Bluebird Bio, BMS/Celgene, Celularity, Cerecor, Janssen Research & Development, Legend Biotech, Medimmune, Millenium, and Takeda. **AD** has received consultancy/advisory board fees from BMS, Imbrium, Janssen, Pfizer, and Prothena; and research funding from Caelum, Prothena, Sanofi, Takeda, and TeneoBio. **AO** has served in a consulting role for Celgene/BMS, Sanofi, and Janssen; and has served on a speakers' bureau for Celgene/BMS, Sanofi, and GSK. **LR** has received honoraria from Amgen, Celgene, GSK, Janssen, Sanofi, and Takeda. **NB** has served in a consulting role for AbbVie, Amgen, BMS, Forus, Genentech, GSK, Janssen, Pfizer, Sanofi, and Takeda; has received honoraria from AbbVie, Amgen, BMS, Forus, Janssen, Pfizer, Sanofi; has received research funding from Pfizer; and served on the IRC and steering committee for Janssen. **KB**, **LK**, **LV**, and **MDS** are employees and/or shareholders of Janssen. **RW** has nothing to disclose. **NWCJvdD** has served in a consulting/advisory role for Adaptive Biotechnologies, Amgen, Bayer, BMS, Celgene, Janssen, Novartis, Roche, Servier, and Takeda; and has received research funding from Amgen, BMS, Celgene, Cellectis, Janssen, and Novartis. **AC** has served in a consulting/advisory role for Amgen, BMS, Celgene, Janssen, Karyopharm, Sanofi, and Takeda; and has received research funding from GSK, Novartis, Pharmacyclics, and Seattle Genetics.

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**Presented at the 11th Annual Meeting of the Society of Hematologic Oncology (SOHO); September 6–9, 2023; Houston, TX, USA**