Talquetamab + Daratumumab + Pomalidomide in Patients With Relapsed/Refractory Multiple Myeloma: Results From the Phase 1b TRIMM-2 Study

Nizar J Bahlis[1], Niels WCJ van de Donk[2], Donna Reece[3], Manisha Bhutani[4], Bhagirathbhai Dholaria[5], Anita D'Souza[6], Thomas G Martin[7], John McKay[8], Alfred Garfall[9], Amrita Krishnan[10], Kalpana Bakshi[11], Lijuan Kang[11], Lien Vandenberk[12], Thomas Prior[11], Jaszianne Tolbert[11], Ajai Chari[13]

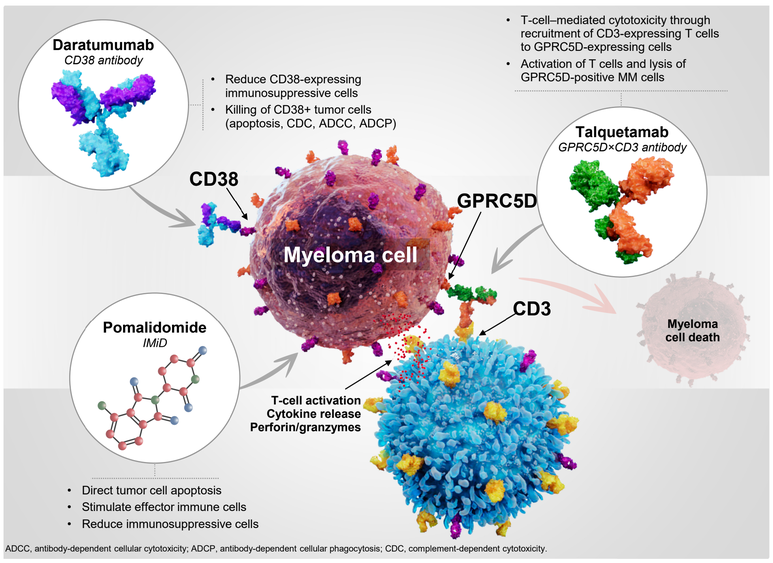
[1]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; [2]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [3]Princess Margaret Cancer Centre, Toronto, ON, Canada; [4]Levine Cancer Institute / Wake Forest School of Medicine, Charlotte, NC, USA; [5]Vanderbilt University Medical Center, Nashville, TN, USA; [6]Medical College of Wisconsin, Milwaukee, WI, USA; [7]Helen Diller Family Comprehensive Cancer Center, San Francisco Medical Center, University of California, San Francisco, San Francisco, CA, USA; [8]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [9]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [10]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [11]Johnson & Johnson, Spring House, PA, USA; [12]Johnson & Johnson, Antwerp, Belgium; [13]University of California, San Francisco, San Francisco, CA, USA

The 11th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

BACKGROUND

- Talquetamab (Tal) is the first approved G protein–coupled receptor class C group 5 member D (GPRC5D)-targeting bispecific antibody for triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM)[1-3]
  - Overall response rates (ORRs) of ≥70% in the MonumenTAL-1 study[1]
- Daratumumab (Dara) is a foundational therapy in multiple myeloma (MM) with direct on-tumor and immunomodulatory actions[4]
- Pomalidomide (Pom) is a third-generation immunomodulatory drug (IMiD) used in multiple regimens for RRMM[5]
- Preclinical data suggest that the immunomodulatory effects of Dara + Pom potentiate the efficacy of Tal (**Figure 1**)[6]
- We present first results (data cut-off: July 29, 2024) from the Tal-Dara-Pom cohort of TRIMM-2 (NCT04108195; **Figure 2**)

FIGURE 1: Mechanism of action for Tal-Dara-Pom



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity.

FIGURE 2: TRIMM-2 study design: Tal-Dara-Pom cohort

Key eligibility criteria
- MM per IMWG
- ≥3 prior LOT[a] or double refractory to PI and IMiD
- Permitted:
  - Anti-CD38 mAb >90 days and IMiD >7 days prior
  - Refractory to anti-CD38 mAb
  - Prior bispecific antibody or CAR-T exposure

Tal[b] + **Dara[c] 1800 mg SC** + **Pom 2 mg PO**

Tal[b]	Dara[c] 1800 mg SC	Pom 2 mg PO
SUD followed by 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W	QW cycles 1–2 Q2W cycles 3–6 Q4W cycles ≥7	Starting cycle 2
May change schedule from QW to Q2W after cycle 4 if in PR and from Q2W to Q4W after cycle 8 if in VGPR		*May be reduced in response to hematologic AEs*

Key objectives
- Safety and antitumor activity

[a]Including a PI and an IMiD. [b]2–3 SUD before first full dose. Premedication including glucocorticoid, antihistamine, and antipyretic at step-up and first full dose. [c]Given with 2-week corticosteroid taper (steroid-free administration after first full treatment dose). AE, adverse event; CAR, chimeric antigen receptor; IMWG, International Myeloma Working Group; LOT, line of therapy; mAb, monoclonal antibody; PI, proteasome inhibitor; PO, orally; PR, partial response; Q2W, every other week; Q4W, every 4 weeks; QW, weekly, SC, subcutaneous; SUD, step-up dose; VGPR, very good partial response.

RESULTS

- Majority of patients were Dara and Pom refractory (**Table 1**)

TABLE 1: TRIMM-2 Tal-Dara-Pom cohort baseline characteristics

Characteristic	Tal 0.4 mg/kg QW + Dara + Pom (n=18)	Tal 0.8 mg/kg Q2W + Dara + Pom (n=59)
Age (years), median (range)	62 (42–75)	64 (33–81)
Male, n (%)	12 (66.7)	31 (52.5)
Race, n (%)		
White	12 (66.7)	51 (86.4)
Black/African American	4 (22.2)	4 (6.8)
Asian	1 (5.6)	1 (1.7)
American Indian/Alaska Native	0 (0)	1 (1.7)
Not reported	1 (5.6)	2 (3.4)
Soft tissue plasmacytoma(s),[a] n (%)	4 (22.2)	14 (23.7)
High cytogenetic risk,[b] n (%)	4 (22.2)	13 (27.7)
ISS stage,[c] n (%)		
I	8 (50.0)	29 (52.7)
II	3 (18.8)	15 (27.3)
III	5 (31.3)	11 (20.0)
Time since diagnosis (years), median (range)	5.7 (0.3–18.3)	7.2 (0.7–17.5)
Prior LOT (n), median (range)	6 (3–11)	6 (1–17)
Prior stem cell transplantation, n (%)	16 (88.9)	50 (84.7)
Prior therapies, n (%)		
Anti-CD38	17 (94.4)	55 (93.2)
IMiD	18 (100.0)	59 (100.0)
Triple class[d]	17 (94.4)	55 (93.2)
Penta drug[e]	12 (66.7)	41 (69.5)
BCMA-targeted therapy	13 (72.2)	40 (67.8)
CAR-T	5 (27.8)	19 (32.2)
Bispecific antibody[f]	6 (33.3)	17 (28.8)
ADC	3 (16.7)	12 (20.3)
Refractory status, n (%)		
Anti-CD38[g]	15 (83.3)	49 (83.1)
Pom	13 (72.2)	45 (76.3)
Triple class[d]	15 (83.3)	45 (76.3)
Penta drug[e]	4 (22.2)	20 (33.9)
Any prior bispecific antibody	7 (38.9)	22 (37.3)
To last line of therapy	17 (94.4)	53 (89.8)

[a]Soft tissue plasmacytomas not associated with the bone were included. [b]del(17p), t(4;14), and/or t(14;16); percentages calculated from n=18 for Tal QW and n=47 for Tal Q2W. [c]Percentages calculated from n=16 for Tal QW and n=55 for Tal Q2W. [d]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [e]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. [f]6 patients received non-BCMA–directed bispecific antibodies. [g]All patients in the Tal QW cohort received Dara; in the Tal Q2W cohort, 89.8% received Dara, 13.6% received isatuximab, and 1.7% received other anti-CD38 therapies.
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; ISS, International Staging System.

- Cytokine release syndrome (CRS)/immune effector cell–associated neurotoxicity syndrome (ICANS) were consistent with Tal monotherapy (**Table 2**)
- CRS was mostly confined to step-up and cycle 1 dosing
  - No grade ≥3 CRS
  - All events recovered
- ICANS in 3 patients (all Q2W)
  - 1 grade 4 ICANS led to discontinuation

TABLE 2: CRS[a]/ICANS[a] characteristics by treatment group

Characteristic	Tal 0.4 mg/kg QW + Dara + Pom (n=18)	Tal 0.8 mg/kg Q2W + Dara + Pom (n=59)
Patients with CRS,[a] n (%)	10 (55.6)	47 (79.7)
Grade 1	7 (38.9)	32 (54.2)
Grade 2	3 (16.7)	15 (25.4)
Time to onset (days),[b] median (range)	3 (1–5)	2 (1–7)
Duration (days), median (range)	2 (1–6)	2 (1–7)
Received supportive measures,[c] n (%)	10 (55.6)	42 (71.2)
Tocilizumab	7 (38.9)	34 (57.6)
Acetaminophen	7 (38.9)	27 (45.8)
Corticosteroids	0 (0)	8 (13.6)
Oxygen	0 (0)	2 (3.4)
Other	8 (44.4)	30 (50.8)

[a]CRS and ICANS were graded per ASTCT criteria. [b]Relative to most recent dose (day of most recent dose = day 1). [c]A patient could receive >1 supportive therapy.
ASTCT, American Society for Transplantation and Cellular Therapy.

- Hematologic AEs were consistent with addition of Dara + Pom to Tal (**Table 3**)
- 4 (5.2%) patients had febrile neutropenia (all Q2W)

TABLE 3: Hematologic AEs

Most common AEs,[a] n (%)	Tal 0.4 mg/kg QW + Dara + Pom (n=18)		Tal 0.8 mg/kg Q2W + Dara + Pom (n=59)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	15 (83.3)	14 (77.8)	47 (79.7)	42 (71.2)
Anemia	9 (50.0)	6 (33.3)	30 (50.8)	22 (37.3)
Thrombocytopenia	6 (33.3)	4 (22.2)	31 (52.5)	20 (33.9)
Leukopenia	4 (22.2)	4 (22.2)	22 (37.3)	19 (32.2)
Lymphopenia	9 (50.0)	9 (50.0)	16 (27.1)	16 (27.1)

[a]AEs were graded by CTCAE v5.0. Only AEs occurring in ≥30% are included. CTCAE, Common Terminology Criteria for Adverse Events.

- Grade 3/4 infection rates were generally low despite neutropenia being common (**Table 4**)
- Of patients with grade 3/4 infections, 84.0% had onset within the first 6 months
- Baseline and posttreatment immunoglobulin G <400 mg/dL observed in 33.8% and 72.7% of patients, respectively
- 53.2% received ≥1 dose of intravenous immunoglobulin

TABLE 4: Infection rates

AEs,[a] n (%)	Tal 0.4 mg/kg QW + Dara + Pom (n=18)		Tal 0.8 mg/kg Q2W + Dara + Pom (n=59)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Infections	13 (72.2)	3 (16.7)	46 (78.0)	22 (37.3)
COVID-19	7 (38.9)	0 (0)	16 (27.1)	0 (0)
Upper respiratory tract infection (undefined)	2 (11.1)	0 (0)	15 (25.4)	1 (1.7)
Pneumonia	0 (0)	0 (0)	10 (16.9)	4 (6.8)
Viral upper respiratory tract infection	3 (16.7)	0 (0)	6 (10.2)	0 (0)
Sinusitis	4 (22.2)	0 (0)	4 (6.8)	3 (5.1)

[a]AEs were graded by CTCAE v5.0. Only AEs occurring in ≥10% are included.

- Nonhematologic AEs were consistent with the profile of individual agents (**Table 5**)
- Median duration of treatment (months): 13.6 (Tal), 13.6 (Dara), 6.7 (Pom)
- No dose-limiting toxicities
- Tal dose reduction or schedule changes due to AEs
  - 33.3% (QW) and 52.5% (Q2W)
- Discontinuation of ≥1 drug due to AEs
  - 27.8% (QW) and 47.5% (Q2W)
- 2 deaths due to AEs (hemorrhagic transformation stroke and pseudomonal sepsis)
- Taste, skin, and nail AEs were mostly low grade; no discontinuations
  - Rash (including maculopapular rash, erythematous rash, and erythema) in 27.8% (QW) and 25.4% (Q2W) of patients

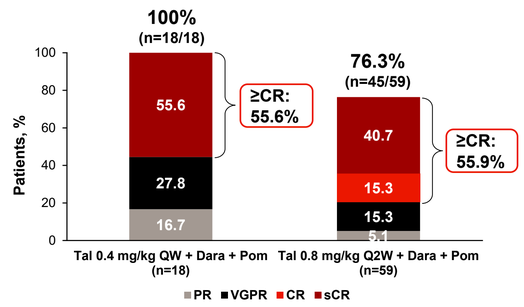
TABLE 5: Nonhematologic AEs

Most common AEs,[a] n (%)	Tal 0.4 mg/kg QW + Dara + Pom (n=18)		Tal 0.8 mg/kg Q2W + Dara + Pom (n=59)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Oral events[b]	18 (100.0)	0 (0)	50 (84.7)	4 (6.8)
CRS	10 (55.6)	0 (0)	47 (79.7)	0 (0)
Nonrash skin events[c]	16 (88.9)	0 (0)	40 (67.8)	0 (0)
Nail events[d]	15 (83.3)	0 (0)	33 (55.9)	0 (0)
Fatigue	11 (61.1)	0 (0)	34 (57.6)	4 (6.8)
Weight decrease ≥10%	12 (66.7)	2 (11.1)	29 (49.2)	10 (16.9)
Pyrexia	7 (38.9)	0 (0)	28 (47.5)	0 (0)
Cough	7 (38.9)	0 (0)	26 (44.1)	2 (3.4)

[a]AEs were graded by CTCAE v5.0, except for CRS, which was graded per ASTCT criteria. Only AEs occurring in ≥40% are included. [b]Oral AEs include dysgeusia, ageusia, taste disorder, hypogeusia, dry mouth, dysphagia, cheilitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral mucosal erythema, oral pain, stomatitis, swollen tongue, tongue discomfort, tongue erythema, tongue edema, and tongue ulceration. Per CTCAE, the maximum grade for dysgeusia (part of oral AEs) is 2. Dysgeusia (Preferred Term) occurred in 88.9% of patients in the Tal 0.4 mg/kg QW + Dara + Pom cohort and in 76.3% in the Tal 0.8 mg/kg Q2W + Dara + Pom cohort. [c]Skin AEs include skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysaesthesia syndrome. [d]Nail AEs include nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging.

- Most patients achieved a stringent complete response (sCR) or complete response (CR) (**Figure 3**)
- Combined ORR was 82% and combined ≥CR rate was 56% (**Table 6**)

FIGURE 3: ORR[a]



[a]Response was assessed by investigators, based on IMWG criteria. Percentages are calculated with the number of patients in each group as denominator.

TABLE 6: Combined ORR and ≥CR rate

	Tal 0.4 mg/kg QW + Dara + Pom (n=18)	Tal 0.8 mg/kg Q2W + Dara + Pom (n=59)
Median (range) follow-up, months	15.8 (3.2–37.9)	17.5 (0.2–37.7)
Median (range) time to first response, months	1.0 (0.9–3.6)	1.0 (0.9–6.7)
Combined ORR, % (n/N)	**81.8** (63/77)	
Combined ≥CR, % (n/N)	**55.8** (43/77)	

Response was assessed by investigators, based on IMWG criteria. Percentages are calculated with the number of patients in each group as denominator.

- High ORRs were observed in prior exposure subgroups (**Figure 4**)

FIGURE 4: ORR (QW + Q2W Tal)[a]

Anti-CD38 naive = never received anti-CD38 therapy; anti-CD38 sensitive = minimal response or better during treatment; anti-CD38 refractory = best response of SD or PD during treatment or within 60 days of completing anti-CD38 therapy. [a]Response was assessed by investigators, based on IMWG criteria. Percentages are calculated with the number of patients in each group as denominator. [b]All 29 patients who received prior bispecific antibody therapy were refractory. PD, progressive disease; SD, stable disease.

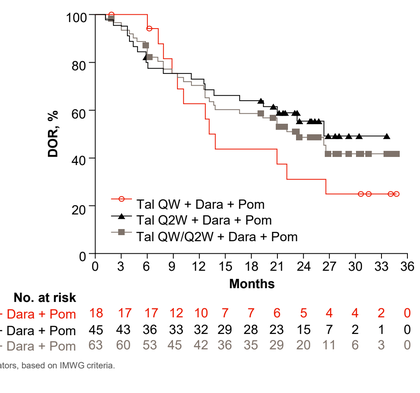
- Durable responses (**Table 7** and **Figure 5**), including in key exposure subgroups 12-month duration of response (DOR) (QW + Q2W Tal)
  - Anti-CD38 naive/sensitive (n=13): 83.9%
  - Pom naive/sensitive (n=16): 80.8%
  - Anti-CD38 refractory (n=50): 67.0%
  - Pom refractory (n=47): 67.0%
  - Bispecific antibody refractory (n=24): 70.2%
  - Prior CAR-T (n=20): 84.4%

TABLE 7: Median and 12-month DOR

Parameter	Tal 0.4 mg/kg QW + Dara + Pom (n=18)	Tal 0.8 mg/kg Q2W + Dara + Pom (n=45)
Median (range) follow-up, months	15.8 (3.2–37.9)	17.5 (0.2–37.7)
Median DOR, months (95% CI)	13.8 (8.8–26.6)	26.4 (16.7–NE)
12-month DOR, % (95% CI)	62.7 (35.1–81.3)	73.1 (57.5–83.7)

Response and progression were assessed by investigators, based on IMWG criteria. NE, not estimable.

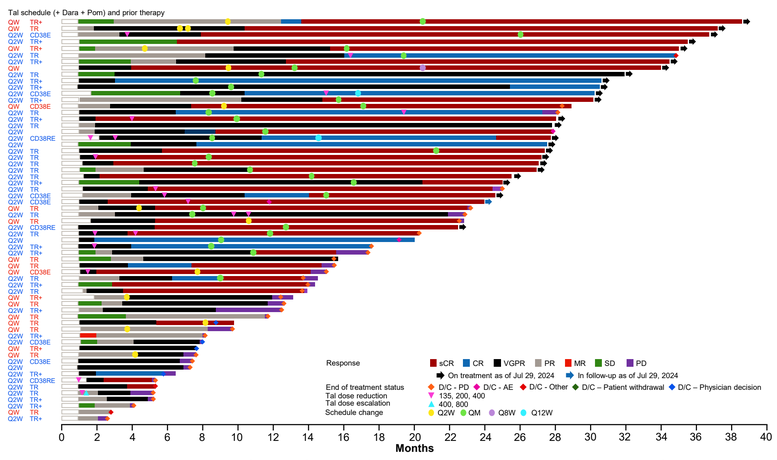
FIGURE 5: DOR[a]



[a]Response and progression were assessed by investigators, based on IMWG criteria.

- Responses deepened over time, irrespective of dose intensity reductions (**Figure 6**)

FIGURE 6: Depth of response



+, penta-drug refractory; CD38E, anti-CD38 therapy exposed; CD38RE, anti-CD38 therapy refractory; D/C, discontinuation; MR, minimal response; Q8W, every 8 weeks; Q12W, every 12 weeks; QM, monthly; TR, triple-class refractory.

- Promising progression-free survival (PFS) was observed (**Figure 7** and **Table 8**), including in key exposure subgroups 12-month PFS (QW + Q2W Tal)
  - Anti-CD38 naive/sensitive (n=13): 84.6%
  - Pom naive/sensitive (n=19): 68.4%
  - Anti-CD38 refractory (n=64): 56.9%
  - Pom refractory (n=58): 59.4%
  - Bispecific antibody refractory (n=29): 69.2%
  - Prior CAR-T (n=24): 73.9%

FIGURE 7: PFS over time

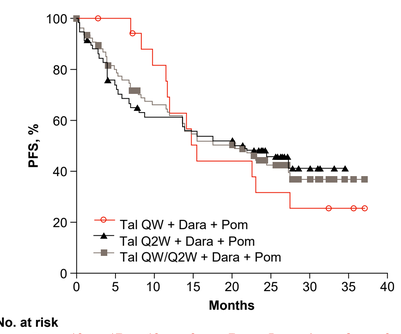


TABLE 8: Median and 12-month PFS

Parameter	Tal 0.4 mg/kg QW + Dara + Pom (n=18)	Tal 0.8 mg/kg Q2W + Dara + Pom (n=59)
Median (range) follow-up, months	15.8 (3.2–37.9)	17.5 (0.2–37.7)
Median PFS, months (95% CI)	15.4 (11.5–27.5)	20.3 (7.9–NE)
12-month PFS, % (95% CI)	62.7 (35.1–81.3)	61.1 (47.1–72.4)

CONCLUSIONS

- **Novel Tal-Dara-Pom triplet therapy showed deep and durable responses in patients with RRMM, particularly those with bispecific antibody-, CD38- and/or Pom-refractory disease**
  - ORR 82% and ≥CR 56% overall
  - ORR 78–83% and ≥CR 52–59% across refractory subgroups
  - With Q2W Tal dosing, 76% ORR, median DOR 26 months, and median PFS 20 months
- **Safety of triplet therapy was consistent with known profiles of individual agents, supporting combinability of Tal**
  - Despite high rate of neutropenia, grade 3/4 infections were consistent with addition of Dara + Pom to Tal
  - Taste, skin, and nail AEs were low grade, with no discontinuations of Tal
- **Novel triplet combination with Q2W Tal warrants further investigation**
  - Phase 3 MonumenTAL-3 trial of Tal + Dara ± Pom vs Dara + Pom + Dexamethasone in patients with RRMM and ≥1 prior LOT (NCT05455320)

References:

1. Rasche L, et al. Presented at EHA; June 13–16, 2024; Madrid, Spain. 2. TALVEY (talquetamab). Summary of product characteristics. Horsham, PA: Janssen Biotech, Inc.; 2023. 3. TALVEY (talquetamab-tgvs). Prescribing information. Horsham, PA: Janssen Biotech, Inc.; 2023. 4. DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use. Package insert. Horsham, PA: Janssen Biotech, Inc.; 2022. 5. POMALYST® (pomalidomide) capsules, for oral use. Package insert. New York, NY; Bristol Myers Squibb; 2023. 6. Verkleij CPM, et al. *Blood Adv* 2021;5:2196-215.

Acknowledgments:

- We thank the patients who are participating in this study and their caregivers, the physicians and nurses who care for them, the staff at study sites, and the staff involved in data collection and analyses.
- This study was funded by Johnson & Johnson.
- Medical writing support was provided by Craig Turner, MSc, of Eloquent Scientific Solutions, and funded by Johnson & Johnson.

https://comylive.cme-congresses.com