P915

Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma

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Key Takeaway

With long-term follow-up, tal continues to demonstrate deep and durable responses and no new safety signals in pts with RRMM

Conclusions

- High ORRs of ≥70% in the QW and Q2W TCR-naive cohorts and 67% in the prior TCR cohort were achieved with long-term follow-up at the approved tal doses
- Pts continued to demonstrate durable responses, with longer DORs observed in pts with deeper response
- The safety profile was consistent with previous reports; together with the efficacy data, these results highlight the overall clinical benefit of the approved tal doses and the flexibility to adjust dosing once response is achieved

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Poster

Supplementary material

https://www.congresshub.com/Oncology/EHA2024/Talquetamab/Rasche

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Disclosures
LR has received travel, accommodations, and expenses from BeiGene and Johnson & Johnson; has received honoraria from and reports a consulting/advisory role with Amgen, BeiGene, BMS, GSK, Pfizer, and Sanofi; and reports a leadership or fiduciary role within the International Myeloma Working Group and International Myeloma Society.

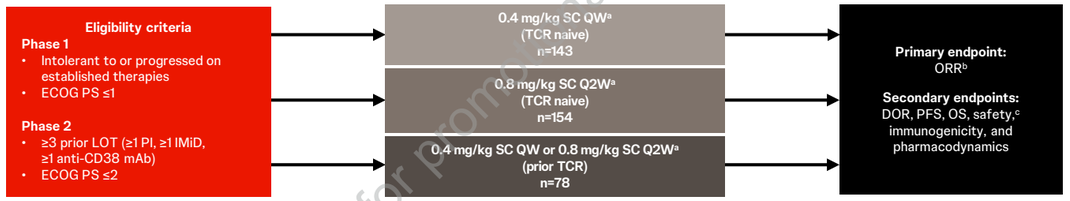
Introduction

- Talquetamab (tal) is the first approved bispecific antibody (BsAb) targeting the novel antigen G protein–coupled receptor class C group 5 member D (GPRC5D) for the treatment of patients (pts) with relapsed/refractory multiple myeloma (RRMM)[1,2]
- In previously reported results from MonumenTAL-1, tal showed overall response rates (ORRs) of >71% in pts naive to prior T-cell redirection therapy (TCR) and 65% in pts with prior TCR at the approved subcutaneous (SC) doses of 0.4 mg/kg weekly (QW) and 0.8 mg/kg every other week (Q2W)[3]
- Exposure–response (E–R) analyses showed increased ORRs with SC doses that plateaued at or above the approved doses (**Supplemental Figure 1**)[4,5]
  - An E–R relationship was observed for grade 1/2 dysgeusia; however, rates were similar at both approved doses (**Supplemental Figure 2**)[4,5]
- Early onset of GPRC5D-related adverse events (AEs), including dysgeusia, is associated with a higher likelihood of response; prior data support flexibility to adjust tal dosing in responders to mitigate AEs while maintaining efficacy[6]
- Here, we report the long-term follow-up results of pts receiving tal at the approved doses

Methods

- MonumenTAL-1 (NCT03399799/NCT04634552) enrolled pts with RRMM who were naive or exposed to prior TCR (**Figure 1**)

Figure 1: MonumenTAL-1 phase 1/2 study design



[a]With 2–3 step-up doses. [b]Assessed by IRC using International Myeloma Working Group criteria.[7,8] [c]CRS and ICANS were graded by ASTCT criteria[9]; all other AEs were graded by CTCAE v4.03. ASTCT, American Society of 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; IMiD, immunomodulatory drug; IRC, independent review committee; LOT, line of therapy; mAb, monoclonal antibody; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor.

Results

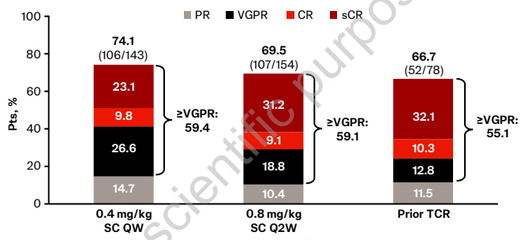
Baseline characteristics

- Baseline characteristics across the QW, Q2W, and prior TCR cohorts were similar to previous reports,[3] with the exception of more African American pts in the current analysis (n=32/375, 9%)

Efficacy

- As of January 29, 2024, ORR was 74%, 70%, and 67% for pts in the QW, Q2W, and prior TCR cohorts, respectively (**Figure 2**)
  - ORRs were consistent across high-risk subgroups, except for pts with extramedullary disease, who had lower ORRs (**Supplemental Table 1**)
  - In pts with prior TCR, ORR was 71% (n=40/56) with prior chimeric antigen receptor (CAR)-T cell therapy and 58% (n=15/26) with prior BsAb therapy
- Median time to first response (range) was 1.2 (0.2–10.9), 1.3 (0.2–4.9), and 1.2 (0.2–7.5) months, respectively
  - Median time to very good partial response (VGPR) as best response was 2.2 (0.8–6.2), 2.3 (0.3–18.9), and 1.8 (0.8–6.4) months and to complete response (CR) or better as best response was 3.0 (1.1–12.7), 5.8 (1.2–16.8), and 2.7 (1.2–18.7) months, respectively
- DOR, PFS, and OS are shown in **Table 1**
  - Better durability was observed in the Q2W vs QW cohort
  - In pts with prior TCR, the median PFS (mPFS) was 12.3 months with prior CAR-T cell therapy and 4.1 months with prior BsAb therapy
- In the Q2W cohort, 40% of pts achieved a ≥CR, most by ~12 months (**Figure 3A**); although a ≥CR may take longer to achieve, pts with deeper responses had a longer DOR (**Figure 3B**)

Figure 2: ORR[a]



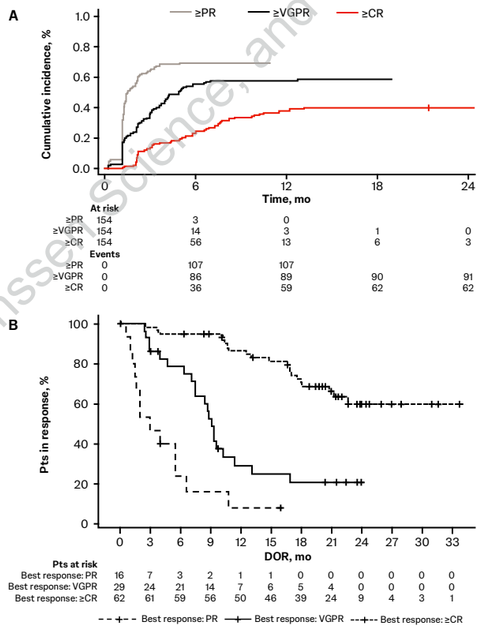
[a]Due to rounding, individual response rates may not sum to the ORR.
PR, partial response; sCR, stringent complete response.

Table 1: Efficacy outcomes

Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
mFU, mo	29.8	23.4	20.5
mDOR (95% CI),[a] mo	9.5 (6.7–13.4)	17.5 (12.5–NE)	N/A[b]
mDOR in pts with ≥CR (95% CI), mo	28.6 (19.4–NE)	NR (21.2–NE)	N/A[b]
mPFS (95% CI), mo	7.5 (5.7–9.4)	11.2 (8.4–14.6)	7.7 (4.1–14.5)
24-mo OS rate (95% CI), %	60.6 (51.7–68.4)	67.1 (58.3–74.4)	57.3 (43.5–68.9)

[a]n=106 (QW), n=107 (Q2W), and n=52 (prior TCR). [b]NR due to heavy censoring from 12 to 20 mo; the estimate may not be reliable at this time point. See **Supplemental Table 2** for efficacy outcomes in the USPI population (≥4 prior LOT). mDOR, median duration of response; mFU, median follow-up; N/A, not available; NE, not estimable; NR, not reported; USPI, United States prescribing information.

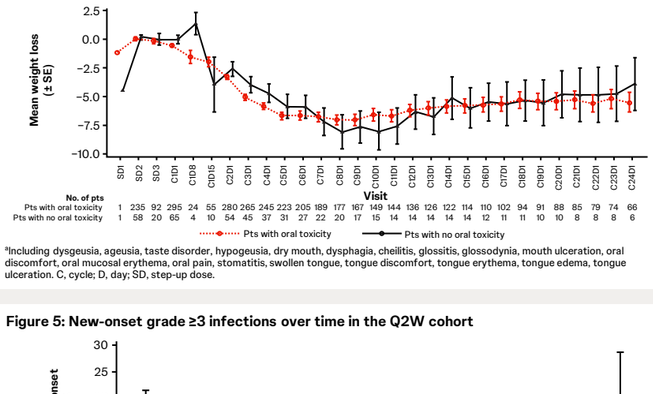
Figure 3: Time to first confirmed response per IRC (A) and DOR by depth of response (B) in the Q2W cohort



Safety

- The safety profile across cohorts was consistent with previous results[3]; no new safety signals were reported
- Weight loss, as assessed by vital signs, occurred in 39%, 34%, and 39% of pts in the QW, Q2W, and prior TCR cohorts, respectively
  - Weight loss was evident early, then stabilized and improved over time, including in pts with oral toxicities (**Figure 4**)
- Infection rates remained lower than in studies of B-cell maturation antigen–targeted BsAbs,[10,11] consistent with previous reports[3]; no increase in grade 3/4 infections was observed with longer follow-up (shown for the Q2W cohort; **Figure 5**)
- Modest intravenous immunoglobulin was required (16%, 14%, and 24% of pts, respectively)
- GPRC5D-associated AEs led to few dose reductions and discontinuations (**Table 2**); only 1 additional pt discontinued treatment since previous report[3]
- Similarly, overall rates of dose reductions and discontinuations due to AEs remained low at 15%, 10%, and 12% and 5%, 10%, and 5%, respectively
- There were no treatment-related deaths

Figure 4: Weight loss in pts with oral toxicity[a] in the QW and Q2W cohorts



[a]Including 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, tongue ulceration. C, cycle; D, day; SD, step-up dose.

Figure 5: New-onset grade ≥3 infections over time in the Q2W cohort

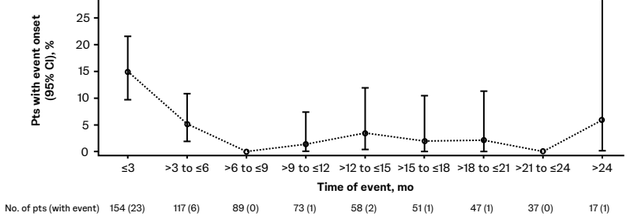


Table 2: GPRC5D-associated AEs

Any-grade AE, n (%)	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
Taste-related[a]			
Total	103 (72.0)	110 (71.4)	59 (75.6)
Leading to dose reduction	10 (7.0)	6 (3.9)	4 (5.1)
Leading to discontinuation	0	3 (1.9)	0
Skin-related[b]			
Total	81 (56.6)	113 (73.4)[e]	50 (64.1)
Leading to dose reduction	5 (3.5)	1 (0.6)	2 (2.6)
Leading to discontinuation	2 (1.4)	1 (0.6)	0
Nail-related[c]			
Total	79 (55.2)	82 (53.2)	46 (59.0)
Leading to dose reduction	1 (0.7)	1 (0.6)	1 (1.3)
Leading to discontinuation	0	0	0
Rash-related[d]			
Total	57 (39.9)[f]	46 (29.9)[g]	25 (32.1)[h]
Leading to dose reduction	1 (0.7)	1 (0.6)	0
Leading to discontinuation	0	0	0

[a]Including ageusia, dysgeusia, hypogeusia, and taste disorder. [b]Including skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome. [c]Including nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging. [d]Including rash, maculopapular rash, erythematous rash, and erythema. [e]Including 1 (0.6%) grade 3/4 event. [f]Including 2 (1.4%) grade 3/4 events. [g]Including 8 (5.2%) grade 3/4 events. [h]Including 2 (2.6%) grade 3/4 events.

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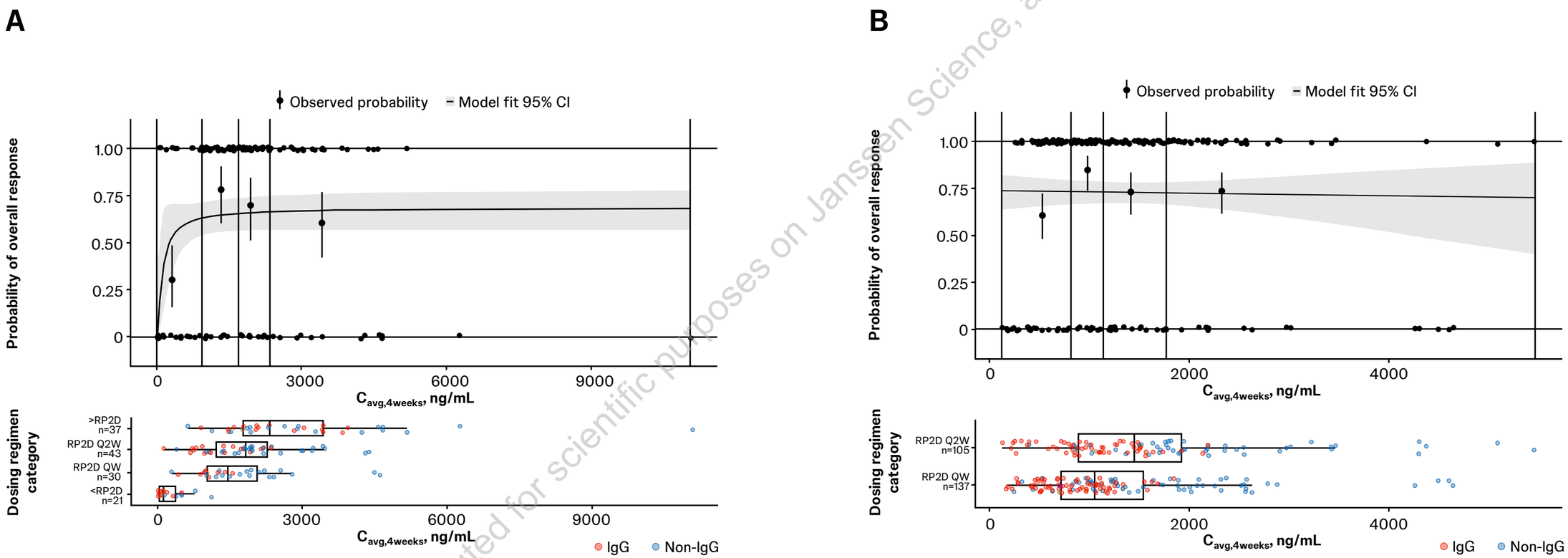
Multiple Myeloma

Presented by L Rasche at the European Hematology Association (EHA) 2024 Hybrid Congress; June 13–16, 2024; Madrid, Spain

Supplemental Figure 1: E-R Relationship for Phase 1 (A) and RP2D ORR (B) vs Estimated $C_{avg,4weeks}$



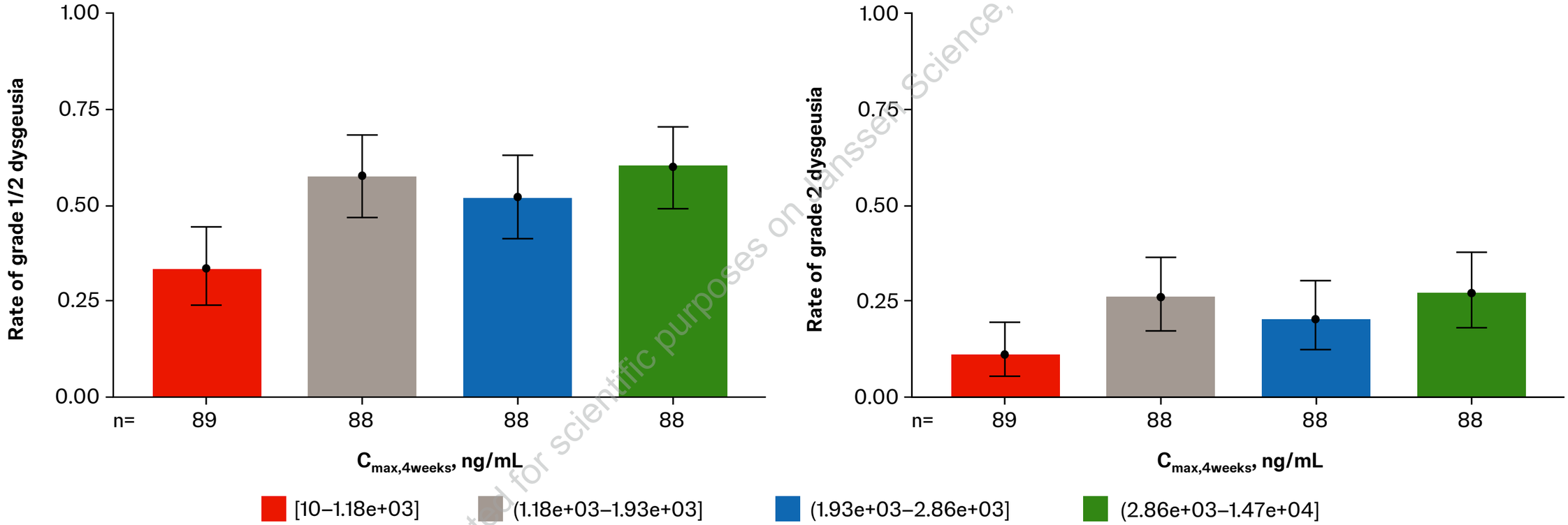
Previously presented at ASCO 2023 and ACOP 2023.[1,2]

Error bars represent the 95% CI of ORR in the respective exposure quartile groups. Shaded areas of the logistic regression plots represent the 95% CI of the estimated ORR.

$C_{avg,4weeks}$, estimated average concentration during the first 4 weeks of full treatment doses; E-R, exposure-response; IgG, immunoglobulin G; ORR, overall response rate; Q2W, every other week; QW, weekly; RP2D, recommended phase 2 dose (now approved doses).

1. Ma X, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. #8041. 2. Zhou J, et al. Presented at ACOP; November 5–8, 2023; Oxon Hill, MD, USA. #T-015.

Supplemental Figure 2: Dysgeusia Rates by the Estimated $C_{max,4weeks}$ Quartiles for Pooled Phase 1/2 SC Cohorts



Previously presented at ASCO 2023 and ACOP 2023.[1,2]
Error bars are the 95% CI of dysgeusia occurrence rates in the respective exposure quartile groups.
$C_{max,4weeks}$, estimated maximum concentration during the first 4 weeks of full treatment doses; SC, subcutaneous.
1. Ma X, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. #8041. 2. Zhou J, et al. Presented at ACOP; November 5–8, 2023; Oxon Hill, MD, USA. #T-015.

Supplemental Table 1: ORR Among High-Risk Subgroups

ORR in subgroups, % (95% CI)	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
Age ≥75, years	71.4 (47.8–88.7)	75.8 (57.7–88.9)	80.0 (28.4–99.5)
High-risk cytogenetics[a]	70.7 (54.5–83.9)	75.0 (58.8–87.3)	52.0 (31.3–72.2)
ISS stage III	64.3 (44.1–81.4)	59.5 (42.1–75.2)	76.9 (46.2–95.0)
Baseline renal function, ≤60 mL/min/1.73 m^2	65.0 (48.3–79.4)	65.2 (49.8–78.6)	63.2 (38.4–83.7)
Refractory status			
Triple-class[b]	72.9 (63.4–81.0)	67.3 (57.7–75.9)	65.2 (52.4–76.5)
Penta-drug[c]	71.1 (55.7–83.6)	69.2 (52.4–83.0)	58.8 (40.7–75.4)
≥1 extramedullary plasmacytoma[d]	48.5 (30.8–66.5)	41.5 (26.3–57.9)	44.0 (24.4–65.1)

[a]Defined by del(17p), t(4;14), and/or t(14;16). [b]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [c]≥2 PIs, ≥2 IMiDs, and ≥1 anti–CD38 mAb. [d]Soft tissue plasmacytomas not associated with the bone were included.
IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; ORR, overall response rate; PI, proteasome inhibitor; Q2W, every other week; QW, weekly; SC, subcutaneous; TCR, T-cell redirection therapy.

Supplemental Table 2: Efficacy Outcomes in the USPI Population

Outcome	0.4 mg/kg SC QW (n=100)	0.8 mg/kg SC Q2W (n=87)	Prior TCR[a] (n=32)
ORR, %	73.0	71.3	75.0
≥CR	35.0	43.7	50.0
VGPR	22.0	18.4	12.5
PR	16.0	9.2	12.5
Median time to first response (range), mo[b]	1.2 (0.2–10.9)	1.3 (0.2–3.6)	1.1 (0.2–6.4)
Median time to best response (range), mo[b]	2.1 (1.1–12.7)	4.7 (0.3–18.9)	2.1 (1.1–14.8)
≥CR[c]	2.3 (1.1–12.7)	6.4 (1.9–16.8)	4.4 (1.2–14.8)
VGPR[d]	2.0 (1.1–6.2)	3.1 (0.3–18.9)	2.0 (1.3–2.1)
PR[e]	1.3 (1.1–2.9)	2.1 (1.2–2.8)	1.1 (1.1–1.4)
Median DOR (95% CI), mo[b]	10.2 (6.6–15.7)	18.0 (14.8–NE)	15.8 (3.7–NE)
≥CR[c]	28.6 (18.9–NE)	NR (21.2–NE)	24.1 (11.2–NE)
VGPR[d]	6.4 (4.4–9.5)	9.3 (7.4–16.8)	4.3 (2.1–NE)
PR[e]	3.0 (1.9–5.6)	4.2 (0.9–NE)	2.4 (1.9–NE)
Median PFS (95% CI), mo	6.8 (5.5–10.4)	12.5 (9.6–18.3)	6.8 (3.4–22.2)
24-mo PFS, %	21.0 (13.4–29.7)	31.1 (20.1–42.8)	28.9 (13.9–45.9)
Median OS (95% CI), mo	32.1 (21.7–NE)	NR (24.4–NE)	24.3 (7.6–NE)
24-mo OS, %	60.3 (49.8–69.4)	67.7 (55.2–77.4)	51.6 (32.7–67.6)

Data are reported from phase 2 only.
[a]Phase 2 data includes the 0.4 mg/kg QW cohort only. [b]n=73 (QW), n=62 (Q2W), and n=24 (prior TCR). [c]n=35 (QW), n=38 (Q2W), and n=16 (prior TCR). [d]n=22 (QW), n=16 (Q2W), and n=4 (prior TCR). [e]n=16 (QW), n=8 (Q2W), and n=4 (prior TCR).
CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Q2W, every other week; QW, weekly; SC, subcutaneous; TCR, T-cell redirection therapy; USPI, United States prescribing information; VGPR, very good partial response.