P-058

Cytokine Release Syndrome in Patients Receiving Alternative Step-Up Doses of Talquetamab for Relapsed/Refractory Multiple Myeloma: Results From the Phase 1/2 MonumenTAL-1 Study

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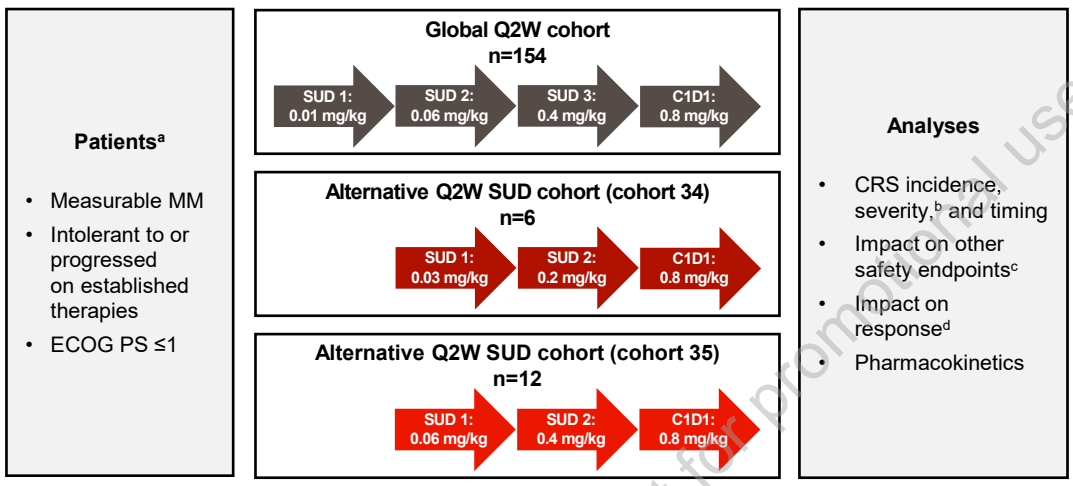
Introduction

- Talquetamab is the first and only G protein–coupled receptor family C group 5 member D–targeting bispecific antibody (BsAb) approved for the treatment of patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM)[1-3]
- Cytokine release syndrome (CRS) is a common adverse event reported with T-cell redirecting BsAbs[4,5]
- In MonumenTAL-1, patients with RRMM received step-up doses (SUDs) of talquetamab to mitigate the risk of CRS[2,6]
  - For the talquetamab 0.4 mg/kg weekly (QW) and 0.8 mg/kg every-other-week (Q2W) approved doses, patients received 2 (0.01 and 0.06 mg/kg) or 3 (0.01, 0.06, and 0.4 mg/kg) SUDs, respectively[2]
  - With 3 SUDs in the Q2W cohort, CRS occurred in 74.5% of patients[6]; most CRS events occurred during SUDs and cycle 1
- Patients were monitored for 48 hours after each SUD and first full treatment dose
- We evaluated the impact of alternative, fewer SUDs in the talquetamab Q2W schedule on key parameters of CRS

Methods

- In phase 1 of MonumenTAL-1 (NCT03399799), alternative SUD cohorts were added for the 0.8 mg/kg Q2W schedule (**Figure 1**); patients in these cohorts could switch to 0.8 mg/kg monthly at confirmed partial response (PR) or better

Figure 1: MonumenTAL-1 global Q2W and alternative SUD cohorts



Administration was 24–72 hours between SUDs and first treatment dose, with inpatient monitoring through 48 hours after the first treatment dose. [a]Phase 1 alternative Q2W SUD cohorts only; criteria for the global Q2W cohort includes patients in phase 2 who had received ≥3 prior lines of therapy and had an ECOG PS ≤2. [b]CRS was graded per Lee criteria.[7] [c]Adverse events were graded per CTCAE v4.03. [d]Response was assessed per investigator and according to International Myeloma Working Group criteria.[8] C1D1, cycle 1 day 1; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; MM, multiple myeloma.

Key Takeaway

These results showed that the use of fewer SUDs to reach the talquetamab Q2W dose was associated with a higher incidence of grade 2 CRS, suggesting that the approved schedule with 3 SUDs may be more clinically manageable until additional prophylactic measures are investigated

Conclusions

With alternative, fewer SUDs, the proportion of patients with grade 2 CRS was increased in both alternative SUD cohorts compared with the global Q2W cohort

Outside of the CRS profile, no other early safety signals or impact on pharmacokinetics were observed with the alternative SUD schedules

Studies are evaluating use of prophylactic tocilizumab to continue to explore approaches to optimize the SUD schedule to allow safe but efficient use of talquetamab (see Poster P-077)

Results

Baseline characteristics

- Across cohorts 34 and 35, a total of 18 patients were included in the analysis, with median follow-up of 6.7 months (range, 2.2–9.9)
- Most patients had high-risk cytogenetics (n=10/18), were triple-class refractory (n=11/18), and were refractory to their last line of therapy (n=11/18); extramedullary plasmacytomas were present in 3/18 patients

CRS incidence, severity, timing, and treatment

- CRS occurred in all (n=6/6) patients in cohort 34 and in 91.7% (n=11/12) of patients in cohort 35 (**Figure 2**)
  - Although rates of grade 1 and 3 events were consistent between the alternative SUD cohorts and the global Q2W cohort (median follow-up, 23.4 months [range, 0.2–37.4]), rates of grade 2 events were higher with the alternative SUD schedules
- Multiple CRS events occurred in 16.7% (n=1/6) and 25.0% (n=3/12) of patients in cohorts 34 and 35, respectively, and in 33.1% (n=51/154) of patients in the global Q2W cohort
- CRS events predominantly occurred during SUDs across all cohorts (**Table 1**); most CRS events occurred during the second (66.7%) and first (75.0%) SUD in cohorts 34 and 35, respectively, and in the second SUD in the global Q2W cohort (40.9%)
- In the global Q2W cohort, more CRS events occurred during cycle 1 (n=22) and after cycle 2 (n=5) vs the alternative SUD cohorts (both n=1)
- Median time to CRS onset and median duration of CRS were the same across alternative SUD and global Q2W cohorts (2 days each measure)
- Across alternative SUD cohorts and the global Q2W cohort, respectively, 77.8% and 37.0% of patients received tocilizumab treatment for CRS
  - No patients who received tocilizumab had a subsequent grade 2 event
- No patients discontinued talquetamab due to CRS in the alternative SUD cohorts compared with 1 patient in the global Q2W cohort

Figure 2: CRS incidence and severity

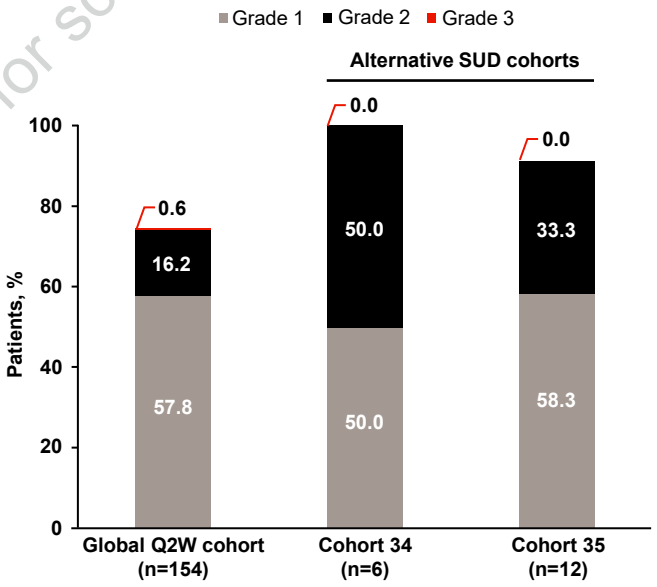


Table 1: CRS timing

	SUDs			C1D1
Global Q2W cohort approved SUDs, mg/kg	**0.01**	**0.06**	**0.4**	**0.8**
CRS, n (%)	41/154 (26.6)	63/154 (40.9)	56/154 (36.4)	22/154 (14.3)
Cohort 34 SUDs, mg/kg	**NA**	**0.03**	**0.2**	**0.8**
CRS, n (%)	NA	3/6 (50.0)	4/6 (66.7)	0
Cohort 35 SUDs, mg/kg	**NA**	**0.06**	**0.4**	**0.8**
CRS, n (%)	NA	9/12 (75.0)	5/12 (41.7)	1/12 (8.3)

NA, not applicable.

Other safety endpoints

- No patients in cohort 34 experienced neurotoxicity
- One (8.3%) patient in cohort 35 experienced grade 1 neurotoxicity during the first SUD and concurrently with CRS; this event resolved and did not lead to discontinuation of talquetamab
- There were no discontinuations of talquetamab or deaths due to treatment-emergent adverse events in the alternative SUD cohorts

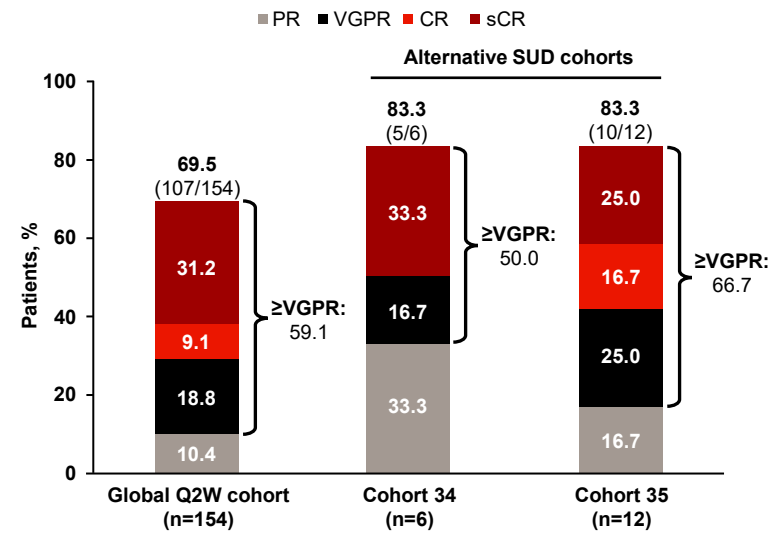
Efficacy

- As of July 31, 2024, overall response rate (ORR) was 83.3% in each of the alternative SUD cohorts (**Figure 3**)
  - ORR appeared higher than in the global Q2W cohort with the caveat of small patient numbers in the alternative SUD cohorts
- Time to first response (range) was 1.2 months (1.1–2.1) in cohort 34 and 1.2 months (0.3–4.2) in cohort 35
- Time to best response (range) was 2.1 months (1.1–4.7) in cohort 34 and 2.7 months (1.1–5.5) in cohort 35

Pharmacokinetics

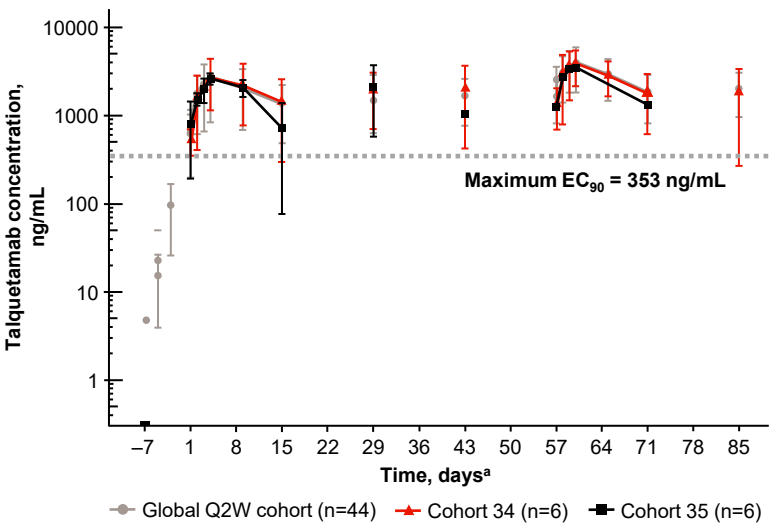
- Preliminary analysis showed that starting from C1D1, talquetamab serum exposure was comparable between the alternative SUD cohorts and global Q2W cohort (**Figure 4**)
  - In cohorts 34 and 35, respectively, the median number of treatment cycles (range) received was 10.0 (4–11) and 5.0 (2–10)

Figure 3: ORR



CR, complete response; VGPR, very good partial response; sCR, stringent complete response.

Figure 4: Mean talquetamab serum concentration–time profiles



[a]Day 1 denotes C1D1. EC_{90}, concentration associated with the 90% maximal drug effect.

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Disclosures

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Multiple Myeloma

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