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Analysis of Repeat Step-Up Dosing and Cytokine Release Syndrome Events Following Prolonged Dosing Intervals of Teclistamab in the Phase 1/2 MajesTEC-1 Study

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Key Takeaway

The incidence of CRS was low after restarting teclistamab treatment following dosing intervals 28–111 days, which supports updated guidelines on restarting teclistamab

Conclusions

- Only 2/61 (3.3%) patients who restarted teclistamab after prolonged dosing intervals >28 days experienced CRS (all events grade 1/2)
- Recommendations for reinitiating teclistamab have been updated and should occur at SUD2 for dosing intervals of 63–111 days and at SUD1 for intervals ≥112 days based on popPK modeling and clinical data
- This retrospective analysis of MajesTEC-1 supported the updated guidance on restarting teclistamab after dose delays, which is now included in the European Medicines Agency–approved label

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Poster

Supplementary material

https://www.congresshub.com/ASH2024/Oncology/Teclistamab/Donk

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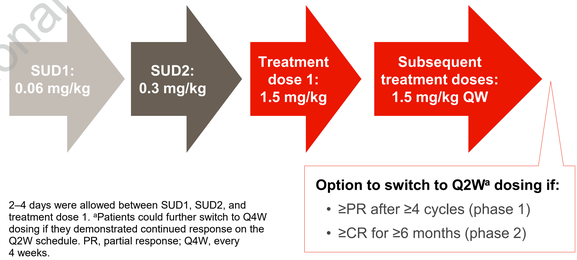
Introduction

- Teclistamab is the first approved B-cell maturation antigen (BCMA) × CD3 bispecific antibody (BsAb) for the treatment of patients with triple-class exposed relapsed/refractory multiple myeloma (RRMM), with weight-based dosing and the longest study follow-up of any BsAb in multiple myeloma (30.4 months)[1-4]
  - After 2 step-up doses (SUDs) to mitigate the risk of cytokine release syndrome (CRS), teclistamab is dosed weekly (QW) with the option to transition to every other week (Q2W) based on response[1,2]
- Teclistamab demonstrated rapid, deep, and durable responses in the pivotal phase 1/2 MajesTEC-1 study (NCT03145181/NCT04557098); overall response rate (ORR), 63.0%; complete response (CR) or better rate, 46.1%[4]
- Depending on the duration following prolonged dosing intervals (permitted for management of adverse events), teclistamab can be safely restarted with or without repeat SUD; this recommendation was informed by population pharmacokinetic (popPK) modeling and a retrospective clinical analysis

Methods

- In the MajesTEC-1 recommended phase 2 dose (RP2D) cohort, patients received teclistamab at the RP2D (1.5 mg/kg subcutaneous QW; **Figure 1**)
- A previously established popPK model of teclistamab was used to determine the longest time window wherein serum concentrations would not drop below levels following SUD1 and SUD2[5]
- The time windows based on popPK estimations were applied to a retrospective clinical analysis of MajesTEC-1 (data cut-off: August 22, 2023) to evaluate repeat SUD and CRS events in the setting of prolonged dosing intervals (>28–62 days, ≥63–111 days, and ≥112 days)

Figure 1: Teclistamab dosing schedule in MajesTEC-1



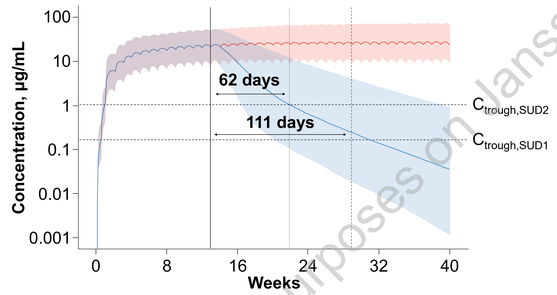
2–4 days were allowed between SUD1, SUD2, and treatment dose 1. [a]Patients could further switch to Q4W dosing if they demonstrated continued response on the Q2W schedule. PR, partial response; Q4W, every 4 weeks.

Results

PopPK modeling and simulation

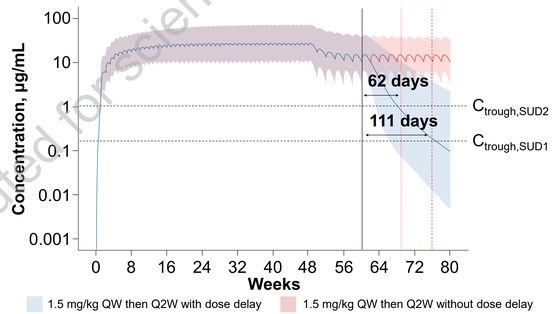
- Dosing intervals <62 days result in teclistamab serum concentrations similar to or higher than serum concentrations after SUD2; therefore, re-introducing SUD2 after a prolonged delay of <62 days may not be needed (**Figures 2** and **3**; **Supplemental Table**)
- Dosing intervals of 62–111 days result in teclistamab serum concentrations that were lower than those after SUD2 and are similar to or higher than those after SUD1; therefore, repeat SUD2 may be needed (**Figures 2** and **3**; **Supplemental Table**)

Figure 2: Teclistamab serum concentration-time profiles for 1.5 mg/kg QW at steady state ± prolonged dosing intervals



C_{trough}, trough concentration.

Figure 3: Teclistamab serum concentration-time profiles for 1.5 mg/kg QW then Q2W ± prolonged dosing intervals



The final popPK model was used to simulate teclistamab concentration-time profiles. Solid lines show the median serum concentration-time profiles for the dosing scenarios described in the legend. The corresponding shaded area represents the 90% prediction interval obtained from randomly sampling a total of 1000 patients from the analysis dataset. The horizontal dashed lines show the predicted median C_{trough} for the first (C_{trough},SUD1) and second (C_{trough},SUD2) SUDs. The vertical solid lines show the time of last dose administered prior to a delay. The vertical dotted and dashed red lines show the time points that dose is delayed for 62 days and 111 days, respectively.

Retrospective clinical analysis of prolonged dosing intervals

- 61 patients had prolonged dosing intervals; some patients had >1 prolonged intervals for a total of 128 intervals >28 days; only 2 intervals led to CRS at restart (**Table 1**)
  - 1 patient delayed the start of cycle 2, repeated both SUDs, and had grade 2 CRS after repeat SUD2
  - The second patient delayed cycle 6, repeated both SUDs, and had 2 events of grade 1 CRS after repeat SUD2 and the subsequent full treatment dose

Table 1: Prolonged intervals >28 days in retrospective clinical analysis

	Total
Patients with prolonged intervals, n	61
With CRS at restart	2
Number of prolonged intervals	128
With CRS at restart	2

- 52 patients had intervals >28–62 days, 15 had intervals ≥63–111 days, and 7 had intervals ≥112 days
- For dosing intervals >28–62 days, the rate of CRS events was low, and most patients did not repeat SUD (**Table 2**)
- For dosing intervals ≥63 days, no CRS events occurred at restart, and the majority of patients repeated SUD2 or both SUD1 and SUD2 (**Table 2**)
- Based on the predicted teclistamab serum concentrations after prolonged dosing intervals and the clinical experience following prolonged dosing intervals, updated recommendations for repeat SUD are presented in **Table 3**

Table 2: Low CRS occurrence after prolonged dosing intervals in retrospective clinical analysis

	>28–62 days (n=52)	≥63–111 days (n=15)	≥112 days (n=7)
Patients with CRS at restart,[a] n (%)	2 (3.8)	0	0
Prolonged intervals, n	102	18	8
Number of intervals with CRS events at restart after:	2[b]	0	0
SUD1 and SUD2, n (%)	3 (2.9)[b]	0	0
Number of intervals without CRS events after:	100	18	8
No SUD,[c] n (%)	78 (78.0)	1 (5.6)	0
SUD1 only,[c] n (%)	0	1 (5.6)[d]	0
SUD2 only,[c] n (%)	17 (17.0)	9 (50.0)	4 (50.0)
SUD1 and SUD2,[c] n (%)	5 (5.0)	7 (38.9)	4 (50.0)

[a]Percentages calculated with the total number of patients within corresponding interval as denominator. Patients could be counted more than once in each category. [b]1 patient had 2 CRS events after teclistamab restart after prolonged dose interval. [c]Percentages calculated with the number of intervals with or without CRS in the corresponding interval as denominator. [d]Discontinued treatment after SUD1 and did not receive repeat SUD.

Table 3: Updated SUD recommendations based on dosing interval

Dosing interval	SUD recommendation
≤62 days	No repeat SUD
63–111 days	Restart at SUD2
≥112 days	Restart at SUD1

References
1. TECVAYLI® (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc.; 2022. 2. TECVAYLI® (teclistamab). Summary of product characteristics. Leiden, Netherlands: Janssen Biologics BV; 2022. 3. Moreau P, et al. *N Engl J Med* 2022;387:495-505. 4. Garfall AL, et al. Presented at ASCO; May 31–June 4, 2024; Chicago, IL, USA & Virtual. Poster #7540. 5. Miao X, et al. *Target Oncol* 2023;18:667-84.

Multiple Myeloma

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