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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Introduction

- Teclistamab is the first approved BCMA × CD3 BsAb for the treatment of patients with TCE RRMM, with weight-based dosing and the longest study follow-up of any BsAb in MM (30.4 months)[1-4]
  - After 2 SUDs to mitigate the risk of CRS, teclistamab is dosed QW with the option to transition to Q2W based on response[1,2]
- Teclistamab demonstrated rapid, deep, and durable responses in the pivotal phase 1/2 MajesTEC-1 study (NCT03145181/NCT04557098); ORR, 63.0%; ≥CR 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 popPK modeling and a retrospective clinical analysis

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CR, complete response; CRS, cytokine release syndrome; MM, multiple myeloma; ORR, overall response rate; popPK, population pharmacokinetic; Q2W, every other week; QW, weekly; RRMM, relapsed/refractory multiple myeloma; SUD, step-up dose; TCE, triple-class exposed.

1. TECVAYLI® (teclistamab). Summary of product characteristics. Leiden, Netherlands: Janssen Biologics BV; 2022. 2. TECVAYLI® (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2022. 3. Moreau P, et al. *New 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.

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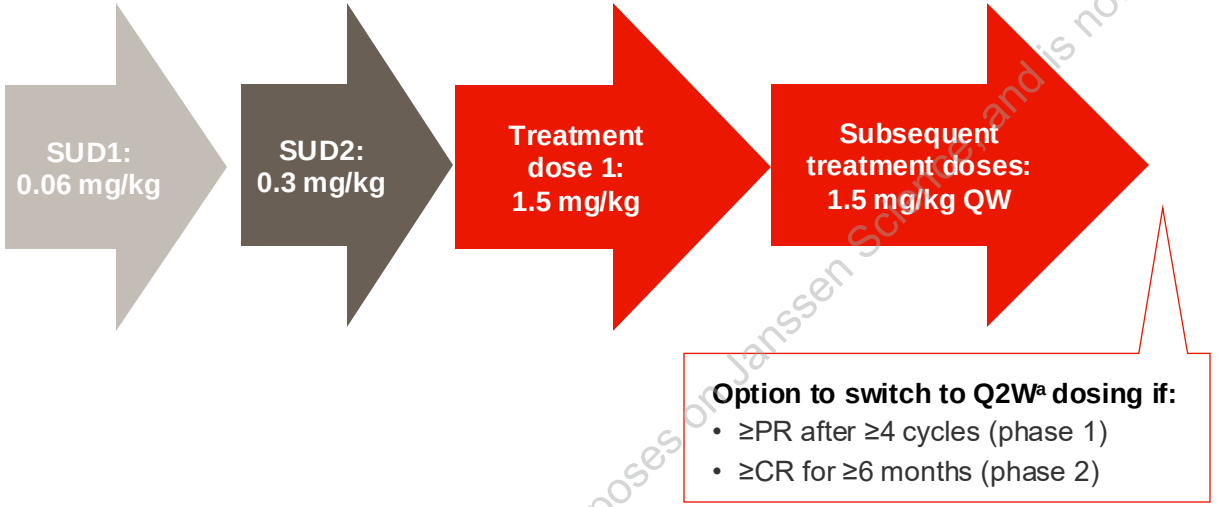
Teclistamab Dosing Schedule in MajesTEC-1



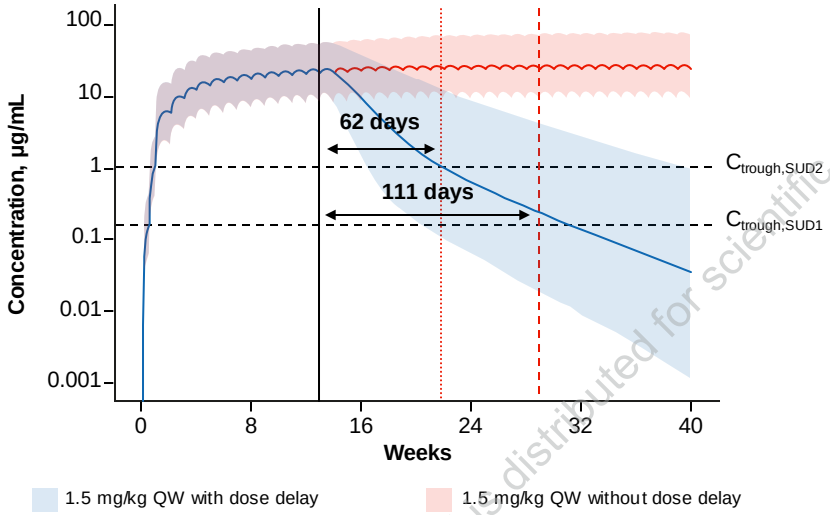
- In the MajesTEC-1 RP2D cohort, patients received teclistamab at the RP2D[b]
- A previously established popPK model of teclistamab was used to determine the longest time window wherein serum concentrations would not drop below levels following SUD1 and SUD2[1]
- The time windows based on popPK estimations 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)

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. [b]1.5 mg/kg subcutaneous QW.
CR, complete response; CRS, cytokine release syndrome; popPK, population pharmacokinetic; PR, partial response; Q2W, every other week; Q4W, every 4 weeks; QW, weekly; RP2D, recommended phase 2 dose; SUD, step-up dose. 1. Miao X, et al. *Target Oncol* 2023;18:667-84.

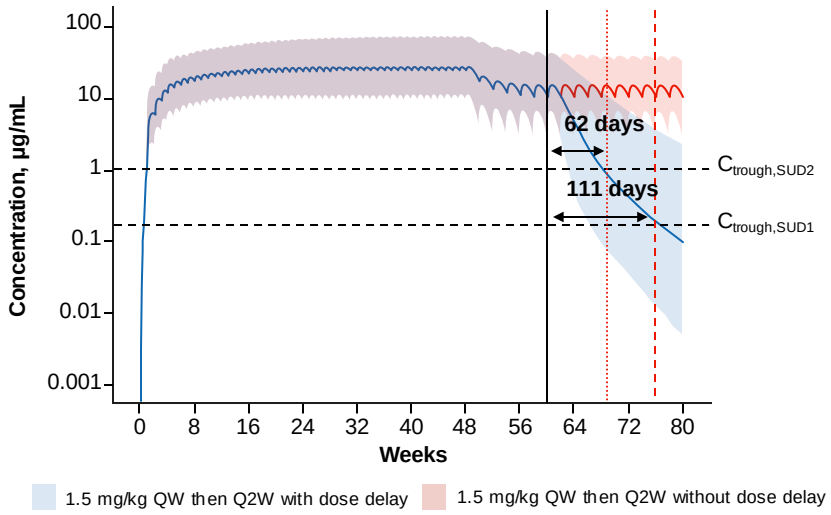
PopPK Modeling and Simulation

- 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
- 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

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



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.
C_{trough}, trough concentration; popPK, population pharmacokinetics; Q2W, every other week; QW, weekly; SUD, step-up dose.

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Retrospective Clinical Analysis of Prolonged Dosing Intervals >28 Days

- 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
  - 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

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

CRS, cytokine release syndrome; SUD, step-up dose.

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Low CRS Occurrence After Prolonged Dosing Intervals in Retrospective Clinical Analysis

- 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
- For dosing intervals ≥63 days, no CRS events occurred at restart, and the majority of patients repeated SUD2 or both SUD1 and SUD2

	>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,[c] 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 with 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.
CRS, cytokine release syndrome; SUD, step-up dose.

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Updated SUD Recommendations Based on Dosing Interval

- 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 the **Table**

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

SUD, step-up dose.

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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

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

CRS, cytokine release syndrome; EMA, European Medicines Agency; popPK, population pharmacokinetic; SUD, step-up dose.

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