1989

Less Frequent Teclistamab Dosing in Responders: Modeling and Simulation Data From the MajesTEC-1 Study in Relapsed/Refractory Multiple Myeloma

Yue Guo[1], Jin Niu[1], Natalia A Quijano Cardé[1], Liviawati S Wu[2], Xin Miao[1], Shalla Hanson[1], Yaming Su[3], Carlos Pérez Ruixo[4], Deeksha Vishwamitra[1], Katherine Chastain[3], Mahesh N Samtani[3], Weirong Wang[1], Nahor Haddish-Berhane[1]

[1]Janssen Research & Development, Spring House, PA, USA; [2]Janssen Research & Development, South San Francisco, CA, USA; [3]Janssen Research & Development, Raritan, NJ, USA; [4]Janssen-Cilag, Madrid, Spain

Key Takeaway

Modeling and simulation results from MajesTEC-1 support the approved switch to teclistamab 1.5 mg/kg Q2W in patients maintaining a response for ≥6 months, and indicate comparable PK between the 1.5 mg/kg Q2W and 3 mg/kg Q4W teclistamab doses

Conclusions

- Exposure-response trends suggest that switching from QW to Q2W dosing did not affect maintenance of response to teclistamab
- Maintenance of tumor volume reduction and DOR were comparable between virtual patients who switched to Q2W dosing after maintaining a response for ≥6 months and those who remained on QW dosing, based on QSP modeling
- Results from teclistamab population PK modeling suggest that the 3 mg/kg Q4W schedule may provide maintenance of response comparable with the 1.5 mg/kg Q2W schedule
- Teclistamab 3 mg/kg Q4W dosing will be evaluated in >800 patients in 3 phase 3 studies in early line RRMM (MajesTEC-3, MajesTEC-9, and MonumenTAL-6) and in 100 patients in the phase 1 MajesTEC-10 study

Please scan QR code

Poster

Supplementary material

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

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Acknowledgments
We thank the patients who participated in the study and their families and caregivers, the physicians and nurses who cared for patients and supported this clinical trial, the staff members at the study sites, and staff members involved in data collection and analyses. This study was funded by Janssen Research & Development, LLC. Medical writing support was provided by Jas Bhachu, PhD, of Eloquent Scientific Solutions, and was funded by Janssen Global Services, LLC.

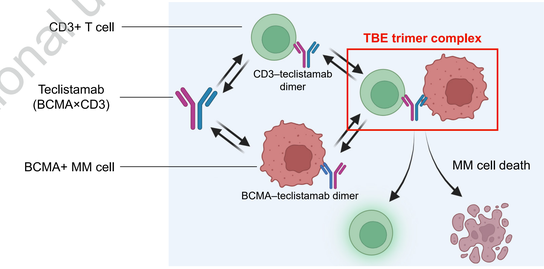
Introduction

- Teclistamab is currently approved at a dose of 1.5 mg/kg weekly (QW) in patients with relapsed/refractory multiple myeloma (RRMM), with the option to switch to 1.5 mg/kg every other week (Q2W) in patients who have maintained complete response or better for ≥6 months[1-3]
- Population pharmacokinetics (PK) and quantitative systems pharmacology (QSP) modeling were used to evaluate the PK, pharmacodynamics, and anticancer activity of teclistamab 1.5 mg/kg Q2W, and the PK of teclistamab 3 mg/kg every 4 weeks (Q4W)
  - These are established approaches to support the evaluation and optimization of dose selection in oncology[4-7]
  - These models have been previously developed for teclistamab[8-10]

Methods

- Teclistamab PK was assessed using a population PK approach[8]
- Exposure-response analysis was performed for duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
- A multiscale QSP model[9] was used to estimate the impact in responders of switching to Q2W teclistamab dosing on simultaneous engagement of B-cell maturation antigen (BCMA) on target multiple myeloma (MM) cells, and CD3 on effector T cells, to form a target cell–biologic–effector cell (TBE) trimer (**Figure 1**)
  - Trimers are formed by either the BCMA–teclistamab dimer binding to unbound CD3 or the CD3–teclistamab dimer binding to unbound BCMA
  - Virtual patients who maintained response for 6 cycles were simulated with continuous 1.5 mg/kg QW dosing or with a switch to 1.5 mg/kg Q2W dosing
- Teclistamab PK at steady state was also simulated for the 1.5 mg/kg Q2W and 3 mg/kg Q4W doses using the population PK model

Figure 1: Simultaneous engagement of BCMA on target MM cells and CD3 on effector T cells by teclistamab to form a TBE trimer complex



Teclistamab engages BCMA on MM cells and CD3 on effector T cells to form a TBE trimer complex with 2 associated dimer complexes.

Results

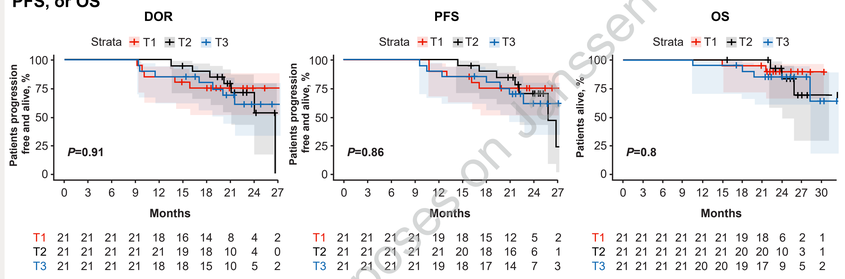
Population PK analysis

- Median estimated teclistamab trough concentration (C_{trough}) was lower after switching from QW to Q2W dosing, but remained above the maximum 90% effective concentration ($EC_{90,max}$) of 6.039 µg/mL[10] (**Supplemental Table**)

Exposure-response analysis

- There was no apparent exposure-response trend between teclistamab exposures and DOR, PFS, and OS in 63 responders who switched to Q2W dosing in MajesTEC-1 (observed response data; **Figure 2**), suggesting that Q2W dosing did not lead to a difference in maintenance of response across exposures

Figure 2: No significant exposure-response trend between teclistamab $C_{trough,1stQ2Wdose}$ and DOR, PFS, or OS

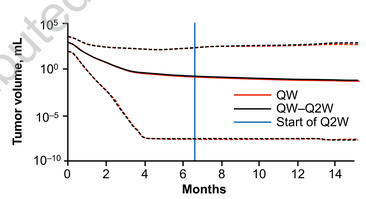


Endpoints were stratified by tertiles of the estimated exposure metrics ($C_{trough,1stQ2Wdose}$) in patients who switched from QW to Q2W teclistamab dosing in MajesTEC-1, based on population PK analysis. Numbers below the plots represent the number of patients at risk at each timepoint. $C_{trough,1stQ2Wdose}$, trough concentration after the first Q2W teclistamab dose; T1, lowest exposure tertile group; T2, middle exposure tertile group; T3 highest exposure tertile group.

QSP model validation and simulation

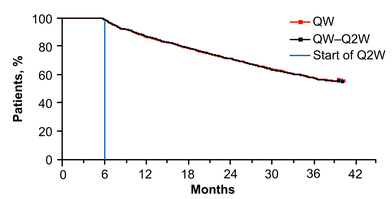
- Although the QW–Q2W switch was estimated to result in less dimer formation on target MM cells (**Figure 3A**) and effector T cells (**Figure 3B** and **3C**) than QW due to teclistamab concentration, this increased the availability of unbound BCMA and CD3, and the QW–Q2W switch therefore had minimal impact on TBE trimer formation (**Figure 3D**)
- Median reduction in tumor volume over time (**Figure 4**) and estimated DOR (**Figure 5**) were comparable between the QW and QW–Q2W scenarios

Figure 4: Comparable tumor volume reduction with QW vs QW–Q2W teclistamab



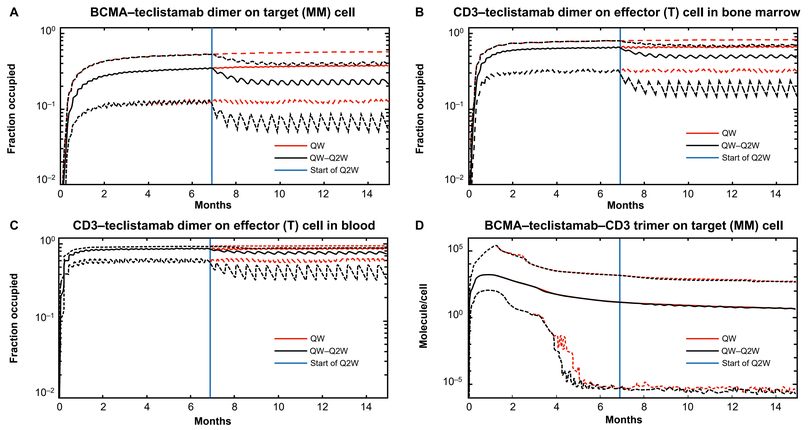
Based on QSP model simulation. Solid lines represent median estimated values and dashed lines represent 90% estimation intervals. The x-axis represents the time after treatment began in the virtual population.

Figure 5: Comparable estimated DOR with QW vs QW–Q2W teclistamab



Based on QSP model simulation. Estimated percentage of virtual patients in response when receiving 1.5 mg/kg QW or 1.5 mg/kg Q2W dosing after maintaining response for 6 months. The x-axis represents the time after achieving response.

Figure 3: Lower estimated (A) BCMA–teclistamab dimer formation and (B) CD3–teclistamab dimer formation in bone marrow, and (C) CD3–teclistamab dimer formation in blood and comparable estimated (D) BCMA–teclistamab–CD3 trimer formation, with QW vs QW–Q2W teclistamab dosing

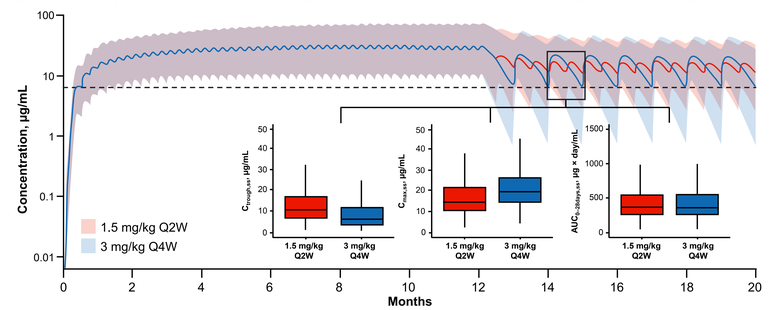


Based on QSP model simulation, in which sustained responders (response maintained for 6 cycles) were simulated with QW and QW–Q2W scenarios. Solid lines represent median estimated values and dashed lines represent 90% estimation intervals. The x-axis represents the time after treatment began in the virtual population.

Comparison of teclistamab PK for 1.5 mg/kg Q2W and 3 mg/kg Q4W doses

- PK simulations were based on teclistamab concentration-time profiles in 1000 virtual patients
- Steady-state teclistamab PK parameters (C_{trough}, maximum concentration, and area under the curve) were estimated to be comparable between the 1.5 mg/kg Q2W and 3 mg/kg Q4W doses (**Figure 6**)
  - Indicates that the 3 mg/kg Q4W schedule may provide maintenance of response comparable with the 1.5 mg/kg Q2W schedule

Figure 6: Comparable estimated steady-state teclistamab PK with 1.5 mg Q2W vs 3 mg/kg Q4W



Based on population PK simulation. $AUC_{0-28\ day,ss}$, area under the serum concentration vs time curve during a dose interval time period (28 days) at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state.

References
1. Usmani SZ, et al. *J Clin Oncol* 2023;41(16_suppl):8034. 2. TECVAYLI® (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2024. 3. TECVAYLI® (teclistamab). Summary of product characteristics. Leiden, Netherlands: Janssen Biologics BV; 2024. 4. Ball K, et al. *MAbs* 2023;15:2181016. 5. Helmlinger G, et al. *CPT Pharmacometrics Syst Pharmacol* 2019;8:380-95. 6. Peterson MC, Riggs MM. *CPT Pharmacometrics Syst Pharmacol* 2015;4:e00020.
7. Aghaee M, et al. *Eur J Pharm Sci* 2023;187:106492. 8. Miao X, et al. *Target Oncol* 2023;18:667-84. 9. Niu J, et al. Presented at ACoP; November 5–8, 2023; Oxon Hill, MD, USA. 10. Girgis S, et al. *Target Oncol* 2022;17:433-9.

Multiple Myeloma

Presented by Y Guo at the 66th American Society of Hematology (ASH) Annual Meeting; December 7–10, 2024; San Diego, CA, USA