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

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

Introduction

- Teclistamab is currently approved at a dose of 1.5 mg/kg QW in patients with RRMM, with the option to switch to 1.5 mg/kg Q2W in patients who have maintained ≥CR for ≥6 months[1-3]
- Using population PK and QSP modeling, we evaluated the PK, pharmacodynamics, and anticancer activity of teclistamab 1.5 mg/kg Q2W and 3 mg/kg Q4W
- PK and QSP modeling 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]

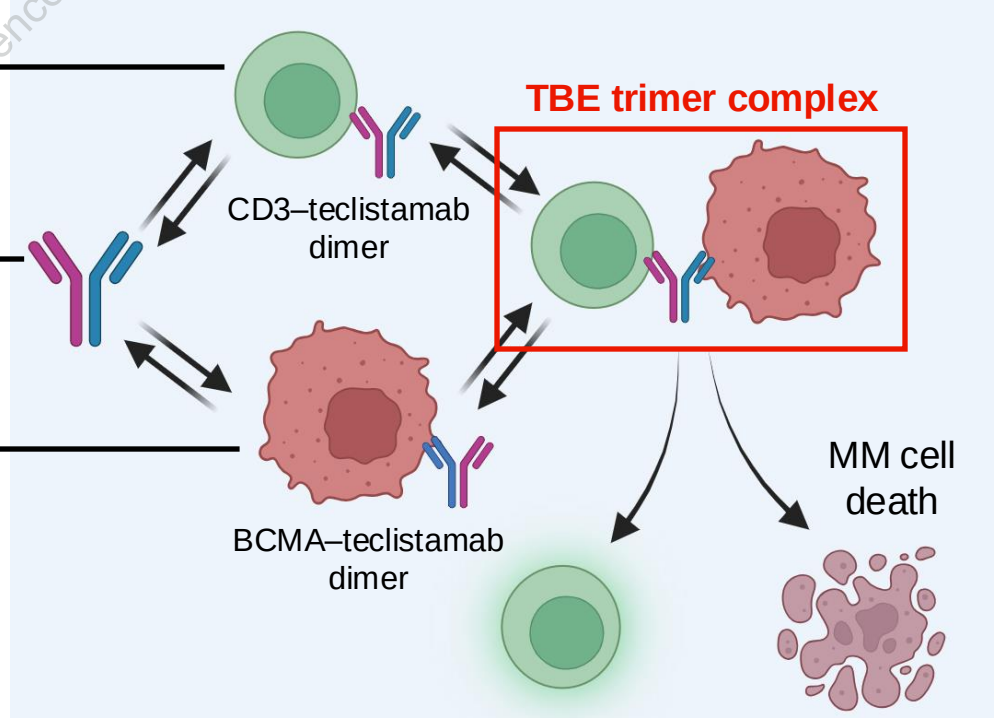
CR, complete response; PK, pharmacokinetics; Q2W, every other week; Q4W, every 4 weeks; QSP, quantitative systems pharmacology; QW, weekly; RRMM, relapsed/refractory multiple myeloma.

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.

PK and QSP Modeling and Analyses

- Teclistamab PK for the 1.5 mg/kg Q2W and 3 mg/kg Q4W doses was assessed using a population PK approach[1]
  - Exposure-response was analyzed for DOR, PFS, and OS in patients switching from teclistamab 1.5 mg/kg QW to 1.5 mg/kg Q2W
- A multiscale QSP model[2] was used to estimate the impact of Q2W teclistamab dosing on TBE trimer complex formation

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



BCMA, B-cell maturation antigen; DOR, duration of response; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every other week; Q4W, every 4 weeks; QSP, quantitative systems pharmacology; QW, weekly; TBE, target cell–biologic–effector cell.

1. Miao X, et al. *Target Oncol* 2023;18:667-84. 2. Niu J, et al. Presented at ACoP; November 5–8, 2023; Oxon Hill, MD, USA.

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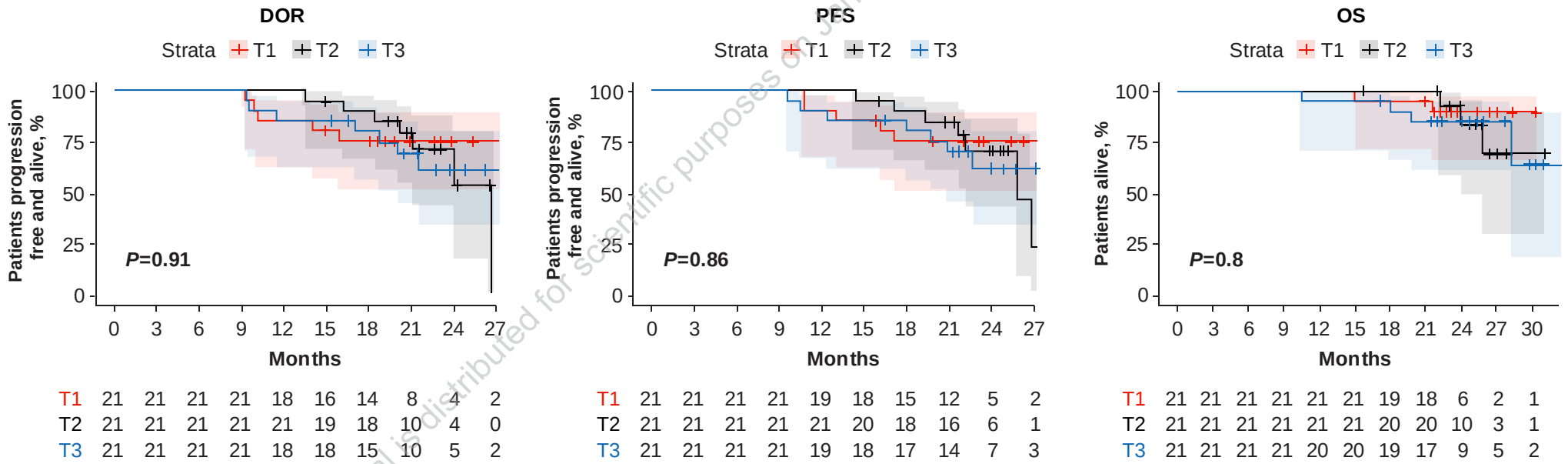
Population PK and Exposure-Response Analysis

- Median estimated teclistamab C_{trough} was lower after switching from QW to Q2W dosing, but remained above the maximal EC_{90} of 6.039 µg/mL[1]
- No apparent exposure-response trend was observed between teclistamab exposures and DOR, PFS, and OS in 63 responders who switched to Q2W dosing in MajesTEC-1[a]



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. [a]Observed response data.

C_{trough}, trough concentration; $C_{trough,1stQ2Wdose}$, trough concentration after the first Q2W teclistamab dose; DOR, duration of response; EC_{90}, 90% effective concentration; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every other week; QW, weekly; T1, lowest exposure tertile group; T2, middle exposure tertile group; T3 highest exposure tertile group. 1. Girgis S, et al. *Target Oncol* 2022;17:433-9.

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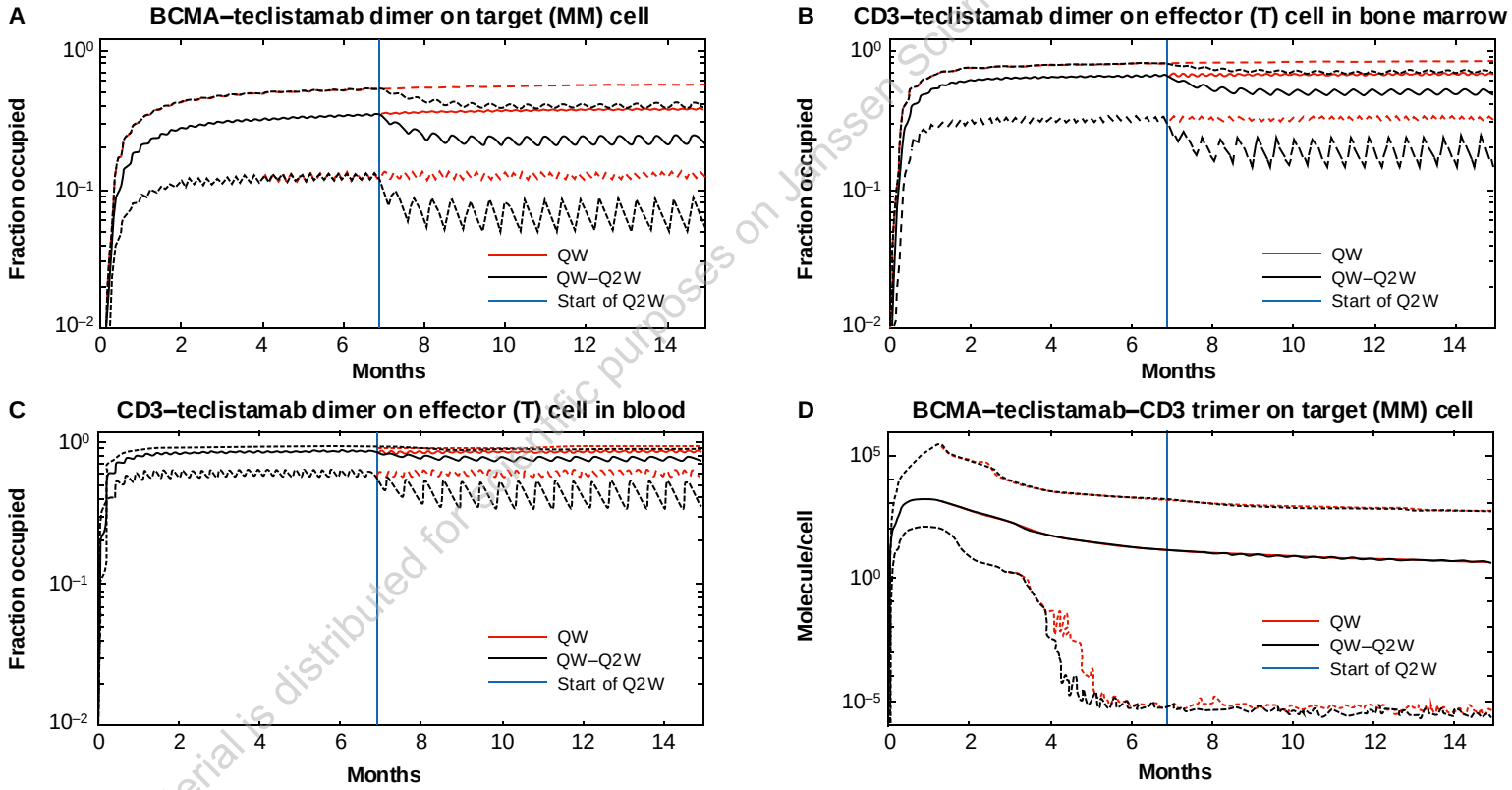
QSP Simulation: Impact of QW–Q2W Switch on TBE Trimer Formation

- Although the QW–Q2W switch was estimated to result in less dimer formation than QW dosing, there was minimal impact on TBE trimer formation

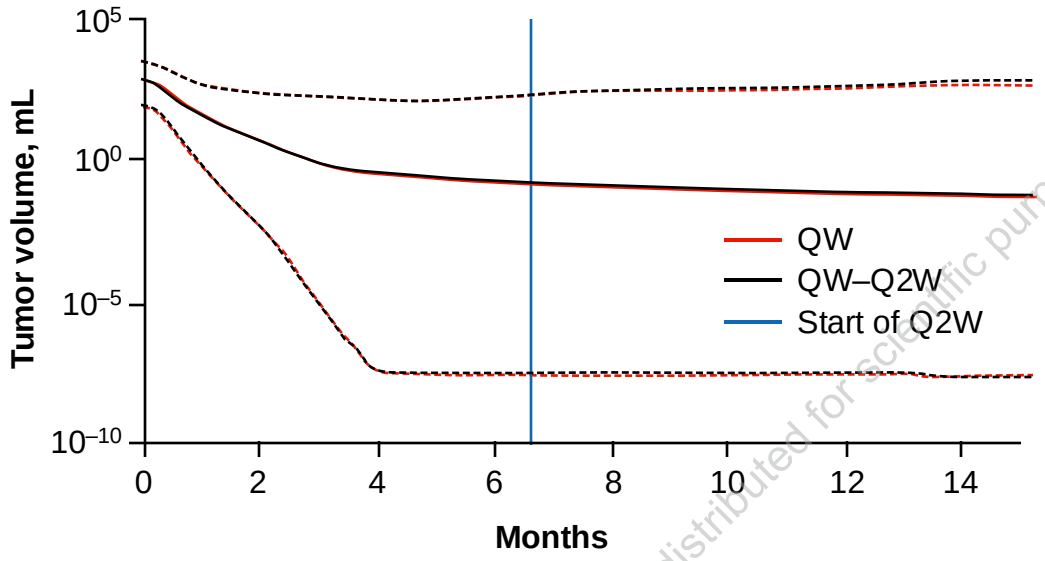


Based on QSP model simulation, in which sustained responders (response maintained for 6 cycles) were simulated with QW and QW–Q2W scenarios. Solid lines represent median estimated values, and dashed lines represent 90% estimation intervals. The x axis represents the time after treatment began in the virtual population.
BCMA, B-cell maturation antigen; MM, multiple myeloma; QSP, quantitative systems pharmacology; Q2W, every other week; QW, weekly; TBE, target cell–biologic–effector cell.

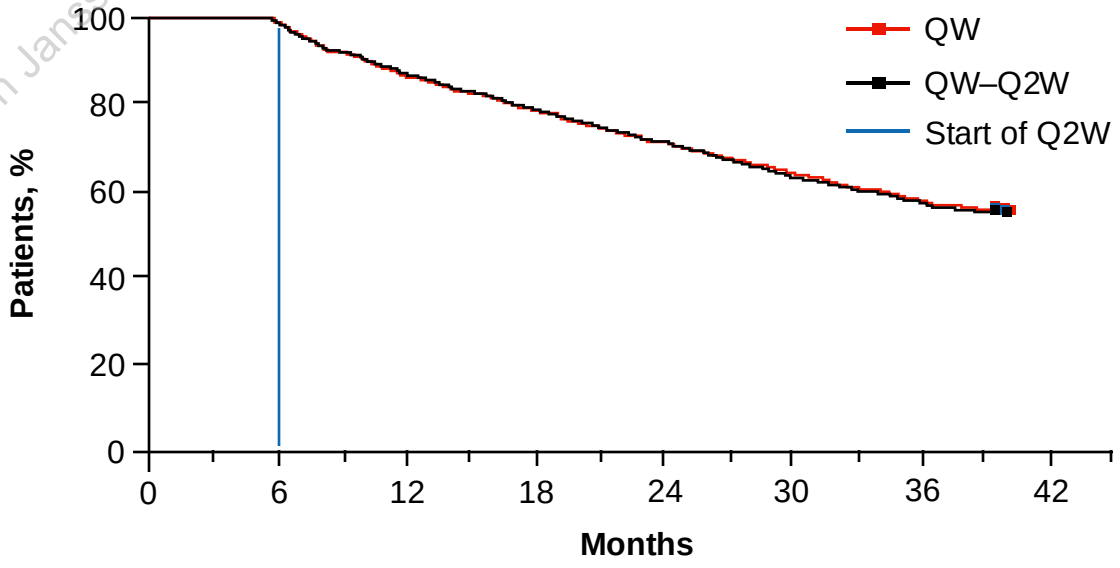
QSP Simulation: Impact of QW–Q2W Switch on Tumor Reduction and DOR

- Median reduction in tumor volume over time and estimated DOR were comparable between the QW and QW–Q2W scenarios

Tumor volume reduction[a]



DOR[b]



Based on QSP model simulation. [a]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. [b]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.
DOR, duration of response; Q2W, every other week; QSP, quantitative systems pharmacology; QW, weekly.

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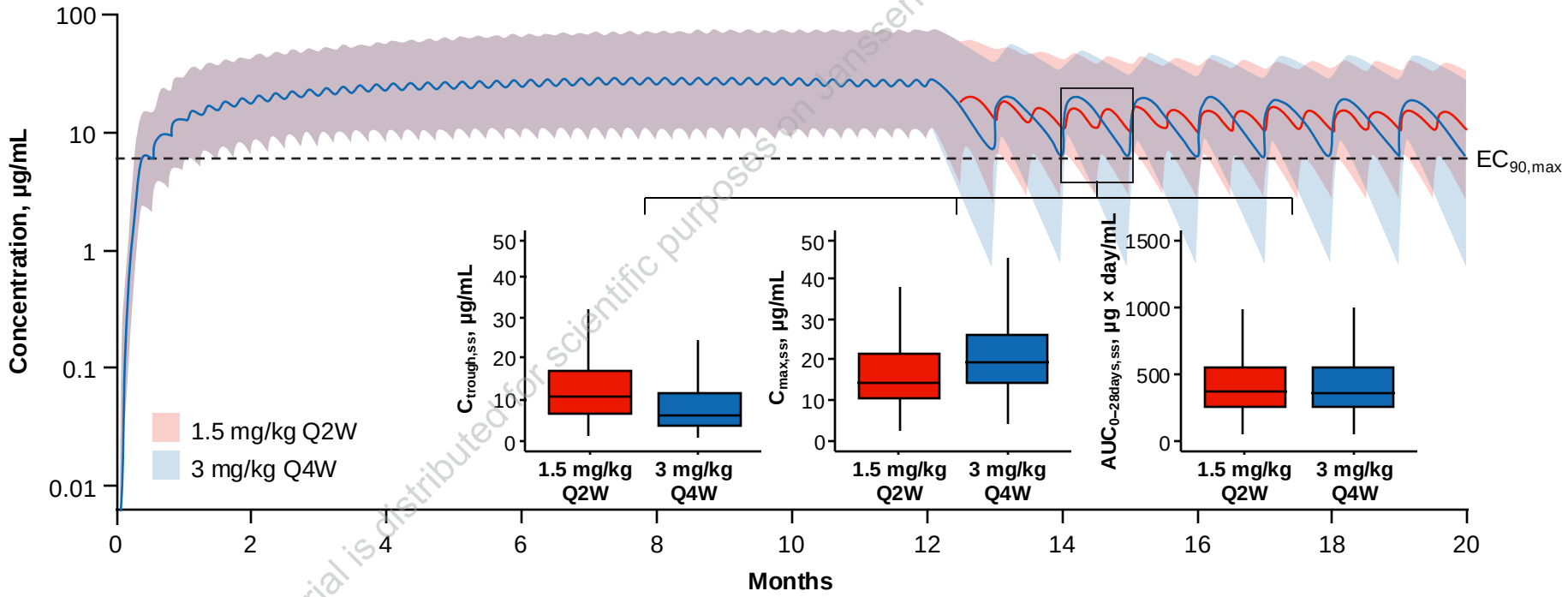
Population PK Analysis: Teclistamab 1.5 mg/kg Q2W vs 3 mg/kg Q4W

- Steady-state teclistamab PK parameters (C_{trough}, C_{max}, and AUC) were estimated to be comparable between the 1.5 mg/kg Q2W and 3 mg/kg Q4W doses
  - Indicates that 3 mg/kg Q4W may provide maintenance of response comparable with 1.5 mg/kg Q2W



Based on population PK simulation.
$AUC_{0–28days,ss}$, 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; $EC_{90,max}$, maximum 90% effective concentration; PK, pharmacokinetics; Q2W, every other week; Q4W, every 4 weeks.

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

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

DOR, duration of response; PK, pharmacokinetics; QSP, quantitative systems pharmacology; Q2W, every other week; Q4W, every 4 weeks; QW, weekly; RRMM, relapsed/refractory multiple myeloma.

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