Pharmacokinetic and Immunogenicity Results From the China Cohort of the MajesTEC-1 Study of Teclistamab for Relapsed/Refractory Multiple Myeloma

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Key Takeaway

Overall, PK and immunogenicity data in the MajesTEC-1 China cohort supported using the same dosing regimen of teclistamab in the Chinese patient population as recommended for the overall pivotal RP2D cohort

Conclusions

- Observed PK data in Chinese patients were well characterized by the global population PK model, indicating no notable ethnic PK differences between the China and pivotal RP2D cohorts
- Median PK exposure values were ~40% lower in the China vs pivotal RP2D cohort, which can be explained by the distribution of significant covariates and has no clinically meaningful impact
- ADA risk is low in Chinese patients and had no impact on teclistamab PK

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Disclosures
All authors are employees of Janssen.

Introduction

- Teclistamab is the first approved B-cell maturation antigen × CD3 bispecific antibody (BsAb) for the treatment of triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM), with weight-based dosing and the longest study follow-up of any BsAb in MM[1]
- In the phase 1/2 MajesTEC-1 study, teclistamab demonstrated rapid, deep, and durable responses with a manageable safety profile[2]
- Efficacy and safety in the MajesTEC-1 China cohort were generally consistent with that of the pivotal recommended phase 2 dose (RP2D) cohort[3]
- The National Medical Products Administration (NMPA) approved teclistamab for the treatment of TCE RRMM in China on June 18, 2024
- Here, we characterize the pharmacokinetics (PK) and immunogenicity of teclistamab at the RP2D in the China cohort of MajesTEC-1 and evaluate whether the proposed dose provides adequate systemic exposure relative to the pivotal RP2D cohort

Methods

Teclistamab dosing

- Patients in the China cohort (N=26) had RRMM and had received ≥3 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody. Patients were given teclistamab as outlined in **Figure 1**

Figure 1: Teclistamab dosing schedule

2–4 days were allowed between SUD 1, SUD 2, and treatment dose 1. Patients could switch to Q2W dosing if they achieved ≥CR for ≥6 months. Patients could subsequently switch to less frequent dosing if they continued to respond on the Q2W schedule.
CR, complete response; Q2W, every other week; QW, weekly; SUD, step-up dose.

PK and immunogenicity

- Serum samples were analyzed for PK and anti-drug antibodies (ADAs) by electrochemiluminescence immunoassay
- Teclistamab PK data in the China cohort were assessed using a 2-compartment population PK model with first-order absorption and parallel time-independent and time-dependent (decrease over time) elimination pathways established using data from patients in the pivotal RP2D MajesTEC-1 cohort[4]
  - The covariate effects were retained in the final model and included body weight, International Staging System (ISS) staging, and the type of myeloma (immunoglobulin [Ig] G type vs non-IgG type)
- A quantitative systems pharmacology (QSP) modeling approach representative of the mechanism of action of T-cell redirecting antibodies[5] was used to estimate the response to teclistamab in the China cohort compared with the pivotal RP2D cohort, based on a virtual population generated for RRMM

Results

Baseline characteristics

- As of clinical cut-off (Sept 27, 2023), 26 patients in the China cohort had received teclistamab at the RP2D (**Table**)

Table: Baseline characteristics

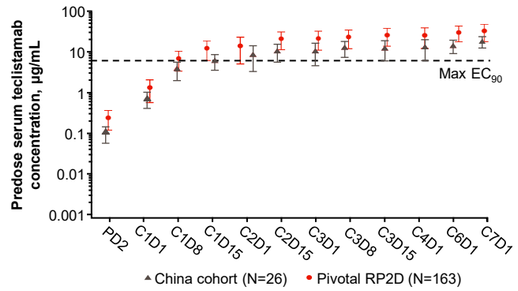
Characteristic	China cohort (N=26)
Age (years), median (range)	66.0 (42–84)
Age category, n (%)	
<65 years	12 (46.2)
65 to <75 years	12 (46.2)
≥75 years	2 (7.7)
Female, n (%)	19 (73.1)
Race, n (%)	
Asian	26 (100.0)
Weight (kg), median (range)	58.2 (42–82)
Bone marrow plasma cells ≥60%, n (%)	4 (15.4)
≥1 extramedullary plasmacytoma, n (%)	9 (34.6)
High-risk cytogenetics, n (%)[a]	15 (57.7)
Type of myeloma	
IgG	13 (50.0)
Non-IgG	13 (50.0)
ISS stage, n (%)	
I	9 (34.6)
II	10 (38.5)
III	7 (26.9)
Time since diagnosis (years), median (range)	4.9 (1.3–11.3)
Prior lines of therapy, median (range)	5 (3–11)
Prior stem cell transplantation, n (%)	3 (11.5)
Exposure status, n (%)	
Triple-class[b]	26 (100.0)
Penta-drug[c]	14 (53.8)
Refractory status, n (%)	
Triple-class	16 (61.5)
Penta-drug	3 (11.5)
To last line of therapy	23 (88.5)

[a]High-risk cytogenetics: patients who are positive for any of del(17p), t(14;16), or t(4;14) by FISH.
[b]PI, IMiD, and anti-CD38 monoclonal antibody. Note: PI includes bortezomib, carfilzomib, ixazomib; IMiD includes thalidomide, lenalidomide, and pomalidomide; anti-CD38 includes daratumumab and other investigational anti-CD38 monoclonal antibodies (TJ202 and CM313).
[c]Penta includes at least 2 PIs, at least 2 IMiDs, and an anti-CD38 monoclonal antibody.
FISH, fluorescence in situ hybridization.

PK

- Consistent with the pivotal RP2D cohort, teclistamab mean trough concentrations (C_{trough}) from cycle 2 day 1 onwards were maintained above the ex vivo 90% maximal effective concentration (EC_{90})[1] in the China cohort (**Figure 2**)

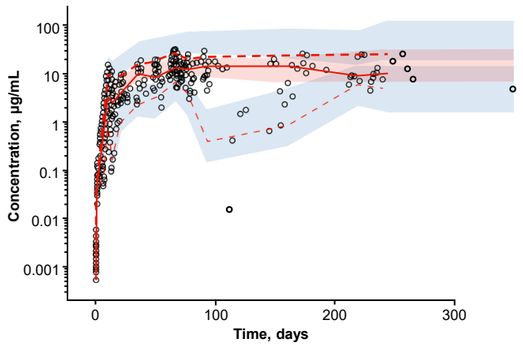
Figure 2: Mean (SD) predose serum concentration-time profiles of teclistamab following SC administration of teclistamab RP2D



PK cut-off was December 30, 2022, for the China cohort and August 9, 2021, for the global pivotal RP2D cohort. The global pivotal RP2D population included patients in the phase 1 and phase 2 RP2D cohorts of MajesTEC-1, with 163 patients who had PK-evaluable data as of the PK cut-off date. The China cohort included 26 patients from phase 2 of MajesTEC-1, who had PK-evaluable data as of the PK cut-off date.
C, cycle; D, day; PD, priming dose; SC, subcutaneous.

- The previously developed 2-compartment global population PK model[4] adequately captured the central tendency and the variability of the observed PK data from the China cohort (**Figure 3**)
  - This demonstrated the consistency of teclistamab PK characteristics between the China cohort and the pivotal RP2D cohort after teclistamab administration

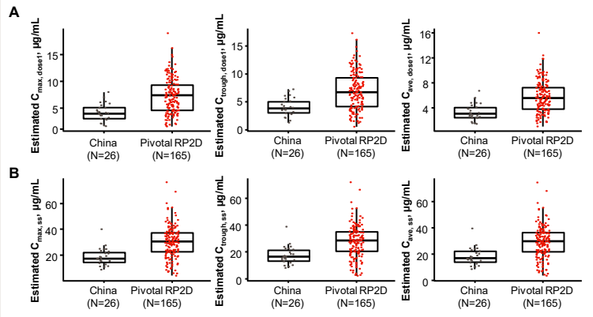
Figure 3: Visual estimation check using the previously developed global population PK model in Chinese patients treated with teclistamab RP2D



Black circles represent observations. The red solid and dashed lines represent the median and 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% CI of the median and 5th and 95th percentiles estimated by the model, respectively.

- The model estimated that exposure metrics following the first and steady state treatment doses of teclistamab in the China cohort overlapped with those in the pivotal RP2D cohort, albeit with an ~40% lower median in the China cohort (**Figure 4**)
  - This is likely due to the small sample size in the China cohort (N=26) and the imbalanced covariate distribution in the China cohort compared with the pivotal RP2D cohort, such as the higher proportion of ISS stage III patients (26.9% vs 12.1%)

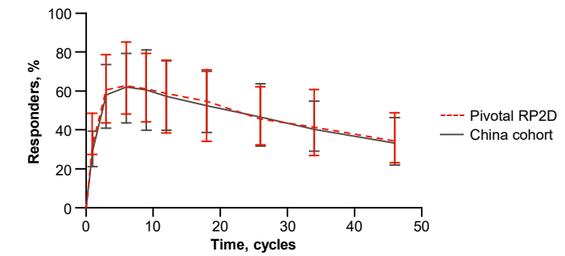
Figure 4: Distribution of the estimated maximum concentration, estimated C_{trough}, and estimated average concentration (A) after the first treatment dose and (B) at steady state[a] with teclistamab RP2D administration



[a]C_{max}/C_{trough}/C_{avg} post cycle 4 day 1 was regarded as steady state PK metrics.
C_{avg}, average concentration; C_{max}, maximum concentration; ss, steady state.

- The lower exposure metrics observed or estimated in the China cohort were not considered clinically relevant
  - A flat exposure-response relationship was observed in the pivotal RP2D cohort,[4] and efficacy and safety in the China cohort were consistent with that of the pivotal RP2D cohort[3]
  - The QSP model also supported RP2D selection for teclistamab in the China cohort, with the estimated best response rate similar to the pivotal RP2D cohort (**Figure 5**)

Figure 5: Percent of responders treated with teclistamab RP2D from QSP estimation



Error bars represent 95% CI.

Immunogenicity

- Only 1 patient was identified as positive for teclistamab ADAs in the China cohort
- ADAs were transient and had low titer (ie, 20)
- No impact of ADAs on teclistamab PK was observed in the China cohort

References
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Multiple Myeloma

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