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Longer-Term Follow-Up of Patients Receiving Prophylactic Tocilizumab for Reduction of Cytokine Release Syndrome in the Phase 1/2 MajesTEC-1 Study of Teclistamab in Relapsed/Refractory Multiple Myeloma

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Key Takeaway

Prophylactic tocilizumab reduced the overall incidence of CRS with teclistamab by 65% relative to the pivotal MajesTEC-1 population, with no new safety signals or impact on response at longer follow-up

Conclusions

- Incidence of CRS with teclistamab was reduced from 72.1%, without prophylactic tocilizumab in the pivotal cohort of MajesTEC-1, to 25% in the prophylactic tocilizumab cohort (all events grade 1/2)
- With longer follow-up, no new safety signals or impact on response to teclistamab were observed
- Further data to inform potential risk factors for higher-grade CRS are needed
- Prophylactic tocilizumab may be considered to mitigate risk of CRS for outpatient dosing of teclistamab

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Poster

Supplementary material

https://www.congresshub.com/Oncology/EHA2024/Teclistamab/Uttervall

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Disclosures
KU has served in a consulting or advisory role for BMS, Janssen, and Sanofi; and participated in speakers' bureaus for BMS and Janssen.

Introduction

- Teclistamab is the first approved B-cell maturation antigen × CD3 bispecific antibody (BsAb) for the treatment of triple-class exposed relapsed/refractory multiple myeloma, with weight-based dosing and the longest study follow-up of any BsAb in multiple myeloma[1-3]
- In the pivotal MajesTEC-1 study, 72.1% of patients had cytokine release syndrome (CRS; all grade 1/2 except 1 grade 3 event in 1 patient)[3,4]
- Teclistamab has been given successfully in the outpatient setting, using prophylactic tocilizumab to manage CRS[5-9]
- In a separate cohort, prophylactic tocilizumab prior to step-up dose (SUD) 1 reduced the incidence of CRS to 26% (all grade 1 and 2) at 2.6 months median follow-up[10]
  - Here, we present data with a longer median follow-up of 8.1 months in the prophylactic tocilizumab cohort (n=24) in MajesTEC-1

Methods

- Patients received teclistamab 1.5 mg/kg weekly (QW; phase 1 exploratory cohort) or a comparable fixed dose after a single dose of tocilizumab and SUD (**Figure 1**)
  - Tocilizumab 8 mg/kg was administered intravenously ≤4 hours before the first teclistamab SUD
  - Premedications during the teclistamab SUD schedule were dexamethasone, acetaminophen, and diphenhydramine
  - Hospitalization was required for 48 hours after each SUD and after the first treatment dose
- CRS management with tocilizumab treatment was permitted for grade 1 and recommended for grade ≥2
- CRS as an adverse event (AE) was graded per Lee et al[11]

Figure 1: Dosing schedule for patients receiving teclistamab and prophylactic tocilizumab

[a]2–4 days were allowed between SUD 1, SUD 2, and treatment dose. [b]Less frequent dosing (eg, Q2W) starting cycle 3. Q2W, every other week; Q4W, every 4 weeks.

Results

- 24 patients received prophylactic tocilizumab prior to SUD 1 of teclistamab
  - Median follow-up: 8.1 months (range, 0.9–13.2)
- Patient demographics and disease characteristics were generally consistent with the MajesTEC-1 pivotal population[3] (**Table 1**)

Table 1: Baseline characteristics

Characteristics	All patients (N=24)
Age, median (range), years	72 (50–82)
Male, n (%)	14 (58.3)
Race, n (%)	
White	19 (79.2)
Other	2 (8.3)
Not reported	3 (12.5)
ECOG PS score, n (%)	
0	13 (54.2)
1	11 (45.8)
Extramedullary plasmacytomas,[a] n (%)	
0	19 (79.2)
≥1	5 (20.8)
High-risk cytogenetics,[b] n (%)	6 (26.1)
ISS stage, n (%)	
I	16 (66.7)
II	7 (29.2)
III	1 (4.2)
Prior lines of therapy, median (range)	4 (2–9)
Triple-class refractory,[c] n (%)	14 (58.3)
% BMPCs (biopsy or aspirate), n (%)	
<30	16 (66.7)
30–59	3 (12.5)
≥60	5 (20.8)

Data cut-off: Nov 1, 2023. [a]≥1 soft tissue plasmacytoma not associated with bone. [b]n=23; high-risk cytogenetics included del(17p), t(4;14), t(14;16). [c]≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and an anti-CD38 monoclonal antibody. BMPC, bone marrow plasma cell; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

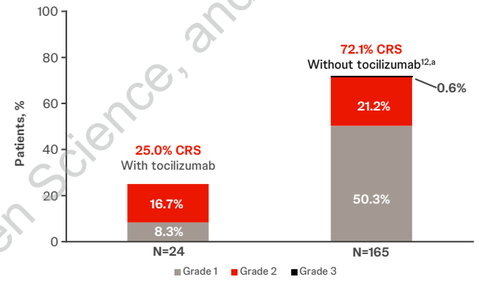
CRS incidence and severity

- 25% CRS with prophylactic tocilizumab (**Figure 2**)
  - Grade 1 (n=2), grade 2 (n=4); no grade 3 events
  - All initial events occurred during SUD; 3 recurrent events
  - Median time to onset: 2 days (range, 1–3)
  - Median duration: 2 days (range, 2–4)
  - All events resolved

CRS and baseline disease characteristics

- No disease characteristic associated with CRS, consistent with the MajesTEC-1 pivotal population[4] (**Table 2**)
  - Small sample size precludes clinically meaningful conclusions

Figure 2: CRS incidence and severity



[a]Pivotal MajesTEC-1 population.

Table 2: CRS by grade and baseline characteristics

Prophylactic tocilizumab cohort (N=24)			
Characteristic	No CRS (n=18)	CRS Grade 1 (n=2)	CRS Grade 2 (n=4)
BMPCs, median (range), %	8.0 (0–80)	19.0 (8–30)	62.5 (30–80)
ISS stage,[a] %			
I	72.2	50	50
II	22.2	50	50
III	5.6	0	0
No. of EMPs, median (range)	0 (0–4)	0 (0)	0 (0–2)

Data cut-off: Nov 1, 2023.
[a]Derived based on the combination of serum β_2-microglobulin and albumin.
EMP, extramedullary plasmacytoma.

Safety

- The safety profile of this cohort was generally consistent with the pivotal MajesTEC-1 population,[12] including incidence of any-grade and grade 3/4 infections (**Table 3**)
- Grade 3/4 infections (25%) included:
  - Pneumonia (n=4)
  - Bacterial infection (n=1)
  - Diverticulitis (n=1)
  - Cytomegalovirus infection (n=1)
  - Sepsis (n=1)
  - Septic shock (n=1)
- 5 patients had 10 neurotoxicity events (ie, neurological AE considered related by investigator) including:
  - Headache, immune effector cell–associated neurotoxicity syndrome, myoclonus, dizziness, and insomnia
  - All events were grade 1/2
  - All events resolved except for grade 2 headache
- Grade 5 pulmonary embolism occurred 20 days after the last teclistamab dose

Table 3: AEs observed with teclistamab and prophylactic tocilizumab

Prophylactic tocilizumab cohort (N=24)		
TEAE, n[a] (%)	Any Grade	Grade 3/4
Infections[b]	19 (79.2)	6 (25.0)
Neutropenia	15 (62.5)	15 (62.5)
Anemia	14 (58.3)	6 (25.0)
Thrombocytopenia	12 (50.0)	6 (25.0)
Lymphopenia	9 (37.5)	9 (37.5)
Leukopenia	6 (25.0)	5 (20.8)
Increased lipase	6 (25.0)	5 (20.8)

[a]Rate of any-grade TEAEs are listed if occurring at grade 3/4 in ≥20% of patients. [b]Rates of any-grade and grade 3/4 infections in the MajesTEC-1 pivotal population were 63.0% and 30.9%, respectively, at 7.2 months median follow-up.

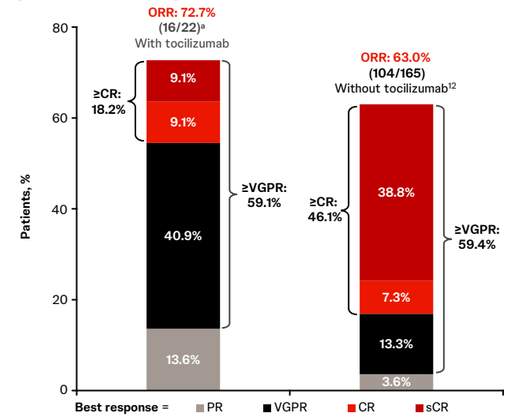
Response to teclistamab

- Responses were similar to the MajesTEC-1 pivotal population[12] (**Figure 3**)
  - The lower complete response (CR) or better rate in the prophylactic tocilizumab cohort is likely due to limited availability of bone marrow samples to confirm CR and duration of follow-up
  - At 8.1 months median follow-up, no impact on teclistamab efficacy was observed

Cytokine profiles

- A single dose of prophylactic tocilizumab blocks interleukin-6 receptor occupancy for ~10 days, covering the teclistamab SUD schedule (**Supplemental Figure 1** and **Supplemental Figure 2**)

Figure 3: Teclistamab response rates



[a]22 of 24 patients evaluable. Response-evaluable were defined as patients who have received ≥1 study treatment and have ≥1 postbaseline response evaluation by the investigator. ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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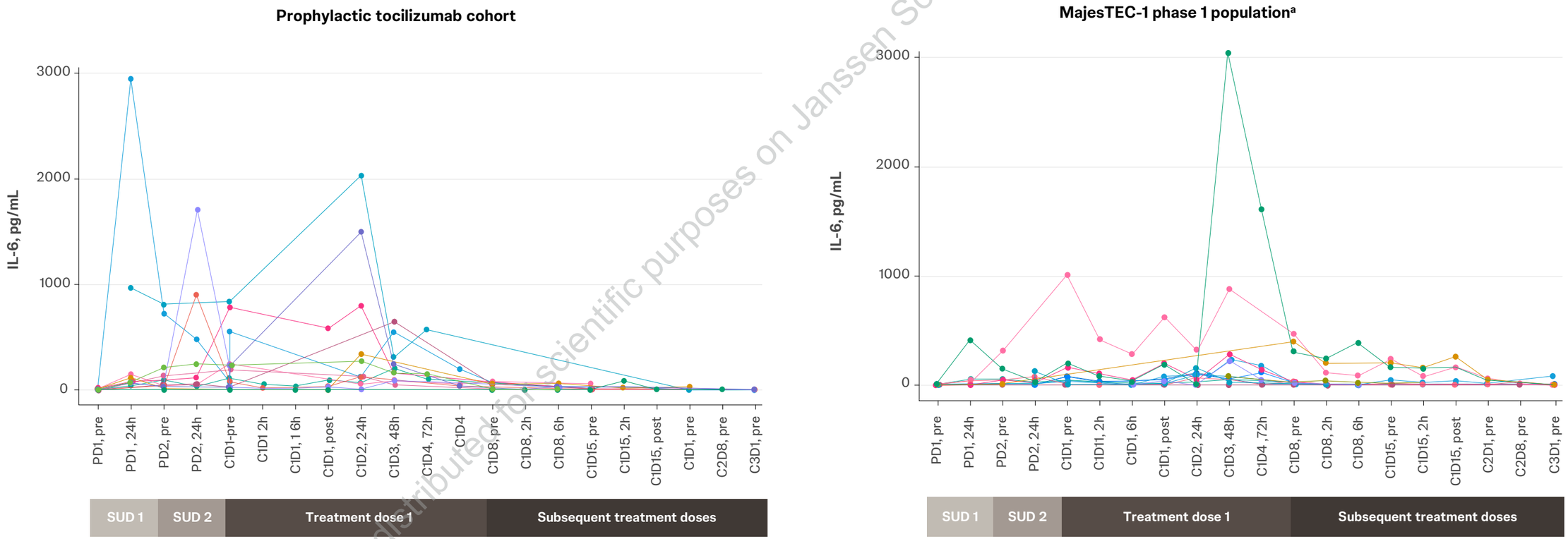
Multiple Myeloma

Presented by K Uttervall at the European Hematology Association (EHA) 2024 Hybrid Congress; June 13–16, 2024; Madrid, Spain

Supplemental Figure 1: IL-6 Induction in Patients Treated With Teclistamab With or Without Prophylactic Tocilizumab

- Timing of IL-6 induction was consistent with phase 1 MajesTEC-1 population[1]
  - Magnitude of IL-6 induction was greater with prophylactic tocilizumab

IL-6 induction in patients treated with teclistamab with or without prophylactic tocilizumab

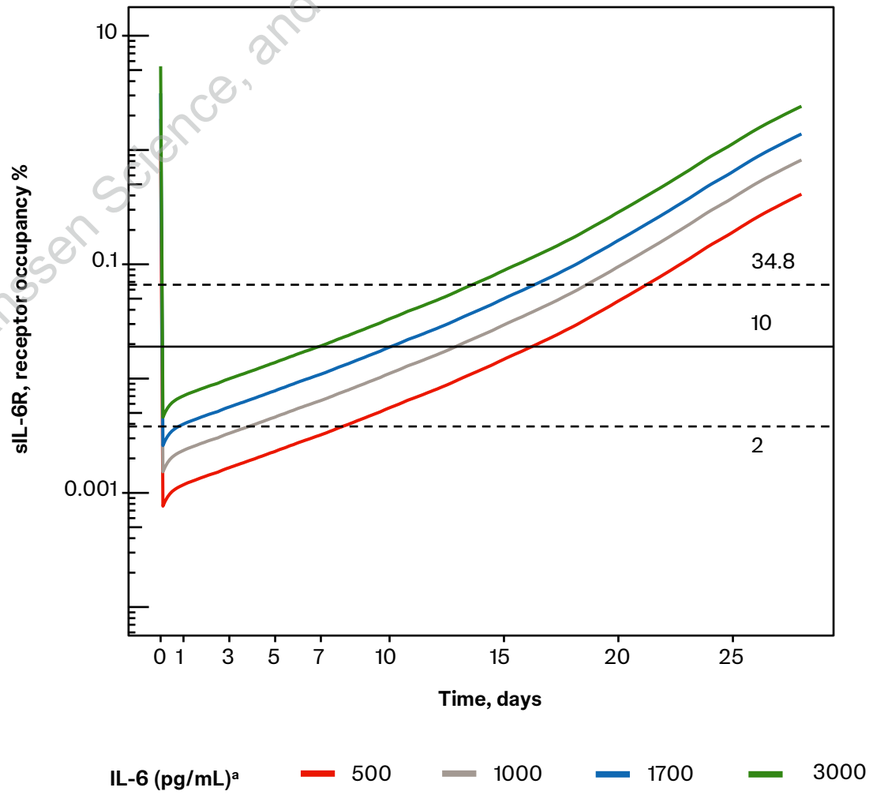


[a]Treated with the recommended phase 2 dose of teclistamab (1.5 mg/kg weekly), without prophylactic tocilizumab. C, cycle; D, day; IL-6, interleukin-6; IL-6R, IL-6 receptor; PD, priming dose; post, post dose; pre, pre dose; sIL-6R, soluble IL-6 receptor. 1. van de Donk NWCJ, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. Poster #8033.

Supplemental Figure 2: Percent sIL-6R Occupied by IL-6 (IL-6 Pathway Activity)

- Based on modeling data, a single dose of prophylactic tocilizumab blocks IL-6 receptor occupancy for ~10 days[1]
- Duration of IL-6 signaling blockade spans the teclistamab dosing schedule, supporting the approach for lowering overall risk of CRS during teclistamab SUD

Percent sIL-6R occupied by IL-6 (IL-6 pathway activity)[a]



[a]Curves indicate percent sIL-6R receptor occupancy by IL-6 in the presence of tocilizumab at different IL-6 concentrations (500, 1000, 1700, and 3000 pg/mL). Horizontal lines indicate sIL-6R in the absence of tocilizumab at different IL-6 concentrations (2, 10, and 34.8 pg/mL). IL-6, interleukin-6; IL-6R, IL-6 receptor; sIL-6R, soluble IL-6 receptor. 1. Zhou J, et al. Presented at ASH; December 9–12, 2023; San Diego, CA, USA. Poster #4670.