Higher Teclistamab Step-up Dosing in Patients With Relapsed or Refractory Multiple Myeloma (RRMM): Results From the MajesTEC-1 Trial

Jeffrey Matous[1], Niels WCJ van de Donk[2], Albert Oriol[3], Alfred L Garfall[4], Paula Rodriguez-Otero[5], Thomas Chalopin[6], Laura Rosiñol[7], Katarina Uttervall[8], María-Victoria Mateos[9], Danielle Trancucci[10], Natalia A Quijano Cardé[11], Caroline Hodin[12], Tara Stephenson[11], Athena F Zuppa[11], Katherine Chastain[10], Lionel Karlin[13]

[1]Colorado Blood Cancer Institute and Sarah Cannon Research Institute, Denver, CO, USA; [2]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [3]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; [4]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Cancer Center Clínica Universidad de Navarra, Pamplona, Navarra, Spain; [6]Centre Hospitalier Universitaire de Tours, Hôpital Bretonneau, Tours, France; [7]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; [8]Karolinska University Hospital and Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden; [9]University Hospital of Salamanca/Instituto de Investigación Biomédica de Salamanca/Centre for Cancer Research Institute of Cancer Molecular and Cellular Biology, Salamanca, Spain; [10]Janssen Research & Development, LLC, Raritan, NJ, USA; [11]Janssen Research & Development, LLC, Spring House, PA, USA; [12]Janssen Research & Development, LLC, Beerse, Belgium; [13]Lyon University Hospital, Hematology Centre Hospitalier Lyon-Sud, Pierre-Bénite, France

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Introduction

- Teclistamab is a first-in-class B-cell maturation antigen (BCMA) × CD3 bispecific antibody (BsAb) approved for the treatment of triple-class–exposed relapsed/refractory multiple myeloma (RRMM), with weight-based dosing, extensive real-world evidence, and the longest study follow-up of any BsAb in multiple myeloma (median: 30.4 months)[1-6]
- In the phase 1/2, single-arm MajesTEC-1 study, teclistamab demonstrated manageable safety with rapid, deep, and durable responses[3,4]
- In MajesTEC-1, patients received step-up doses (SUDs) of 0.06 and 0.3 mg/kg followed by 1.5 mg/kg weekly (recommended phase 2 dose [RP2D])[3]
  - Cytokine release syndrome (CRS) occurred in 72% of patients (nearly all grade 1/2); although most events occurred during step up, 24% of patients experienced CRS following the first treatment dose
- Higher SUDs may shorten the period of risk of CRS, potentially shortening the CRS monitoring window and facilitating prompt transition of care to the outpatient setting
- We evaluated higher SUDs in exploratory phase 1 cohorts from MajesTEC-1

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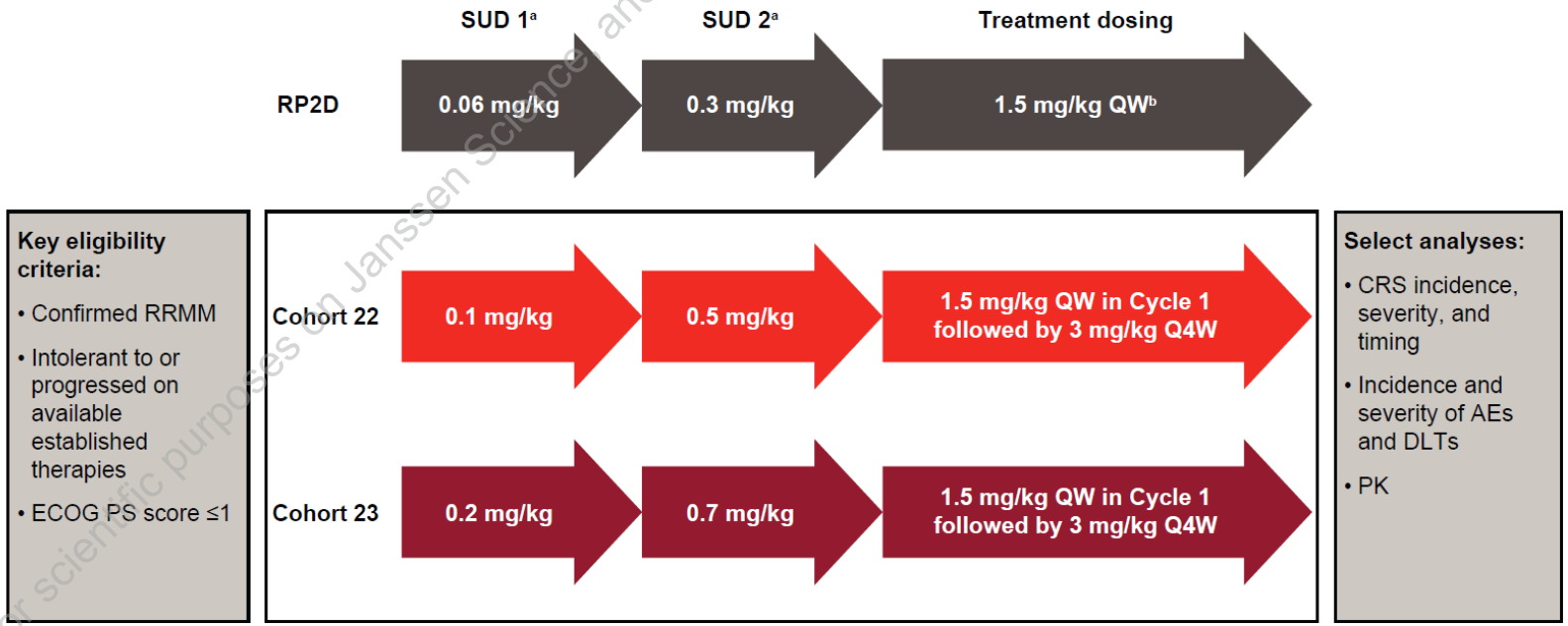
Methods

- Two exploratory cohorts of MajesTEC-1 were evaluated (phase 1, ClinicalTrials.gov Identifier: NCT03145181; **Figure 1**)
  - Cohort 22: SUDs of 0.1 and 0.5 mg/kg (2-4 days between doses)
  - Cohort 23: SUDs of 0.2 and 0.7 mg/kg (2-4 days between doses)
- Following SUDs, patients received 1.5 mg/kg on Days 1, 8, and 15 of Cycle 1 followed by 3 mg/kg every 4 weeks (Q4W) in subsequent cycles
- Premedication requirements and permitted supportive treatments for CRS were the same as for the RP2D cohort[3]
  - Prophylactic tocilizumab was not permitted

Figure 1: Treatment schedule in MajesTEC-1 RP2D[3] and exploratory higher SUD cohorts



- CRS was graded per Lee criteria[7] and converted to American Society for Transplantation and Cellular Therapy (ASTCT) criteria[8] to allow comparison with the RP2D[3]
- All adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03
- Serum samples were collected to assess teclistamab pharmacokinetics (PK)

[a]2 to 4 days between each SUD. Hospitalization was required after each SUD and after the first treatment dose. [b]Patients in phase 1 had the option to transition to Q2W if they achieved ≥PR after ≥4 cycles of therapy.[4]
C, Cycle; D, Day; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; QW, weekly; Q2W, every 2 weeks.

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Baseline Characteristics

- A total of 21 patients were enrolled (Cohort 22: n=10; Cohort 23: n=11)
- Patient demographics and baseline disease characteristics were generally consistent with those of the RP2D population[3] (**Table 1**)

Table 1: Demographics and baseline disease characteristics

Characteristic	Cohort 22 (n=10)	Cohort 23 (n=11)	RP2D (N=165)[3]
Age, years, median (range)	68.5 (51-76)	70.0 (52-78)	64.0 (33-84)
Male, n (%)	5 (50.0)	7 (63.6)	96 (58.2)
Race, n (%)			
White	3 (30.0)	7 (63.6)	134 (81.2)
Black/African American	1 (10.0)	0	21 (12.7)
Unknown	2 (20.0)	0	–
Not reported	4 (40.0)	4 (36.4)	–
≥1 extramedullary plasmacytoma, n (%)	1 (10.0)	1 (9.1)	28 (17.0)
ECOG PS score, n (%)			
0	5 (50.0)	4 (36.4)	55 (33.3)
1	5 (50.0)	7 (63.6)	110 (66.7)
High cytogenetic risk,[a] n/N (%)	4/10 (40.0)	1/9 (11.1)	38/148 (25.7)
≥60% BMPCs,[b] n/N (%)	2/10 (20.0)	1/10 (10.0)	18/160 (11.2)
ISS stage, n/N (%)			
I	7/10 (70.0)	4/11 (36.4)	85/162 (52.5)
II	3/10 (30.0)	5/11 (45.5)	57/162 (35.2)
III	0	2/11 (18.2)	20/162 (12.3)
Time since diagnosis, years, median (range)	5.5 (0.8-9.5)	5.5 (0.8-7.6)	6.0 (0.8-22.7)
Number of prior lines, median (range)	3 (1-4)	3 (1-4)	5 (2-14)
Prior therapy exposure, n (%)			
Triple-class	10 (100)	11 (100)	165 (100)
Penta-drug	2 (20.0)	4 (36.4)	116 (70.3)
Refractory status, n (%)			
Anti-CD38 mAb	8 (80.0)	9 (81.8)	148 (89.7)
Triple-class	4 (40.0)	5 (45.5)	128 (77.6)
Penta-drug	1 (10.0)	2 (18.2)	50 (30.3)

Data cut-off: September 4, 2024.

[a]High-risk cytogenetics was defined as the presence of del(17p), t(4;14), or t(14;16) by FISH/karyotype. [b]Bone marrow biopsy or aspirate. Maximum value from bone marrow biopsy or aspirate was selected if both results were available. BMPC, bone marrow plasma cell; FISH, fluorescence in situ hybridization; ISS, International Staging System; mAb, monoclonal antibody; PL, prior line.

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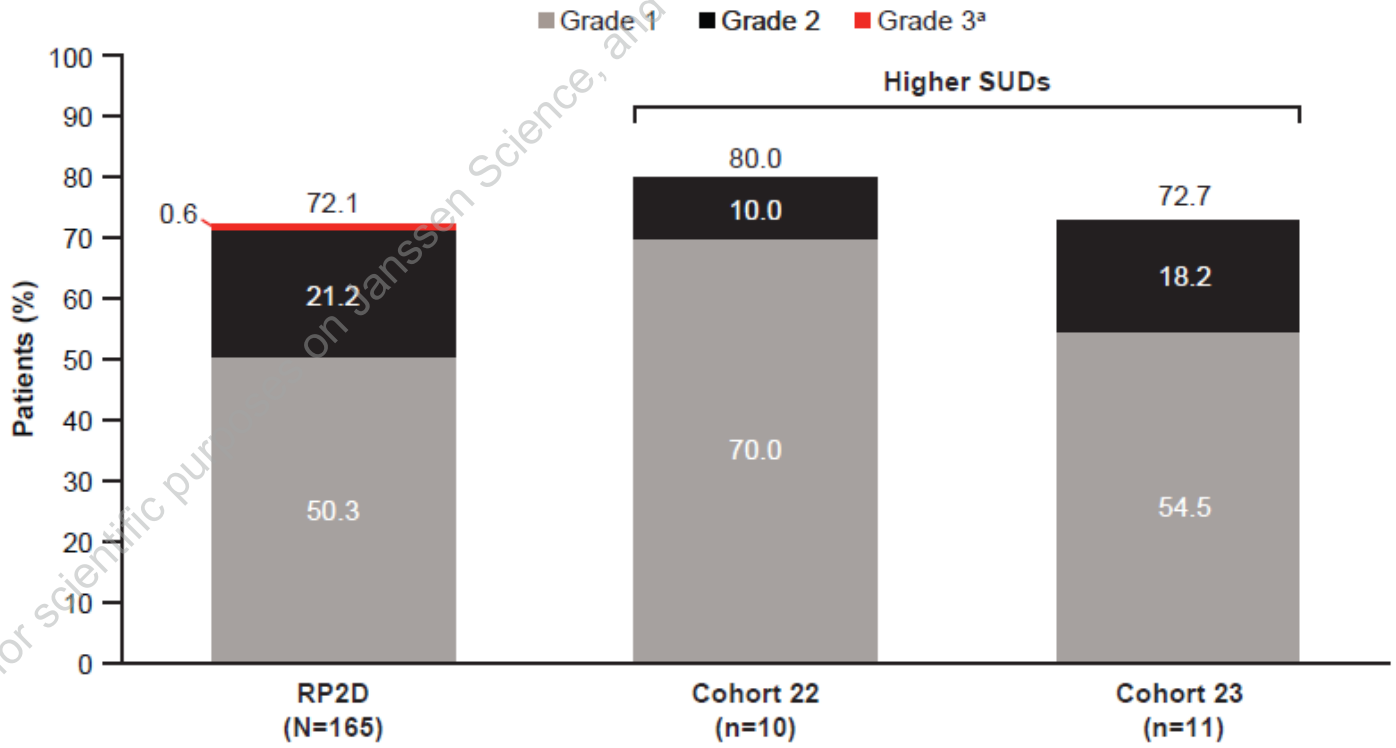
CRS Incidence, Severity, Timing, and Supportive Treatment

- Median follow-up was 10.2 months (range, 3.4-12.5) for Cohort 22 and 3.2 months (range, 1.8-8.1) for Cohort 23
- Overall, 22 CRS events were reported in 16 patients (8 patients in each cohort); all events were grade 1/2 (**Figure 2**)
- The overall incidence and severity of CRS events were comparable to results with the RP2D SUD (median follow-up: 14.1 months [range, 0.3-24.4])[3]
- Median onset of CRS through Cycle 1 Day 1 was 2.0 days in Cohort 22 and 2.5 days in Cohort 23; median event duration was 2 days in both cohorts
- All CRS events resolved, and none led to treatment discontinuation

Figure 2: CRS incidence and severity with the RP2D[3] and higher SUD cohorts



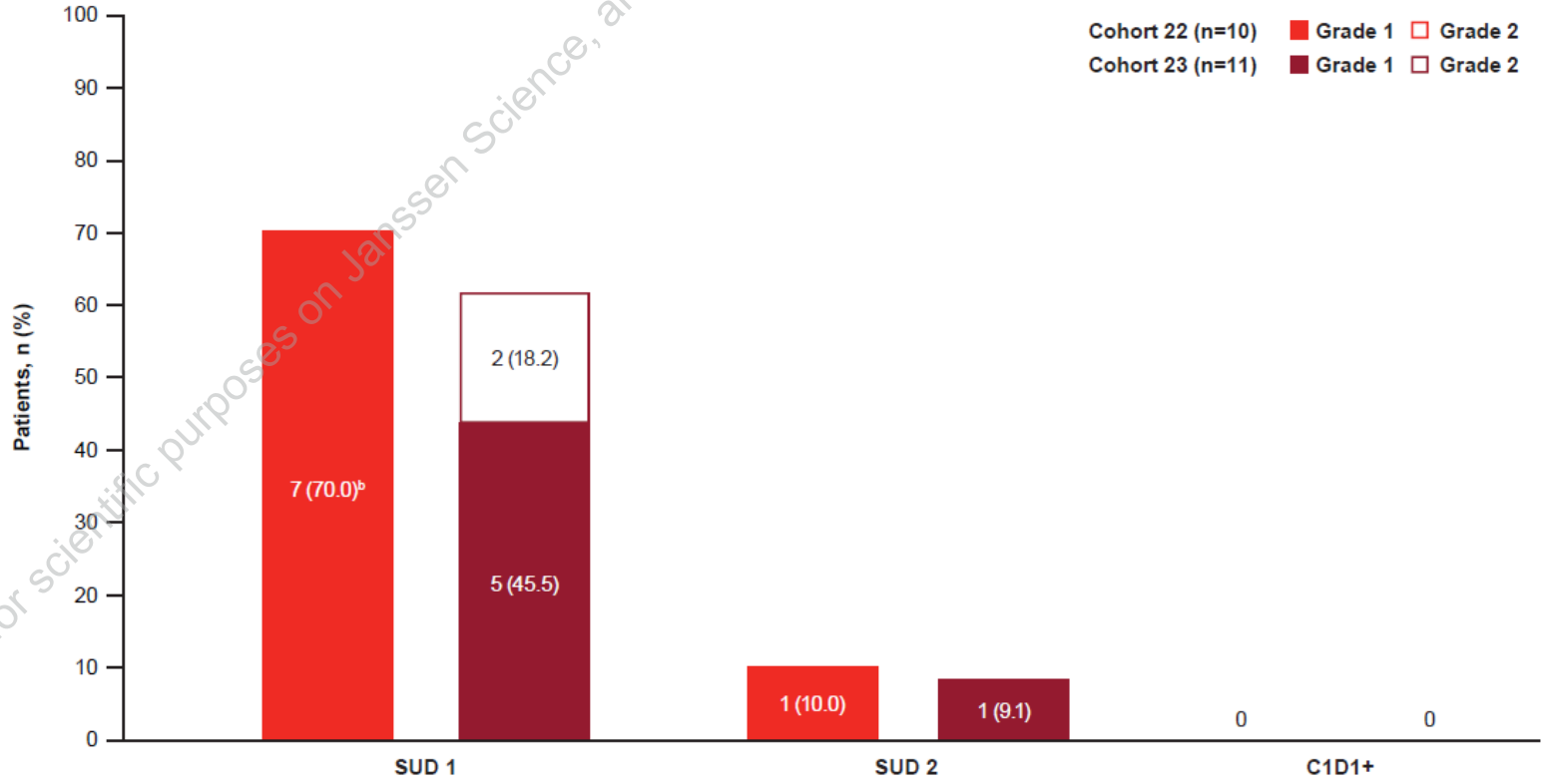
- All 16 (100%) patients who experienced CRS received supportive treatment
  - Overall, 5 of 8 (62.5%) patients in Cohort 22 and 4 of 8 (50.0%) patients in Cohort 23 who experienced CRS received tocilizumab
  - Of the 2 patients who experienced recurrent CRS during step up, 1 (Cohort 22; grade 2) received tocilizumab for the recurrent event
  - Neither of the 2 patients who experienced recurrent CRS after Cycle 1 Day 1 received tocilizumab at any time during treatment

[a]No grade 4 or 5 CRS events were reported.

CRS Incidence, Severity, Timing, and Supportive Treatment

- All initial CRS events occurred during SUDs (**Figure 3**)
  - With RP2D, 14 (8.5%) patients had their initial CRS event after Cycle 1 Day 1[9]
- Four (19.0%) patients in the higher SUD cohorts experienced recurrent CRS events (2 patients in each cohort)
  - 2 patients in Cohort 22 had recurrent events; 1 after SUD 2 (grade 2) and 1 after Cycle 1 Day 15 (grade 1)
  - 2 patients in Cohort 23 had recurrent events; 1 after SUD 2 (grade 1) and 1 after Cycle 1 Days 1, 8, and 15 (all grade 1)

Figure 3: Timing by cycle and grade for the initial CRS event[a]



[a]Time points are mutually exclusive. Occurrence was based on the last treatment visit on or prior to the day in which the event occurred. [b]One patient in Cohort 22 experienced grade 1 CRS after repeat SUD 1 in initial priming.

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Safety

- At an overall median follow-up of 7.4 months, the safety profiles of the higher SUD cohorts were generally comparable to that of the RP2D[3] (**Table 2**)
- Grade 3/4 TEAEs occurred in 7 (70.0%) patients in Cohort 22 and 8 (72.7%) patients in Cohort 23
  - Most common: neutropenia, anemia, and leukopenia
- Hypogammaglobulinemia TEAEs were reported in 6 (28.6%) patients; in addition, immunoglobulin G laboratory values <500 mg/dL were reported in 14 (66.7%) patients
- No cases of immune effector cell–associated neurotoxicity were reported; 1 patient in Cohort 22 experienced grade 1 neurotoxicity (dysgeusia, headache, and dizziness)
- The overall incidence of infections across both higher SUD cohorts (66.7%; grade 3/4: 23.8%) was generally similar to that of the RP2D (76.4%; grade 3/4: 44.8%)[3]
- DLTs were reported in 3 patients in Cohort 22 (*Escherichia* bacteremia, neutropenia, and bone pain); no DLTs were reported in Cohort 23
- One patient in Cohort 23 died from pneumonia related to COVID-19

Table 2: TEAEs observed with higher teclistamab SUDs

TEAEs (any grade: ≥20%),[a] n (%)	Cohort 22 (n=10)		Cohort 23 (n=11)		RP2D (N=165)[3]	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic						
Anemia	3 (30.0)	2 (20.0)	6 (54.5)	2 (18.2)	86 (52.1)	61 (37.0)
Neutropenia	4 (40.0)	3 (30.0)	3 (27.3)	3 (27.3)	117 (70.9)	106 (64.2)
Thrombocytopenia	4 (40.0)	1 (10.0)	2 (18.2)	0	66 (40.0)	35 (21.2)
Leukopenia	3 (30.0)	3 (30.0)	0	0	29 (17.6)	12 (7.3)
Nonhematologic						
CRS	8 (80.0)	0	8 (72.7)	0	119 (72.1)	1 (0.6)
Injection-site erythema	5 (50.0)	0	4 (36.4)	0	43 (26.1)	0
Nausea	4 (40.0)	0	4 (36.4)	0	45 (27.3)	1 (0.6)
Hypogammaglobulinemia[b]	3 (30.0)	0	3 (27.3)	2 (18.2)	24 (14.5)	3 (1.8)
Diarrhea	4 (40.0)	0	1 (9.1)	0	47 (28.5)	6 (3.6)
Constipation	4 (40.0)	0	1 (9.1)	0	34 (20.6)	0
COVID-19	1 (10.0)	0	4 (36.4)	1 (9.1)	29 (17.6)	20 (12.1)
Cough	3 (30.0)	0	1 (9.1)	0	33 (20.0)	0
Fatigue	2 (20.0)	0	2 (18.2)	0	46 (27.9)	4 (2.4)
Hypophosphatemia	2 (20.0)	1 (10.0)	2 (18.2)	0	20 (12.1)	10 (6.1)
URTI	2 (20.0)	0	2 (18.2)	0	18 (10.9)	0
Headache	2 (20.0)	0	1 (9.1)	0	39 (23.6)	1 (0.6)
ALT increased	2 (20.0)	0	2 (18.2)	0	NR	NR
Insomnia	3 (30.0)	0	0	0	NR	NR
Asthenia	2 (20.0)	0	1 (9.1)	0	18 (10.9)	1 (0.6)
Dysgeusia	2 (20.0)	0	1 (9.1)	0	NR	NR
Dyspnea	2 (20.0)	0	1 (9.1)	0	17 (10.3)	1 (0.6)
Bone pain	2 (20.0)	1 (10.0)	0	0	29 (17.6)	6 (3.6)
Hypocalcemia	2 (20.0)	0	1 (9.1)	0	NR	NR
Pyrexia	2 (20.0)	0	1 (9.1)	1 (9.1)	45 (27.3)	1 (0.6)
Pain in extremity	2 (20.0)	0	0	0	21 (12.7)	1 (0.6)
General physical health deterioration	2 (20.0)	1 (10.0)	0	0	NR	NR
Blood creatinine increased	2 (20.0)	0	0	0	NR	NR
Confusional state	2 (20.0)	0	0	0	NR	NR

[a]Any grade TEAEs occurring in ≥20% of patients in the higher SUD cohorts. [b]Hypogammaglobulinemia as determined by means of AE reporting. ALT, alanine aminotransferase; NR, not reported; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

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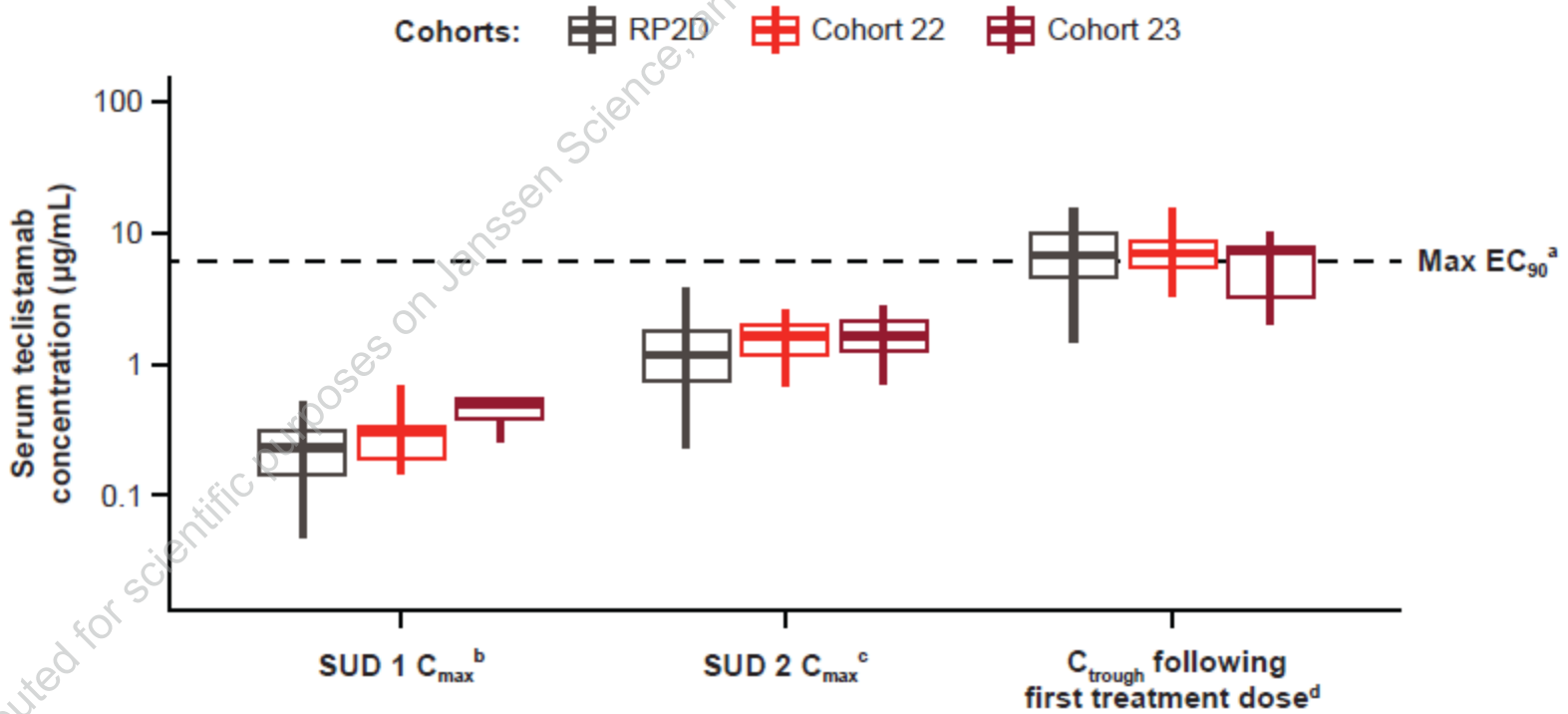
Pharmacokinetics

- Median maximal serum teclistamab concentrations following SUD administration were slightly higher in the higher SUD cohorts compared with the RP2D cohort[3]
- Trough concentrations of patients primed with higher SUDs were comparable to that observed with the RP2D[3] after the treatment dose of 1.5 mg/kg (**Figure 4**)

Figure 4: Serum teclistamab concentrations



[a]From an ex vivo cytotoxicity assay using bone marrow mononuclear cells from patients with multiple myeloma. [b]RP2D: n=40; Cohort 22: n=9; Cohort 23: n=9. [c]RP2D: n=165; Cohort 22: n=9; Cohort 23: n=9. [d]RP2D: n=150; Cohort 22: n=9; Cohort 23: n=9. C_{max}, maximal concentration; C_{trough}, trough concentration; Max EC_{90}, maximum 90% effective concentration.

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Key Takeaway and Conclusions

Key Takeaway

- Higher teclistamab SUDs resulted in similar overall CRS incidence and grades compared with the RP2D, but with a notable earlier occurrence of CRS events

Conclusions

- Rates of CRS in the higher SUD cohorts were similar to those with the RP2D; all events were grade 1/2, most occurred after the first SUD, and none led to treatment discontinuation
- The overall safety profiles were similar to that of the RP2D
- Higher SUDs resulted in slightly higher teclistamab serum concentrations during step up relative to the RP2D but did not have an impact on teclistamab exposure following treatment doses
- Alternate SUDs may shorten the time needed for CRS monitoring and potentially facilitate the earlier transition to outpatient monitoring

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Acknowledgments and References

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