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TECLISTAMAB, A B-CELL MATURATION ANTIGEN (BCMA) X CD3 BISPECIFIC ANTIBODY, IN RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA (RRMM): UPDATED PHASE 1 RESULTS

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INTRODUCTION

- Prognosis is poor for patients with RRMM who progress on available classes of therapies, with ORR ~30%, mPFS of ~3 months, and median overall survival between 6–11 months[1]
- Teclistamab (JNJ-64007957) is a humanized BCMA × CD3 bispecific IgG-4 antibody that redirects CD3+ T cells to BCMA-expressing myeloma cells
- Teclistamab induces T cell-mediated killing of myeloma cells from heavily-treated patients and in xenograft models[2-4]
- Updated results from an ongoing phase 1 study of teclistamab administered IV or SC in patients with RRMM (NCT03145181) are presented here[5]

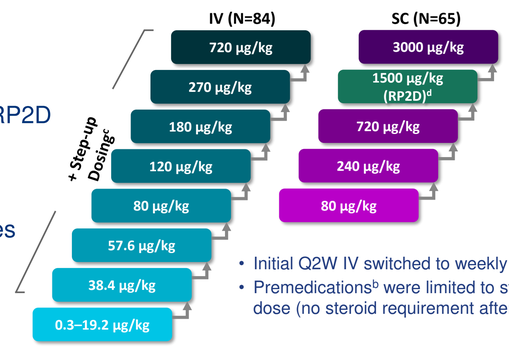
METHODS

Primary objectives

- Part 1: Identify RP2D
- Part 2: Safety and tolerability at proposed RP2D
- Antitumor activity, PK, pharmacodynamics

Key eligibility criteria

- Adults with measurable MM
- RR or intolerant to established MM therapies
- Hb ≥8 g/dL, platelets ≥75×10^9/L,[a] ANC ≥1.0×10^9/L
- No prior BCMA-targeted therapy



- Initial Q2W IV switched to weekly IV or SC ± step-up dosing
- Premedications[b] were limited to step-up doses and first full dose (no steroid requirement after first full dose)

ANC, absolute neutrophil count; BCMA, B-cell maturation antitgen; Hb, hemoglobin; IV, intravenous; MM, multiple myeloma; PK, pharmacokinetics; Q2W, once every 2 weeks; RP2D, recommended phase 2 dose; RR, relapsed/refractory; SC, subcutaneous;Tec, teclistamab. [a]≥50×10^9/L for patients with ≥50% bone marrow plasma cells. [b]Glucocorticoid, antihistamine, and antipyretic. [c]1-3 step-up doses given within 1 week before a full dose. [d]With 60 and 300 µg/kg step-up doses.

RESULTS

Table 1. Demographics and Baseline Characteristics

Characteristic, n (%)	Total N=149	1500 µg/kg SC (RP2D) n=33
Median age (range), years	63 (24–84)	61 (39–84)
≥70 years	33 (22)	8 (24)
Male	81 (54)	22 (67)
Bone marrow plasma cells ≥60%[a]	34 (25)	3 (10)
Extramedullary plasmacytomas ≥1	18 (12)	6 (18)
Median years since diagnosis (range)	7 (1–26)	6 (1–12)
High-risk cytogenetics[b]	36 (32)	8 (38)
Prior transplantation	127 (85)	28 (85)
Median prior lines of therapy (range)	6 (2–14)	5 (2–11)
Triple-class[c] exposed	143 (96)	33 (100)
Penta-drug[d] exposed	102 (69)	21 (64)
Refractory status		
Carfilzomib	99 (66)	22 (67)
Pomalidomide	115 (77)	24 (73)
Anti-CD38[e]	138 (93)	32 (97)
Triple-class[c] refractory	121 (81)	28 (85)
Penta-drug[d] refractory	58 (39)	12 (36)
Refractory to last line of therapy[f]	136 (91)	29 (88)

26 Oct 2020 data cutoff. RP2D, recommended phase 2 dose. [a]Percentages calculated from n=138 for total and n=29 at RP2D. [b]Based on FISH or karyotype testing and includes del(17p), t(4;14), t(14;16); n=111 for total, n=12 for RP2D. [c]Proteasome inhibitor (PI), immunomodulatory drug (IMiD), and anti-CD38, [d]2 PIs, 2 IMiDs, and an anti-CD38. [e]Includes daratumumab or isatuximab. [f]Progressive disease on or within 60 days of last regimen.

Table 2. Adverse Events

AEs (≥20% of Total) n (%)	Total N=149		1500 µg/kg SC (RP2D) n=33	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic				
Neutropenia	85 (57)	69 (46)	17 (52)	11 (33)
Anemia	82 (55)	47 (32)	13 (39)	7 (21)
Thrombocytopenia	59 (40)	32 (22)	11 (33)	4 (12)
Leukopenia	41 (28)	21 (14)	11 (33)	6 (18)
Nonhematologic				
CRS	82 (55)	0	21 (64)	0
Pyrexia	45 (30)	0	6 (18)	0
Diarrhea	34 (23)	1 (1)	4 (12)	0
Nausea	33 (22)	1 (1)	6 (18)	0
Fatigue	33 (22)	2 (1)	8 (24)	1 (3)
Headache	32 (22)	0	4 (12)	0
Cough	31 (21)	3 (2)	1 (3)	0

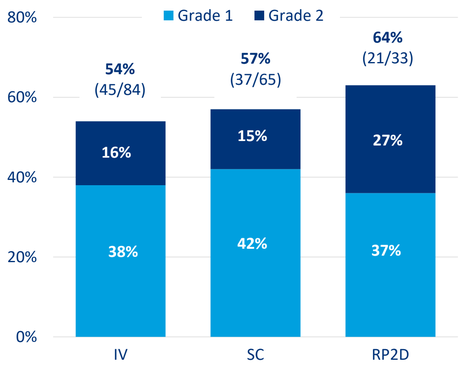
AE, adverse event; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; Gr, grade; IV, intravenous; RP2D, recommended phase 2 dose; SC, subcutaneous; TRAE, treatment-related adverse event.

- **2 DLTs across all doses; no DLT at RP2D**
  - Gr 4 delirium (20 µg/kg IV step-up dose)
  - Gr 4 thrombocytopenia (180 µg/kg IV)
- **Maximum tolerated dose not reached**
- **Infections in 52% of patients; 27% at RP2D**
  - 15% had Gr ≥3 infections across all doses
  - 6% had Gr ≥3 infections at RP2D
- **Neurotoxicity in 7 patients (5%); 1 (3%) at RP2D**
  - 2 Gr ≥3 events with IV dosing; none with SC
- **Injection-site reactions in 32% of patients; 36% at RP2D (all Gr 1–2)**
- **1 TRAE leading to death; none at RP2D**
  - Gr 5 pneumonia at 80 µg/kg IV

Table 3. Cytokine Release Syndrome

Parameter, n (%)	Total (N=149)	IV (n=84)	SC (n=65)
Patients with CRS	82 (55)	45 (54)	37 (57)
Median time to CRS onset[a] (range), days	2 (1–5)	1 (1–3)	2 (1–5)
Median duration of CRS (range), days	2 (1–8)	1 (1–7)	2 (1–8)
Patients with supportive measures to treat CRS[b]	76 (51)	43 (51)	33 (51)
Tocilizumab	35 (23)	22 (26)	13 (20)
Steroids	19 (13)	15 (18)	4 (6)
Low flow oxygen	9 (6)	6 (7)	3 (5)
Single low-dose vasopressor	1 (1)	1 (1)	0

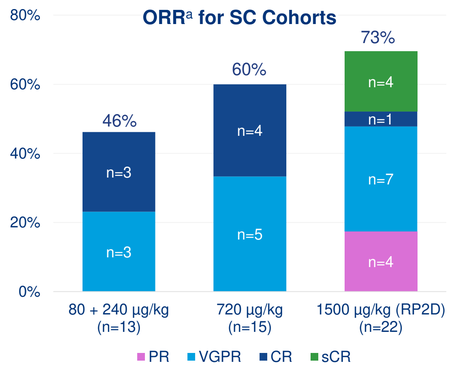
Maximum CRS Grade by Dose Groups[c]



CRS, cytokine release syndrome; IV, intravenous; SC, subcutaneous. [a]Day 1 was day of most recent dose. [b]A patient could receive >1 supportive therapies. [c]Graded according to Lee et al. *Blood* 2014;124:188

- No treatment discontinuations due to CRS, and CRS was generally confined to step-up and first full doses
- Step-up dosing was implemented to mitigate risk of severe CRS; no grade ≥3 CRS events were observed

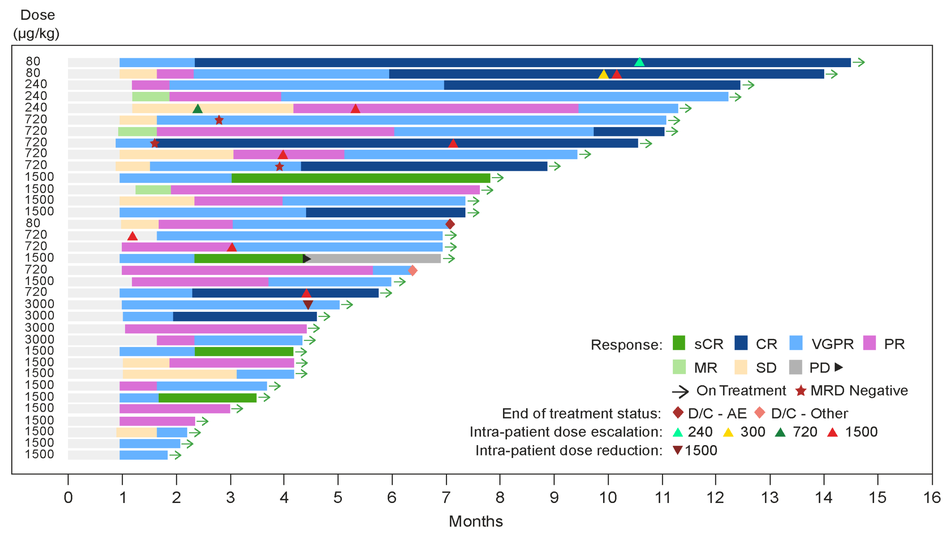
Figure 1. Overall Response Rate



- At the RP2D of 1500 µg/kg SC:
  - Median time to first confirmed response was 1 month (0.3–3)
  - 14/20 (70%) triple-class refractory patients responded
  - 6/8 (75%) penta-drug refractory patients responded
- Most active doses were 270–720 µg/kg IV and 720–3000[b] µg/kg SC
  - ORR[a] at these doses was 69% (47/68)
  - ≥VGPR was 59%; ≥CR was 26%
  - 67% (18/27) ORR in IV cohorts and 71% (29/41) ORR in SC cohorts
- Of 11 evaluable patients across all IV and SC doses so far, 8 had MRD-neg CR at 10^{-6} and 1 at 10^{-5} sensitivity[c]

CR, complete response; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response. [a]Among response-evaluable patients who had ≥1 study treatment and ≥1 postbaseline disease evaluation; includes unconfirmed responses.[b]4/4 patients responded at 3000 µg/kg SC dose. [c]Patient with MRD-neg CR at 10^{-5} was indeterminate at 10^{-6} due to insufficient cell counts.

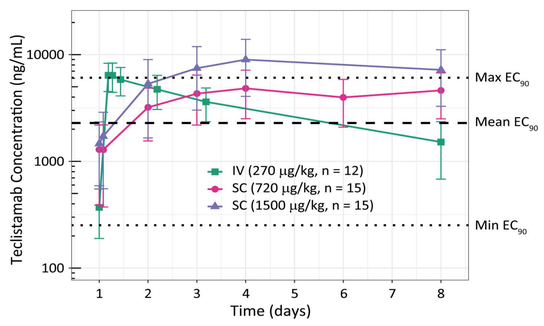
Figure 2. Duration of Response



AE, adverse events; CR, complete response; D/C, discontinued; mF/U, median follow-up; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

- Responses were durable and deepened over time
- Among responders treated at the RP2D, 15/16 (94%) are alive and progression-free after median follow-up of 3.9 months (1.7–7.4)
- Among responders in SC cohorts, 32/35 (91%) remain on treatment with ongoing responses after median follow-up of 6.5 months (1.7–14)
- Among responders treated at the most active IV and SC doses, 44/47 (94%) remain on treatment with ongoing responses after median follow-up of 6.5 months (1.7–14)
- 5/5 evaluable patients across IV and SC cohorts showed sustained MRD negativity

Figure 3. Pharmacokinetics Support RP2D of 1500 µg/kg SC

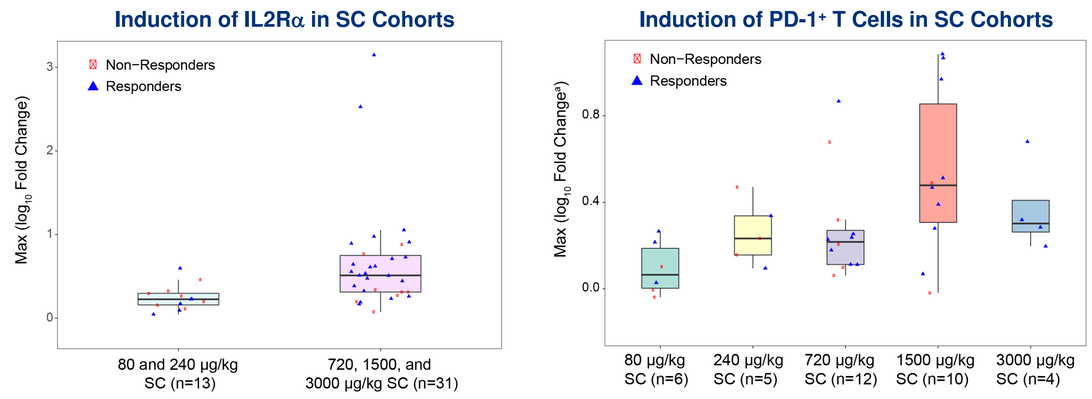


SC Dosing:

- Exposure was dose proportional following the first treatment dose (80–3000 µg/kg SC)
- 1500 µg/kg SC has low peak/trough ratio and maintains exposure over the max EC$_{90}$
- Opportunity for less frequent SC dosing
- Immunogenicity: 2 of 107 patients (2%) had antidrug antibodies of low titer
- From preliminary population PK analysis, soluble BCMA does not appear to impact teclistamab exposure

EC$_{90}$ values from ex vivo cytotoxicity assay using bone marrow mononuclear cells from patients with multiple myeloma. BCMA, B-cell maturation antigen; EC$_{90}$, 90% effective concentration; PK, pharmacokinetic; RP2D, recommended phase 2 dose; SC, subcutaneous.

Figure 4. Pharmacodynamics Support RP2D of 1500 µg/kg SC



26 Oct 2020 data cutoff. IL, interleukin; IL2Rα, interleukin-2 receptor subunit alpha; PD-1, programmed cell death protein-1; RP2D, recommended phase 2 dose; SC, subcutaneous; . [a]Fold change of total T cells that were PD-1+.

- Highest induction of cytokines (IL-10, IL2Rα, IL-6) occurred at doses ≥720 mg/kg SC
- PD-1+ T cells were induced in the periphery, indicating T cell activation
- Consistent T cell activation was observed at the RP2D (1500 µg/kg SC)

CONCLUSIONS

- **Teclistamab was well-tolerated at the RP2D of 1500 µg/kg SC**
  - Maximum tolerated dose has not been identified
  - All CRS events were grade 1–2 and generally confined to step-up and first full doses
  - One grade 1 reversible neurotoxicity at RP2D
  - No new safety signals were identified
- **High response rate observed at the RP2D**
  - ORR at the RP2D (1500 µg/kg SC) was 73%; ≥VGPR was 55% and ≥CR was 23%
    - 14/20 (70%) triple-class refractory patients responded; 6/8 (75%) penta-drug refractory patients responded
  - Responses appeared durable and deepened over time
  - At median 3.9-month follow-up, 15/16 (94%) responders are alive and progression-free
- **Selection of the 1500 µg/kg SC RP2D was supported by promising safety, efficacy, PK, and pharmacodynamics**
- **Teclistamab, an off-the-shelf therapy targeting BCMA, showed promising efficacy in heavily-pretreated patients with RRMM**
  - Phase 1 of the study is ongoing, and phase 2 expansion study has started

REFERENCES

1. Ghandi *Leukemia* 2019;33:2266. 2. Labrijn AF *PNAS*. 2013;110:5145. 3. Frerichs KA *Clin Cancer Res*. 2020;26:2203. 4. Pillarisetti K *Blood Adv*. 2020;4:4538. 5. Usmani SZ. *JCO* 2020:38 (Suppl) Abstract 100.

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