The 7th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

TALQUETAMAB, A G PROTEIN-COUPLED RECEPTOR FAMILY C GROUP 5 MEMBER D (GPRC5D) X CD3 BISPECIFIC ANTIBODY, IN RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA (RRMM): RESULTS FROM AN ONGOING PHASE 1 STUDY

Paula Rodriguez-Otero[1], Jesus G. Berdeja[2], Albert Oriol[3], Niels W.C.J. van de Donk[4], Ajai Chari[5], Elham Askari[6], Maria-Victoria Mateos[7], Monique C. Minnema[8], Raluca Verona[9], Suzette Girgis[9], Thomas Prior[9], Brandi W. Hilder[9], Jeffery Russell[9], Jenna D. Goldberg[9], Amrita Krishnan[10]

[1]Clínica Universidad de Navarra, Navarra, Spain; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Institut Català d'Oncologia and Institut Josep Carreras. Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [4]Amsterdam University Medical Center, Location VU University Medical Center, Amsterdam, The Netherlands; [5]Mount Sinai Medical Center, New York, NY, USA; [6]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [7]Hospital Clínico Universitario de Salamanca, Salamanca, Spain; [8]University Medical Center Utrecht, Utrecht, The Netherlands; [9]Janssen R&D, Spring House, PA, USA; [10]City of Hope, Duarte, CA, USA

INTRODUCTION

- Orphan G protein-coupled receptor of unknown function with limited expression in healthy human tissue[1-2]
- GPRC5D is highly expressed in myeloma cells and associated with poor prognostic factors in multiple myeloma (MM)[1-3]
- Talquetamab is a first-in-class DuoBody® IgG4 PAA antibody that binds to both GPRC5D and CD3 to redirect T cells to GPRC5D-expressing myeloma cells to mediate cell killing
- Antitumor activity was demonstrated in primary myeloma cells and xenograft models of MM[1-2, 4]
- A first-in-human phase 1 study is ongoing to evaluate talquetamab in relapsed/refractory MM (NCT03399799)

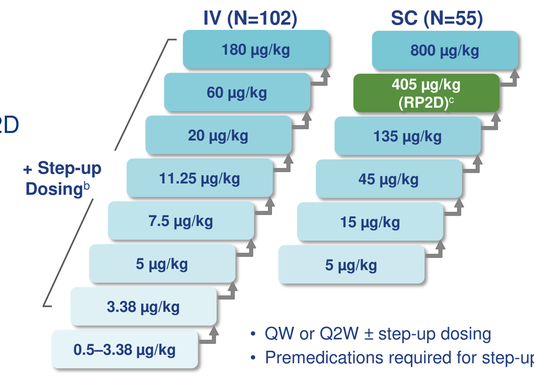
METHODS

Primary objectives

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

Key eligibility criteria

- 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
- Prior BCMA-targeted therapy allowed



- QW or Q2W ± step-up dosing
- Premedications required for step-up and first full dose

24 Oct 2020 data cut. [a]Glucocorticoid, antihistamine, and antipyretic. [b]1 to 3 step-up doses. [c]With 10 and 60 µg/kg step-up doses. ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; Hb, hemoglobin; IV, intravenous; PK, pharmacokinetics; QW, weekly; Q2W, every 2 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous

RESULTS

Table 1. Demographics and Baseline Characteristics

Characteristic, n (%)	Total (N=157)	405 µg/kg SC RP2D (n=19)
Median age (range), years	64 (33–80)	61 (49–80)
≥70 years	47 (30)	5 (26)
Male	89 (57)	11 (58)
Bone marrow plasma cells ≥60%[a]	31 (22)	3 (19)
Extramedullary plasmacytomas ≥1	31 (20)	7 (37)
Median years from diagnosis (range)	7 (1–27)	6 (2–20)
High-risk cytogenetics[b]	18 (13)	1 (6)
Prior transplantation	135 (86)	15 (79)
Median prior lines of therapy (range)	6 (2–20)	4.5 (2–14)
Triple-class[c] exposed	155 (99)	18 (95)
Penta-drug[d] exposed	120 (76)	13 (68)
Prior anti-BCMA therapy[e]	27 (17)	3 (16)
Refractory Status		
Carfilzomib	105 (67)	11 (58)
Pomalidomide	119 (76)	15 (79)
Anti-CD38	149 (95)	18 (95)
Triple-class[c]	128 (82)	13 (68)
Penta-drug[d]	51 (33)	4 (21)
Refractory to last line of therapy	136 (87)	15 (79)

[a]Percentages based on n=144 for total and n=16 at RP2D. [b]Based on FISH or karyotype testing and includes del(17p), t(4;14), t(14;16); denominator is n=134 for total and n=17 for RP2D. [c]Proteasome inhibitor (PI), immunomodulatory drug (IMiD), and anti-CD38, [d]2 PIs, 2 IMiDs, and anti-CD38, [e]27/157 were quad-class exposed (PI, IMiD, anti-CD38, and anti-BCMA agent) with 6 treated with BCMA chimeric antigen receptor T (CAR-T) cell therapy and 12 with non-CAR-T BCMA agent (1 patient received both). RP2D, recommended phase 2 dose; SC, subcutaneous

Table 2. Adverse Events

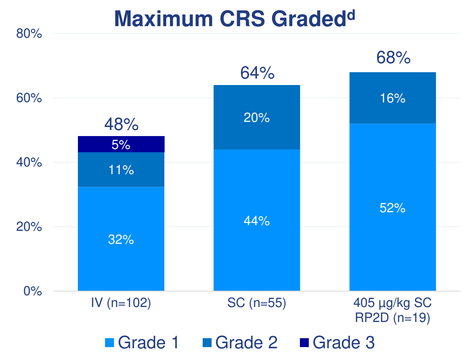
AEs (≥25% of Total)	Total (N=157) 3.6-mo (0.1–28.1) mF/U		405 µg/kg SC RP2D (n=19) 2.7-mo (0.1–6.5) mF/U	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic, n (%)				
Anemia	76 (48)	43 (27)	5 (26)	0
Neutropenia	74 (47)	48 (31)	9 (47)	8 (42)
Lymphopenia	62 (40)	57 (36)	3 (16)	3 (16)
Leukopenia	50 (32)	25 (16)	4 (21)	3 (16)
Thrombocytopenia	50 (32)	20 (13)	4 (21)	1 (5)
Nonhematologic, n (%)				
CRS	84 (54)	5 (3)	13 (68)	0
Dysgeusia	60 (38)	NA	9 (47)	NA
Fatigue	46 (29)	1 (1)	3 (16)	0
Headache	43 (27)	2 (1)	3 (16)	0
Pyrexia	42 (27)	1 (1)	2 (11)	0
Diarrhea	39 (25)	4 (3)	3 (16)	0

- **3 DLTs across all doses; no DLT at RP2D**
  - Gr 4 increased lipase (7.5 µg/kg IV)
  - Gr 3 maculopapular rash (n=2; 135 and 800 µg/kg SC)
- **Dose reductions at the RP2D were less frequent and occurred later compared with the 800 µg/kg dose**
- **Infections in 38% of patients; 16% at RP2D**
  - 8% had Gr ≥3 infections across all doses
  - No Gr ≥3 infections at RP2D
- **Neurotoxicity in 9 patients (6%); 1 (5%) at RP2D**
  - 6 (6%) with IV and 3 (6%) with SC dosing
  - 3 Gr ≥3 events with IV dosing; none with SC
  - Gr 2 encephalopathy at RP2D (resolved)
- **Injection-site reactions in 18% of patients; 21% at RP2D (all events were Gr 1–2)**
- **Skin-related AEs in 45%; 58% at RP2D (majority Gr 1–2)**
- **Nail disorders[a] in 17% of patients; 21% at RP2D**
- **No Gr 5 AEs across all doses**

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

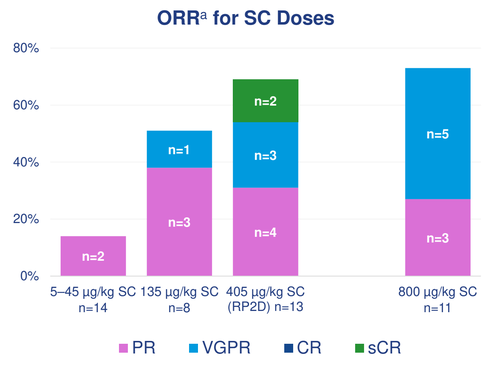
Table 3. Cytokine Release Syndrome

Parameter, n (%)	Total N=157	IV n=102	SC n=55
Patients with CRS	84 (54)	49 (48)	35 (64)
Median time to CRS onset[a] (range), days	2 (1–5)	1 (1–3)	2 (1–5)
Median duration of CRS (range), days	2 (1–9)	2 (1–9)	2 (1–7)
Patients receiving supportive treatments[b]	81 (52)	47 (46)	34 (62)
Tocilizumab	63 (40)	38 (37)	25 (46)
Steroids	13 (8)	11 (11)	2 (4)
Oxygen	12 (8)	8 (8)	4 (7)
Single low-dose vasopressor	3 (2)	2 (2)	1 (2)
Anakinra	2 (1)	1 (1)	1 (2)
Other[c]	68 (43)	44 (43)	24 (44)



[a]Day 1 was day of most recent dose. [b]Patients could receive more than 1 supportive therapy. [c]Includes fever-reducing medications, IV fluids, and other supportive care. [d]Graded according to Lee 2014 *Blood* 124(2):188. CRS, cytokine release syndrome; IV, intravenous; SC, subcutaneous

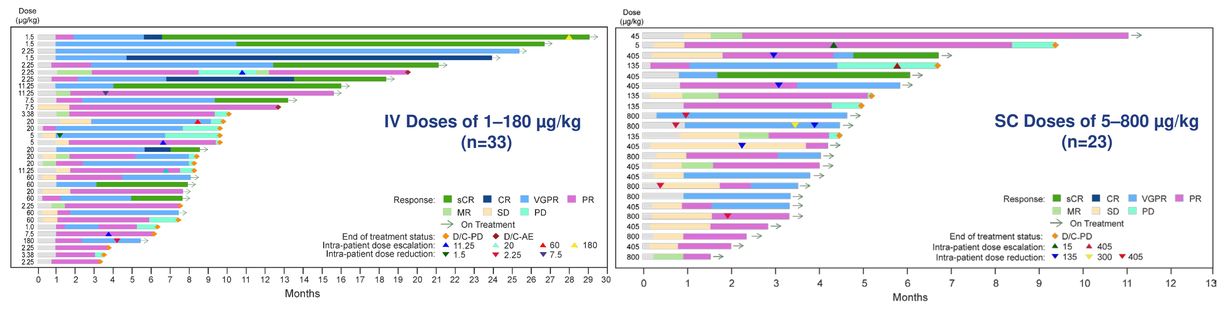
Figure 1. Overall Response Rate



- **At the RP2D of 405 µg/kg SC**
  - 69% ORR (9/13)
  - Median 3.7-month (1.7–6.5) follow-up for responders
  - Median time to first confirmed response was 1 month (1–2)
  - 67% (6/9) of triple-class refractory patients responded
  - 100% (2/2) of penta-drug refractory patients responded
- **At most active doses of 20–180 µg/kg IV and 135–800 µg/kg SC**
  - 66% ORR (33/50)
  - ≥VGPR was 42%
  - 67% ORR (12/18) in IV cohorts and 66% ORR[a] (21/32) in SC cohorts

[a]Among response-evaluable patients who had at least 1 study treatment and 1 postbaseline disease evaluation; includes unconfirmed responses. CR, complete response; IV, intravenous; ORR, overall response rate; PR, partial response; SC, subcutaneous; sCR, stringent complete response, VGPR, very good partial response

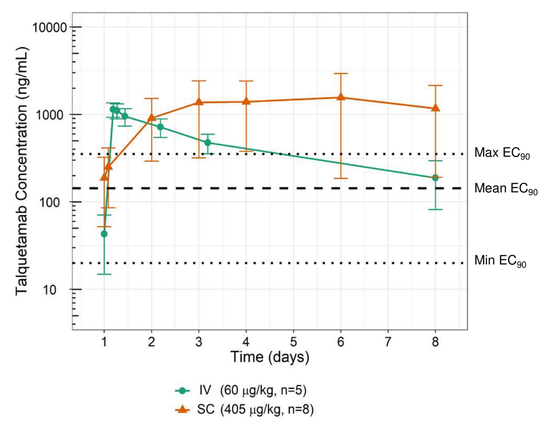
Figure 2. Duration of Response



AE, adverse event; CR, complete response; D/C, discontinued; IV, intravenous; MR, minimal response; PD, progressive disease; PR, partial response; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

- Median time to first confirmed response across all doses was 1 month (0.2–3)
- Responses were durable and deepened over time
- Data for IV cohorts are more mature
  - **Only** 1 of 6 responders at doses ≥60 µg/kg IV has progressed at median follow-up of 7.4-month (5.1–7.8)
  - None of the 17 responders at doses ≥405 µg/kg SC have progressed at median follow-up of 3.7-month (1.4–6.5)
  - In the 8 responders with duration of >12 months, all have ongoing responses, with 7 ≥CR and 3 with duration of response >2 years

Figure 3. Pharmacokinetics Support RP2D



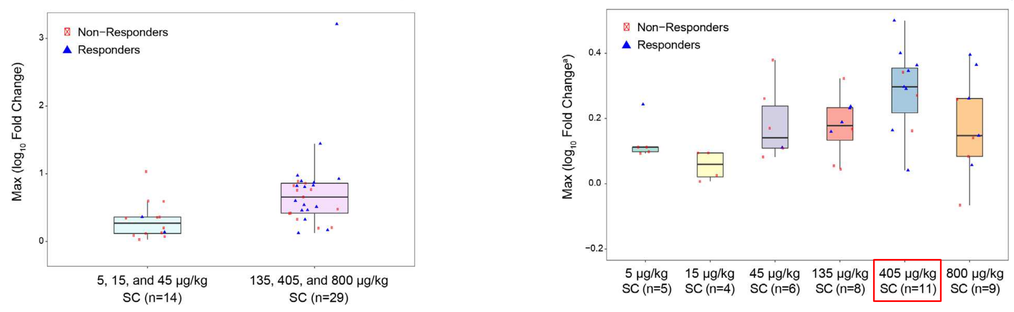
- Exposure is dose-proportional following the first dose (5–405 µg/kg SC)
- 405 µg/kg SC has lower peak/trough ratio than 60 µg/kg IV and maintains exposure over the maximum EC_{90}

Immunogenicity:

- Generally low-titer ADA in 12% of patients (11/95) for IV and 8% (3/38) for SC
- ADA did not appear to impact safety, PK, or efficacy

EC_{90} values from ex vivo cytotoxicity assay using bone marrow mononuclear cells from patients with multiple myeloma (n=6). ADA, antidrug antibody; EC_{90}, concentration at 90% of maximum effect; max, IV, intravenous; maximum; min, minimum; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SC, subcutaneous

Figure 4. Pharmacodynamics Support RP2D of 405 µg/kg SC



24 Oct 2020 data cut. Maximum induction calculated from baseline through pre-cycle 2 day 1. [a]Fold change of total T cells that were PD-1+. IL, interleukin; IL2Rα, interleukin-2 receptor subunit alpha; PD-1, programmed cell death protein-1; RP2D, recommended phase 2 dose; SC, subcutaneous

- Consistent induction of cytokines (IL-10, IL-6, IL2Rα) was observed at doses >45 µg/kg SC
- PD-1$^+$ T cells were induced in the periphery, indicative of T cell activation; consistent T cell activation observed at RP2D of 405 µg/kg SC

CONCLUSIONS

- **Talquetamab has a tolerable safety profile at the RP2D of 405 µg/kg SC**
  - Safety profile at the RP2D was generally consistent with safety at lower doses, with low incidence of infections
  - Early DLT of Gr 3 maculopapular rash and dose reductions due to certain toxicities (skin rash, oral toxicity, back pain) were observed in 4/11 patients (36%) at 800 µg/kg SC weekly
  - CRS was generally low grade with no grade ≥3 CRS with SC dosing
  - Low incidence of neurotoxicity with no grade ≥3 events with SC dosing
- **High response rate observed at the RP2D**
  - ORR was 69% (9/13) at the RP2D of 405 µg/kg SC; 39% ≥VGPR
    - Median time to first confirmed response was 1 month
    - 6/9 triple-class refractory patients responded; 2/2 penta-drug refractory patients responded
  - Responses were durable and continued to deepen over time
- **PK results indicate target exposure levels at the RP2D, and pharmacodynamic data demonstrate consistent T cell activation, cytokine production, and redistribution at the RP2D**
- **SC dosing is more convenient and may offer an opportunity for less frequent dosing**
- **Talquetamab, a first-in-class, off-the-shelf therapy targeting GPRC5D, showed encouraging efficacy in heavily-pretreated patients with RRMM**
  - Dose expansion is ongoing and phase 2 is planned

REFERENCES

[1]Smith *Sci Transl Med* 11(485):eaau7746. [2]Pillarisetti *Blood* 135(15):1232. [3]Atamaniuk *Eur J Clin Invest* 42(9):953. [4]Verkleij *HemaSphere* 3(S1):230, Poster #PF556.

https://comylive.cme-congresses.com/

Previously presented at ASH 2020