TALQUETAMAB, A G PROTEIN-COUPLED RECEPTOR FAMILY C GROUP 5 MEMBER D (GPRC5D) × CD3 BISPECIFIC ANTIBODY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): UPDATED RESULTS OF A PHASE 1, FIRST-IN-HUMAN STUDY

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Additional information can be viewed by accessing this link: https://oncologysciencehub.com/IMW2021/talquetamab/vandedonk.

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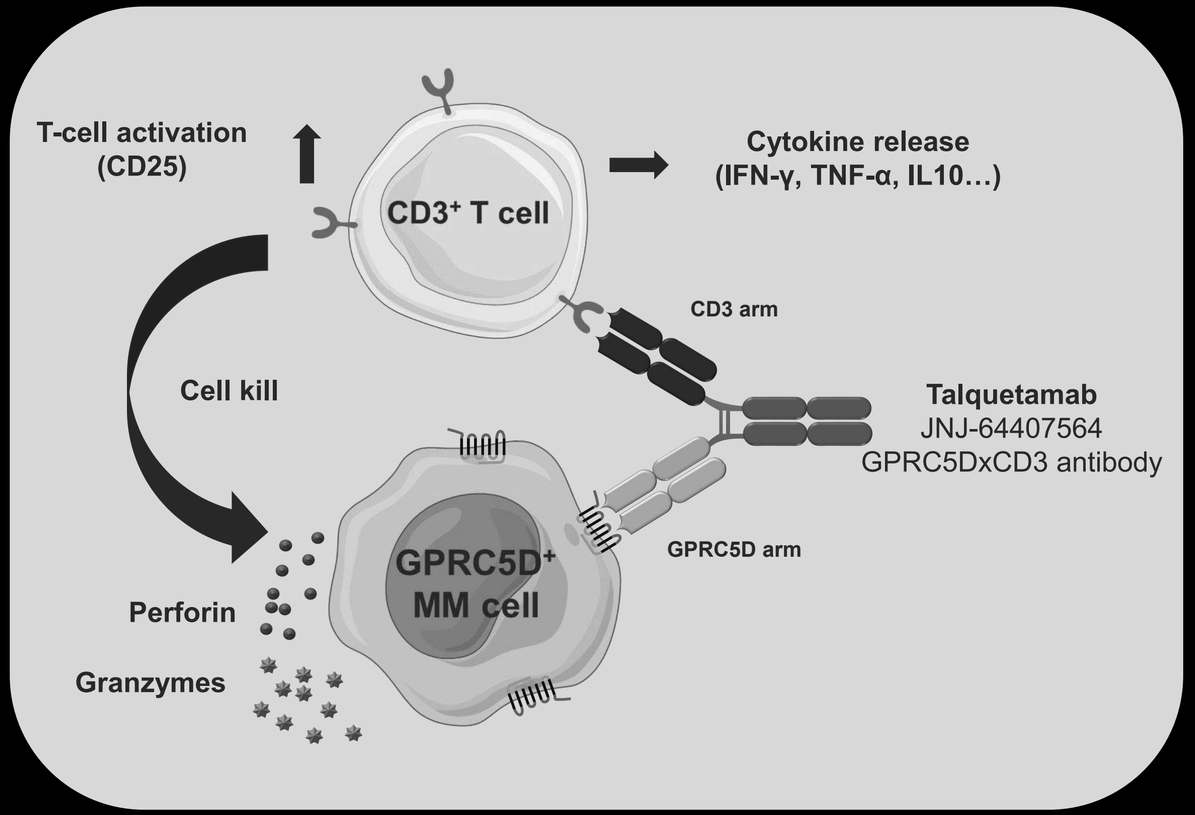
TALQUETAMAB

GPRC5D × CD3 Bispecific Antibody

- GPRC5D is a highly expressed receptor in MM, with limited expression in healthy human tissue[1-2]
- Talquetamab is a first-in-class antibody that binds to CD3 and GPRC5D to redirect T cells to kill MM cells[2-3]
- In the ongoing, phase 1, first-in-human study of talquetamab in patients with RRMM, the RP2D was identified as a QW SC dose of 400 µg/kg[a] (MonumenTAL-1; NCT03399799)[4]
- Here we present updated results of safety and efficacy of talquetamab at the RP2D, with additional patients and longer follow-up



[a]400 µg/kg was selected as final dosing concentration in phase 2 for operational convenience; In phase 1, 405 µg/kg was the RP2D.

GPRC5D, G protein-coupled receptor family C group 5 member D; IFN, interferon; IL, interleukin; MM, multiple myeloma; QW, once weekly; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; TNF, tumor necrosis factor.

1. Smith EL, et al. *Sci Transl Med* 2019;11:eaau7746. 2. Pillarisetti K, et al. *Blood* 2020;135:1232-43. 3. Verkleij CPM, et al. *Blood Adv* .2021; 5:2196-2215. 4. Chari A, et al. 62nd ASH Annual Meeting and Exposition 2020, Abstract 290.

Presented By: **Niels W.C.J. van de Donk**

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MonumenTAL-1 Study Design

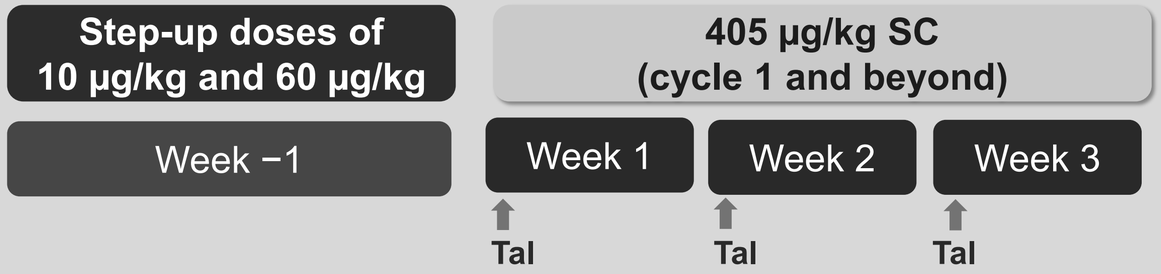
Key Objectives

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

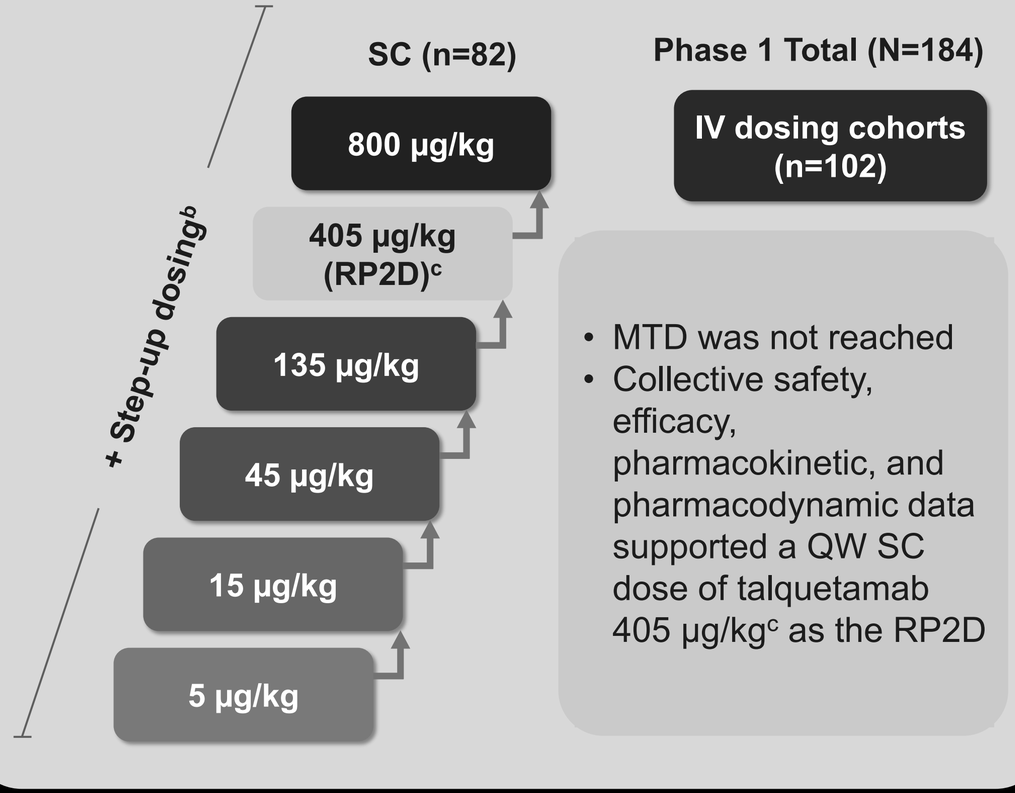
Key Eligibility Criteria

- Adults with measurable MM
- RR or intolerant to established MM therapies
- Hemoglobin ≥8 g/dL, platelets ≥50×10^9/L, ANC ≥1.0×10^9/L
- Prior BCMA-targeted therapy allowed

Dosing Schedule at RP2D



- Premedications[a] were limited to step-up doses and first full dose
  - No steroid requirement after first full dose



- The data cut-off date for these analyses was April 18, 2021

[a]Glucocorticoid, antihistamine, and antipyretic; [b]1-3 step-up doses given within 1 week before a full dose; [c]Step-up doses of 10 and 60 µg/kg.
ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; IV, intravenous; MM, multiple myeloma; MTD, maximum tolerated dose; QW, every week; RP2D, recommended phase 2 dose; RR, relapsed/refractory; SC, subcutaneous.

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Patient Demographics and Disease Characteristics

Characteristic	SC Total n=82	RP2D (405 µg/kg SC QW)[a] n=30
Age, years, median (range)	63.0 (42–80)	61.5 (46–80)
Age ≥70 years, n (%)	22 (27)	7 (23)
Sex, n (%)		
Male	47 (57)	19 (63)
Female	35 (43)	11 (37)
Years since diagnosis, median (range)	5.9 (1–20)	5.6 (2–20)
Extramedullary plasmacytomas ≥1, n (%)[b]	27 (33)	10 (33)
Bone marrow plasma cells ≥60%, n (%)[c]	13 (17)	6 (21)
ISS stage, n (%)[d]		
I	26 (32)	12 (40)
II	36 (44)	13 (43)
III	13 (16)	3 (10)
Prior transplantation, n (%)	71 (87)	27 (90)

Characteristic	SC Total n=82	RP2D (405 µg/kg SC QW)[a] n=30
Prior lines of therapy, n, median (range)	6.0 (2–17)	6.0 (2–14)
Exposure status, n (%)		
Prior BCMA therapy[e]	20 (24)	8 (27)
Triple-class[f]	81 (99)	30 (100)
Penta-drug[g]	64 (78)	24 (80)
Refractory status, n (%)		
PI[h]	69 (84)	25 (83)
Carfilzomib	54 (66)	19 (63)
IMiD[i]	76 (93)	28 (93)
Pomalidomide	67 (82)	26 (87)
Anti-CD38 mAb[j]	77 (94)	30 (100)
BCMA[e]	14 (17)	5 (16)
Triple-class[f]	62 (76)	23 (77)
Penta-drug[g]	23 (28)	6 (20)
To last line of therapy	69 (84)	26 (87)

[a]Step-up doses of 10 µg/kg and 60 µg/kg; [b]Soft-tissue component of a bone-based plasmacytoma not included; [c]Percentages calculated from n=76 for SC total and n=29 at RP2D; [d]Percentages calculated from n=66 for SC total and n=27 at RP2D; [e]BCMA CAR-T therapy or BCMA non-CAR-T therapy; [f]≥1 PI, ≥1 IMiD, and 1 anti-CD38 mAb; [g]≥2 PI, ≥2 IMiD, and 1 anti-CD38 mAb; [h]Bortezomib, carfilzomib, and/or ixazomib; [i]Thalidomide, lenalidomide, and/or pomalidomide; [j]Daratumumab and/or isatuximab.
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

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Safety Profile

AE (≥20% of total SC), n (%)	SC Total n=82		RP2D (405 µg/kg SC QW)[a] n=30	
	Any grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	47 (57)	40 (49)	20 (67)	18 (60)
Anemia	37 (45)	23 (28)	17 (57)	8 (27)
Thrombocytopenia	23 (28)	15 (18)	10 (33)	6 (20)
Leukopenia	21 (26)	16 (20)	11 (37)	8 (27)
Lymphopenia	19 (23)	19 (23)	9 (30)	9 (30)
Nonhematologic				
CRS	55 (67)	1 (1)	22 (73)	1 (2)
Dysgeusia	38 (46)	NA	18 (60)	NA
Fatigue	26 (32)	0	9 (30)	0
Pyrexia	23 (28)	1 (1)	7 (23)	1 (2)
Dry mouth	22 (27)	0	8 (27)	0
Dysphagia	21 (26)	0	11 (37)	0
Headache	19 (23)	1 (1)	7 (23)	0
Diarrhea	18 (22)	0	7 (23)	0
Nausea	18 (22)	0	7 (23)	0

[a]Step-up doses of 10 µg/kg and 60 µg/kg; [b]Includes skin exfoliation, pruritis, rash, and nail disorders; [c]Includes nail disorders, onychomadesis, and nail dystrophy.
AE, adverse event, CRS, cytokine release syndrome; DLT, dose-limiting toxicity; NA, not applicable; RP2D, recommended phase 2 dose; SC, subcutaneous.

- Talquetamab has a tolerable safety profile at the RP2D of 405 µg/kg SC
  - No DLTs at the RP2D
  - Cytopenias mostly confined to step-up doses and cycles 1/2
  - Neutropenias generally resolved within a week and were limited to cycles 1/2
- Infections in 37% of SC and RP2D patients (grade 3/4: 9% for SC total, 3% for RP2D)
- Neurotoxicities (all grade 1/2) in 4 patients with SC dosing; 2 patients (7%) at RP2D
- Injection-site reactions in 17% of SC patients (including RP2D) were mild and manageable (all grade 1/2)
- Skin-related AEs[b] in 67% of SC patients; 77% at RP2D (majority grade 1/2)
  - Nail disorders[c] in 21% of patients; 27% at RP2D
- No deaths due to AEs at the RP2D

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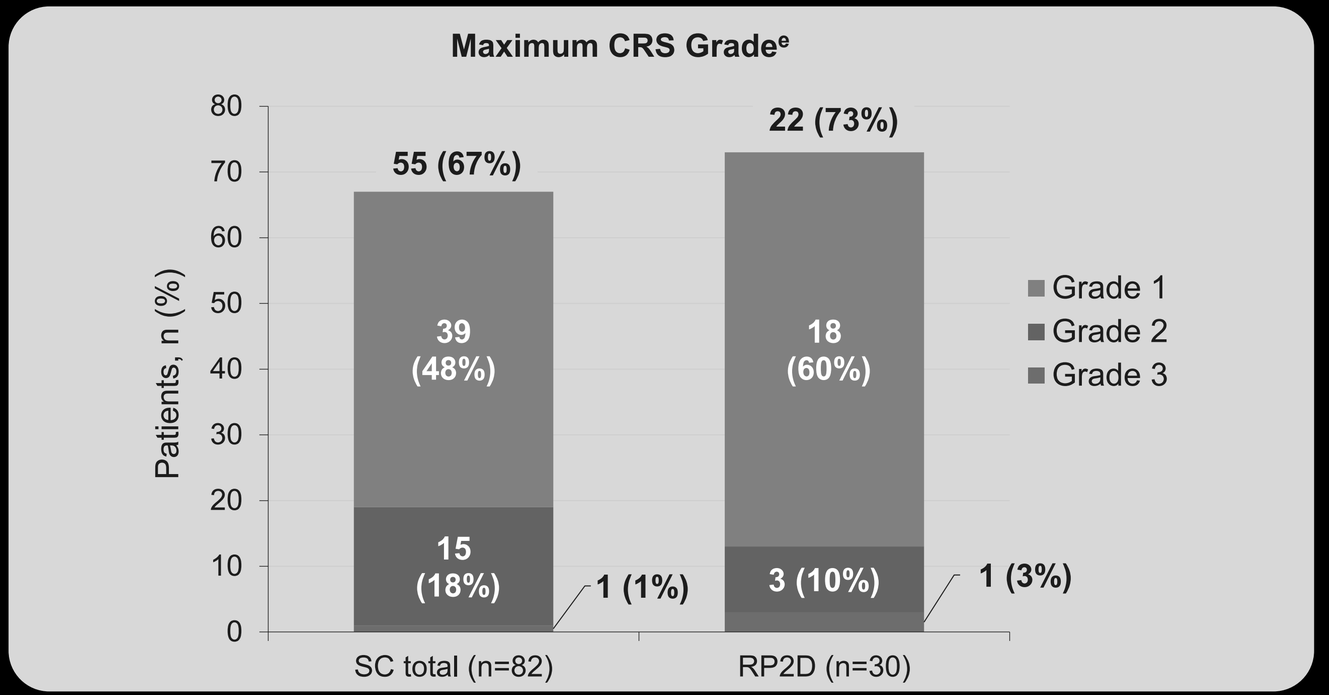
Cytokine Release Syndrome

Parameter	SC Total n=82	RP2D (405 µg/kg SC QW)[a] n=30
Patients with CRS, n (%)	55 (67)	22 (73)
Time to onset, days,[b] median (range)	2 (1–22)	2 (1–22)
Duration, days, median (range)	2 (1–7)	2 (1–3)
Supportive measures, n (%)[c]	55 (67)	22 (73)
Tocilizumab[d]	43 (52)	18 (60)
Steroids	5 (6)	1 (3)
Low-flow oxygen by nasal cannula	6 (7)	1 (3)
Vasopressor	2 (2)	1 (3)



- CRS was generally confined to step-up and first full doses
- Across all SC cohorts, CRS was limited to grade 1/2 in all patients, with the exception of 1 patient with grade 3 CRS
  - Majority of patients only had 1 dose of tocilizumab as a supportive measure for CRS

[a]Step-up doses of 10 µg/kg and 60 µg/kg; [b]Relative to the most recent dose; [c]A patient could receive >1 supportive therapy; [d]Tocilizumab was allowed for all CRS events; [e]Graded according to Lee et al. *Blood* 2014;124:188.
CRS, cytokine release syndrome; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

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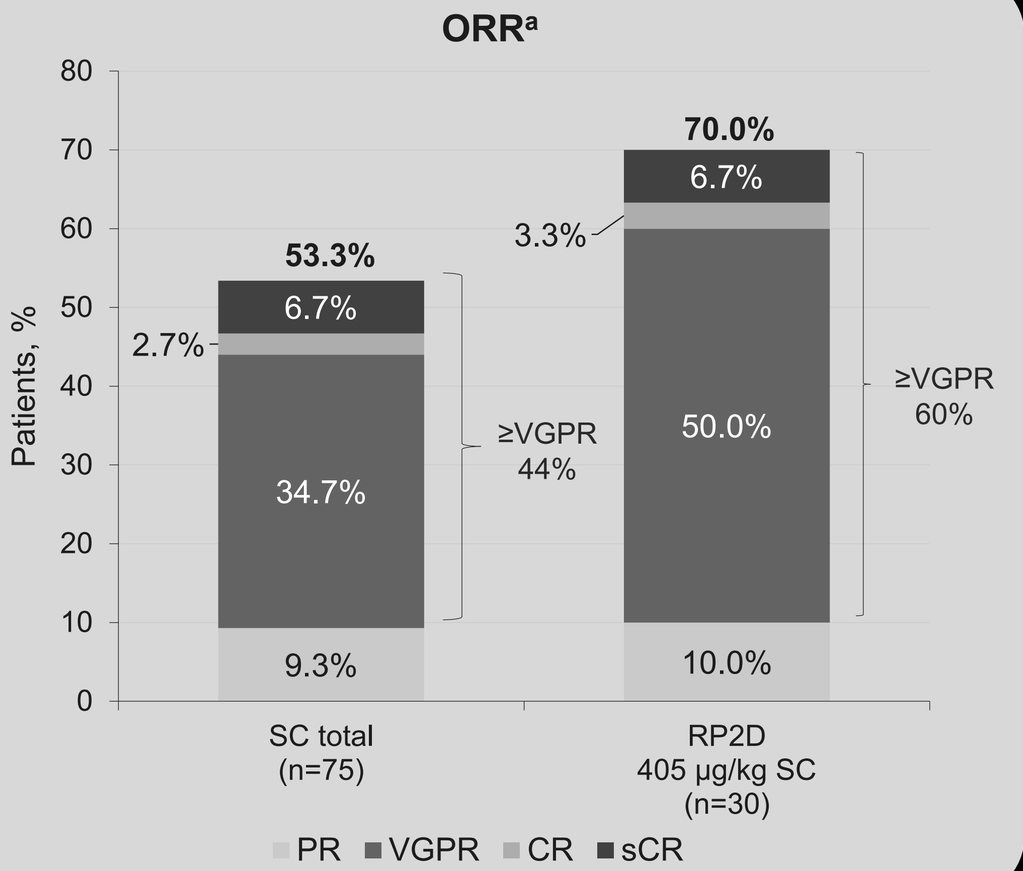
Overall Response Rate



- The RP2D of 405 µg/kg SC QW has been administered to 30 patients with a median follow-up of 6.3 months (range: 1.4–12.0) for responders
- At the RP2D:
  - 70.0% ORR (21/30)
  - Median time to first confirmed response was 1 month (range: 0.2–3.8)
  - 65.2% (15/23) of triple-refractory patients responded
  - 83.3% (5/6) of penta-refractory patients responded
- Of 6 evaluable patients across IV and SC cohorts, 4 had MRD-negative CR/sCR at 10^{-6}, including 1 patient in RP2D cohort
  - MRD negativity was sustained 7 months post CR in 1 evaluable patient

[a]Investigator assessment of evaluable patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation per 2011 International Myeloma Working Group response criteria; includes unconfirmed response.
CR, complete response; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

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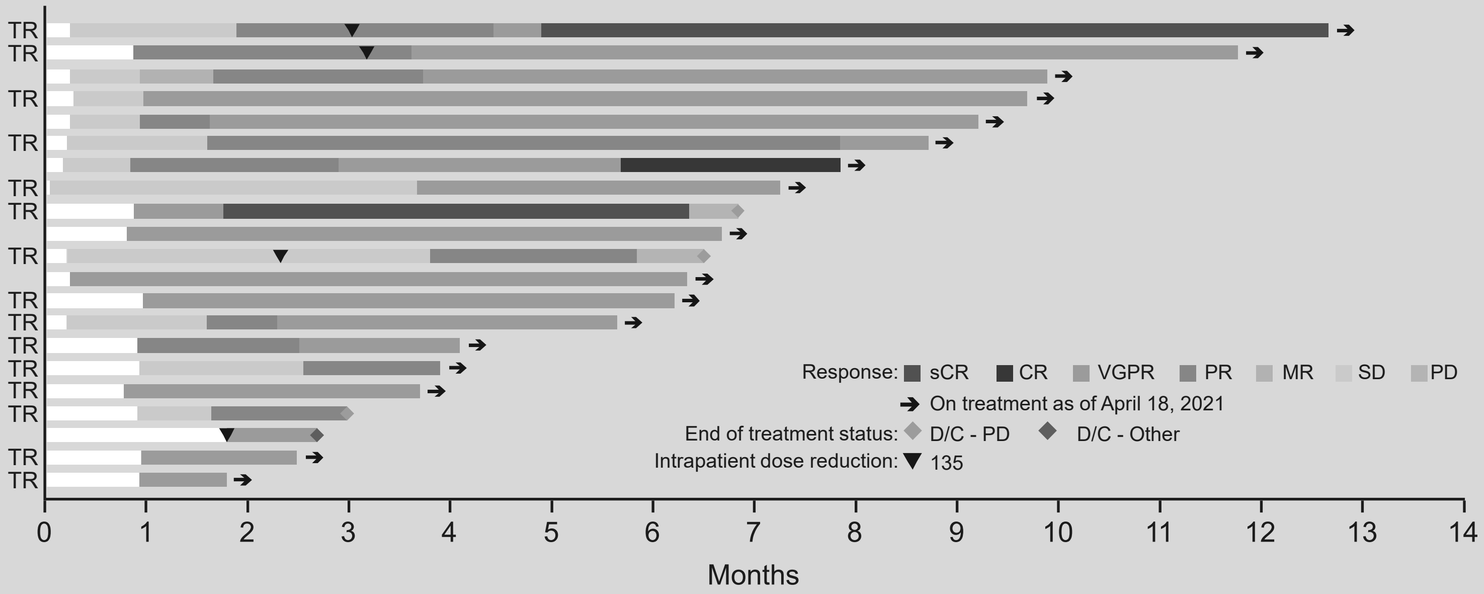
Duration of Response



- Responses were durable and deepened over time
- At the RP2D of 405 µg/kg SC QW:
  - Median duration of response was not reached
  - 17/21 responders (81%) were continuing on treatment, after median follow-up of 6.3 months (range: 1.4–12.2)
- Data from IV cohorts (not shown) were more mature
  - Even at subtherapeutic doses, responses are ongoing at 22+ months in patients with longer follow-up

CR, complete response; D/C, discontinued; IV, intravenous; MR, minimal response; PD, progressive disease; PR, partial response; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; TR, triple-class refractory; VGPR, very good partial response.

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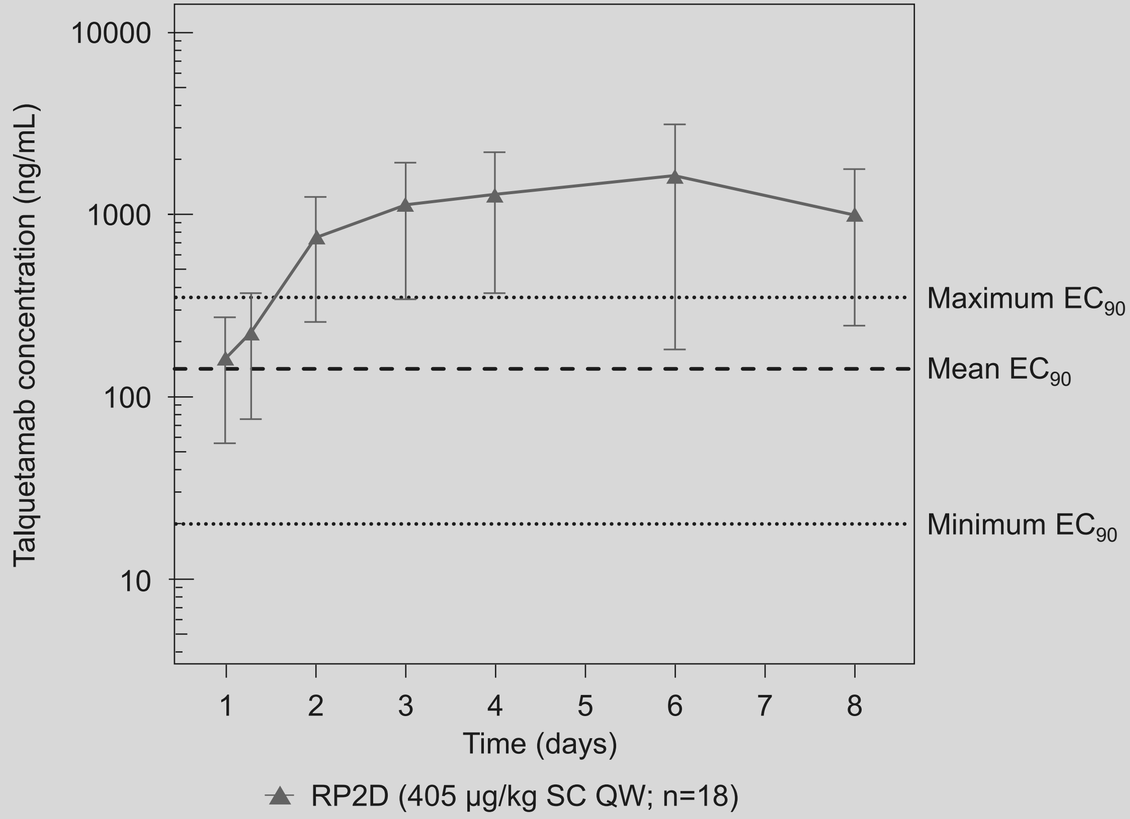
Pharmacokinetics

Pharmacokinetic Profile Following the First 405 µg/kg SC Dose



- 405 µg/kg SC has low peak/trough ratio and maintains exposure over the maximum EC_{90}[a]
- Immunogenicity
  - 6 of 50 patients (12%) treated with talquetamab SC had antidrug antibodies, generally of low titer
  - Antidrug antibodies did not appear to impact safety, pharmacokinetics, or efficacy

[a]EC90 was experimentally determined from an ex vivo cytotoxicity assay
EC_{90}, 90% effective concentration; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

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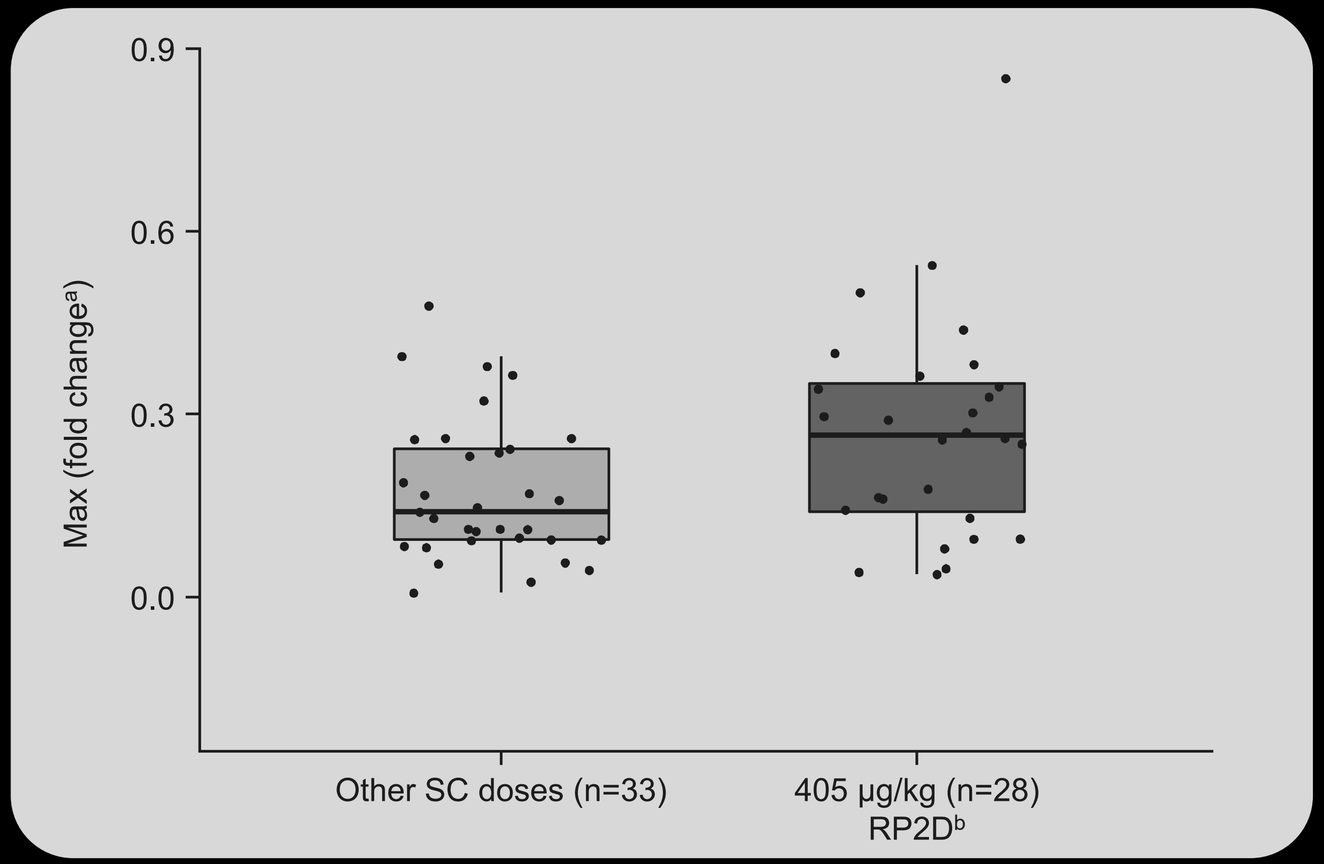
Pharmacodynamics

Induction of PD-1–Positive T Cells With SC Dosing



- Post talquetamab administration, PD-1–positive T cells were induced in the periphery, indicative of T cell activation
  - Consistent induction of PD-1+ T cells is observed in RP2D cohorts
- Consistent induction of cytokines (ie, IL-10, IL-6, IL-2Rα) is observed at doses >45 µg/kg SC

[a]Fold change of total T cells that were PD-1 positive; [b]Step-up doses of 10 µg/kg and 60 µg/kg.
IL, interleukin; IL-2Rα, interleukin-2 receptor subunit alpha; PD-1, programmed cell death protein-1; RP2D, recommended phase 2 dose; SC, subcutaneous.

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Conclusions

- Talquetamab is an off-the-shelf T-cell redirecting, GPRC5D targeting agent that requires limited steroid use and has a manageable safety profile at a dose of 405 µg/kg SC QW
- Additional patients and longer follow-up support the RP2D
  - A high response rate (70% ORR) was observed
  - High response rate was maintained in triple-refractory and penta-refractory patients (65% and 84%, respectively)
  - Responses were durable and continued to deepen over time
  - Pharmacokinetic and pharmacodynamic data continue to support the RP2D
- Talquetamab showed encouraging efficacy in heavily pretreated patients with RRMM
  - A phase 2 expansion study of talquetamab at the RP2D[a] is in progress (NCT04634552)

[a]400 µg/kg selected as final dosing concentration in phase 2 for operational convenience.
GPCR5D, G protein–coupled receptor family C group 5 member D; ORR, overall response rate; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; QW, weekly.

Acknowledgments

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