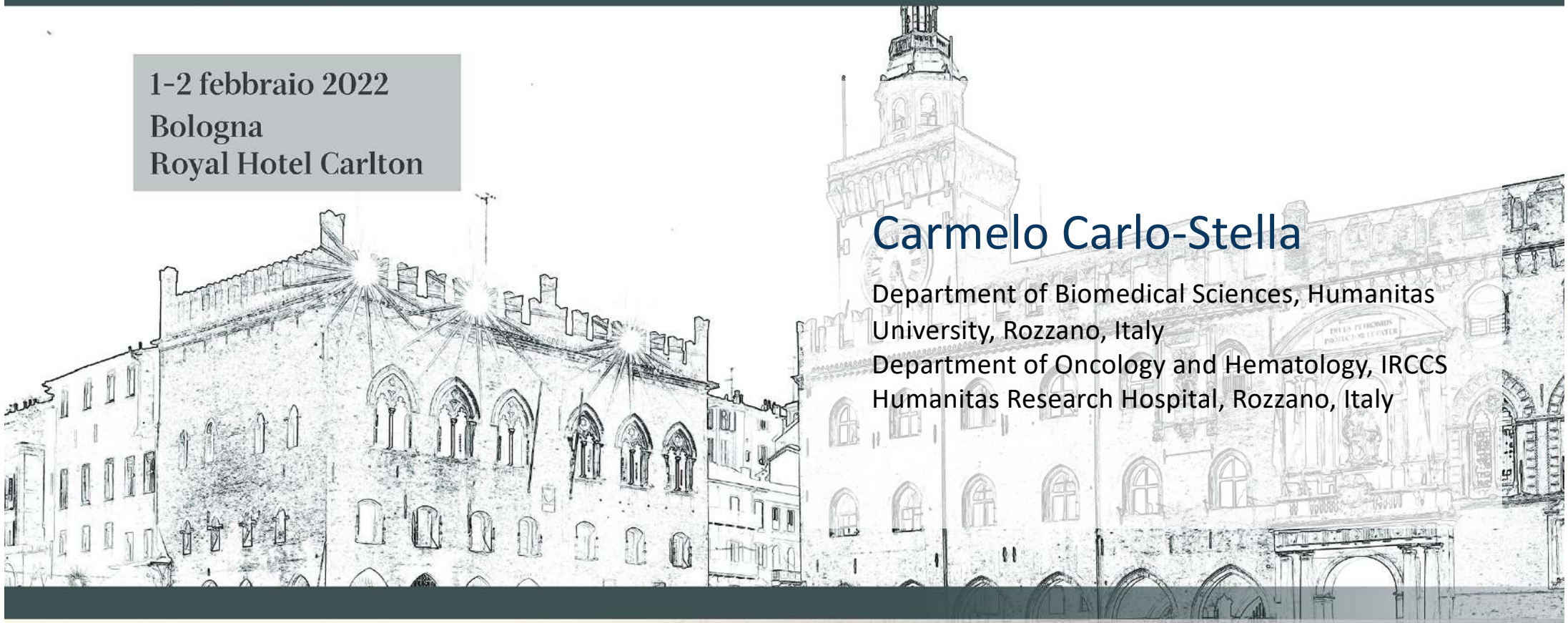
Highlights from IMW 2021



1-2 febbraio 2022
Bologna
Royal Hotel Carlton

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Disclosures of Carmelo Carlo-Stella

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi	X		X			X	
ADC Therapeutics	X		X			X	
Karyopharm Therapeutics						X	
Celgene/Bristol-Myers Squibb						X	Honoraria
Incyte					X		
F. Hoffmann-La Roche Ltd	X					X	Travel grants
Janssen Oncology							Travel grants, honoraria
Takeda							Travel grants, honoraria
Merck Sharp & Dohme					X		Honoraria
AstraZeneca							Honoraria
Gilead					X		Honoraria

Bispecific Antibodies Targeting BCMA, GPRC5D, FcRH5

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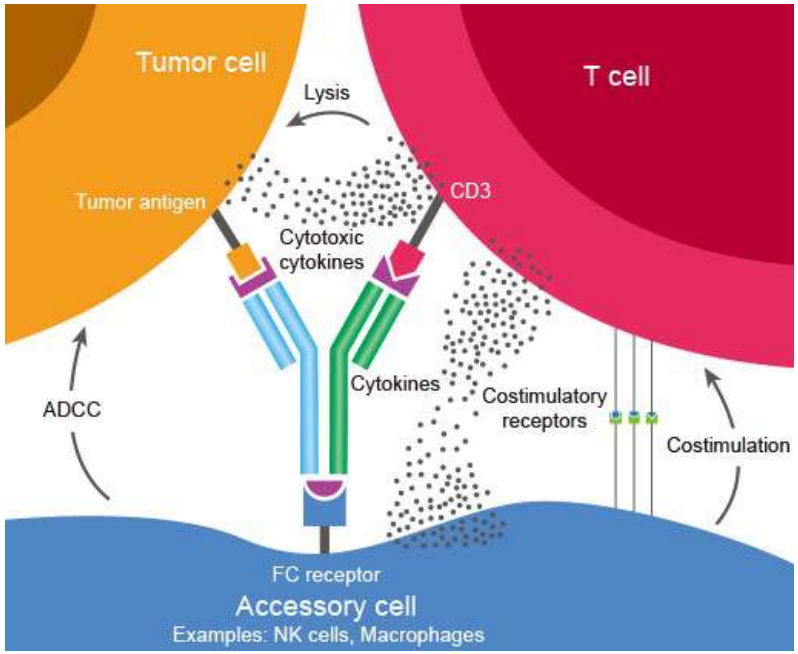
Highlights from IMW 2021 - Bologna, 1-2 FEB 2022

Background

- MM remains incurable and most patients eventually relapse after exposure to:
  - ✓ intensive induction/stem cell transplant
  - ✓ proteasome inhibitors (PIs)
  - ✓ immunomodulatory drugs (IMiDs)
  - ✓ CD38-targeting therapy
- T cell-mediated killing of MM cells can result in clinical benefit as has been shown for CAR T cell therapy

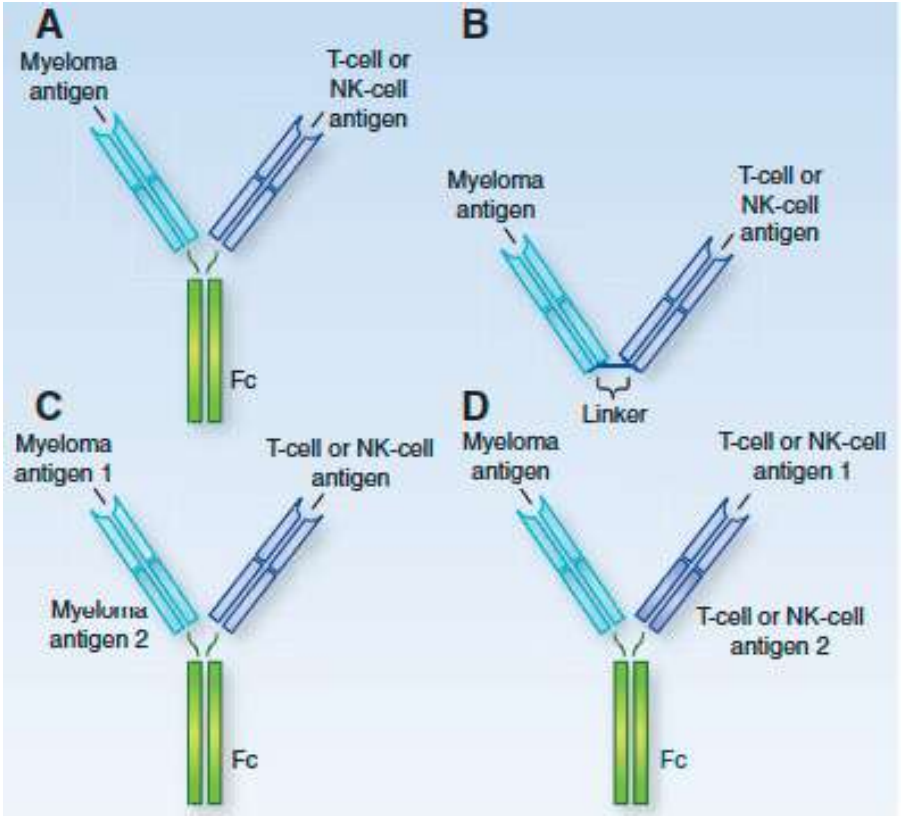
Bispecific Antibodies



- BsAbs can act as a bridge to redirect immune effector cells in close proximity to malignant cells
- T cells undergo activation due to CD3 cross-linking, which is associated with cytokine release (IFN-g, TNF-a, IL-2, -6, -10) and cytotoxic granule release (granzyme B)
- T-cell activation is MHC-unrestricted and no longer depends on the native TCR specificity of the activated T cell

Bispecifics in Development

- BCMA - Teclistamab
- GPRC5D - Talquetamab
- FcRH5 - Cevostamab



Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study

Saad Z Usmani, Alfred L Garfall, Niels W C J van de Donk, Hareth Nahi, Jesus F San-Miguel, Albert Oriol, Laura Rosinol, Ajai Chari, Manisha Bhutani, Lionel Karlin, Lotfi Benboubker, Lixia Pei, Raluca Verona, Suzette Girgis, Tara Stephenson, Yusri Elsayed, Jeffrey Infante, Jenna D Goldberg, Arnob Banerjee, María-Victoria Mateos, Amrita Krishnan

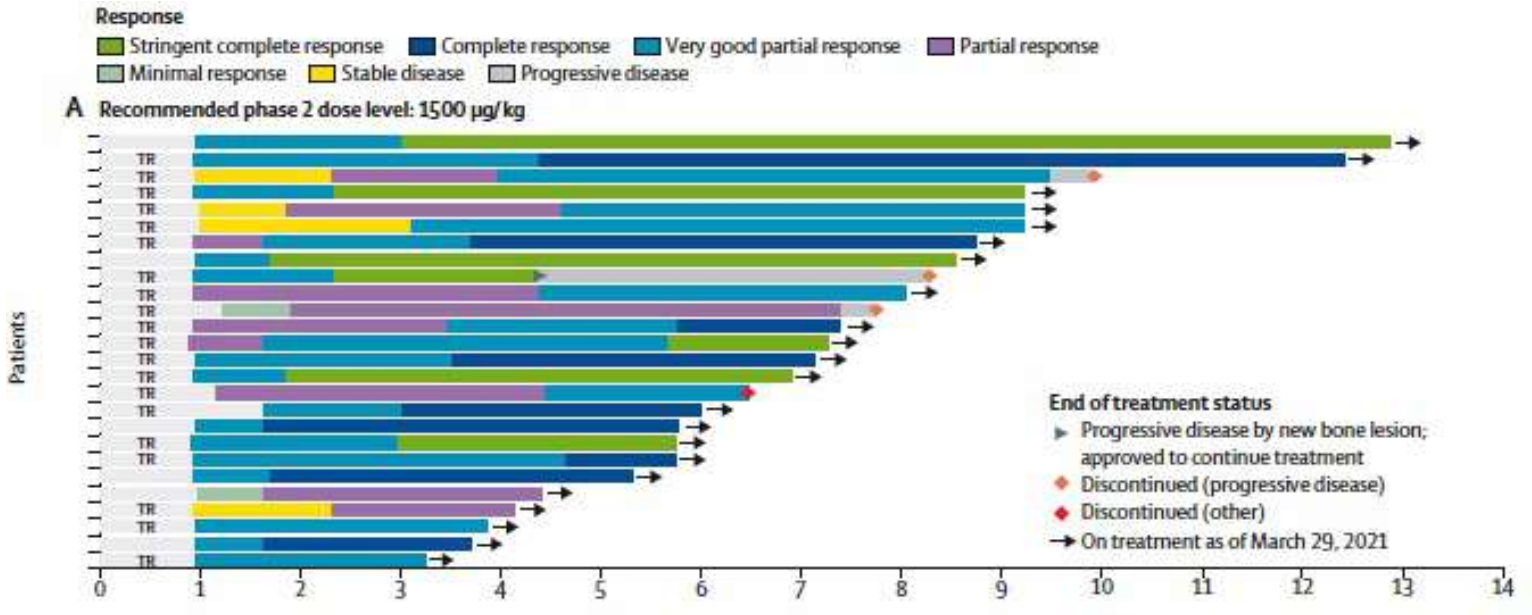
The Lancet, 398:665-674, 2021

Findings Between June 8, 2017, and March 29, 2021, 219 patients were screened for study inclusion, and 157 patients (median six previous therapy lines) were enrolled and received at least one dose of teclistamab (intravenous n=84; subcutaneous n=73). 40 patients were administered the recommended phase 2 dose, identified as once per week subcutaneous administration of teclistamab at 1500 µg/kg, after 60 µg/kg and 300 µg/kg step-up doses (median follow-up 6·1 months, IQR 3·6–8·2). There were no dose-limiting toxicities at the recommended phase 2 dose in part one. In the 40 patients treated at the recommended phase 2 dose, the most common treatment-emergent adverse events were cytokine release syndrome in 28 (70%; all grade 1 or 2 events) and neutropenia in 26 (65%) patients (grade 3 or 4 in 16 [40%]). The overall response rate in response-evaluable patients treated at the recommended

Patients Treated at the RP2D

ORR was 65%
VGPR or > 58%
CR or > 40%

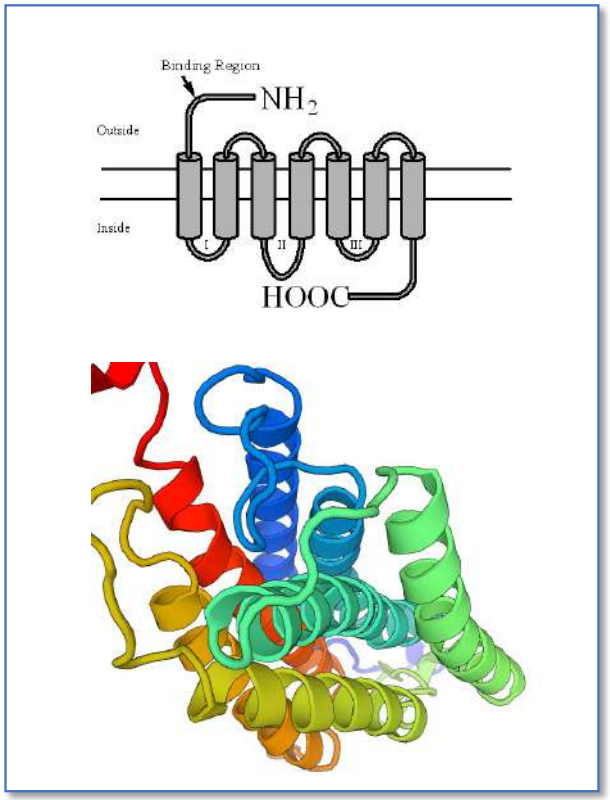
Median DoR, NR
22/26 responders (85%) on treatment as of the cutoff date
Follow-up 7.1 mos



The Lancet, 398:665-674, 2021

GPRC5D

- G-protein coupled receptor family C group 5 (PRC5D) is an orphan receptor with no known ligands or functions in human (and human cancer)
- GPRC5D has seven transmembrane segments and is expressed in cell membranes
- The GPRC5D gene that is mapped on chromosome12p13.3 contains three exons and spans about 9.6 kb. The large first exon encodes the seven-transmembrane domain
- Restricted RNA expression in normal tissue observed in testis & skin/hair follicles

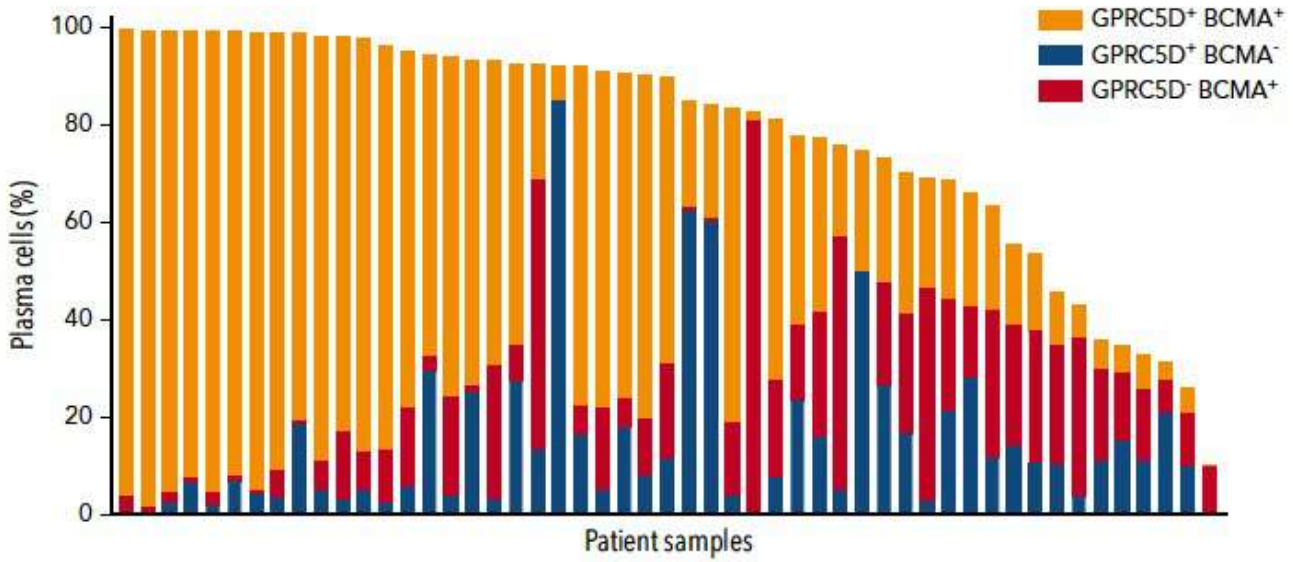


[1]Venkateshaiah, Blood 2013; [2]Atamaniuk, ESCI 2012; [3]Cohen, Hematology 2013; [4]Smith, Sci Transl Med 2019

A T-cell–redirecting bispecific G-protein–coupled receptor class 5 member D x CD3 antibody to treat multiple myeloma

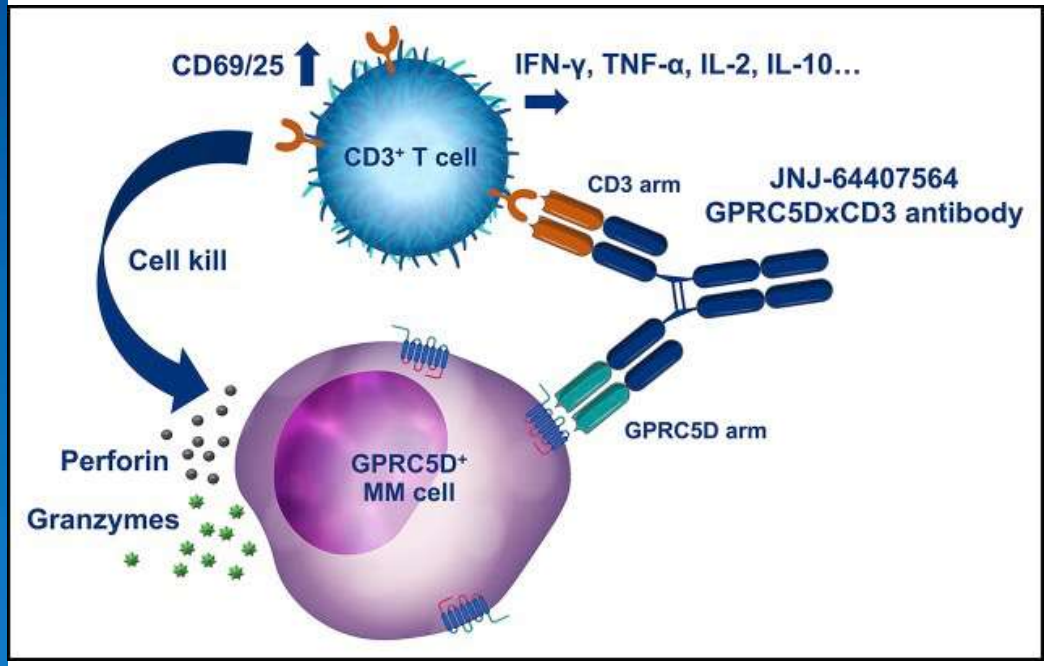
Kodandaram Pillarisetti,[1] Suzanne Edavettal,[2] Mark Mendonça,[1] Yingzhe Li,[1] Mark Tornetta,[3] Alexander Babich,[1] Nate Majewski,[3] Matt Husovsky,[2] Dara Reeves,[1] Eileen Walsh,[3] Diana Chin,[1] Leopoldo Luistro,[1] Jocelin Joseph,[1] Gerald Chu,[1] Kathryn Packman,[1] Shoba Shetty,[4] Yusri Elsayed,[1] Ricardo Attar,[1] and François Gaudet[1]

(*Blood*. 2020;135(15):1232-1243)



Talquetamab: A GPRC5D × CD3 Bispecific Antibody

- GPRC5D is highly expressed on MM plasma cells, making it a promising target for MM therapy[1-5]
- Talquetamab (JNJ-64407564) is a first-in-class antibody that binds to GPRC5D and CD3 receptors, mediating T cell recruitment, activation and subsequent lysis of GPRC5D+ MM cells[6]
- In the ongoing, phase 1, first-in-human study of talquetamab in patients with RRMM (MonumenTAL-1; NCT03399799), the first RP2D was identified as a weekly SC dose of 405 µg/kg[a,7–8]
- Here we present
  - Updated data from patients treated at the first RP2D[a]
  - Initial results from patients treated at a second RP2D of 800 µg/kg Q2W



MonumenTAL-1: Nonhematologic Safety Profile

AEs (≥20 of total SC population), n (%)	405 µg/kg SC QW[a] n=30		800 µg/kg SC Q2W[a] n=25	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Nonhematologic				
CRS	23 (77)	1 (3)	18 (72)	0 (0)
Dysgeusia	18 (60)	N/A	9 (36)	N/A
Dysphagia	11(37)	0 (0)	4 (16)	0 (0)
Skin exfoliation	11(37)	0 (0)	9 (36)	0 (0)
Fatigue	9 (30)	1 (3)	7 (28)	0 (0)
Weight decreased	9 (30)	0 (0)	6 (24)	0 (0)
Nail disorder[b]	9 (30)	N/A	5 (20)	N/A
Pyrexia	6 (20)	0 (0)	4 (16)	0 (0)
Dry mouth	8 (27)	0 (0)	10 (40)	0 (0)
Diarrhea	8 (27)	0 (0)	3 (12)	0 (0)
Nausea	7 (23)	0 (0)	3 (12)	0 (0)
ALT increased	6 (20)	1 (3)	8 (32)	1 (4)

- **Infections occurred in 33% (18/55) of patients**
  - 3 (5%) patients had grade 3/4 infections
- Dysgeusia generally mild with few dose adjustments required
- **Skin-related and nail disorder AEs[c] occurred in 75% of patients**
  - Most commonly reported was exfoliation (all grade 1/2)
  - Rashes were mostly grade 1/2
    - Grade 3 rashes reported in 7.5% (4/55) of patients[d]; all patients successfully rechallenged (3 at the same dose level)
  - See poster #1658 (Saturday 5:30-7:30 pm) for further details
- Injection-site reactions in 16% (9/55) of patients (all grade 1/2)
- **No AE deaths related to talquetamab**
  - One AE death due to basilar artery thrombosis, in a patient with significant history of vascular disease

MonumenTAL-1: Overall Safety and Hematologic Safety Profile

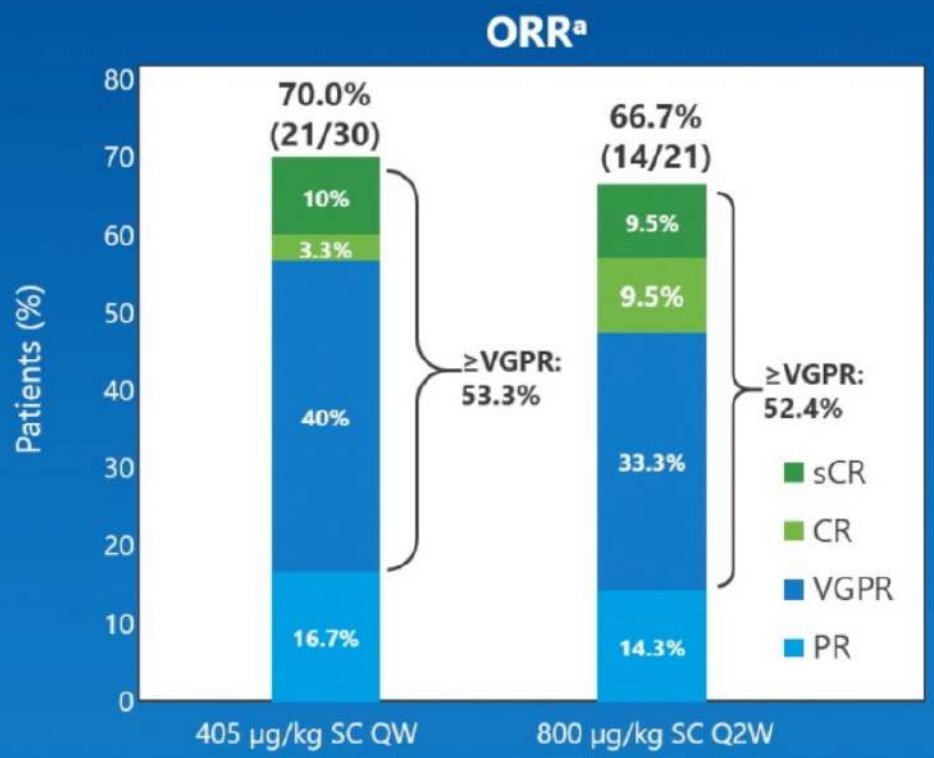
AEs (≥20% of total SC population), n (%)	405 µg/kg SC QW[a] n=30		800 µg/kg SC Q2W[a] n=25	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	20 (67)	18 (60)	11 (44)	9 (36)
Anemia	18 (60)	8 (27)	9 (36)	2 (8)
Lymphopenia	12 (40)	12 (40)	6 (24)	6 (24)
Thrombocytopenia	11 (37)	7 (23)	5 (20)	2 (8)
Leukopenia	12 (40)	9 (30)	4 (16)	4 (16)

Talquetamab has a tolerable safety profile at both RP2Ds

- No new AEs were observed
- The majority of AEs were grade 1 or 2
- 1 patient (1.8%) discontinued due to an AE

- Cytopenias were mostly confined to step-up and cycle 1/2 doses
  - Cytopenias were reversible
  - Neutropenias generally resolved within a week and were limited to cycles 1/2

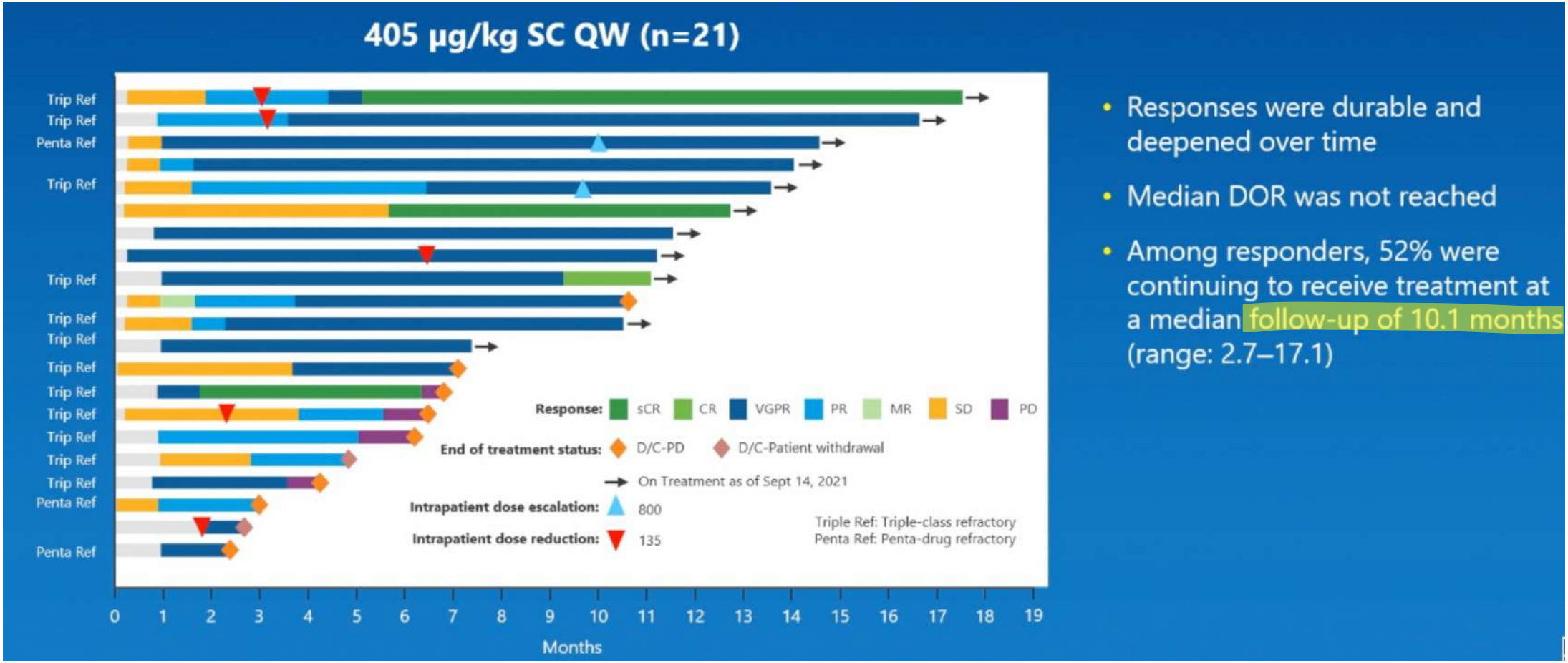
MonumenTAL-1: Overall Response Rate



Response	405 µg/kg SC QW[b] n=30	800 µg/kg SC Q2W[b] n=25
Median follow-up (months), median (range)	9.0 (0.9–17.1)	4.8 (0.4–11.1)
Response-evaluable patients,[c] n	30	21
ORR, n (%)	21 (70.0)	14 (66.7)
ORR in triple-class–refractory patients, n/N (%)	15/23 (65.2)	12/18 (66.7)
ORR in penta-drug–refractory patients, n/N (%)	5/6 (83.3)	5/6 (83.3)
Median time to first confirmed response (months), median (range)	0.9 (0.2–3.8)	1.2 (0.2–6.8)

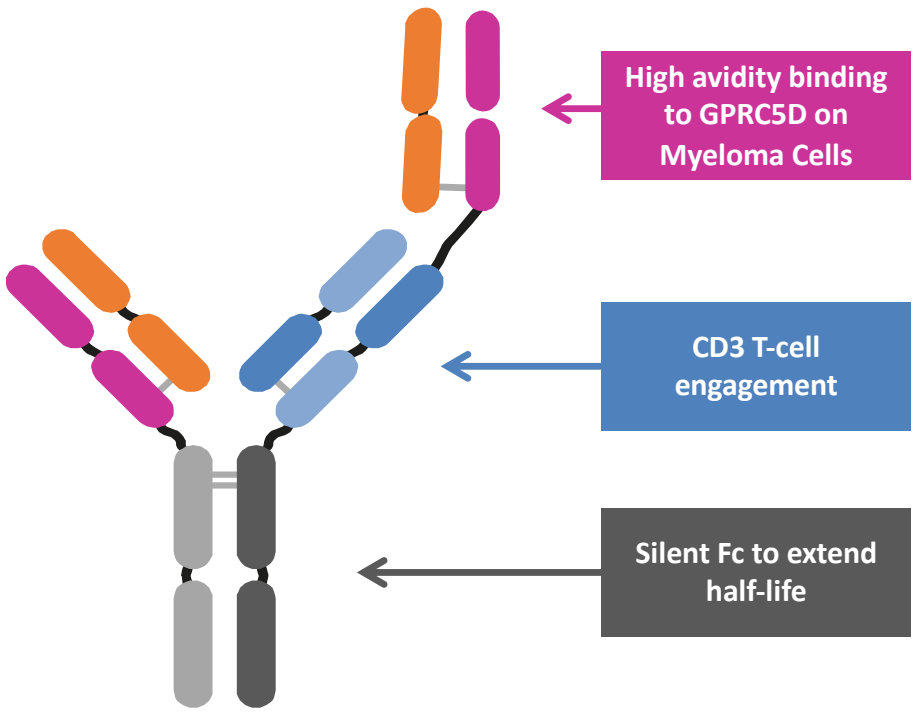
- ORR appears to be comparable across both RP2Ds

Talquetamab: DoR



- Responses were durable and deepened over time
- Median DOR was not reached
- Among responders, 52% were continuing to receive treatment at a median follow-up of 10.1 months (range: 2.7–17.1)

GPRC5D CD3 T-cell bispecific antibody ("GRACE") - RO7425781



Mechanism of action

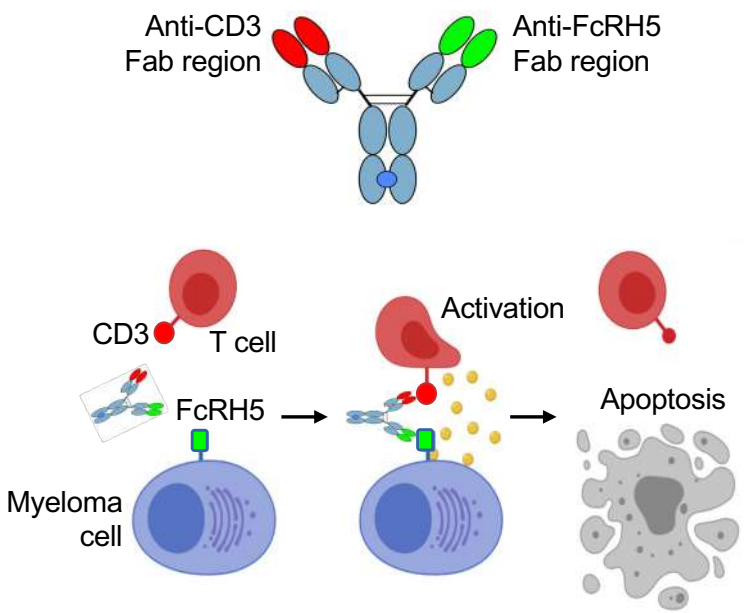
Bispecific antibody binds to GPRC5D on myeloma cells and CD3 on T cells, recruiting T cells to target and destroys malignant plasma cells

Differentiation

- 2:1 format clinically validated as BIC (CD20-TCB, Celgene BCMA TCB)
- Strong prevalence in malignant plasma cells. No shedding of target, as compared to BCMA
- Preclinical data demonstrates
  1) Greater efficacy over competitor JNJ-64407564, 1:1 format)
  2) Rescue of BCMA-TCB escaping Multiple Myeloma with GPRC5D TCB

Cevostamab: FcRH5xCD3 bispecific antibody

- Fc receptor-homolog 5 (FcRH5)
  - expressed exclusively in B-cell lineage (myeloma cells > normal B cells)[1]
  - near ubiquitous expression on myeloma cells[1,2]
- Cevostamab bispecific antibody
  - targets membrane-proximal domain of FcRH5 on myeloma cells and epsilon domain of CD3 on T cells[1]
  - dual binding results in T-cell directed killing of myeloma cells[1]
- Previously reported Phase I dose-finding experience (NCT03275103)[3]
  - promising activity in patients with heavily pre-treated RRMM
  - manageable safety, with C1 single step-up dosing providing effective CRS mitigation



Aims: (1) share updated Phase I dosing-finding results, and
(2) evaluate the impact of C1 single step-up and C1 double step-up dosing on CRS

C, Cycle; CRS, cytokine release syndrome;
Fab, fragment antibody binding; RRMM, relapsed/refractory multiple myeloma

1. Li et al. Cancer Cell 2017;31:383–95
2. Sumiyoshi et al. EHA 2021; 3. Cohen et al. ASH 2020

Cytokine release syndrome

	N=161
N (%) of patients with CRS*	130 (80.7)
Grade 1	69 (42.9)
Grade 2	59 (36.6)
Grade 3	2 (1.2)
N (%) of patients with ICANS associated with CRS	23 (14.3)
Grade 1	13 (8.1)
Grade 2	9 (5.6)
Grade 3	1 (0.6)
Most common ICANS symptoms associated with CRS	
Confusional state	4 (2.5)
Aphasia	2 (1.2)
N (%) of patients with CRS leading to treatment discontinuation	1 (0.8)
N (%) of patients with CRS receiving CRS management with:	
Tocilizumab only	60 (37.3)
Steroids only	35 (21.7)
Tocilizumab and steroids	26 (20.0)

- CRS primarily observed in C1
- CRS onset within 24 hours of administration in 70% of patients
- CRS resolution within 48 hours of onset in 85% of patients
- All but one patient with ICANS associated with CRS had resolution of their ICANS symptoms
  - the patient whose symptoms did not resolve discontinued due to disease progression soon afterwards

- C1 step-up dosing provided effective CRS mitigation. CRS was generally confined to C1 and was mostly low Grade.

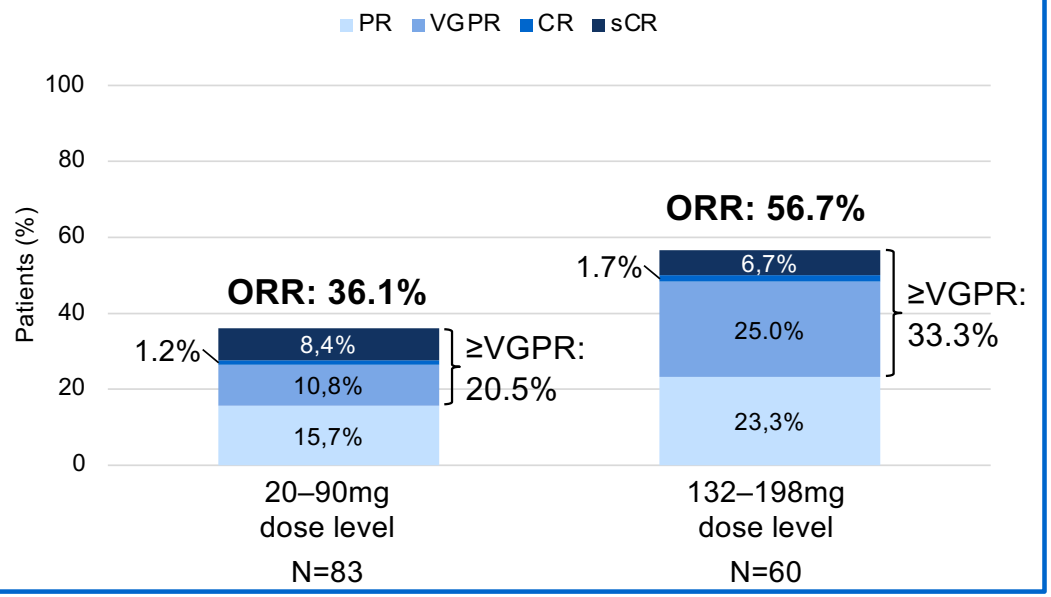
*assessed using ASTCT 2019 criteria[1]; ICANS, immune effector cell-associated neurotoxicity syndrome

1. Lee et al. Biol Blood Marrow Transplant 2019;25:625–38

Response

- Response observed at the 20mg target dose level and above (N=143 patients)
- ORR increases with target dose
  - ORR in C1 single step-up expansion (3.6/90mg): 29.0%
  - ORR in C1 double step-up expansion (0.3/3.6/160mg): 54.8%
- Response occurs early
  - median time to first response: 1.0 mo (range: 0.7–5.9)
- Response deepens over time
  - median time to best response: 2.1 mo (range: 0.7–11.4)
- MRD negativity by NGS ($<10^{-5}$) detected in 7/10 evaluable patients with ≥VGPR

Best response rates in efficacy-evaluable patients by dose level



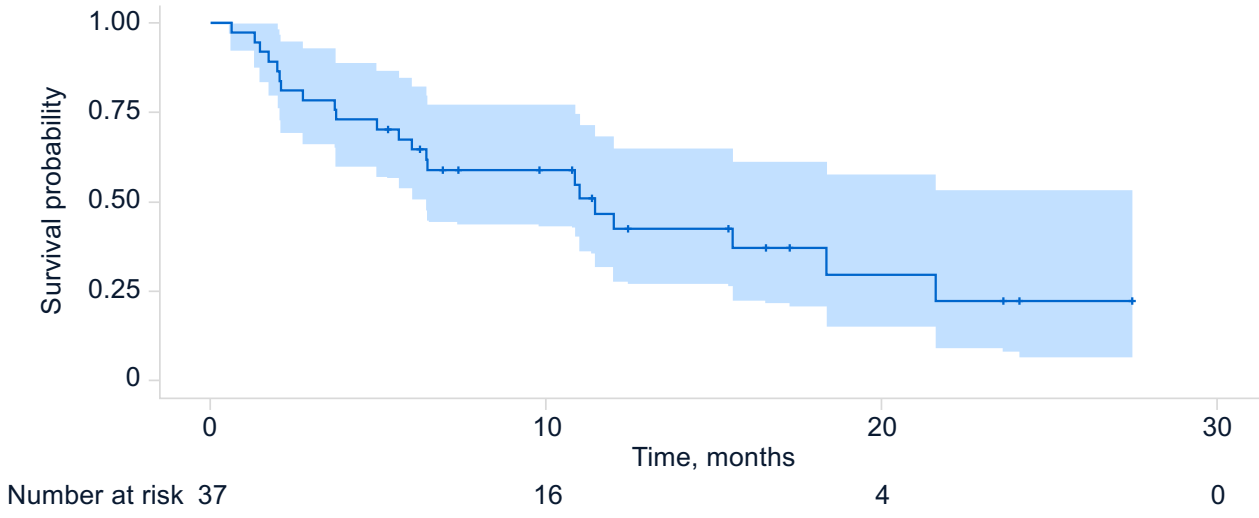
- Cevostamab was efficacious in patients with heavily pre-treated RRMM. ORR increased with target dose.

CR, complete response; MRD, minimal residual disease; NGS, next generation sequencing; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Duration of response

- Median follow-up in responders
  - C1 single step-up cohorts: 14.3 months (range: 2.7–31.8)
  - C1 double step-up cohorts: 6.5 months (range: 4.8–21.4)
- 6 patients in the C1 single step-up cohorts continued in response for ≥6 months after cessation of treatment

Median duration of response among responders in the C1 single step-up cohorts



Median duration of response: 11.5 months (95% CI: 6.0, 18.4)

- Responses were durable. Responses were maintained after cessation of treatment.

Conclusions

- Bispecifics are available as off-the-shelf products
- High response rates
- CRS grade 1-2
- Mechanisms of action
- Duration of therapy and response
- Mechanisms of resistance