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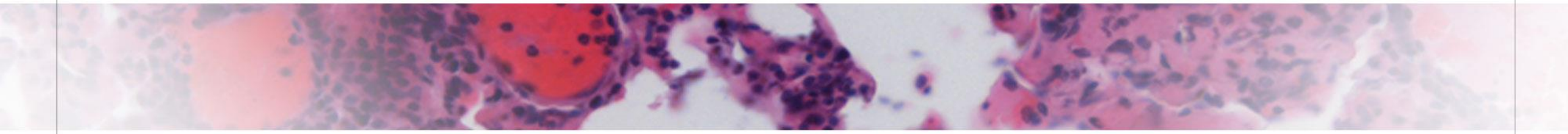

Modakafusp Alfa (TAK-573), an Immunocytokine, Shows Clinical Activity in Patients with Relapsed/Refractory Multiple Myeloma; Updated Results from a First-In-Human Phase 1 Study

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Oral presentation at the 63rd Annual Meeting of the American Society of Hematology (ASH), December 11–14, 2021
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Disclosures

I disclose the following relevant financial relationships:

- Consultancy: Takeda, Karyopharm, GSK, Oncopeptides, Janssen, Sanofi, CSL Behring
- Research funding: Takeda, Active Biotech

Co-author disclosures:

- **JLK:** Consultancy: AbbVie, Janssen, Incyte, Celgene, BMS, Roche/Genentech, TecnoPharma; Research funding: Genentech, Abbvie, Janssen, Amgen, BMS, Fortis Therapeutics, Heidelberg Pharma, Novartis, Sutro, Takeda; Honoraria: TecnoPharma, AbbVie, Janssen, Roche/Genentech; Membership of board of directors/advisory committee: Incyte, TG Therapeutics
- **SAH:** Research funding: Oncopeptides; Honoraria: Celgene, Genentech, GSK, Janssen, Secura Bio, Sorrento, Takeda; Member of board of directors/advisory committee: Oncopeptides, Celgene, Takeda
- **SA:** Research funding: Janssen, Amgen, GSK; Speakers' bureau: Janssen
- **ON:** Member of board of directors/advisory committee: Takeda, BMS, GSK, Karyopharm, Adaptive Biotechnologies
- **MJ:** Research funding: ADC Therapeutics, Fate Therapeutics, Takeda; Honoraria: Kyowa Kirin Therapeutics
- **KS, YL, XP, and SC:** Employee: Takeda
- **MC:** None

Off-label disclosure:

This presentation contains information about investigational use of modakafusp alfa (TAK-573) in patients with relapsed refractory multiple myeloma

Modakafusp alfa is a novel, first-in-class immunocytokine designed to deliver IFNα2b to CD38+ cells

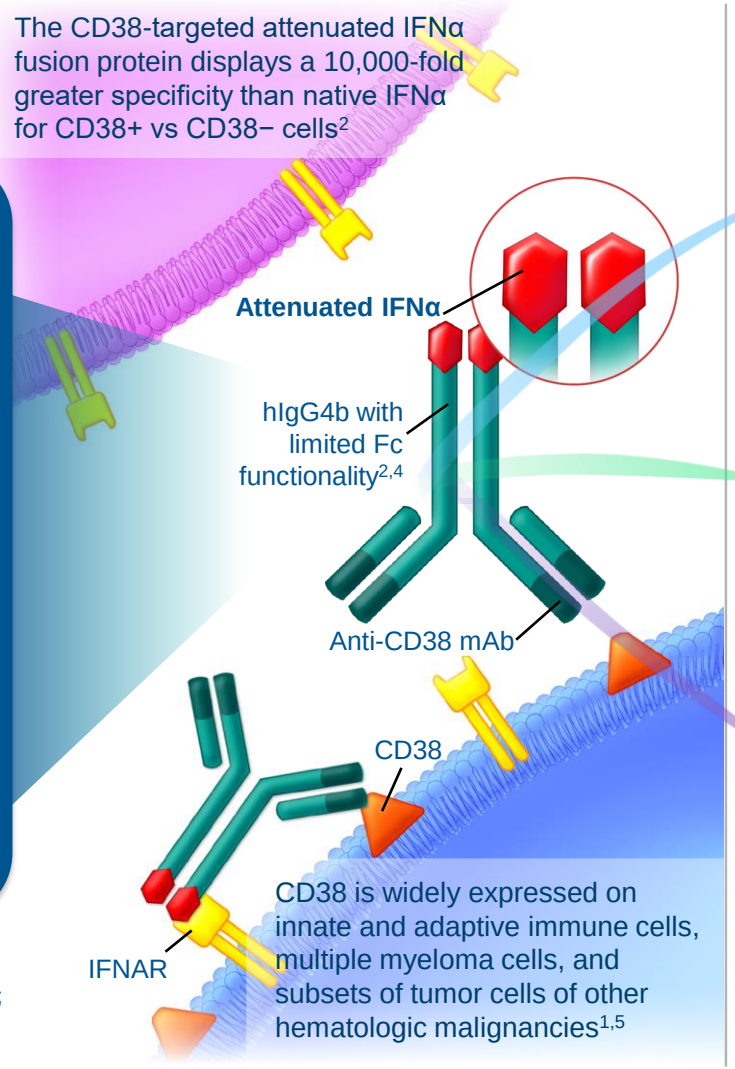
Modakafusp alfa

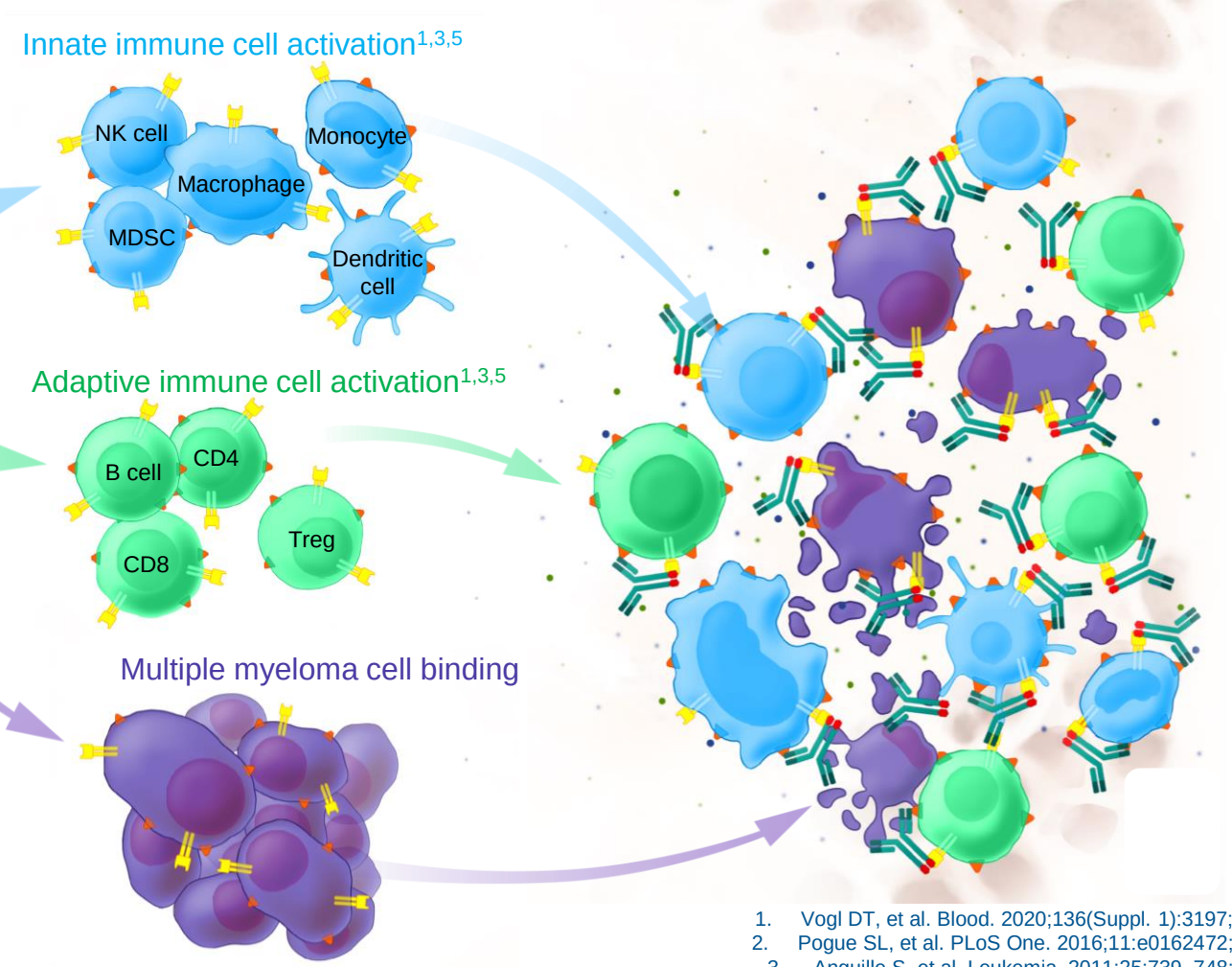
Binds with high affinity to unique epitope of CD38[1,2]

Signals through IFNAR[2] to:

- activate innate and adaptive immune cells[1]
- direct anti-proliferative/ apoptotic signals to tumor cells[2,3]

The CD38-targeted attenuated IFNα fusion protein displays a 10,000-fold greater specificity than native IFNα for CD38+ vs CD38− cells[2]





Fc, fragment crystallizable; hIgG4b, human immunoglobulin 4b; IFN, interferon; IFNAR, interferon α receptor; mAb, monoclonal antibody; MDSC, myeloid-derived suppressor cell; NK, natural killer; Treg, regulatory T cell

1. Vogl DT, et al. Blood. 2020;136(Suppl. 1):3197;
2. Pogue SL, et al. PLoS One. 2016;11:e0162472;
3. Anguille S, et al. Leukemia. 2011;25:739–748;
4. Cresioli S, et al. Curr Allergy Asthma Rep. 2016;16:7;
5. Calabretta E, Carlo-Stella C. Cells. 2020;9:802.

Study eligibility criteria and objectives

Key eligibility criteria

- RRMM
- ≥3 prior lines of MM therapy
- Refractory to or intolerant of ≥1 PI and 1 IMiD
- Daratumumab washout of 90 days required for patients with >5 months of therapy in escalation phase
  - Daratumumab washout not required for patients in expansion phase

Study objectives

Primary:

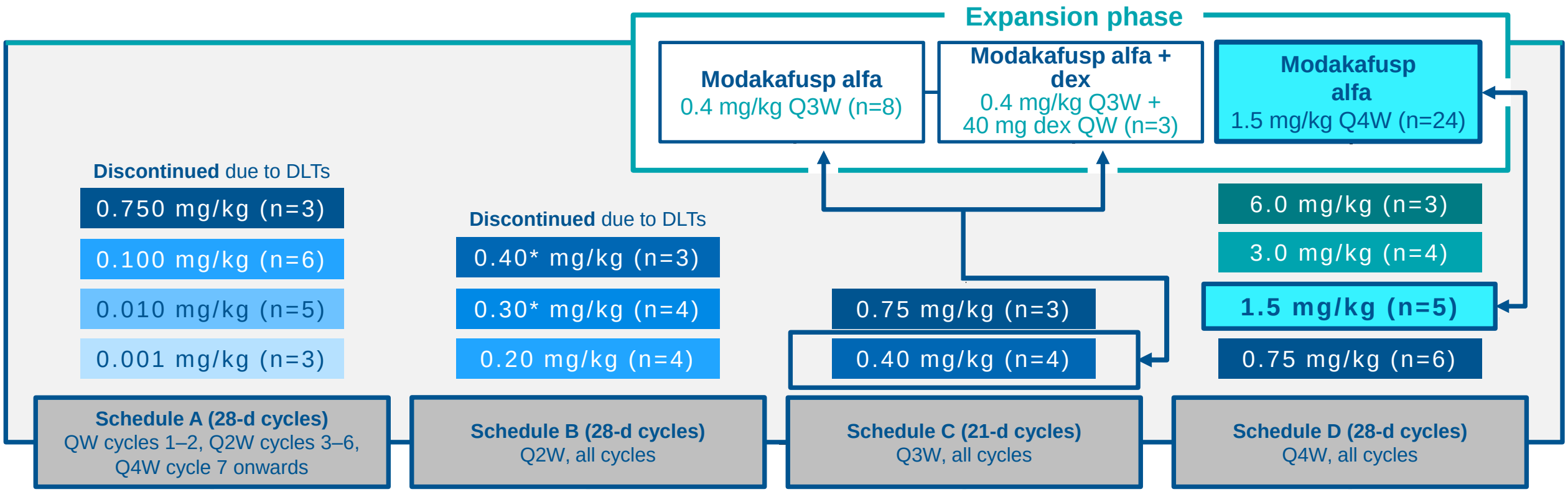
- OBD and/or MTD with 1 or more schedules

Secondary:

- Preliminary anti-tumor activity: ORR, DOR, and PFS
- PK and immunogenicity

DOR, duration of response; IMiD, immunomodulatory drug; MM, multiple myeloma; MTD, maximum tolerated dose; OBD, optimal biological dose; ORR, overall response rate; PFS; progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; RRMM, relapsed/refractory MM

Study design



Data cutoff date: **6 August 2021**

*Per protocol version available, patients may have been enrolled under schedule A.

Dex, dexamethasone; DLT, dose-limiting toxicity; QW, weekly; Q2/3/4W, every 2/3/4 weeks

Patient characteristics

Characteristic	1.5 mg/kg Q4W (n=29)
Median age, years (range)	66.0 (40–83)
Female sex, n (%)	15 (51.7)
Race,* n (%):	
White	23 (79.3)
Black or African American	2 (6.9)
Asian	2 (6.9)
ECOG performance status, n (%)	
0	4 (13.8)
1	25 (86.2)

*Race not reported for 2 patients in the 1.5 mg/kg cohort.

Characteristic	1.5 mg/kg Q4W (n=29)
Median time from diagnosis, years (range)	6.0 (0.7–16.1)
MM type,* n (%)	
IgG	13 (44.8)
IgA	5 (17.2)
Light chain only	9 (31.0)
ISS stage at study entry,† n (%)	
I	12 (41.4)
II	11 (37.9)
III	3 (10.3)
High-risk cytogenetics [del17p, t(4;14), or t(14;16)], n/N (%)	7/25 (28.0)

*1 patient had MM type under review and 1 had MM type missing.

†ISS stage missing for 3 patients.

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System

Prior therapies and refractoriness

Prior therapies	1.5 mg/kg Q4W (n=29)
Median prior lines of therapy, n (range)	7.0 (3–16)
Prior ASCT, n (%)	23 (79.3)
Prior CD38 mAb,* n (%)	28 (96.6)
Prior anti-BCMA therapy, n (%)	15 (51.7)
Prior CAR-T cell therapy,† n (%)	8 (27.6)
Prior T-cell engagers,‡ (%)	6 (20.7)

*Daratumumab and isatuximab.
†All CAR-T cell therapy assumed to be BCMA-directed.
‡BCMA-targeted in 2 patients.

Refractoriness	1.5 mg/kg Q4W (n=29)
PI + IMiD-refractory, n (%)	27 (93.1)
Triple class-refractory,* n (%)	25 (86.2)
Anti-CD38 mAb†-refractory, n (%)	26 (89.7)
Triple class-refractory* and penta-exposed,‡ n (%)	22 (75.9)
Last line-refractory, n (%)	23 (79.3)
Last line anti-CD38 mAb†-refractory, n (%)	4 (13.8)

*Refractory to PI, IMiD, and anti-CD38 mAb; refractoriness defined as disease progression while on treatment or <60 days from last exposure to the drug.
†Daratumumab and isatuximab.
‡Exposed to two PIs, two IMiDs, and one anti-CD38 mAb.

ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor

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Disposition and treatment exposure

	1.5 mg/kg Q4W (n=29)
Ongoing on study drug, n	13
Discontinued study drug, n	16
Progressive disease	12
Adverse events	3
Patient withdrawal	1
Lost to follow-up	0
Median duration of exposure, weeks (range)	13.6 (1.6–71.4)
Median number of cycles (range)	3 (1–18)

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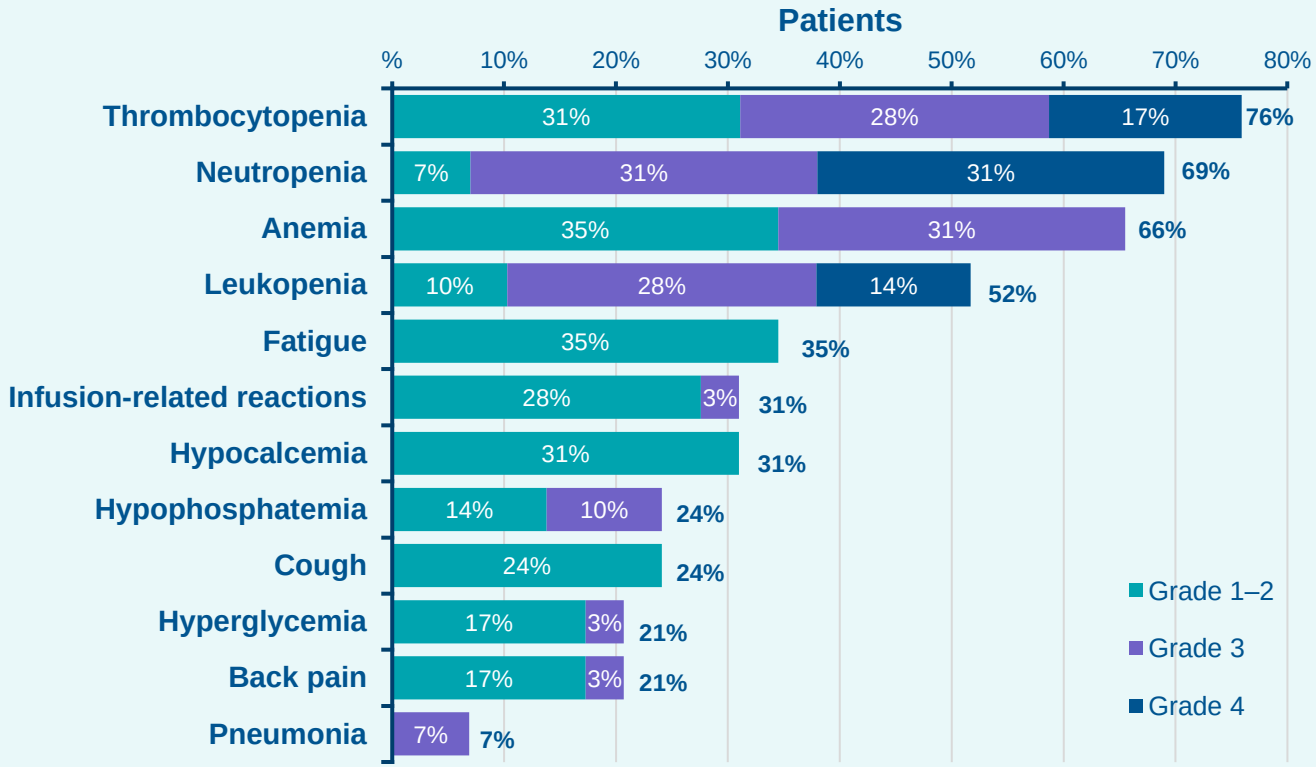
Safety profile

- **The MTD was exceeded with 6 mg/kg Q4W dose due to DLTs:**
  - Grade 3 infusion reaction
  - Prolonged grade 4 thrombocytopenia and neutropenia, which delayed the start of cycle 2 by >14 days
- **With 1.5 mg/kg Q4W modakafusp alfa:**
  - One patient had a grade 3 bleeding event and continued on study treatment at the time of data cut-off
  - Three patients had grade 3 infections (pneumonia, n=2; sinusitis, n=1)

Most common TEAEs with 1.5 mg/kg Q4W modakafusp alfa (n=29)



TEAEs reported in >20% of patients (or >25% for hematological TEAEs) overall or at grade ≥3 severity in >5% of patients overall. Overall total % may not equal grade 1–2 plus grade ≥3 %s due to rounding.

TEAE, treatment-emergent adverse event

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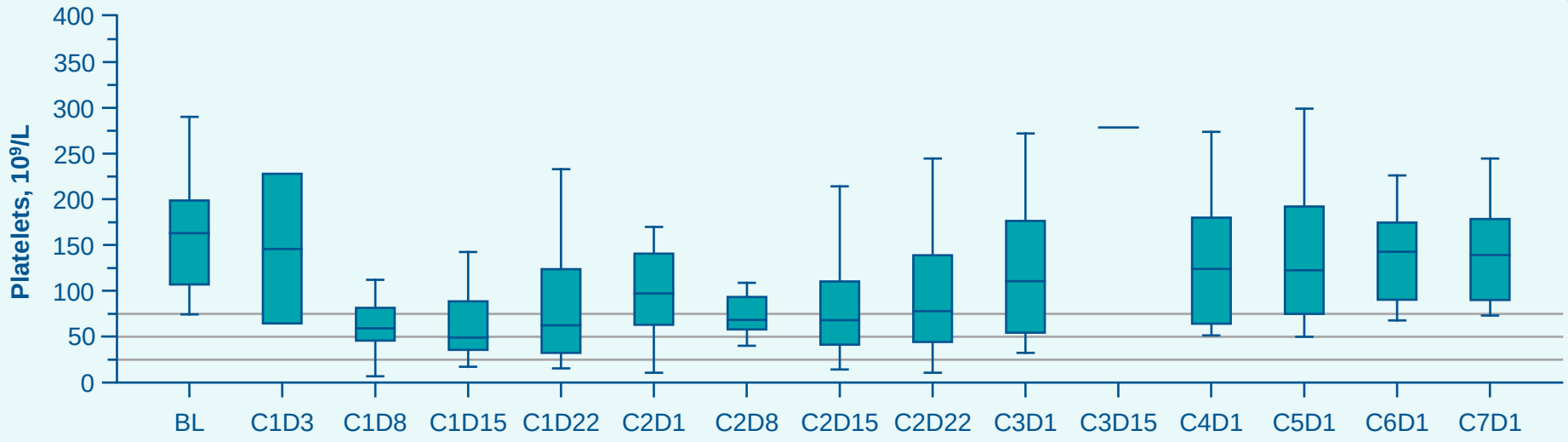
Platelet count over time with 1.5 mg/kg Q4W

Mean platelet count was lowest at days 8 and 15 of the first 2 cycles, but recovered over time



Number of patients:

	BL	C1D3	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D15	C4D1	C5D1	C6D1	C7D1
Total	29	2	26	26	26	20	18	17	18	17	1	14	11	10	9
Dose escalation	5	0	4	4	4	3	3	3	3	3	1	3	3	3	3
Dose expansion	24	2	22	22	22	17	15	14	15	14	0	11	8	7	6

Within each box, horizontal lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values; whiskers denote minimum and maximum values, excluding outliers.

BL, baseline

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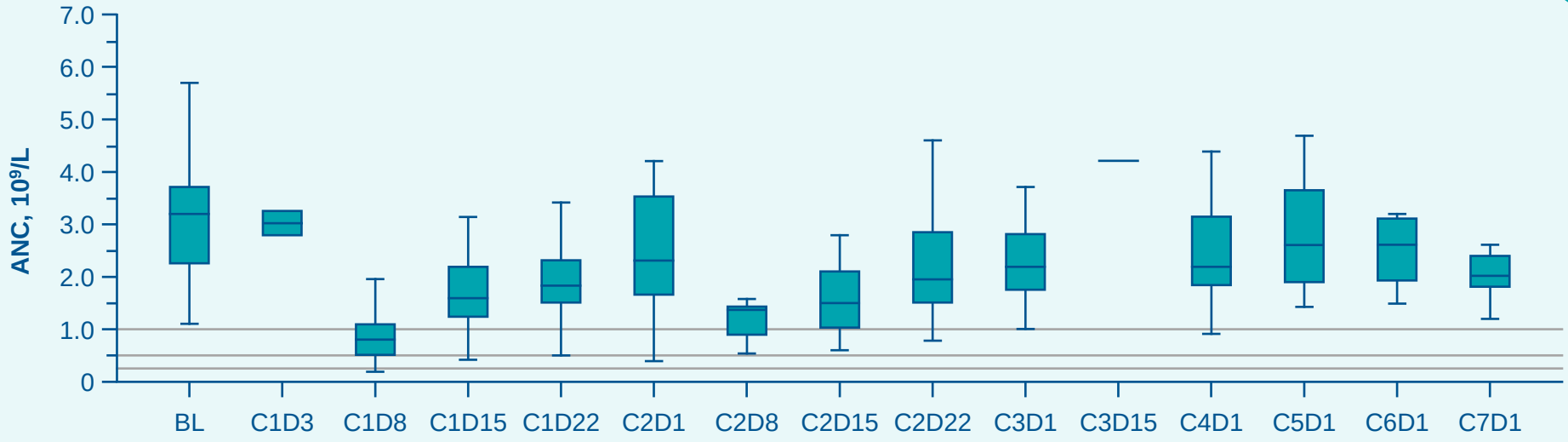
ANC over time with 1.5 mg/kg Q4W

Mean ANC was lowest at the beginning of each cycle, particularly the first 2 cycles, but recovered towards the end of each cycle



Number of patients:

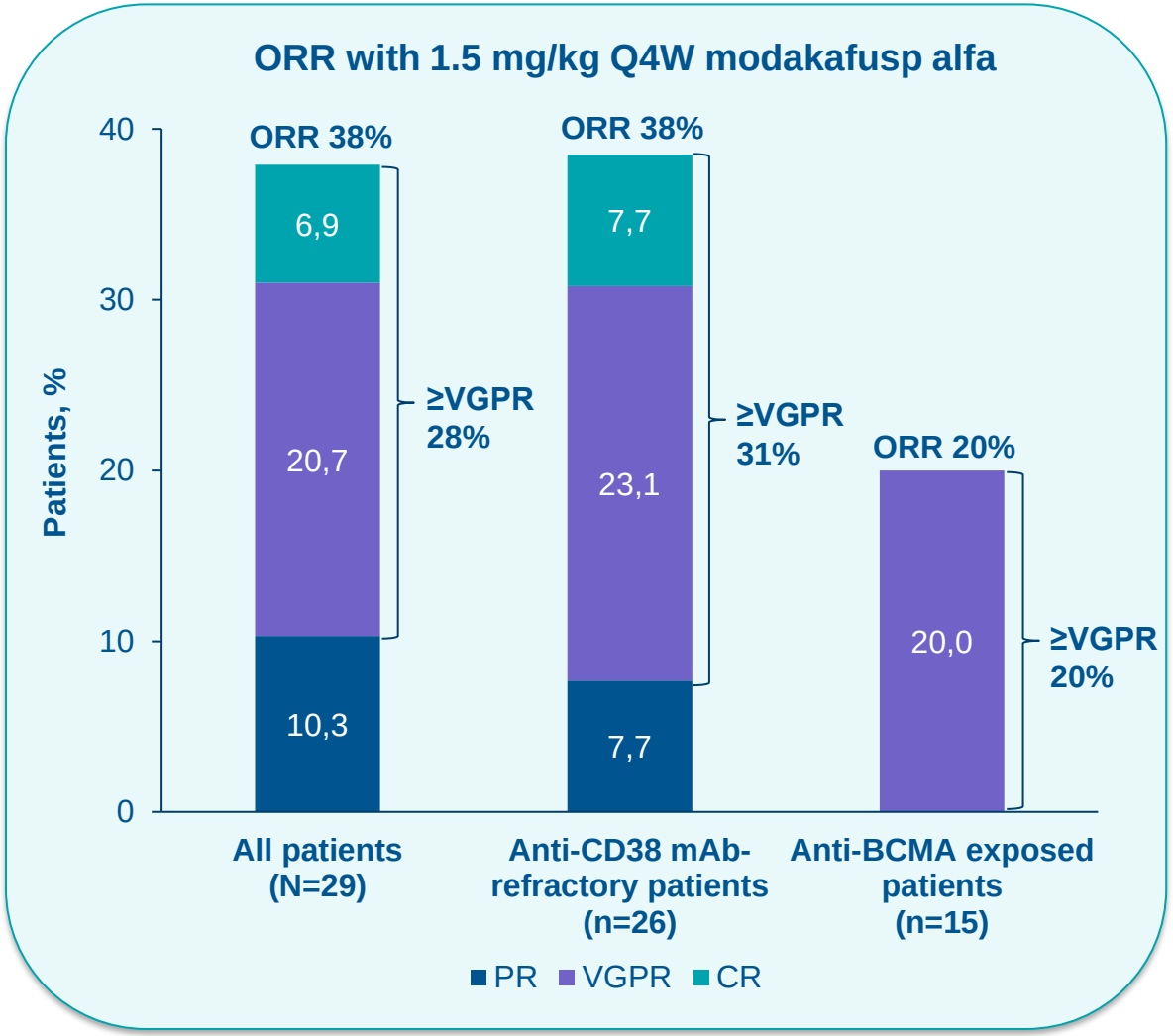
	BL	C1D3	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D15	C4D1	C5D1	C6D1	C7D1
Total	28	2	26	25	25	19	18	17	17	16	1	14	12	10	9
Dose escalation	5	0	4	3	4	2	3	3	3	3	1	3	3	3	3
Dose expansion	23	2	22	22	21	17	15	14	14	13	0	11	9	7	6

Within each box, horizontal lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values; whiskers denote minimum and maximum values, excluding outliers.

ANC, absolute neutrophil count

Overall response rate

- **Among 29 patients who received modakafusp alfa 1.5 mg/kg Q4W (5 in dose escalation and 24 in ongoing dose expansion):**
  - 11 patients had ≥PR (ORR 38%), including 6 with VGPR and 2 with CR (28% ≥VGPR)
- **Among 26 anti-CD38 mAb-refractory patients, ORR was also 38% (31% ≥VGPR):**
  - Among the 4 patients who received an anti-CD38 mAb in their most recent line of therapy, 1 achieved a CR, and 2 achieved a VGPR (ORR 75%)
- **Of the 15 patients with prior anti-BCMA therapy, 3 (20%) had a VGPR**



CR, complete response; PR, partial response; VGPR, very good partial response

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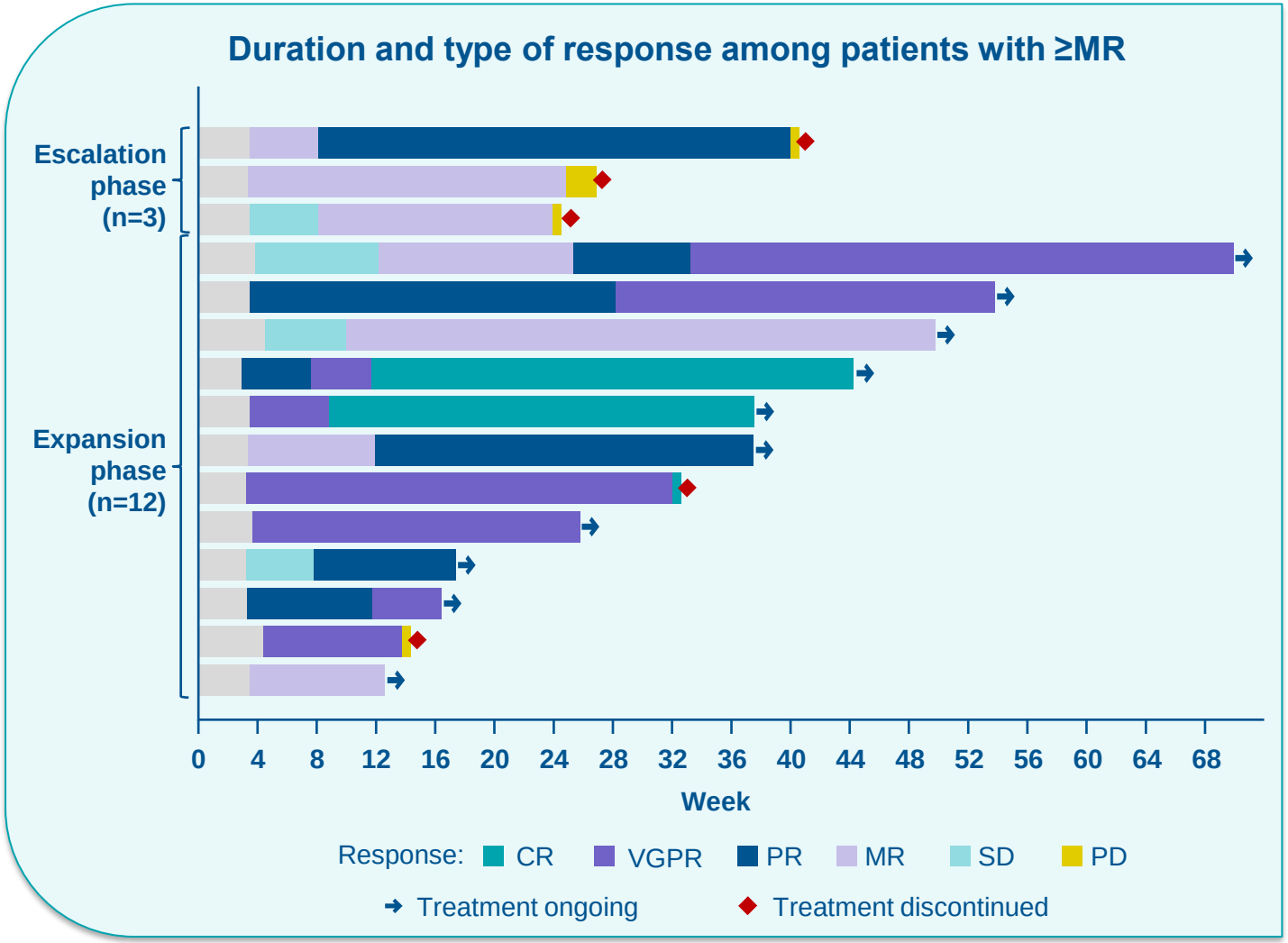
Duration of response

- **After a median follow-up of 4.2 months (range: 0.4–17.6 months), 10 patients* remain on treatment**
- **Among 11 patients with ≥PR:**
  - Median time to response was 1 month (range: 0.8–5.8 months)
  - Median time to best response was 2 months (range: 0.9–7.7 months)
  - Median duration of response has not been reached (range: 2.1–11.3† months)
  - Two patients achieved a CR after 2 and 3 cycles; both are ongoing on treatment in CR
- **Among all patients in the 1.5 mg/kg cohort (n=29), median PFS was 5.7 months (95% CI, 0.99–NR)**



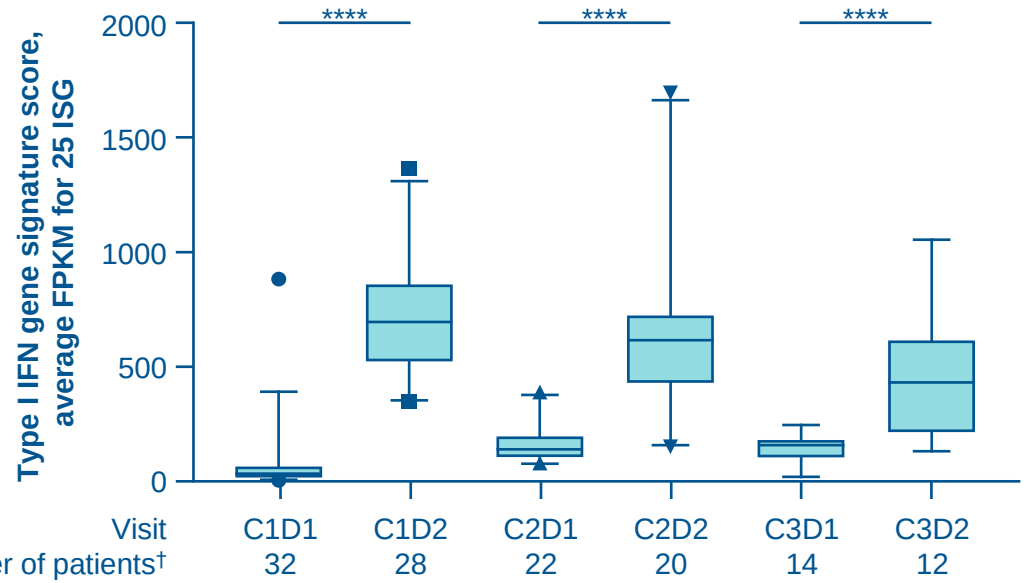
*Among patients who had at least one response assessment and have at least a MR.
†Patient censored.
MR, minimal response; NR, not reached; PD, progressive disease; SD, stable disease

Innate and adaptive immune activation

Administration of modakafusp alfa leads to:

- induction of type I IFN gene signature
- activation of CD8 T cells and NK cells

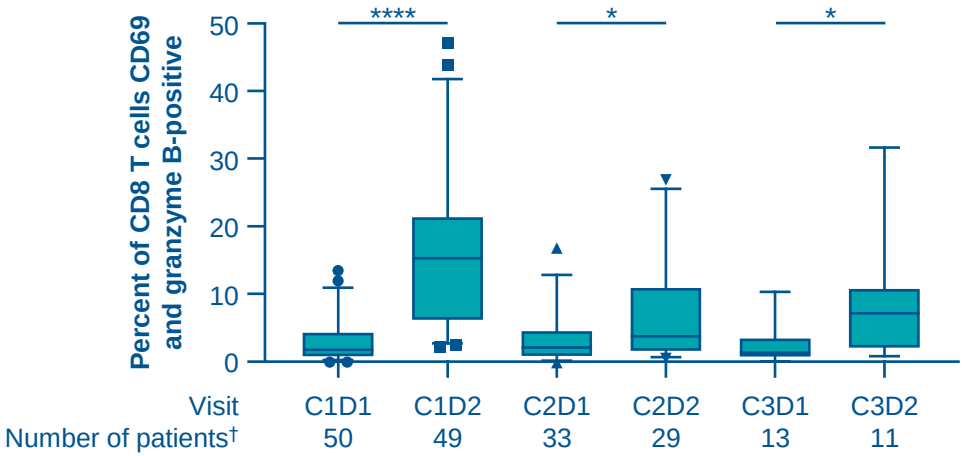
Peripheral blood type I IFN pathway activation



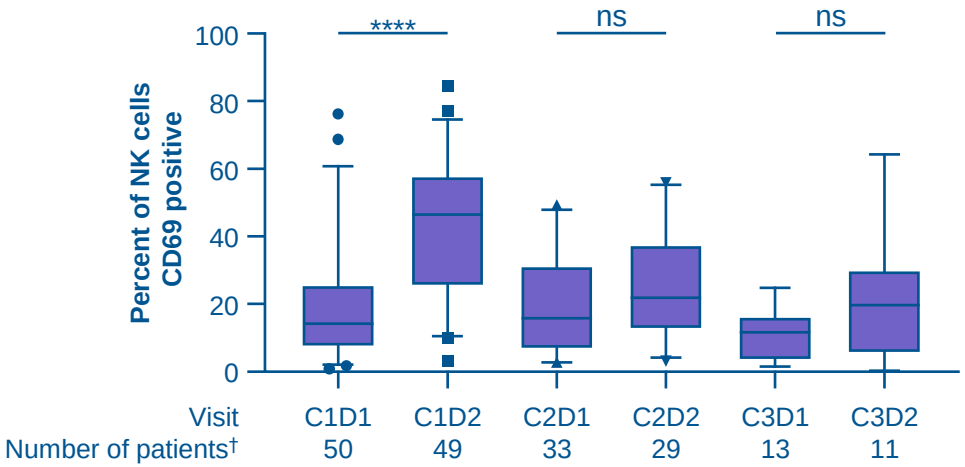
****p-value ≤0.0001; *p-value ≤0.05; ns, not significant.
†Data available for samples from patients treated with 0.4 mg/kg, 0.75 mg/kg, and 1.5 mg/kg.

FPKM, fragments per kilobase of transcript per million mapped reads; ISG, interferon-stimulated genes

Peripheral blood CD8 T cell activation



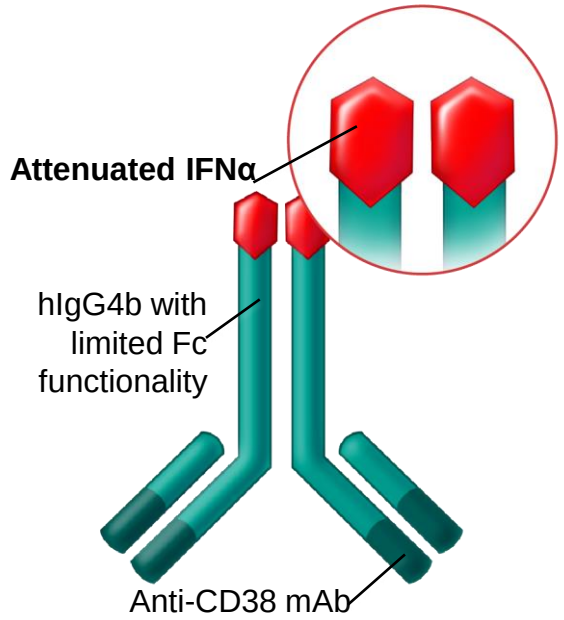
Peripheral blood NK cell activation



Conclusions

- **Modakafusp alfa is a novel immunocytokine with:**
  - Promising single-agent activity in patients with heavily pre-treated myeloma, including those with disease refractory to an anti-CD38 mAb
  - A manageable safety/tolerability profile
  - A unique structure and mechanism of action
  - Evidence of immune activation

- **Q4W is the optimal dosing interval for multiple myeloma**
  - Further enrollment has identified the maximum tolerated dose as 3 mg/kg
  - A randomized phase 2 trial is planned to define the optimal single-agent dose



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Acknowledgements and QR code

- This study was funded by Takeda Development Center Americas, Inc. (TDCA)

- The authors would like to thank all patients and their families, as well as all investigators for their valuable contributions to this study

- Medical writing support for the development of this oral presentation, under the direction of the authors, was provided by Luisa Madeira, PhD, of Ashfield MedComms, an Ashfield Health company, funded by Takeda Pharmaceuticals, U.S.A., Inc., and complied with the Good Publication Practice-3 (GPP3) guidelines (Battisti WP, et al. Ann Intern Med 2015;163:461–4); Victoria Enwemadu, PharmD, of Takeda Development Center Americas, Inc. (TDCA) provided editorial assistance

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QR, quick response