Randomized Phase 2 Dose Optimization Trial of Modakafusp Alfa in Relapsed/Refractory Multiple Myeloma

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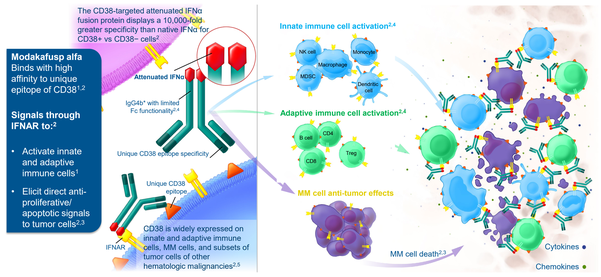
Background

- Modakafusp alfa is a first-in-class, innate immunity enhancer designed to deliver attenuated interferon (IFN) to innate and adaptive immune cells, as well as myeloma cells (**Figure 3**)[1,2]
- Modakafusp alfa comprises two attenuated IFNα2b molecules genetically fused to the Fc portion of a humanized IgG4 monoclonal antibody (mAb), which binds to a unique epitope on CD38
- Our previously reported phase 1/2 trial identified two potential phase 2 doses of modakafusp alfa in patients with RRMM: 1.5 mg/kg and 3 mg/kg every 4 weeks (Q4W), both at which the overall response rate (ORR) was 43% and toxicities were primarily hematologic[1]
- Here, we describe the results of a non-comparative, randomized, phase 2 dose optimization study evaluating modakafusp alfa at the fixed-dose equivalents of 3.0 mg/kg and 1.5 mg/kg Q4W, 240 mg and 120 mg Q4W, respectively (NCT03215030)

Figure 3. Modakafusp alfa mode of action

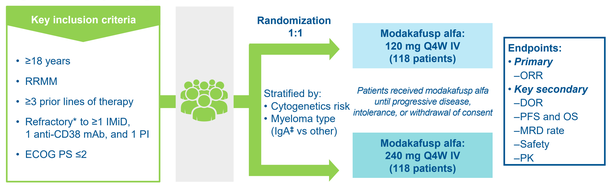


*IgG4 is a poor inducer of Fc-mediated effector functions, such as antibody-dependent cellular cytotoxicity and phagocytosis.[4]
Fc, fragment crystallizable; IgG4b, immunoglobulin 4b; IFNAR, interferon α receptor; MDSC, myeloid-derived suppressor cell; MM, multiple myeloma; NK, natural killer; Treg, regulatory T cell.

Methods

- Eligible patients were randomized 1:1 to receive modakafusp alfa Q4W at 240 mg or 120 mg intravenously over 1 hour, with corticosteroid use limited to dexamethasone 20 mg as premedication with each dose of modakafusp alfa (**Figure 4**)
- No formal statistical comparison between the two doses was planned
- Dose selection was to be based on the totality of the data, i.e. safety and tolerability, efficacy, and clinical pharmacokinetic and pharmacodynamic data[6]

Figure 4. Study design



*Defined as <25% reduction in M-protein or progression of disease during treatment or ≤60 days after cessation of treatment. †236 planned patients, per study protocol. ‡Based on historical data showing higher ORR in patients with IgA myeloma.[7]
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; IV, intravenous; MRD, minimal (measurable) residual disease; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PI, proteasome inhibitor.

Results

Patients

- In total, 146 patients (71 patients in the 120 mg cohort and 75 in the 240 mg cohort) were accrued over 57 global sites and started treatment between Jun 2022 and Sep 2023
- Due to business reasons, the sponsor decided to discontinue the development of modakafusp alfa and therefore terminate the study early; the data cutoff date for this final analysis was Feb 9, 2024

Question What is the efficacy and safety profile of modakafusp alfa in patients with relapsed/refractory multiple myeloma (RRMM)?

Study design

Patients with RRMM refractory to a PI, IMiD, and an anti-CD38 mAb → Randomized 1:1

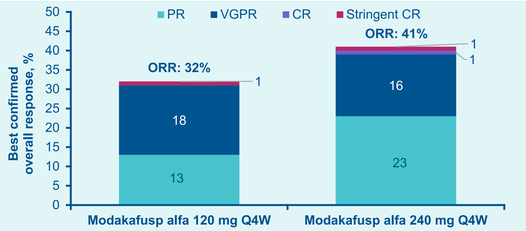
- Modakafusp alfa 120 mg Q4W IV
- Modakafusp alfa 240 mg Q4W IV

Primary endpoint: ORR (partial response [PR] or better)

Key secondary endpoints: DOR, Safety

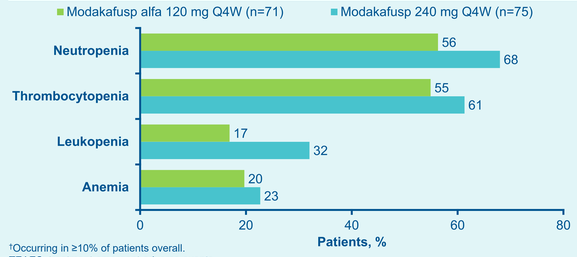
Results

Figure 1. Overall response rates with modakafusp alfa*



*The proportion of patients who achieved a confirmed PR or better during the study (IMWG Uniform Response Criteria).
CR, complete response; IMWG, International Myeloma Working Group; VGPR, very good partial response.

Figure 2. Most common grade ≥3 TEAEs with modakafusp alfa†



†Occurring in ≥10% of patients overall.
TEAES, treatment-emergent adverse events.

Key take aways Our results confirm the efficacy and acceptable safety profile of single-agent modakafusp alfa in patients with RRMM.

Table 1. Baseline patient demographics and characteristics

	Modakafusp alfa 120 mg (n=71)	Modakafusp alfa 240 mg (n=75)	Total (N=146)
Age, years, median (range)	67 (36–82)	68 (42–90)	67 (36–90)
Male, n (%)	37 (52.1)	36 (48.0)	73 (50.0)
Race, n (%)			
White	38 (53.5)	51 (68.0)	89 (61.0)
Black/African American	10 (14.1)	4 (5.3)	14 (9.6)
Asian	5 (7.0)	9 (12.0)	14 (9.6)
NR	18 (25.4)	11 (14.7)	29 (19.9)
No. of prior lines of therapy, median (range)	6 (3–17)	6 (3–15)	6 (3–17)
Prior therapy, n (%)			
Anti-CD38 mAb (in last line)	13 (18.3)	15 (20.0)	28 (19.2)
Anti-BCMA	34 (47.9)	32 (42.7)	66 (45.2)
Antibody drug conjugate	13 (18.3)	19 (25.3)	32 (21.9)
CAR T-cell therapy	12 (16.9)	9 (12.0)	21 (14.4)
T-cell engager	20 (28.2)	13 (17.3)	33 (22.6)
Penta-exposed*	48 (67.6)	49 (65.3)	97 (66.4)
Refractory status, n (%)			
Triple-refractory† and penta-exposed*	47 (66.2)	49 (65.3)	96 (65.8)
Penta-refractory‡	30 (42.3)	20 (26.7)	50 (34.2)

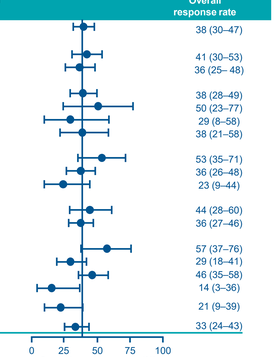
*Exposed to 2 PIs, 2 IMiDs, and an anti-CD38 mAb; †Refractory to an IMiD, a PI, and an anti-CD38 mAb; ‡Refractory to 2 PIs, 2 IMiDs, and an anti-CD38 mAb.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; NR, not reported.

Efficacy

- At a median follow-up of 7.3 months, the ORR was 32% (95% confidence interval [CI], 22–45%) in the 120 mg cohort and 41% (95% CI, 30–53%) in the 240 mg cohort (**Summary Panel**, **Figure 1**)
- ORRs in the combined cohort of 146 patients by prior treatment received and type of myeloma are shown in **Figure 5**
  - ORR was 29% in patients exposed to an anti-B-cell maturation agent (BCMA), and 46% in non-anti-BCMA-exposed patients

Figure 5. ORR subgroup analysis

Subgroup analysis Subgroup	No. of patients	Prior lines of therapy median (range)	Overall response rate
All patients	146	6 (3–17)	38 (30–47)
Gender			
Male	73	6 (3–15)	41 (30–53)
Female	73	6 (3–17)	36 (25– 48)
Race			
White	89	6 (3–17)	38 (28–49)
Black or African American	14	7 (3–13)	50 (23–77)
Asian	14	7 (3–13)	29 (8–58)
Other	29	6 (3–12)	38 (21–58)
Type of myeloma*			
IgA	32	6 (3–10)	53 (35–71)
IgG	80	6 (3–17)	36 (26–48)
Light Chain Only	26	7 (3–15)	23 (9–44)
Cytogenetics risk†			
High risk	39	6 (3–17)	44 (28–60)
Non-High risk	107	6 (3–15)	36 (27–46)
Prior treatment			
Anti-CD38 in last line of therapy	28	5 (3–17)	57 (37–76)
Anti-BCMA exposed	66	7 (4–17)	29 (18–41)
Non Anti-BCMA exposed	80	4 (3–15)	46 (35–58)
Anti-BCMA exposed (CAR-T)	21	8 (4–17)	14 (3–36)
Anti-BCMA exposed (Bispecific TP-cell engagers)	33	7 (4–15)	21 (9–39)
Penta exposed	97	6 (3–17)	33 (24–43)



*Myeloma type from disease characteristics; †Cytogenetics results from local testing.
ADC, antibody drug conjugate; LoT, line of therapy.

- Among 7 patients tested for MRD (120 mg, n=6; 240 mg, n=1), 4 patients were MRD-negative at 10^{-5}
- The median DOR was not reached (95% CI, 6.7–not evaluable [NE]) in the 120 mg Q4W arm and was 9.2 (95% CI, 4.9–NE) months in the 240 mg Q4W arm
- Median investigator-assessed PFS was 4.1 (95% CI, 2.8–7.6) months in the 120 mg Q4W arm and 5.3 (95% CI, 2.8–6.5) months in the 240 mg Q4W arm

Safety

- A summary of TEAEs reported in each arm are shown in **Table 2**
- Rates of grade ≥3 TEAEs were 90.1% in the 120 mg cohort and 96.0% in the 240 mg cohort
- The most common grade ≥3 TEAEs were hematologic in nature and occurred more frequently with the 240 mg versus 120 mg dose (**Summary panel**, **Figure 2**)
- Rates of grade 3–4 infections were 21.1% and 14.7% for patients who received modakafusp alfa 120 mg Q4W and 240 mg Q4W, respectively
- Infusion-related reactions (IRRs) were observed in 25.4% of patients in the 120 mg cohort, and 16.0% of patients in the 240 mg cohort, with rates of grade 3 IRRs of 2.8% and 2.7%, respectively
  - The most common IRR symptoms across both treatment groups were chills (6.2%), flushing (4.8%), and back pain, nausea, and pruritus (each 4.1%)

Table 2. Safety overview with modakafusp alfa

n (%)	Modakafusp alfa 120 mg (n=71)	Modakafusp alfa 240 mg (n=75)	Total (N=146)
Any TEAE	70 (98.6)	75 (100)	145 (99.3)
Drug-related	67 (94.4)	72 (96.0)	139 (95.2)
Grade ≥3 TEAEs	64 (90.1)	72 (96.0)	136 (93.2)
Drug-related	61 (85.9)	64 (85.3)	125 (85.6)
Serious TEAEs	28 (39.4)	33 (44.0)	61 (41.8)
Drug-related	12 (16.9)	13 (17.3)	25 (17.1)
TEAEs leading to drug discontinuation	7 (9.9)	10 (13.3)	17 (11.6)
On-study deaths	4 (5.6)	5 (6.7)	9 (6.2)
Most common TEAEs*			
Thrombocytopenia	53 (74.6)	63 (84.0)	116 (79.5)
Neutropenia	48 (67.6)	55 (73.3)	103 (70.5)
Anemia	31 (43.7)	33 (44.0)	64 (43.8)
Fatigue	21 (29.6)	28 (37.3)	49 (33.6)
Leukopenia	18 (25.4)	25 (33.3)	43 (29.5)
Cough	12 (16.9)	21 (28.0)	33 (22.6)
IRR	18 (25.4)	12 (16.0)	30 (20.5)
Nausea	9 (12.7)	21 (28.0)	30 (20.5)

*Experienced by ≥20% of patients overall.

Conclusions

- These data confirm the single-agent efficacy and tolerability of modakafusp alfa, a first-in-class immunocytokine with novel mechanism of action delivering IFNα signalling to CD38-positive cells in patients with RRMM
- Despite these favorable data, further development of modakafusp alfa has been discontinued by Takeda due to business reasons
- This highlights the complexities surrounding drug development for RRMM in the current era witnessing rapid advances in immunotherapies

References

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;25:739–48
4. Crescioli S, et al. *Curr Allergy Asthma Rep.* 2016;16:7
5. Calabretta E, Carlo-Stella C. *Cells.* 2020;9:802
6. FDA. Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases. Guidance for Industry. U.S. Department of Health and Human Services. Aug 2024. Available online: https://www.fda.gov/media/164555/download (accessed: Oct 2024)
7. Ohno R and Kimura J. *Cancer.* 1986;57:1685–88

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Disclosures

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