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Tagraxofusp in combination with pomalidomide and dexamethasone in relapsed and / or refractory multiple myeloma shows encouraging preliminary efficacy with a manageable safety profile

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Key words: Multiple myeloma, tagraxofusp, pomalidomide, relapsed, refractory, CD123

Two-sentence article summary: This non-randomized, open-label, multicenter, dose-escalation study (NCT02661022) evaluated the safety of tagraxofusp, a first-in-class CD123-targeted therapy, in adult patients with relapsed/refractory multiple myeloma. Tagraxofusp showed a manageable safety profile with 100% of relative dose intensity maintained over a median 5 cycles and no unexpected toxicities, as well as a promising signal for clinical benefit (including a median progression-free survival of 8.8 months and overall response rate of 83.3%).

Letter

Cancer stem cells (CSCs) are present in virtually all tumor types and are potentially responsible for tumor initiation, propagation, and metastasis.[1-3] Relative to normal hematopoietic stem cells and mature hematopoietic cells, the interleukin-3 receptor (IL-3R) is overexpressed on CSCs and in a wide array of hematopoietic malignancies, including multiple myeloma (MM),[2-5] and may correspond with poor outcomes.[6] IL-3 promotes hematopoietic cell line proliferation and differentiation,[7] and targeting IL-3R in MM may confer clinical benefit due to its ubiquitous and differential expression on cells that play a key role in disease pathogenesis, aggressiveness, and treatment resistance.[2,4,5] This may be especially relevant for patients with heavily pretreated, relapsed/refractory (RR) MM, as the unique characteristics of CSCs (eg, slow growth and anti-cell death mechanisms) enable resistance to traditional therapeutics.[2,3] In addition to CSCs, high quantities of IL-3R–expressing plasmacytoid dendritic cells (pDCs) are contained within the bone marrow of MM patients.[4] Interactions between pDCs and MM cells trigger IL-3 release, further promoting cancer growth and survival.[4,5] Tagraxofusp (TAG), a first-in-class CD123-targeted therapy, is a recombinant fusion protein consisting of human IL-3 conjugated to a truncated diphtheria toxin payload that targets cells overexpressing IL-3R, leading to receptor-mediated endocytosis and treatment localization to early endosomes.[5,8] In preclinical research, TAG blocked the growth of pDCs and MM cells without affecting normal peripheral blood mononuclear cells, while TAG administered in combination with bortezomib, dexamethasone (DEX), melphalan, and/or pomalidomide (POM) blocked monocyte-derived osteoclast formation, helping to restore bone marrow-induced osteoblast formation.[4]

TAG as monotherapy is approved in the US and EU for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm, a rare aggressive acute leukemia. This non-randomized, open label, multicenter, dose escalation study (NCT02661022) evaluated the safety of TAG in adult patients with RRMM. This analysis showed a promising signal for clinical benefit, a manageable safety profile, and no unexpected toxicities with single-agent TAG and triplet TAG/POM/DEX therapy in patients with RRMM.

The primary study objectives were to evaluate the safety of single-agent TAG in an initial run-in cycle in patients with RRMM, determine the maximum tolerated dose (MTD) of TAG given in combination with POM/DEX, and characterize the safety and tolerability profiles of triplet TAG/POM/DEX at the MTD. Eligible patients had RRMM; had received ≥2 prior lines of therapy (including a proteasome inhibitor and lenalidomide); and had achieved stable disease or better response to ≥1 treatment cycle of ≥1 prior treatment line, followed by documented disease progression within ≤90 days of last treatment. Patients were also required to have a serum albumin ≥3.2 g/dL in the absence of intravenous (IV) albumin within the previous 72 hours and could not have received any anti-cancer therapy in the 14 days preceding initial run-in treatment. The trial was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines on Good Clinical Practice, and institutional review board or independent ethics committee at each center approved the protocol. All patients provided written informed consent.

Patients received TAG by IV infusion over 15 minutes for 5 consecutive days (days 1-5) of a 28-day cycle. During combination therapy cycles, POM and DEX were administered orally (POM: 4 mg on days 1-21; DEX: 40 mg on days 1, 8, 15, and 22, with a lower initial DEX dose acceptable for patients ≥70 years). Dose escalation comprised a 3+3 design with a single-agent run-in cycle followed by an initial combination therapy cycle with POM/DEX. Patients who received ≥1 dose of TAG who experienced any dose-limiting toxicity (DLT) were discontinued, while patients who did not experience DLT had POM and DEX added to their regimen. DLTs were defined as grade ≥4 neutropenia lasting >7 days or grade ≥3 neutropenia with fever; grade ≥4 thrombocytopenia >7 days or grade ≥3 thrombocytopenia with bleeding; grade 4 transaminase or creatine phosphokinase elevations; or any grade ≥3 non-hematologic toxicity (with the exceptions of fatigue lasting <7 days; nausea, vomiting, diarrhea, arthralgia, myalgia, or fever lasting ≤48 hours and resolving to grade ≤1 or baseline; or asymptomatic grade 3 laboratory abnormalities not considered clinically significant). TAG was to be evaluated at a starting dose of 7 mcg/kg/day, with escalation to 9 and 12 mcg/kg/day or higher, as warranted. For dose expansion, all patients were to receive combination therapy at the MTD established during dose escalation. Patients without evidence of progressive disease or unacceptable toxicity could receive up to 6 cycles of TAG in combination with POM/DEX. Combination treatment with TAG could be extended if determined to be of benefit to the patient.

In addition to DLT, safety assessments included adverse events (AEs) and serious AEs, including treatment-emergent adverse events (TEAE) and treatment-related adverse events (TRAE). Efficacy assessments included progression-free survival (PFS), overall response rate (ORR),

clinical benefit rate, and duration of response (DOR). Clinical benefit was calculated as the sum of complete response (CR), very good partial response (VGPR), partial response (PR), and minimal response, based on International Myeloma Working Group–defined response.[9]

A total of 9 RRMM patients were enrolled, all of whom received TAG run-in treatment (n=7 with TAG 7 mcg/kg/day and n=2 with TAG 9 mcg/kg/day) and were included in the safety population. Three patients discontinued after the TAG run-in (primary reasons for discontinuation were 1 each for DLT [hypoxia], physician decision, and patient decision). The remaining 6 patients received combination therapy (n=5 with 7 mcg/kg/day and n=1 with TAG 9 mcg/kg/day) and comprised the modified intent-to-treat (mITT) population, evaluated for treatment efficacy. All enrolled patients discontinued treatment prior to study completion, primarily due to withdrawal (3/9 [33.3%]), progressive disease (3/9 [33.3%]), AE (2/9 [22.2%]), or physician decision (1/9 [11.1%]).

Patient baseline characteristics by TAG dose are shown in Table 1. The time from original MM diagnosis was a median 60 months, and time from relapse was a median 1.5 months. Over one-half (55.6%) showed CR as best response to prior treatment. Patients had a median 2 prior lines of therapy (range, 1-5); all patients received prior immunomodulatory drugs and proteasome inhibitors; 2 (22.2%) were primary refractory; 2 (22.2%) were double-refractory; no patients were triple-refractory; and 6 (66.7%) patients had relapsed after prior transplant.

The 9 safety patients were exposed to a median 5 cycles of TAG therapy (range, 1-8) for a median 138 days of exposure (range, 1-236). The mean relative dose intensity was 100.0%. Respectively, 6 and 3 patients had dose interruptions and dose reductions due to a TEAE. Two patients discontinued treatment due to TEAEs. One patient in the 7 mcg/kg/day run-in TAG monotherapy dose group had a DLT of grade 3 reversible hypoxia as well as metastatic melanoma. One patient in the 9 mcg/kg/day group discontinued due to grade 2 pancreatitis and also had grade 3 thrombocytopenia and grade 2 capillary leak syndrome, which resolved in 4 days. All patients experienced at least one grade ≥3 TEAE, and all patients had ≥1 TRAE. Table 2 shows TRAEs related to TAG by dose and grade. Overall, the most common grade ≥3 hematologic TRAEs were neutropenia (n=3 [33.3%]) and thrombocytopenia (n=3 [33.3%]); the most common grade ≥3 non-hematologic TRAEs were fatigue and elevated aspartate aminotransferase (each n=1 [11.1%]). Evaluation of hematologic and clinical chemistry parameters revealed no clinically relevant changes within or between treatment groups.

In the mITT population, median PFS was 8.8 months (95% CI: not estimable [NE]-NE) for the TAG 7-mcg group and not reached (NR)(95% CI: NE-NE) for the 9-mcg group. Table 3 summarizes patient response rates and DOR by dose: 5/6 (83.3%) showed an overall response and clinical benefit (all received TAG 7 mcg and had PR as best response). The median DOR was NR (95% CI: 5.4-NE).

In this population of patients with RRMM, TAG, administered as both a single agent and in combination with POM/DEX, was generally safe and tolerable, with manageable toxicity and an

encouraging preliminary signal of activity. The median PFS of 8.8 months (95% CI: NE-NE) for the TAG 7-mcg group compares favorably to the median PFS observed in the phase 3 POM/DEX MM-003 trial of 4.0 months (95% CI: 3.6–4.7).[10] Furthermore, an observed clinical benefit in more than 80% of patients is an impressive signal in a relapsed/refractory population, although the small number of patients treated precludes definitive interpretation of these efficacy data. In the current study, over a median of 5 treatment cycles, 100% of relative dose intensity was maintained, indicating good TAG tolerability. Additionally, the frequency and severity of TEAEs and serious AEs, both related and not related to treatment, were within historical references for this patient population.[11-13] Preclinical evidence indicates that TAG directly targets pDCs and inhibits pDC-triggered MM cell growth and osteolytic bone disease.[4] Given that this mechanism of action is distinct from currently available cancer therapeutics, TAG may be an effective addition to the therapeutic armamentarium against hematologic malignancies, and in RRMM in particular, with further studies warranted, including exploring more convenient and outpatient focused schedules.[14]

1. Hermann PC, Huber SL, Heeschen C. Metastatic cancer stem cells: a new target for anti-cancer therapy? Cell Cycle. 2008;7(2):188-193.

2. Jordan CT, Guzman ML, Noble M. Cancer stem cells. N Engl J Med. 2006;355(12):1253-1261.

3. Jordan CT, Upchurch D, Szilvassy SJ, et al. The interleukin-3 receptor alpha chain is a unique marker for human acute myelogenous leukemia stem cells. Leukemia. 2000;14(10):1777-1784.

4. Ray A, Das DS, Ravillah D, et al. SL-401, a novel targeted therapy directed to the interleukin-3 receptor (IL-3R), blocks plasmacytoid dendritic cell (pDC)-triggered myeloma cell growth and prevents osteoclastogenesis. Blood. 2014;124(21):3441.

5. Frankel AE, Woo JH, Ahn C, et al. Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients. Blood. 2014;124(3):385-392.

6. Vergez F, Green AS, Tamburini J, et al. High levels of CD34+CD38low/-CD123+ blasts are predictive of an adverse outcome in acute myeloid leukemia: a Groupe Ouest-Est des Leucemies Aigues et Maladies du Sang (GOELAMS) study. Haematologica. 2011;96(12):1792-1798.

7. Patnaik MM, Mughal TI, Brooks C, Lindsay R, Pemmaraju N. Targeting CD123 in hematologic malignancies: identifying suitable patients for targeted therapy. Leuk Lymphoma. 2021;62(11):2568-2586.

8. Frankel A, Liu JS, Rizzieri D, Hogge D. Phase I clinical study of diphtheria toxin-interleukin 3 fusion protein in patients with acute myeloid leukemia and myelodysplasia. Leuk Lymphoma. 2008;49(3):543-553.

9. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-1473.

10. Miguel JS, Weisel K, Moreau P, et al. Dimopoulos M. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-1066.

11. Stemline Therapeutics, Inc. ELZONRIS® (tagraxofusp-erzs) prescribing information. https://rxmenarinistemline.com/ELZONRIS_US_Full_Prescribing_Information.pdf. Accessed July 2023.

12. Dechow T, Aldaoud A, Behlendorf T, et al. Pomalidomide plus dexamethasone for patients with relapsed or refractory multiple myeloma: final results of the non-interventional study POSEIDON and comparison with the pivotal phase 3 clinical trials. Eur J Haematol. 2022;108(2):133-144.

13. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123(12):1826-1832.

14. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer J. 2018;8(11):109.

Table 1. Patient Characteristics (All Patients)

	TAG 7 mcg/kg/day, n=7	TAG 9 mcg/kg/day, n=2	Total, N=9
Age			
Median, years	66.0	57.0	65.0
Range	57-70	57-57	57-70
Sex			
Female, N (%)	3 (42.9)	1 (50.0)	4 (44.4)
Male, N (%)	4 (57.1)	1 (50.0)	5. (55.6)
Race/Ethnicity			
White, N (%)	7 (100.0)	2 (100.0)	9 (100.0)
ECOG Performance Status			
0, N (%)	3 (42.9)	2 (100.0)	5 (55.6)
1, N (%)	4 (57.1)	0	4 (44.4)
Time Since Diagnosis			
Median, months	54.3	85.7	60.0
Minimum, maximum	24, 90	60, 111	24, 111
Received Prior Systemic Therapy for MM			
Yes, N (%)	7 (100.0)	2 (100.0)	9 (100.0)
Prior Exposure to IMiDs and PIs			
Yes, N (%)	7 (100.0)	2 (100.0)	9 (100.0)
Best Response to Prior Treatment			
CR, N (%)	4 (57.1)	1 (50.0)	5 (55.6)
PR, N (%)	2 (28.6)	0	2 (22.2)
Other, N (%)	1 (14.3)	1 (50.0)	2 (22.2)
Relapse On or After Treatment			
Yes, N (%)	7 (100.0)	2 (100.0)	9 (100.0)
Time Since Relapse			
Median, months	1.7	0.4	1.5
Minimum, maximum	0, 39	0, 0	0, 39
Primary Refractory			
Yes, N (%)	2 (28.5)	0	2 (22.2)
Double Refractory to PI/IMiD			
Yes, N (%)	2 (28.5)	0	2 (22.2)
Relapsed after Prior Transplant			
Yes, N (%)	4 (57.1)	2 (100.0)	6 (66.7)
Lines of Prior Therapy			
Median, N	2	2	2
Minimum, maximum	1, 5	2, 2	1, 5

Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; IMiDs = immunomodulatory drugs; MM = multiple myeloma; PIs = proteasome inhibitors; PR = partial response; TAG = tagraxofusp.

Table 2. Hematologic and Non-Hematologic Treatment-related Adverse Events[a] by Dose and Grade

TRAE, N (%)	TAG 7 mcg/kg/day n=7		TAG 9 mcg/kg/day n=2		Total N=9	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Hematologic (Reported for ≥2 patients)						
Lymphopenia	0	2 (28.6	0	0	0	2 (22.2)
Neutropenia	1 (14.3)	3 (42.9)	0	0	1 (11.1)	3 (33.3)
Thrombocytopenia	1 (14.3)	1 (14.3)	0	1 (50.0)	1 (11.1)	2 (22.2)
Non-hematologic (Reported for ≥3 patients)						
Fatigue	5 (71.4)	1 (14.3)	1 (50.0)	0	6 (66.7)	1 (11.1)
Nausea	5 (71.4)	0	1 (50.0)	0	6 (66.7)	0
Pyrexia	4 (57.1)	0	2 (100.0)	0	6 (66.7)	0
Hypoalbuminemia	4 (57.1)	0	1 (50.0)	0	5 (55.6)	0
Chills	4 (57.1)	0	0	0	4 (44.4)	0
AST increased	2 (28.6)	0	1 (50.0)	1 (50.0)	3 (33.3)	1 (11.1)
Dizziness	3 (42.9)	0	0	0	3 (33.3)	0
Flushing	3 (42.9)	0	0	0	3 (33.3)	0
Headache	2 (28.6)	0	1 (50.0)	0	3 (33.3)	0
Peripheral edema	3 (42.9)	0	0	0	3 (33.3)	0

[a]Treatment-related adverse events are specific to TAG (not POM or DEX).

Abbreviations: AST = aspartate aminotransferase; DEX = dexamethasone; POM = pomalidomide; TAG = tagraxofusp; TRAE, treatment-related adverse event.

Table 3. Summary of Response Rate and Duration of Response by Dose (Modified Intent-to-Treat Population)[a]

	TAG 7 mcg/kg/day, n=5	TAG 9 mcg/kg/day, n=1	Total, N=6
Overall response rate, N (%)	5 (100.0)	0	5 (83.3)
Best response			
Partial response, N (%)	5 (100.0)	0	5 (83.3)
Stable Disease, N (%)	0	1 (100.0)	1 (16.7)
Median DOR, months (95% CI)	NR (5.4-NE)	NA	NR (5.4-NE)
CB rate,[b] N (%)	5 (100.0)	0	5 (83.3)

[a]3 out of 9 enrolled patients discontinued after the run-in cycle, did not receive treatment for Cycle 1, and were not included in the mITT population.
[b]CB is calculated as sum of CR, VGPR, PR, and MR; based on IMWG-defined response.

Abbreviations: CB = clinical benefit; CR = complete response; DOR = duration of response; IMWG = International Myeloma Working Group; mITT = modified intent-to-treat; MR = minimal response; NA = not applicable; NE = not estimable; NR = not reached; PR = partial response; TAG = tagraxofusp; VGPR = very good partial response.