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

Cancer stem cells (CSC) 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 CSC 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 CSC (e.g., slow growth and anti-cell death mechanisms) enable resistance to traditional therapeutics.[2,3] In addition to CSC, high quantities of IL-3R-expressing plasmacytoid dendritic cells (pDC) are contained within the bone marrow of MM patients.[4] Interactions between pDC 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 pDC 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, multi-center, dose escalation study (*clinicaltrials gov. Identifier: 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 Harmonization 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. DLT 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 six 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 (AE) and serious AE, including treatment-emergent AE (TEAE) and treatment-related AE (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 nine 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 six patients received combination therapy (N=5 with 7 mcg/kg/day and N=1 with 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 two prior lines of therapy

Table 1. Patient characteristics (all patients).

	TAG 7 mcg/kg/day N=7	TAG 9 mcg/kg/day N=2	Total N=9
Age in years			
Median	66.0	57.0	65.0
Range	57-70	57-57	57-70
Sex, N (%)			
Female	3 (42.9)	1 (50.0)	4 (44.4)
Male	4 (57.1)	1 (50.0)	5 (55.6)
Race/ethnicity, N (%)			
White	7 (100.0)	2 (100.0)	9 (100.0)
ECOG performance status, N (%)			
0	3 (42.9)	2 (100.0)	5 (55.6)
1	4 (57.1)	0	4 (44.4)
Time since diagnosis in months			
Median	54.3	85.7	60.0
Minimum-maximum	24-90	60-111	24-111
Received prior systemic therapy for MM, N (%)			
Yes	7 (100.0)	2 (100.0)	9 (100.0)
Prior exposure to IMiD and PI, N (%)			
Yes	7 (100.0)	2 (100.0)	9 (100.0)
Best response to prior treatment, N (%)			
CR	4 (57.1)	1 (50.0)	5 (55.6)
PR	2 (28.6)	0	2 (22.2)
Other	1 (14.3)	1 (50.0)	2 (22.2)
Relapse on or after treatment, N (%)			
Yes	7 (100.0)	2 (100.0)	9 (100.0)
Time since relapse in months			
Median	1.7	0.4	1.5
Minimum-maximum	0-39	0-0	0-39
Primary refractory, N (%)			
Yes	2 (28.5)	0	2 (22.2)
Double refractory to PI/IMiD, N (%)			
Yes	2 (28.5)	0	2 (22.2)
Relapsed after prior transplant, N (%)			
Yes	4 (57.1)	2 (100.0)	6 (66.7)
Number of prior lines of therapy			
Median	2	2	2
Minimum-maximum	1-5	2-2	1-5

CR: complete response; ECOG: Eastern Cooperative Oncology Group; ImiD: immunomodulatory drugs; MM: multiple myeloma; PI: proteasome inhibitors; PR: partial response; TAG: tagraxofusp.

(range, 1-5); all patients received prior immunomodulatory drugs and proteasome inhibitors; two (22.2%) were primary refractory; two (22.2%) were double-refractory; no patients were triple-refractory; and six (66.7%) patients had relapsed after prior transplant.

The nine safety patients were exposed to a median five 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, six and three patients had dose interruptions and dose reductions due to a TEAE. Two patients discontinued treatment due to TEAE. 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 TRAE related to TAG by dose and grade. Overall, the most common grade ≥3 hematologic TRAE were neutropenia (N=3 [33.3%]) and thrombocytopenia (N=3 [33.3%]); the most common grade ≥3 non-hematologic TRAE 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.

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	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 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 (TRAE) are specific to tagraxofusp (TAG) (not pomalidomide [POM] or dexamethasone [DEX]). AST: aspartate aminotransferase.

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, N (%) Partial response Stable disease	 5 (100.0) 0	 0 1 (100.0)	 5 (83.3) 1 (16.7)
Median DOR in months (95% CI)	NR (5.4-NE)	NA	NR (5.4-NE)
CB rate,[b] N (%)	5 (100.0)	0	5 (83.3)

[a]Three of 9 enrolled patients discontinued after the run-in cycle, did not receive treatment for cycle 1, and were not included in the modified intent-to-treat (mITT) population. [b]Clinical benefit (CB) is calculated as sum of complete response (CR), very good partial response (VGPR), partial response (PR), and minimal response (MR); based on International Myeloma Working Group-defined response. TAG: tagraxofusp; NA: not applicable; NE: not estimable; NR: not reached; DOR: duration of response; CI: confidence interval.

In the mITT population, median PFS was 8.8 months (95% confidence interval [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: five of six (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 III 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 five treatment cycles, 100% of relative dose intensity was maintained, indicating good TAG tolerability. Additionally, the frequency and severity of TEAE and serious AE, both related and not related to treatment, were within historical references for this patient population.[11-13] Preclinical evidence indicates that TAG directly targets pDC 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]

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Data-sharing statement

Data that underlie the results reported in a published article may be requested for products and the relevant indications that have been authorized by the regulatory authorities in Europe/the United States (or, if not, 2 years have elapsed since the study completion). The Menarini Group will review requests individually to determine whether (i) the requests are legitimate and relevant and meet sound scientific research principles, (ii) the requests are within the scope of the participants' informed consent, and (iii) the request is compliant with any applicable law and regulation and with any contractual relationship that Menarini Group and its affiliates and partners have in place with respect to the study and/or the relevant product. Prior to making data available, requestors will be required to agree in writing to certain obligations, including, without limitation, compliance with applicable privacy and other laws and regulations. Proposals should be directed to medicalinformation@menarinistemline.com.

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