Tagraxofusp, an Anti-CD123 Therapy, in Patients With Blastic Plasmacytoid Dendritic Cell Neoplasm: Sub-analysis of a Pivotal Trial by Age and Baseline Disease Involvement

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INTRODUCTION

BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN)[1]

- BPDCN is an aggressive hematologic malignancy associated with a poor prognosis
- BPDCN is characterized by clonal expansion of plasmacytoid dendritic tumor cells expressing specific markers, including the IL-3 receptor alpha (CD123)
- Median age at diagnosis is 60–70 years, with clinical presentation marked by skin and bone marrow involvement
  - Secondary sites include peripheral blood, lymph nodes, viscera, and CNS involvement

TAGRAXOFUSP (TAG)[2]

- Tagraxofusp (TAG, SL-401) is a first-in-class CD123-targeted agent approved by the United States FDA (December 2018)[3,4] and EMA (January 2021)[5] for patients with BPDCN
- TAG is a recombinant fusion protein composed of human IL-3 fused to a truncated diphtheria toxin payload that irreversibly blocks protein synthesis and induces cell death once internalized in CD123-bearing cells



Aim: To determine whether age or extent of baseline disease involvement impact outcomes following TAG treatment in first-line patients with BPDCN

CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; IL-3, interleukin-3.

STUDY DESIGN

- Multicenter, 4-stage, single-arm, phase 1/2 trial evaluating TAG monotherapy in patients with first-line (1L) or relapsed/refractory (R/R) BPDCN

Stage 1 Lead-in, dose escalation	Stage 2 Expansion	Stage 3 Pivotal, confirmatory	Stage 4 Continued access
▶ 1L and R/R ▶ TAG 7 mcg/kg or 12 mcg/kg	▶ 1L and R/R ▶ TAG 12 mcg/kg	▶ 1L ▶ TAG 12 mcg/kg	▶ 1L and R/R ▶ TAG 12 mcg/kg

TAG administered via IV infusion on days 1–5 of a 21-day cycle

Key Eligibility Criteria

- Albumin ≥3.2 g/dL

Main Outcome Measures

- CR (defined as CR + CRc), ORR, OS, safety

CR, complete response; CRc, complete response with residual skin abnormality not indicative of active disease; IV, intravenous; ORR, overall response rate; OS, overall survival; R/R, relapsed/refractory.

REFERENCES:

1. Pagano L, et al. *Br J Haematol*. 2016;174:188-202; **2.** Pemmaraju N, et al. *N Engl J Med*. 2019;380:1628-1637; **3.** ELZONRIS (tagraxofusp-erzs) [prescribing information]. New York, NY: Stemline Therapeutics, Inc. 2018; **4.** Jen EY, et al. *Clin Cancer Res*. 2020;26(3):532-536; **5.** ELZONRIS [summary of product characteristics]. Amsterdam, Netherlands: Stemline Therapeutics B.V. 2018. **6.** Stevens SR, et al. *Arch Dermatol*. 2002;138:42-48.

RESULTS

- 65 first-line patients received TAG at 12 mcg/kg

Table 1. Demographics and Baseline Characteristics

Parameter	Age Subgroup, years			Baseline Disease Involvement*		
	<60 (n=17)	≥60 to ≤75 (n=39)	>75 (n=9)	Skin-only (n=18)	Systemic-only** (n=4)	Skin + systemic (n=42)
Gender, n (%)						
Male	12 (70.6)	32 (82.1)	8 (88.9)	13 (72.2)	4 (100)	34 (81.0)
Female	5 (29.4)	7 (17.9)	1 (11.1)	5 (27.8)	0	8 (19.0)
Median age, years (range)	41.0 (22-59)	69.0 (61-75)	79.0 (76-84)	67.0 (28-84)	65.0 (57-72)	68.5 (22-84)
ECOG PS, n (%)						
0	11 (64.7)	18 (46.2)	2 (22.2)	12 (66.7)	1 (25.0)	17 (40.5)
1	5 (29.4)	20 (51.3)	6 (66.7)	6 (33.3)	3 (75.0)	22 (52.4)
2	0	1 (2.6)	1 (11.1)	0	0	2 (4.8)
Missing	1 (5.9)	0	0	0	0	1 (2.4)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; TAG, tagraxofusp.
*One patient was excluded from baseline analysis as not meeting criteria for systemic disease – pretreatment bone marrow biopsy confirmed 3% blast count.
**Patients with active or suspected CNS leukemia were excluded.

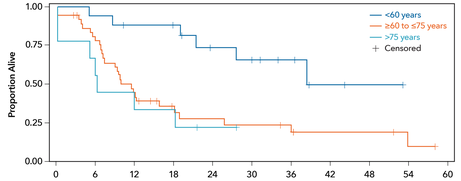
- Similar rates of CR/CRc and ORR were seen across the age cohorts
- Highest number of patients bridging to HSCT was in the <60 years age group
- Greatest survival benefit (median OS, 38.4 months) was seen in the <60 years age group

Table 2. Efficacy Outcomes and Overall Survival Stratified by Age

Parameter	Age Subgroup, years		
	<60 (n=17)	≥60 to ≤75 (n=39)	>75 (n=9)
Response rate, n (%)			
ORR	13 (76.5)	29 (74.4)	7 (77.8)
CR/CRc	10 (58.5)	23 (59.0)	4 (44.4)
Duration of Objective Response, months (95% CI)	NR (4.6, NR)	6.6 (2.3, NR)	3.8 (0.7, NR)
Bridged to HSCT, %	58.8	25.6	11.1
Median OS, months (95% CI)	38.4 (21.5, NR)	11.5 (7.2, 18.0)	6.2 (0.3, NR)
Survival probability, %			
12 months	88.2	44.6	33.3
18 months	88.2	35.5	33.3
24 months	74.0	27.6	22.2

CI, confidence interval; CR, complete response; CRc, complete response with residual skin abnormality not indicative of active disease; HSCT, hematopoietic stem cell transplant; NR, not reached; ORR, objective response rate; OS, overall survival.

Figure 1. Overall Survival Stratified by Age



- Similar response rates were observed across the cohorts stratified by baseline disease involvement
- Highest proportion of patients bridging to HSCT were those with baseline skin-only disease

Table 3. Efficacy Outcomes and Overall Survival Stratified by Baseline Disease Involvement

Parameter	Baseline Disease Involvement*		
	Skin-only (n=18)	Systemic-only** (n=4)	Skin + systemic (n=42)
Response rate, n (%)			
ORR	13 (72.2)	3 (75.0)	32 (76.2)
CR/CRc	13 (72.2)	2 (50.0)	21 (50.0)
Duration of Objective Response, months (95% CI)	24.9 (2.5, NR)	NR (3.0, NR)	NR (2.3, NR)
Bridged to HSCT, %	44.4	0	31.0
Median OS, months (95% CI)	18.2 (7.2, NR)	NR (5.3, NR)	11.9 (7.3, 35.9)
Survival probability, %			
12 months	58.4	50.0	49.5
18 months	50.0	50.0	46.6
24 months	40.0	50.0	39.5

CI, confidence interval; CR, complete response; CRc, complete response with residual skin abnormality not indicative of active disease; HSCT, hematopoietic stem cell transplant; NR, not reached; OS, overall survival.
*One patient was excluded from baseline analysis as not meeting criteria for systemic disease – pretreatment bone marrow biopsy confirmed 3% blast count; **Patients with active or suspected CNS leukemia were excluded.

Figure 2. Overall Survival Stratified by Baseline Disease Involvement

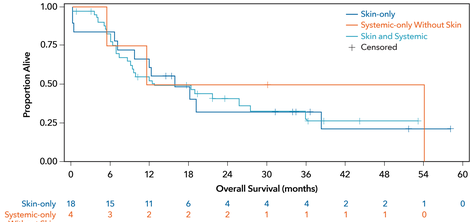


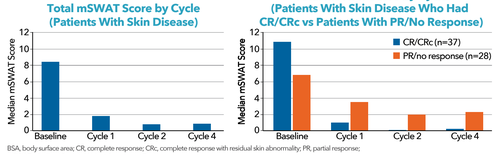
Table 4. Overall Efficacy Outcomes for Patients Who Bridged to HSCT

Parameter, n (%)	Baseline (N=65)	Complete remission	HSCT after CR
Age, years			
≥65	39 (60)	22/39 (56)	9/22 (41)
<65	26 (40)	15/26 (58)	10/15 (67)
Cardiac history*			
Yes	17 (26)	10/17 (59)	4/10 (40)
No	48 (74)	27/48 (56)	15/27 (56)
BM blasts ≥5%			
Yes	32 (49)	17/32 (53)	7/17 (41)
No	33 (51)	20/33 (61)	12/20 (60)
≥2 disease sites			
Yes	45 (69)	23/45 (51)	11/23 (48)
No	20 (31)	14/20 (70)	8/14 (57)

BM, bone marrow; CR, complete response; HSCT, hematopoietic stem cell transplant.
*Cardiac history is defined as having at least 1 of the following: coronary artery disease, congestive heart failure (controlled; non-Class III or IV), myocardial infarction (>6 months prior to study start), controlled atrial fibrillation, atrial flutter, sick sinus syndrome, or ventricular fibrillation.

Figure 3. Modified Severity Weight Assessment Tool (mSWAT) Analysis

- mSWAT is a skin scoring tool, which utilizes a percentage of total BSA involved by patches, plaques, and tumors. The percentage of involved BSA for each type of lesion is then multiplied by a weighting factor (patch =1, plaque =2, tumor =4), and scores are summed together.[6]
- A complete response is defined as 100% clearance of skin lesions or no new lesions in patients without lesions at baseline. A partial response is defined as 50-90% clearance of skin disease from baseline without any new lesions.
- TAG has pronounced and rapid effects on skin disease as measured by mSWAT



BSA, body surface area; CR, complete response; CRc, complete response with residual skin abnormality; PR, partial response; mSWAT, Modified Severity Weight Assessment Tool.

Example of a Dermatologic Response to TAG[2]

- Photographs of chest and back of a 71-year-old female patient participating in clinical trial
- First-line patient with extensive skin and bone BM involvement
- Received 6 cycles of TAG 12 mcg/kg
- Panel A (baseline): Extensive skin and BM involvement
  - BM blasts: 14%
  - mSWAT: 11.3%
- Panel B (day 21): Skin and BM responses
  - BM blasts: 3%
  - mSWAT: 0%
- Bridged to HSCT after achieving CR and 6 cycles of TAG

A. Before Treatment



B. Day 21 After Treatment Initiation



BM, bone marrow; CR, complete response; HSCT, hematopoietic stem cell transplant; mSWAT, Modified Severity Weight Assessment Tool; TAG, tagraxofusp.

- Safety profile was similar across the age groups

Table 5. Safety Outcomes Stratified by Age

Most common TEAEs, n (%)	Age Subgroup, years		
	<60 (n=17)	≥60 to ≤75 (n=39)	>75 (n=9)
Increased ALT	10 (59)	19 (49)	5 (56)
Increased AST	9 (53)	19 (49)	5 (56)
Thrombocytopenia	9 (53)	10 (26)	1 (11)
Pyrexia	7 (41)	7 (18)	4 (44)
Hypoalbuminemia	6 (35)	16 (41)	3 (33)
Chills	5 (30)	5 (13)	1 (11)
Fatigue	4 (24)	6 (15)	1 (11)
Anemia	4 (24)	5 (13)	0
Leukopenia	4 (24)	1 (3)	0
Increased weight	3 (20)	12 (31)	3 (33)
Nausea	3 (20)	10 (26)	2 (22)
Neutropenia	3 (20)	3 (8)	1 (11)
Capillary leak syndrome	1 (6)	9 (23)	2 (18)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Tagraxofusp is the first-in-class CD123-targeted therapy and the first approved treatment for BPDCN in both the United States and Europe

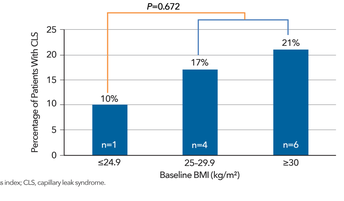
- Site of baseline disease did not predispose patients to different TEAEs

Table 6. Safety Outcomes Stratified by Baseline Disease Involvement

Most common TEAEs, n (%)	Baseline Disease Involvement		
	Skin-only (n=18)	Systemic-only (n=4)	Skin + systemic (n=42)
Increased ALT	10 (53)	3 (75)	30 (71)
Pyrexia	10 (53)	1 (25)	16 (38)
Increased AST	9 (47)	3 (75)	27 (64)
Fatigue	9 (47)	3 (75)	15 (36)
Hypoalbuminemia	9 (47)	1 (25)	18 (43)
Increased weight	9 (47)	0	15 (36)
Nausea	7 (37)	3 (75)	18 (43)
Thrombocytopenia	6 (32)	1 (25)	19 (45)
Hyperglycemia	6 (32)	2 (50)	12 (29)
Edema peripheral	6 (32)	2 (50)	12 (29)
Constipation	6 (32)	2 (50)	11 (26)
Hyperkalemia	2 (11)	2 (50)	5 (12)
Capillary leak syndrome	4 (21)	0	7 (17)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Figure 4. Incidence of CLS in First-Line Patients Stratified by BMI (n=11)



BMI, body mass index; CLS, capillary leak syndrome.

CONCLUSIONS

- This is the largest prospective trial to date evaluating TAG for treatment of BPDCN
- High response rates in first-line patients (ORR=75%; CR/CRc=57%), with median duration of CR/CRc of 24.9 months
  - High rates of durable CRs enabled over half of the patients in CR to be bridged to HSCT, including older adults and patients with extensive baseline disease
- Efficacious across all age cohorts, including older patients and those with significant baseline disease
  - Adverse events were manageable, and the safety profile was similar between older and younger patients
  - Site of baseline disease did not predispose patients to different TEAEs
- TAG is the first-in-class CD123-targeted therapy and the first approved treatment for BPDCN in both the United States and Europe