Findings from an Observational, Multicenter, Retrospective Analysis of Patients With Blastic Plasmacytoid Dendritic Cell Neoplasm Treated With Tagraxofusp in the European Expanded Access Program

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INTRODUCTION

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematologic malignancy with poor prognosis with a median overall survival of around 1 year[1]
- BPDCN is characterized by clonal expansion of plasmacytoid dendritic tumor cells expressing specific markers, including the IL-3 receptor alpha (CD123)[2,3]
- Tagraxofusp (TAG, SL-401) is a first-in-class CD123-targeted agent approved by the United States FDA (December 2018)[4,5] and EMA (January 2021)[6] 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 (**Figure 1**)
- In August 2019, a global Expanded Access Program (EAP) was initiated in Europe to provide patients access to and gather experience on the safety and efficacy of TAG in real-world practice

EMA, European Medicines Agency; FDA, Food and Drug Administration; IL-3, interleukin-3; OS, overall survival.

Figure 1: Tagraxofusp – Novel CD123-Targeted Therapy



CD-123, interleukin-3 receptor alpha chain; IL-3, interleukin-3

METHODS

STUDY DESIGN

- Non-interventional, retrospective, observational, multicenter, single-arm study of patients with BPDCN treated with TAG in a real-world setting from August 2019 to December 2021

ELIGIBILITY CRITERIA

- Key inclusion criteria
  - Diagnosis of BPDCN confirmed by hematopathology and immunophenotyping with established marker panels (including CD123, CD4 and CD56)

PRIMARY OBJECTIVES

- Complete response (CR) after 2-3 cycles of treatment with TAG in first-line and relapsed/refractory settings
- Incidence and severity of capillary leak syndrome (CLS)

SECONDARY OBJECTIVES

- Rate of patients bridged to hematopoietic stem cell transplantation (HSCT)
- Incidence and severity of adverse events (AEs)
- Number of TAG doses administered in each cycle

BPDCN, blastic plasmacytoid dendritic cell neoplasm; TAG, tagraxofusp.

DOSING:

- TAG, 12 mcg/kg IV once daily for a total of 5 doses on days 1-5 (up to day 10 was allowed) of a 21-day cycle
- Hospitalization required only for the first cycle (subsequent cycles could be administered in an outpatient setting)

PATIENT POPULATION:

- 80 patients (n=76 adults and n=4 pediatrics) with BPDCN treated with TAG according to the EU SMPC[6] in a standard clinical practice setting across multiple sites in Europe
- Data was collected from the TAG request form and the current analysis from patient case data on a subset of 15 adult patients

BPDCN, blastic plasmacytoid dendritic cell neoplasm; EU, European; IV, intravenous; SMPC, summary of product characteristics; TAG, tagraxofusp.

RESULTS

As of 11 April 2022, 15 of 76 adult patients enrolled in the European EAP had data available (**Tables 1 & 2**)

Table 1. BPDCN History and Baseline Assessments

	Total (N=15)
Country representation, n (%)	
Germany	5 (33)
France	4 (27)
Italy	2 (13)
Switzerland	2 (13)
Austria	1 (7)
Spain	1 (7)
Median age, yrs (range)	68 (21-82)
Sex, n (%)	
Male	12 (80)
Female	3 (20)
Treatment setting, n (%)	
First-line	12 (80)
Relapsed/refractory	3 (20)
Median number of cycles, n (range)	3 (1-7)
Median duration of treatment, months (range)	2.5 (0.7-8.2)
Disease duration at TAG start[a,b]	
Median months (range)	2.0 (0.5-21.5)
Disease presentation at initial diagnosis, n (%)	
Skin involvement	12 (80)
Bone marrow	12 (80)
Lymph nodes[c]	7 (47)
Spleen	3 (20)
Bulky disease (any lesion >7 cm either single or multiple)	2 (13)
CNS	2 (13)
Liver	1 (7)
Ann Arbor staging, n (%)[d]	
I	3 (20)
II	0
III	2 (13)
IV	6 (40)
Number of lesions, n (%)	
Single	2 (13)
Multiple	10 (67)
Patients with BPDCN assessed, n (%)	
Bone marrow	12 (80)
Infiltration by BPDCN, n	9 (75)
Skin (mSWAT)	11 (73)
Lymph node	9 (60)
Blood	7 (47)
Visceral involvement (other than bone marrow)	5 (33)
Spleen	4 (27)

CNS, central nervous system; mSWAT, Modified Severity-Weighted Assessment Tool; TAG, tagraxofusp.

[a]Calculated as (date of TAG first dose - date of BPCDN first diagnosis + 1)/30.4375. [b]n = 14; 1 patient missing. [c]Multiple sites. [d]CT or PET scan was performed on 15 patients.

Preliminary real-world data on tagraxofusp from an ongoing European early access program reports efficacy and a manageable safety profile

Table 2. Overview of Immunophenotyping Analysis

	Total (N=15)		
	Skin[a]	Bone Marrow	Other Tissue
Type of immunophenotyping analysis, n (%)			
Immunohistochemistry	10 (67)	5 (33)	2 (13)
Flow cytometry	0	5 (33)	0
Other	1 (7)	0	0
Markers, n (%)			
CD123	9 (60)	8 (53)	2 (13)
CD4	11 (73)	8 (53)	2 (13)
CD56	10 (67)	7 (47)	1 (7)

[a]n=1 missing for type of immunophenotyping analysis.

SAFETY

- The majority of Grade 3/4 AEs & SAEs, related/unrelated to TAG occurred on cycle 1

Table 3. Summary of Grade 3/4 AEs or SAEs: Overall Cycles and Cycle 1

	Total (N=15)	
	Overall Cycles	Cycle 1
TEAEs:		
Patients with ≥1 grade 3/4 AE or SAE, n (%)	8 (53)	7 (47)
Total number of cases/incidence rate per 100 person years[a]	11/0.3	7[b]
Grade 3/4 AE or SAE, n (%)		
Anaphylactic reaction	1 (7)	0
Confusional state	1 (7)	1 (7)
Hepatotoxicity	1 (7)	1 (7)
Hypertransaminasemia	1 (7)	1 (7)
Increased AST	1 (7)	1 (7)
TRAEs:		
Patients with ≥1 grade 3/4 AE or SAE related to TAG, n (%)	6 (40)	6 (40)
Total number of cases/incidence rate per 100 person years[a]	8/0.2	9[b]
Grade 3/4 AE or SAE related to TAG, n (%)		
Capillary leak syndrome (grade 3)	2 (13)	2 (13)
Hypertransaminasemia	1 (7)	1 (7)
Increased AST	1 (7)	1 (7)

AE, adverse event; AST, aspartate aminotransferase; SAE, serious adverse event; TAG, Tagraxofusp; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.
[a]Person years calculated from TAG start date to TAG end date. [b]Only relates to total number of cases.

- Seven CLS events occurred in 5 of the 15 patients (33%), with 5 events occurring in 5 patients during cycle 1 (**Table 4**)
- Overall, the majority of all CLS events (5/7 [71%]) were non severe (grade ≤2)
  - No patients experienced a grade 5 event
- All 7 CLS events were resolved

Table 4. Summary of CLS Events: Overall Cycles and Cycle 1

	Overall Cycles	Cycle 1
N (number of events)	7	5
Grade, n (%)		
1	0	0
2	5 (71)	3 (60)
3	2 (29)	2 (40)
4	0	0
Median duration, days (range)	9.0 (4.0-11.0)	8.0 (4.0-11.0)

CLS, capillary leak syndrome; SD, standard deviation.

Table 5. Summary of Grade 1/2 and Grade 3/4 Hematologic AEs: Overall Cycles and Cycle 1

	Total (N=15)	
	Overall Cycles	Cycle 1
Patients with ≥1 hematologic AE, n (%)	10 (67)	10 (67)
Grade 1/2, n (%)	6 (40.0)	4 (26.7)
Grade 3/4, n (%)	7 (46.7)	7 (46.7)
Total number of cases/Incidence rate per 100 person years[a]	26/0.7	15[b]
Grade 1/2, n (%)		
Thrombocytopenia	4 (27)	2 (13)
Anemia	1 (7)	1 (7)
Decreased platelet count	1 (7)	1 (7)
Increased AST	1 (7)	1 (7)
Increased ALT	1 (7)	0
Neutropenia	1 (7)	0
Grade 3/4, n (%)		
Thrombocytopenia	5 (33)	5 (33)
Neutropenia	2 (13)	2 (13)
Anemia	1 (7)	1 (7)
Decreased platelet count	1 (7)	0
Increased ALT	1 (7)	1 (7)
Leukopenia	1 (7)	0
Platelet count	1 (7)	1 (7)
Patients with ≥1 hematologic AE related to TAG, n (%)	5 (33)	5 (33)
Grade 1-2, n (%)	3 (20.0)	2 (13.3)
Grade 3-4, n (%)	3 (20.0)	3 (20.0)
Total number of cases/Incidence rate per 100 person years[a]	11/0.3	6[b]
Grade 1/2 related to TAG, n (%)		
Anemia	1 (7)	1 (7)
Decreased platelet count	1 (7)	1 (7)
Thrombocytopenia	1 (7)	0
Grade 3/4 related to TAG, n (%)		
Thrombocytopenia	3 (20)	3 (20)
Neutropenia	1 (7)	1 (7)

AE, adverse event; AST, aspartate aminotransferase; SAE, serious adverse event; TAG, Tagraxofusp.
[a]Person years calculated from TAG start date to TAG end date. [b]Only relates to total number of cases.

EFFICACY

Table 6. Best Overall Response*

	All Assessed Patients (n=15)	First-line Patients (n=12)	Relapsed/Refractory Patients (n=3)
Complete response, n (%)	6 (40)	5 (50)	0
Partial response, n (%)	5 (33)	4 (13)	1 (33)

- 8 of the 12 first-line patients (67%) were bridged to allogeneic HSCT (**Table 7**)

*As of the data cutoff date

Table 7. Overview of HSCT Data

	Total (N=15)
Patients who received HSCT, n (%)	8 (44)
Disease status prior to transplant, n (%)[a]	
Complete remission	5 (63)
Partial remission	3 (38)
Type of HSCT, n (%)[a]	
Allogeneic	8 (100)
Donor type[b]	
MUD	4 (50)
Other	2 (25)
HALM identical sibling	1 (13)
Haplo	1 (13)
Conditioning regimen[b]	
MAC	2 (25)
RIC	2 (25)
Other	2 (25)
Not available	2 (25)
Autologous	0
Patients with GVHD, n (%)[a]	
Acute GVHD	4 (50)
Chronic GVHD	2 (50)
Disease status after HSCT, n (%)[a]	
Complete remission	6 (75)
Partial remission	1 (13)
Stable disease	0
Progressive disease/relapse	0
Patient restarted TAG[c]	0
SOD or VOD assessed, n (%)[a]	
Yes	1 (13)
No	5 (63)
Unknown	2 (25)

GVHD, graft versus host disease; Haplo, haploidentical; HSCT, hematological stem cell transplant; IV, intravenous; MAC, myeloablative conditioning; MUD, matched unrelated donor; RIC, reduced intensity conditioning; SOD, sinusoidal obstruction syndrome; TAG, Tagraxofusp; VOD, veno-occlusive liver disease.
[a]Percentages calculated from the number of patients eligible and received HSCT. [b]Percentages calculated from the number of patients with allogeneic type of HSCT. [c]Percentage calculated from the number of patients who had progressive disease/relapse following HSCT.

CONCLUSIONS

- As of 11 April 2022, 15 of 76 adult patients enrolled in the European EAP had data available.
- This is the largest retrospective analysis of real-world clinical practice outside of a clinical trial in patients with BPDCN treated with TAG.
- Median age was 68 years (range, 21-82) and the majority of patients were male (80%), representing real-world distribution.
- Of the 12 first-line patients: CR (n=6; 50%); PR (n=4; 33%).
  - 8 of the 12 first-line patients were bridged to allogeneic HSCT.
- AEs and SAEs mainly occurred in cycle 1 in an inpatient setting:
  - Only Grade 2-3 CLS events were reported in this subset analysis of 15 patients.
  - No grade 5 CLS events were reported in the entire population (n=80) enrolled in the EAP.
  - All cases of CLS were resolved.
- These preliminary results confirm the feasibility and safety of TAG, including in elderly patients, with a manageable safety profile.
- The detailed adherence of health care professionals to the EAP guidelines and multidisciplinary training is thought to have positively affected the prevention and management of CLS and other grade 3-4 AEs.
- Data collection is still ongoing for a larger analysis of the remaining patients enrolled in the EAP.

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