Preliminary Results from an Observational Multicenter Study 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 myeloid malignancy with poor prognosis and a median overall survival (OS) of ~1 year[1]
- It is derived from plasmacytoid dendritic cell precursors expressing CD123, the interleukin-3 receptor alpha (IL-3Rα), which is overexpressed in all cases of BPDCN[2,3]
- Tagraxofusp (TAG), a first-in-class CD123-directed therapy, is composed of a recombinant human IL-3 fused to a truncated diphtheria toxin payload (**Figure 1**)[4]
- In the pivotal 0114 BPDCN study (NCT02113982), treatment with TAG 12 mcg/kg demonstrated a well-characterized and manageable safety profile and resulted in an overall response rate of 75% in first-line (1L) and 58% in relapsed/refractory (R/R) patients[5]
  - In 1L patients, complete response (CR) + clinical CR (CRc; CR with residual skin abnormality not indicative of active disease) rate was 57%, with 51% of these patients bridging to hematopoietic stem cell transplant (HSCT). Median duration of CR + CRc was 25 months after 3 years of follow-up
  - In R/R patients, CR + CRc rate was 16% and 5% of patients bridged to HSCT
- TAG was approved by the EMA (01/2021) as monotherapy for the 1L treatment of adult patients with BPDCN and by the US FDA (12/2018) for treatment of BPDCN (1L and R/R) in adult and pediatric patients 2 years and older[6,7]

Figure 1. Tagraxofusp – CD123-Directed Therapy

- In August 2019, an expanded access program (EAP) was established in Europe to
  - Provide adult patients with BPDCN access to TAG prior to its approval by the EMA
  - Gather experience on the safety and efficacy of TAG in real-world practice
- This is the preliminary analysis as of September 15, 2022, including 40 adult patients with BPDCN treated with TAG in the European EAP

METHODS

- The EAP is a noninterventional, retrospective, observational, multicenter, single-arm study in patients with 1L and R/R BPDCN treated with TAG in a real-world setting (**Figure 2**)

Figure 2. EAP Study Design

Patients

Target
- N = 80

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

Main exclusion criterion
- Participation in another study/registry reporting treatment outcomes of BPDCN

TAG treatment[a]

Per EU SmPC[7]
- TAG 12 mcg/kg, IV infusion, once daily
- Total of 5 doses on days 1–5 of a 21-day cycle *(the 5 doses could be administered over up to 10 days)*

Hospitalization required only in cycle 1 *(subsequent cycles could be administered in an outpatient setting)*

Objectives

Primary
- CR after 2-3 TAG cycles in 1L and R/R BPDCN
- CLS incidence and severity

Secondary
- Rate of patients bridging to HSCT
- AE incidence and severity
- Number of TAG doses/cycle

[a]Patients were informed on TAG treatment by the physician who signed the supply form. Prior to TAG administration, physicians, nurses, and pharmacists were trained on dosing, administration, storing, and serious AE reporting.

- Data were collected through retrospective chart review, with the observation period starting from TAG therapy initiation

RESULTS

Patients

- Preliminary analysis of data from 40 patients with BPDCN (**Table 1**)
  - 1L, n = 22 (55%)
  - R/R, n = 18 (45%)
- Male
  - 1L, 86%
  - R/R, 89%
- Skin involvement
  - 1L, 77%
  - R/R, 67%
- Countries
  France (n = 15), Germany (n = 9), Italy (n = 8), Switzerland (n = 6), Austria (n = 1), and Spain (n = 1)

Table 1. Baseline Demographic and Disease Characteristics

Parameter	1L (n = 22)	R/R (n = 18)
Median age, years (range)	68 (21-82)	66 (29-83)
Disease presentation at initial diagnosis, n (%)		
Skin involvement[a]	17 (**77**)	12 (**67**)
Single lesion[b]	3 (**15**)	1 (**7**)
Multiple lesions[b]	13 (**65**)	10 (**71**)
Lymph node involvement	12 (**55**)	11 (**61**)
Single	2 (**9**)	0
Multiple	10 (**46**)	11 (**61**)
Spleen involvement	8 (**36**)	4 (**22**)
CNS involvement[c]	3 (**10**)	4 (**22**)
Previous lines of therapy, n (%)		
0	22 (**100**)	0
1	0	12 (**67**)
2	0	5 (**28**)
3	0	1 (**6**)
Time to TAG start,[d,e] months, median (range)	1.5 (0.4-9.0)	7.5 (1.0-27.3)

[a]Unknown for 1 patient each in the 1L and R/R groups. [b]Includes only patients with computerized tomography or positron emission tomography scans performed. [c]Not evaluated in 1 patient each in the 1L and R/R groups. [d]Missing for 1 patient each in the 1L and R/R groups. [e]Time from the date of diagnosis to the start of TAG therapy.

Efficacy

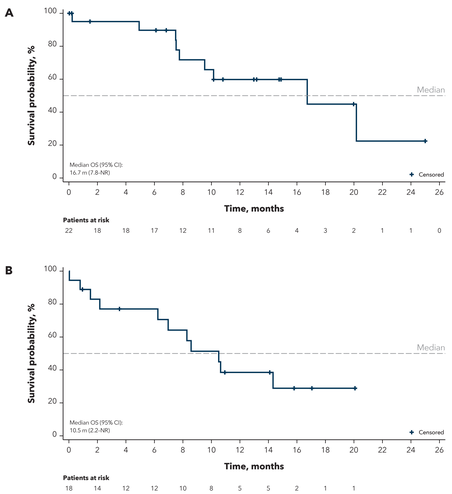
- Best response (**Table 2**)
  - ORR
    - 1L, 88% (15/17)
    - R/R, 67% (10/15)
  - CR rate
    - 1L, 71% (12/17)
    - R/R, 40% (6/15)
- Bridged to allogeneic HSCT (**Table 2**)
  - 1L, 10/22 (45%)
  - R/R, 7/18 (39%)
- Median follow-up time
  - 1L, 10.1 months
  - R/R, 8.4 months
- Median OS
  - 1L (n = 22), 16.7 months (**Figure 3A**)
  - R/R (n = 18), 10.5 months (**Figure 3B**)

Table 2. Objective Response and HSCT

Parameter	1L (n = 22)	R/R (n = 18)
Patients with ≥1 tumor assessment, n (%)	17 (**77**)	15 (**83**)
Best overall response,[a] n (%) [95% CI]		
ORR	15 (**88**) [63.6-98.5]	10 (**67**) [38.4-88.2]
CR	12 (**71**) [44.0-89.7]	6 (**40**) [16.3-67.7]
PR	3 (**18**) [3.8-43.4]	4 (**27**) [7.8-55.1]
SD	1 (**6**)	2 (**13**)
PD	1 (**6**)	3 (**20**)
Median response duration, months, (95% CI) [range]	8.8 (3.2-NR) [0.3–14.1[b]]	5.6 (3.0-NR) [1.4–19.2[b]]
Patients who received HSCT, n (%) [95% CI]	10 (**45**) [24.4-67.8]	7 (**39**) [17.3-64.3]
In CR prior to HSCT, n (%)	7 (**70**)	5 (**71**)
In PR prior to HSCT, n (%)	3 (**30**)	2 (**29**)

[a]Based on all tumor assessments regardless of the cycle in which they were obtained. [b]Last observation censored.

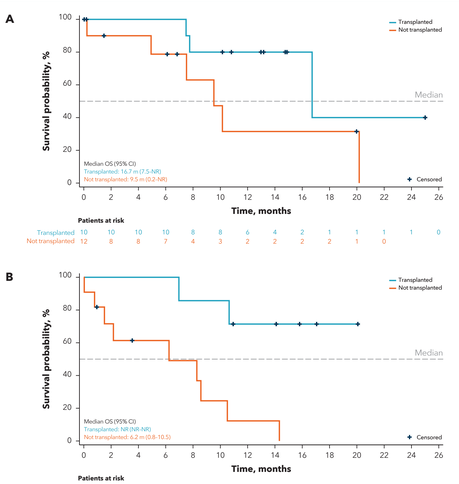
Figure 3. Overall Survival by Line of Treatment in 1L (A) and R/R (B) Patients[a]



[a]Overall survival is the period from tagraxofusp start date to death from any cause.

- Median OS in 1L (**Figure 4A**)
  - Transplanted (n = 10), 16.7 months
  - Not transplanted (n = 12), 9.5 months
- Median OS in R/R (**Figure 4B**)
  - Transplanted (n = 7), not reached
  - Not transplanted (n = 11), 6.2 months

Figure 4. Overall Survival by Transplant Status in 1L (A) and R/R (B) Patients[a]



[a]Overall survival is the period from tagraxofusp start date to death from any cause.

Safety

- Median number of TAG cycles
  - 1L, 3 (range, 1–8)
  - R/R, 2 (range, 1–5)
- TAG-related grade 3/4 adverse events (AEs) or serious AEs (SAEs) (**Table 3**)
  - Overall, the most frequent (in ≥10% of patients) were thrombocytopenia (23%), anemia (18%), and neutropenia (13%)
  - 1L, n = 8 (36%). The most frequent AE was thrombocytopenia (23%)
  - R/R, n = 8 (44%). The most frequent AE was anemia (28%)
- All grade 3/4 AEs and SAEs occurred only during cycle 1
- Mean albumin level prior to TAG therapy
  - 1L, 3.8 g/dL
  - R/R, 3.7 g/dL

Table 3. Grade 3/4 AEs or SAEs Related to TAG in ≥10% of Patients in Either Group

AE, n (%)	1L (n = 22)	R/R (n = 18)
Nonhematologic grade 3/4 AEs or SAEs		
Hepatic cytolysis[a]	1 (**5**)	2 (**11**)
Tumor lysis syndrome	0	2 (**11**)
Increased AST	3 (**14**)	0
Pneumonia	0	2 (**11**)
Hematologic grade 3/4 AEs		
Thrombocytopenia	5 (**23**)	4 (**22**)
Anemia	2 (**9**)	5 (**28**)
Neutropenia	3 (**14**)	2 (**11**)
Pancytopenia	0	2 (**11**)

[a]Definitions collected retrospectively from the clinical dossier.

- A summary of capillary leak syndrome (CLS) events as reported by the investigator is shown in **Table 4**
  - Symptoms associated with CLS events were weight gain, edema, hypotension, and hypoalbuminemia
- In the 1L setting, 9/22 patients had a total of 12 events
  - 8 of the 12 events occurred in cycle 1
- In the R/R setting, 11/18 patients had a total of 13 events
  - 11 of the 13 events occurred in cycle 1
- The majority of CLS events were grade 1/2; no grade 5 events occurred
- CLS was managed by TAG dose interruption and intravenous albumin supplementation
- All CLS events resolved

Table 4. Incidence of CLS Events[a] (All Cycles)

Parameter	1L (n = 22)	R/R (n = 18)
Patients who experienced CLS, n	**9**	**11**
Patients who experienced CLS on 2 occasions	**3**	**2**
Number of CLS events	**12**[b]	**13**[c]
Grade, n		
1	**1**	**0**
2	**8**	**8**
3	**3**	**4**
4	**0**	**1**
Action taken on TAG, n		
Dose reduced	**0**	**0**
Drug interrupted	**6**	**5**
Median duration, days (range)	**8** (3–172)	**5** (3–11)

[a]Symptoms associated with CLS events (as reported by the investigator): weight gain, edema, hypotension, and hypoalbuminemia. [b]Three patients had more than 1 event. [c]Two patients had more than 1 event.

CONCLUSIONS

- This preliminary analysis of real-world data with tagraxofusp (N = 40; 1L, n = 22; R/R, n = 18) as of September 15, 2022, from the ongoing European EAP confirms a positive benefit-to-risk ratio in adult patients with BPDCN
- In the real-world setting, stronger clinical efficacy with higher CR rates than in the pivotal BPDCN study were reported
  - In 1L, the ORR was 88%, with a CR rate of 71%
    - 45% of patients bridged to HSCT
  - In R/R, the ORR was 67%, with a CR rate of 40%
    - 39% of patients bridged to HSCT
- The majority of CLS events were mild/moderate (grade 2/3) and no grade 5 events were reported. This demonstrates the effectiveness of adherence to CLS monitoring and management guidelines

ABBREVIATIONS IN TABLES/FIGURES: 1L, first-line; AE, adverse event; AST, aspartate aminotransferase; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CD123, interleukin-3 receptor alpha chain; CI, confidence interval; CLS, capillary leak syndrome; CNS, central nervous system; CR, complete response; EAP, expanded access program; HSCT, hematopoietic stem cell transplant; IL-3, interleukin 3; IL-3Rα, interleukin-3 receptor alpha; IV, intravenous; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SAE, serious AE; SD, stable disease; SmPC, summary of product characteristics; TAG, tagraxofusp.

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