Durable Outcomes and Manageable Safety With Tagraxofusp in a Real-World Study of Patients With Treatment-Naïve and Relapsed/Refractory Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

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BACKGROUND

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematologic malignancy characterized by clonal expansion of tumor cells with features of plasmacytoid dendritic cells or their precursors that express CD123 as well as other conventional DC and lymphoid/myeloid markers.[1-3]
- Historically, median OS post-induction chemotherapy for treatment-naïve BPDCN ranges from 8 to 14 months, with relapse occurring in the majority of patients treated with chemotherapy alone.[4-7]
- Hematopoietic stem cell transplantation after successful induction and recovery offers the possibility of long-term remission and potential cure.[7]
- Tagraxofusp (TAG), a first-in-class CD123-targeted therapy, is the only drug approved for adults or pediatric patients aged ≥2 years with newly diagnosed or relapsed/refractory BPDCN in the United States, or for adults with newly diagnosed BPDCN in Europe.[8,9]
- In August 2019, a Named Patient Program was initiated in Europe to ensure patient access to TAG.
- To assess real-world safety and clinical efficacy of TAG treatment in patients with BPDCN, a population with a very poor prognosis, we independently and retrospectively analyzed data from patients with treatment-naïve and relapsed/refractory BPDCN enrolled in the NPP.

METHODS

Non-interventional, retrospective, observational, multi-center study of TAG in patients with BPDCN in the European NPP

Key Inclusion Criteria

- BPDCN diagnosis by immunophenotyping with established panels inclusive of conventional myeloid and lymphatic lineage markers as well as CD123, CD4, and CD56
- Adults with treatment-naïve or relapsed/refractory BPDCN

Endpoints

Primary:
- Complete response after 2–3 cycles of TAG treatment
- Incidence and grade of capillary leak syndrome

Secondary:
- Number of patients bridged to SCT
- Progression–free survival
- Overall survival
- Best overall response rate
- Duration of response
- Safety

Study Treatment

Patients treated via European NPP at discretion of treating physician:
- TAG 12 mcg/kg as a daily intravenous infusion on days 1–5 (or by day 10) of each 21–day cycle
- Hospitalization required in the first cycle for at least 24 hours after the last dose
- Subsequent cycles allowed in outpatient setting
- Clinicians received training on CLS monitoring and management guidelines[8,9]

RESULTS

Patient demographics and baseline characteristics

- We analyzed 22 patients (median age, 68 years) with treatment-naïve BPDCN and 18 patients (median age, 66 years) with relapsed/refractory BPDCN enrolled in the European NPP (**Table 1**).
  - The three most common sites of disease involvement were bone marrow, skin, and lymph node.
  - Prior therapy in relapsed/refractory patients is shown in **Table 2**.
  - At a median follow-up of 10 months, treatment-naïve patients received a median of 3 (range 1-8) cycles of TAG.
  - At a median follow-up of 8 months, relapsed/refractory patients received a median of 2 (range 1-5) cycles of TAG.

Table 1. Patient Characteristics

Characteristic	Treatment-naïve Patients (N=22)	Refractory Patients (N=18)
Median age, years (range)	68 (21-82)	66 (29-83)
Gender, n (%)		
Male	19 (86)	16 (89)
Female	3 (14)	2 (11)
Disease involvement at assessment prior to TAG start, n (%)	n=20	n=14
Bone marrow	16 (80)[a]	12 (86)
Skin	15 (75)[a]	10 (71)
Lymph node	13 (65)[a]	8 (57)
Spleen	9 (45)[a]	3 (21)
CNS	2 (10)[a]	4 (29)
Blood	9 (45)[a]	7 (50)
Bulky disease (any lesion >7 cm single or multiple)	5 (23)[a]	4 (22)[a]
Median albumin level prior to TAG start, g/L (range)	39 (26-50)	37 (32-46)
Median time from diagnosis to TAG start, months (range)	1.5 (0.4-9)	7.4 (1-27)

[a]1 patient unknown; [b]2 patients unknown; [c]9 patients missing data

Table 2. Prior Therapy in Relapsed/Refractory Population

	Relapsed/Refractory Patients (N=18)
Number of prior lines of therapy, n (%)	
Median (range)	1 (1-3)
1	12 (66.7)
2	5 (27.8)
3	1 (5.6)
4	0
Allogeneic SCT prior to TAG start, n (%)	
Yes	4 (22)
No	14 (78)
Status regarding last line of treatment, n (%)	
Refractory	6 (33)
Relapsed	6 (33)
Unknown	3 (17)
Missing	3 (17)

Most CLS events occurred in cycle 1 and were mild

- 10 (45%) treatment-naïve and 11 (61%) relapsed/refractory patients had ≥1 CLS event (**Table 3**).
  - 9/10 treatment-naïve and all relapsed/refractory patients had at least one CLS event in cycle 1.
  - Treatment-naïve group: only 2 patients had CLS events in later cycles.
  - Relapsed/refractory group: 1 patient had 2 CLS events in cycle 1 and 1 patient also had a CLS event in cycle 2.
- Median time to CLS resolution was 8 days in treatment-naïve patients and 4 days in relapsed/refractory patients.
- There were no deaths related to CLS events.

Table 3. Incidence and Management of CLS Events[a] (All Cycles)

	Treatment-naïve Patients	Relapsed/Refractory Patients
Patients with ≥1 observed CLS event, n (%)	10 (46)[b]	11 (61)[c]
CLS grade,[d] n (%)		
1	1 (8)	0 (0)
2	8 (62)	8 (62)
3	4 (31)	4 (31)
4	0	1 (8)
5	0	0
Action taken on TAG, n (%)		
No modification	4 (31)	4 (31)
Dose reduced	0	0
Drug interrupted	6 (46)	5 (39)
Drug withdrawn	3 (23)	4 (31)
Median duration of CLS events, days (range)	8 (2-172)	4 (2-11)

[a]As reported by the investigator. [b]Symptoms associated with CLS events were edema (n=9 patients), weight gain (n=8), hypotension (n=5), hypoalbuminemia (n=1), and other (n=4). [c]Symptoms associated with CLS events were edema (n=11 patients), weight gain (n=11), hypotension (n=7), hypoalbuminemia (n=1), and other (n=5). [d]As reported for 13 events in each group (treatment-naïve: 9 in cycle 1 and 4 in later cycles; relapsed/refractory: 11 in cycle 1 and 2 in cycle 2).

The majority of grade 3-4 AEs occurred during cycle 1 and resolved quickly

- **Table 4** summarizes AEs related to TAG, excluding CLS.
- Excluding CLS, 36% of treatment-naïve and 44% of relapsed/refractory patients had a grade 3-4 AE deemed related to TAG.
- 92% and 100% of events occurred in cycle 1 in the treatment-naïve and relapsed/refractory patients, respectively, and resolved quickly.
- No grade 3-4 or SAE infections related to TAG were observed in the treatment-naïve population.
- In both populations, myelosuppression was mild to moderate, transient, and reversible, with no cumulative hematologic toxicity.
- There were no treatment-related deaths.

Table 4. AEs Related to TAG (Excluding CLS) in ≥2 Patients*

	Treatment-naïve Patients (N=22)		Relapsed/Refractory Patients (N=18)	
	Patients, n (%)	Time to resolution, median days (range)	Patients, n (%)	Time to resolution median days (range)
Grade 3-4 Hematologic AEs[†]				
Thrombocytopenia	5 (23)	8 (3-10)	2 (11)	18 (7-28)
Neutropenia	4 (18)	5 (3-23)	*	NA
Pancytopenia	0	-	2 (11)	9 (7-10)
Grade 3-4 and SAE Non-hematologic				
Increased AST	3 (14)	14 (13-14)	0	-
Increased ALT	2 (9)	14 (14-14)	0	-
Hypertransaminasemia	2 (9)	11 (10-20)	0	-
Tumor lysis syndrome	0	-	2 (11)	4 (1-7)
Hepatic cytolysis	*	NA	2 (11)	7 (7-7)
Pneumonia	0	-	2 (11)	8 (5-11)

*Table includes only AEs for ≥2 patients in either treatment-naïve or relapsed/refractory setting (data not shown if <2 patients); time to resolution only available for events with ≥2 patients. [†](SAEs were not collected for hematologic AEs).

Patients with treatment-naïve and relapsed/refractory BPDCN achieved durable outcomes with TAG treatment

- Durable and high response rates in patients with ≥1 tumor assessment in both patient populations (**Figure 1** and **Table 5**).
  - Treatment-naïve patients: ORR of 89% (67% CR and 22% PR)
  - Relapsed/refractory patients: ORR of 67% (40% CR and 27% PR)
- Rapid time to onset of response in both patient populations (**Table 5**).
- Median PFS:
  - Treatment-naïve patients: 10.2 months (95% CI 7.5-NE)
  - Relapsed/refractory patients: 4.3 months (95% CI 1.4-12.9)

Figure 1. Best Overall Response in Patients With ≥1 Tumor Assessment

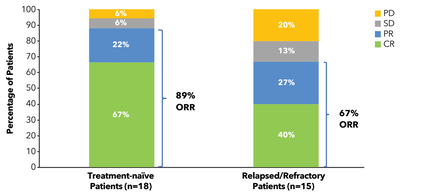


Table 5. Time to and Duration of Response[a]

	Treatment-naïve Patients n=18	Relapsed/Refractory Patients n=15
Median time to onset of response, days (range)	21 (11-74)	20 (15-56)
Median time to CR, days (range)	29 (11-58)	25 (17-56)
Median duration of response, months (95% CI)	8.9 (3.2-NE)	5.0 (3.0-NE)
Probability of continued response at 12 months, % (95% CI)	40 (3.2-NE)	40 (10-70)

[a]Patients with ≥1 tumor assessment.

Of patients with ≥1 tumor assessment, 61% of treatment-naïve and 40% of relapsed/refractory patients were bridged to SCT

- Responses were highly durable in all patients bridged to SCT, with median DOR not reached in either group (**Table 6**).
- Patients bridged to transplant (vs non-transplant) were younger and had a higher response rate:
  - Treatment naïve patients: ORR 91% and median age 64 years vs ORR 86% and median age 71 years
  - Relapsed/refractory patients: ORR 83% and median age 47 years vs ORR 56% and median age 72 years

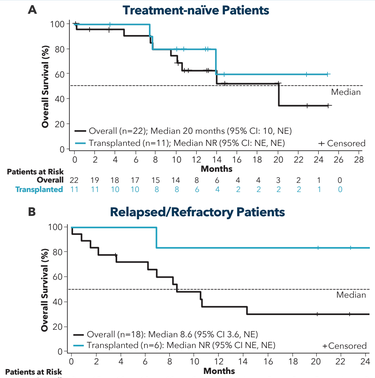
Table 6. Response in Patients Bridged to SCT

	Treatment-naïve Patients	Relapsed/Refractory Patients
Median age, years	64	47
Median follow -up time, months (range)	13 (4-25)	24 (7-26)
Bridge to transplant, n	11/18	6/15
Overall response rate, %	100	83
Complete response, %	78	66.7
Partial response, %	22	16.7
Probability of continued response at 12 months, % (95% CI)	60 (20-80)	80 (20-100)

Real-world TAG treatment for patients with treatment-naïve and relapsed/refractory BPDCN led to prolonged survival, with median OS not reached in patients bridged to SCT

- Treatment-naïve patients: median OS for all patients was 20 months (**Figure 2A**).
- Relapsed/refractory patients: median OS for all patients was 8.6 months (**Figure 2B**).
- Median OS was not reached for all patients bridged to SCT (**Figures 2A and 2B**).

Figure 2. OS* Curves for Overall and Transplanted Patients



*OS is defined as time from start of TAG to death.

Patients with CNS involvement

- **Treatment-naïve patients:**
  - 2 patients with baseline CNS involvement received both intrathecal chemotherapy and TAG treatment.
  - Both patients achieved a BPDCN best response of CR, and both proceeded to SCT.
- **Relapsed/refractory patients:**
  - 4 patients had documented CNS involvement at initial diagnosis and TAG start, 3 of which received intrathecal chemotherapy before initiating TAG.
  - Of the 3 responders, 2 achieved CR in marrow and one achieved PR; 1 patient in CR bridged to SCT.

CONCLUSIONS

- TAG achieved fast and durable responses, high response rates, and prolonged survival in patients with both treatment-naïve or relapsed/refractory BPDCN, poor prognosis populations where historic treatments, including chemotherapy, show limited efficacy.
- With up to 2 years of follow-up, treatment-naïve patients with BPDCN who received TAG achieved responses regardless of CNS involvement and prolonged survival beyond that of chemotherapy's historically shorter median OS (~8–14 months).
  - ORR 89% (CR 67%); median DOR 8.9 months; median OS 20 months.
- In patients with relapsed/refractory BPDCN, TAG was associated with an ORR 67% (CR 40%), median DOR 5.0 months, and median OS of 8.6 months.
- Of patients with ≥1 tumor assessment, 61% of treatment-naïve and 40% of relapsed/refractory patients were bridged to transplant, with median DOR and OS not reached in these patients that bridged to transplant.
- No new safety signals were observed with TAG therapy in all BPDCN patient populations, and there were no treatment-related deaths.
  - With proper selection, monitoring, and directed intervention, CLS is manageable, usually mild, and mostly limited to the first cycle.
  - Myelosuppression was mild to modest, reversible, and was not cumulative with continued TAG treatment.
- These real-world results support the use of TAG for patients with treatment-naïve and relapsed/refractory BPDCN.

ABBREVIATIONS IN TABLES/FIGURES: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CI, confidence interval; CLS, capillary leak syndrome; CNS, central nervous system; CR, complete response; DC, dendritic cell; DOR, duration of response; NA, not available; NE, not estimable; NPP, Named Patient Program; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event; SCT, stem cell transplantation; TAG, tagraxofusp.

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