Tagraxofusp, a CD123-Directed Therapy, in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm and Prior or Concomitant Hematologic Malignancies: Subgroup Analysis of a Pivotal Trial

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INTRODUCTION

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive myeloid malignancy that has a poor prognosis[1]
- BPDCN derives from the precursors of plasmacytoid dendritic cells, which express CD123 (also known as interleukin-3 [IL-3] receptor alpha)[2,3]; CD123 is overexpressed in all cases of BPDCN
- BPDCN may occur as a secondary malignancy, with approximately 10–20% of patients with BPDCN also having prior or concomitant hematologic malignancies (PCHMs)[4-7]
  - These diseases may include myelodysplastic syndrome, chronic myelomonocytic leukemia, chronic myeloid leukemia, and acute myeloid leukemia
  - These PCHMs (and subsequent lines of treatment, such as chemotherapy) likely predispose patients to worse prognosis compared with those without PCHMs
  - The presence of concomitant malignancies underscores the importance of being vigilant and ensuring that BPDCN is correctly diagnosed
  - It also illustrates the need for adequate monitoring for cytopenia, including thrombocytopenia, in patients with BPDCN vs other hematologic malignancies
- Patients with PCHMs likely have a unique disease biology, which may impact their response to therapy
- Tagraxofusp (TAG), a first-in-class CD123-directed therapy comprising a recombinant human IL-3 fused to a truncated diphtheria toxin payload, is US FDA- and EMA-approved for the treatment of patients with BPDCN[8,9]
- In the pivotal trial (NCT02113982), treatment with TAG 12 mcg/kg resulted in[10]
  - An overall response rate (ORR) of 75% in first-line (1L) patients with a median duration of 25 months for patients with complete response plus complete response with residual skin abnormality not indicative of active disease (CR/CRc) after 3 years of follow-up
  - Nineteen of the 37 (51%) 1L patients who achieved CR/CRc were bridged to hematopoietic stem cell transplant (HSCT)
  - A well-characterized and manageable safety profile
- Herein, we report a subgroup analysis of the pivotal trial that evaluated the efficacy and safety of TAG in eight 1L patients with PCHM

METHODS

Study Overview

- This was a multicenter, 4-stage, single-arm, phase 1/2 trial evaluating TAG monotherapy in patients with 1L or relapsed/refractory BPDCN
- The study stages, dosing, and outcome measures are shown in **Figure 1**

Tagraxofusp has demonstrated clinical activity and a manageable safety profile in patients with BPDCN who had prior or concomitant hematologic malignancies

Figure 1. 0114 Study

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

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

Principal endpoints

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

Select Eligibility Criteria

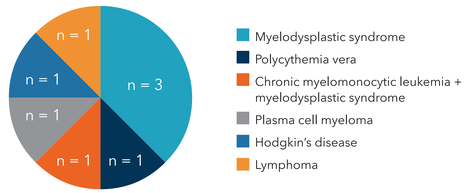
- Diagnosis of BPDCN according to World Health Organization classification[11] or confirmed by hematopathology
- Patients had histologic and/or cytologic evidence of BPDCN by pathologic assessment that can be measured for treatment response
- Aged ≥18 years
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2
- Adequate baseline cardiac, renal, and hepatic function
  - Albumin level of ≥3.2 g/dL
  - Normal left ventricular ejection fraction
- Patients with a past cancer history (within 2 years of entry) with substantial potential for recurrence and/or ongoing active malignancy could be included following discussion with the Sponsor before study entry

RESULTS

Study Population

- In total, 65 1L patients received TAG at 12 mcg/kg
- Of these, 8 (12%) patients had PCHM
  - One patient had 2 different PCHMs
- The PCHMs in the study population are presented in **Figure 2**

Figure 2. Summary of the Different PCHMs Experienced by Individual Patients



Baseline Demographics

- Baseline characteristics were similar between patients with or without PCHMs (**Table 1**)
- For patients with or without PCHM, respectively
  - Median age was 69 years and 68 years
  - Most patients were male (75% vs 81%)
  - The majority had ECOG PS 0/1 (100% vs 95%)
- Time since PCHM diagnosis prior to the BPDCN diagnosis varied, ranging from 4–14 years

Table 1. Patient Demographics and Baseline Disease Characteristics

	Patients with PCHM N = 8	Patients without PCHM N = 57
Median age Years (range)	**69** (40–84)	**68** (22–84)
Gender, n (%)		
Male	**6** (75)	**46** (81)
Female	**2** (25)	**11** (19)
Race, n (%)		
Asian	**0**	**2** (4)
American Indian or Alaska Native	**0**	**1** (2)
Black or African American	**0**	**2** (4)
White	**8** (100)	**49** (86)
Other	**0**	**3** (5)
ECOG PS, n (%)		
0	**2** (25)	**29** (51)
1	**6** (75)	**25** (44)
2	**0**	**2** (4)
Missing	**0**	**1** (2)

Efficacy

- The main efficacy outcomes are presented in **Table 2**
- Similar rates of CR/CRc and ORR were seen across patients with and without PCHM
- TAG enabled 1 patient (13%) with PCHM who had a CR/CRc to be bridged to HSCT
- In total, 18 patients (32%) who had no PCHM were bridged to HSCT after achieving a CR/CRc with TAG

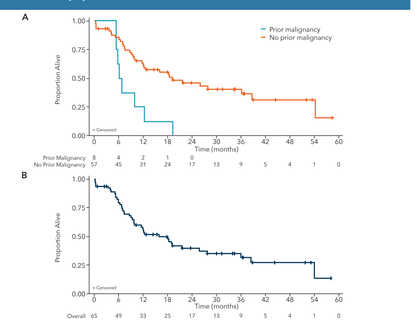
Table 2. Efficacy Outcomes in Patients With or Without PCHM

	Patients with PCHM N = 8	Patients without PCHM N = 57	*P* value
Response rate, n (%)			
ORR	**7** (88)	**42** (74)	**0.6675***
CR/CRc	**4** (50)	**33** (58)	**0.7171***
Median duration of CR/CRc, months (95% CI)	**3.0** (1.0, NR)	**NR** (4.4, NR)	**0.0088†**
Survival probability, %			
12 months	**25**	**59**	**0.0316‡**
18 months	**13**	**55**	**0.0081‡**
Bridged to HSCT , n (%)	**1** (13)	**18** (32)	**0.2592***

*Calculated using Fisher exact test; †Chi square *P* value calculated using log-rank test; ‡Log-rank *P* value determined from truncated Kaplan-Meier analysis where all patients who survived at least 12/18 months were censored at 12/18 months, respectively.

- Median overall survival (OS) was significantly longer in patients without PCHM (18.9 months [95% CI: 11.5, 38.4]) than in patients with PCHM (6.3 months [95% CI: 5.2, 12.1]; *P* = 0.0021*; **Figure 3**)

Figure 3. Median OS of (A) Patients With and Without PCHM and (B) all Patients



*Chi square *P* value calculated using log-rank test.

SAFETY

Treatment-Related Adverse Events

- The most common treatment-related adverse events occurring with an incidence of ≥20% in either patient cohort are presented in **Table 3**

Table 3. TRAEs Occurring With an Incidence of ≥20% in Either Patient Cohort

TRAE, n (%)	Patients with PCHM (N = 8)	Patients without PCHM (N = 57)
At least 1 TRAE	**7** (88)	**53** (93)
Increased ALT	**2** (25)	**32** (56)
Increased AST	**3** (38)	**30** (53)
Hypoalbuminemia	**2** (25)	**23** (40)
Thrombocytopenia	**0**	**20** (35)
Pyrexia	**0**	**18** (32)
Weight gain	**2** (25)	**16** (28)
Nausea	**1** (13)	**14** (25)
Capillary leak syndrome	**0**	**12** (21)

CONCLUSIONS

- Patients with BPDCN who have PCHM represent a population with a high unmet need
- In the 0114 study, patients who had a cancer history within 2 years of entry that could potentially recur and/or an ongoing active malignancy could be enrolled following discussion with the Sponsor
- Eight patients (12%) in study 0114 had PCHM, which is in line with previous reports[4-7]
- While these patients were heterogeneous in terms of type and duration of prior malignancies, as well as treatment history – factors that could worsen prognosis and treatment outcomes – TAG demonstrated efficacy in this patient population
- Patients with PCHM historically have a poorer prognosis
  - In this subanalysis, the observed response rates in patients with PCHM were consistent with those observed in patients without PCHM
  - Median OS was lower than observed in patients without PCHM
- In total, 50% of patients with PCHM achieved a CR/CRc, with TAG treatment enabling one of these patients to be bridged to HSCT
- No new safety findings were observed in patients with PCHM

ABBREVIATIONS IN TABLES/FIGURES: 1L, first line; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete response; CRc, CR with residual skin abnormality not indicative of active disease; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; IV, intravenous; ND, not determined; NR, not reached; ORR, overall response rate; OS, overall survival; PCHMs, prior or concomitant hematologic malignancies; PS, performance status; R/R, relapsed/refractory; TAG, tagraxofusp; TRAE, treatment-related adverse event.

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