Anti-tumor activity and restoration of hematopoiesis achieved with tagraxofusp in patients with treatment-naïve blastic plasmacytoid dendritic cell neoplasm (BPDCN): pivotal trial subanalysis

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INTRODUCTION

- BPDCN is an aggressive, orphan 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 dendritic cells and lymphoid/myeloid markers.[1-3]
- Tagraxofusp (TAG) is a first-in-class CD123-targeted therapy and is the only drug approved for adults or pediatric patients aged ≥2 years with treatment-naïve or relapsed/refractory BPDCN in the US, or for adults with treatment-naïve BPDCN in Europe.[4,5]
- Results from the pivotal phase 2 trial of TAG in BPDCN demonstrated a high overall response rate (ORR) of 75% and CR + CRc of 57%, with rapid and durable responses (23 days median time to response and 24.9 months median duration of CR + CRc) in 65 treatment-naïve patients.[6]
  - In 30 out of 32 patients with bone marrow (BM) disease at baseline (blasts ≥5%), the CR + CRc rate was 53%.[6] Response rates could not be assessed in 2 patients.
- TAG's safety profile is well-characterized and manageable, with transient AEs mostly in cycle 1 and no cumulative hematologic toxicity or myelosuppression.

OBJECTIVE

- To determine hematopoietic and BM effects of TAG treatment in adult patients with BPDCN over time, we assessed changes in hematologic laboratory parameters.

METHODS

- Hematologic laboratory values were assessed in treatment-naïve patients with BPDCN included in a phase 1/2 trial (NCT02113982) of TAG monotherapy.
- All patients received TAG 12 mcg/kg IV on days 1-5 (up to day 10 to allow for dose interruptions if needed) of a 21-day cycle.
- Neutrophils, platelets, hemoglobin (Hb), and peripheral leukemic blasts were assessed at time points through the first 4 TAG cycles and reported as mean values ± standard deviations.
  - Baseline measurements were obtained on the first day of cycle 1 before TAG dosing.
  - The study population was further analyzed by BM involvement at baseline.
- Transfusions over time and hematologic treatment-related adverse events (TRAEs) were measured.

RESULTS

- Sixty-six treatment-naïve patients (median age 69) were included in the safety population, and 32 of these patients (median age 69) had BM disease involvement at baseline (**Table 1**).
- Baseline demographics and disease characteristics were similar in patients with BM disease compared to the overall population.
- The three most common sites of disease involvement overall were skin, lymph node, and bone marrow.
- Baseline abnormal hematologic laboratory findings in the overall population vs patients with BM disease included 52% vs 72% anemia, 50% vs 63% thrombocytopenia, 17% vs 34% neutropenia, and 14% vs 19% leukopenia.
- Patients received a median of 4 (range 1-76) cycles of TAG.

Table 1. Patient Characteristics

Characteristic	Overall Population (N=66)	Patients With BM Disease (n=32)
Median age, years (range)	69 (22-84)	69 (22-82)
Gender, no. (%)		
Male	53 (80)	25 (78)
Female	13 (20)	7 (22)
ECOG PS[a]		
0	32 (49)	8 (25)
1	31 (47)	21 (66)
2	2 (3)	2 (6)
Disease involvement at baseline, no. (%)		
Bone marrow	32 (49)	32 (100)
Skin	61 (92)	28 (88)
Lymph node	33 (50)	19 (59)
Peripheral blood	17 (26)	16 (50)
Visceral	9 (14)	9 (28)
≥2 disease sites	45 (68)	31 (97)
Abnormal hematologic laboratory findings at baseline, no. (%)		
Anemia	34 (52)	23 (72)
Thrombocytopenia	33 (50)	20 (63)
Neutropenia	11 (17)	11 (34)
Leukopenia	9 (14)	6 (19)

[a]Data for one patient in both populations unavailable.

HEMATOLOGIC PARAMETERS

Neutrophils — *Overall, neutrophils gradually increased over the course of therapy; the incidence of neutropenia decreased from baseline, was mostly in cycle 1, and non-cumulative.*

- Neutrophils remained in normal range from baseline during TAG treatment in the overall population (**Figure 1A**).
- For patients with BM disease, neutrophils were slightly lower than normal at baseline and gradually increased to normal.
- Patients without BM disease had consistent neutrophil counts over time and similar to the overall population.
- Granulocyte colony-stimulating factor (G-CSF) administration was concentrated in the first cycles of TAG as neutrophil recovery occurred (**Figure 1A**).
- In the overall population,
  - 10.6% of patients had any grade treatment-related neutropenia, all of which resolved at a median of 9 days.
  - 7.6% of patients had grade 3-4 treatment-related neutropenia with 80% resolution at a median of 10 days; all but one of which occurred in cycle 1.
  - Baseline disease-related neutropenia was 16.7%, whereas treatment-related neutropenia was 10.6% in cycle 1 and not cumulative (**Figure 1B**).
- Treatment-related neutropenia was similar in BM disease group to the overall population.
- Infections or infestations deemed related to TAG occurred in 3% of patients consisting of grade 1-2 cellulitis in one patient (BM disease group) and grade 1-2 gingivitis in one patient.

Platelets — *Overall, platelet counts returned to normal during TAG treatment; thrombocytopenia decreased from baseline, was mostly in cycle 1, and non-cumulative.*

- Platelet counts, which were below normal range at baseline, returned to normal after one cycle of TAG treatment in the overall population (**Figure 2A**) and in the BM disease subgroup. Platelet counts remained normal in subsequent cycles in both populations.
- Patients without BM disease had a platelet count pattern similar to the overall population.
- The percentage of patients who required platelet transfusions declined after the first cycle in the overall population (17% to 2-3%) and the BM disease subgroup (28% to 5-6%).
- In the overall population,
  - 31.8% of patients had any grade treatment-related thrombocytopenia with 81% resolution at a median of 8 days.
  - 19.7% of patients had grade 3-4 thrombocytopenia with 85% resolution at a median of 8 days.
  - Baseline disease-related thrombocytopenia was 50.0% whereas treatment-related thrombocytopenia was 30.3% at cycle 1 and was not cumulative (**Figure 2B**).
- Findings in the BM disease group were similar to the overall population, albeit with higher baseline thrombocytopenia.
- Hemorrhage was not observed in any patients.

Hemoglobin — *Overall, TAG was not associated with decreases in Hb; anemia decreased from baseline, was mostly in cycle 1, and non-cumulative.*

- Cycle day 1 Hb levels remained consistent with baseline Hb over subsequent TAG cycles in the overall population (**Figure 3A**) and in the BM disease subgroup.
- Within cycles, Hb values increased post TAG dosing over time in the overall population and in the BM disease subgroup.
- Patients without BM disease had a hemoglobin pattern similar to the overall population.
- The percentage of patients who received red blood cell (RBC) transfusions decreased over time in the overall population and BM disease subgroup, which was consistent with improved Hb over TAG treatment time.
- In the overall population,
  - 13.6% of patients had any grade treatment-related anemia, with 89% resolution at a median of 13 days.
  - Grade 3-4 treatment-related anemia occurred in 4.5% of patients, and all resolved at a median of 14 days.
  - Baseline disease-related anemia was reported in 51.5% of patients, whereas treatment-related anemia was 10.6% in cycle 1 and not cumulative (**Figure 3B**).
- Findings in the BM disease group were similar to the overall population.

Figure 1A. Neutrophils Over TAG Cycles 1-4: Overall Population

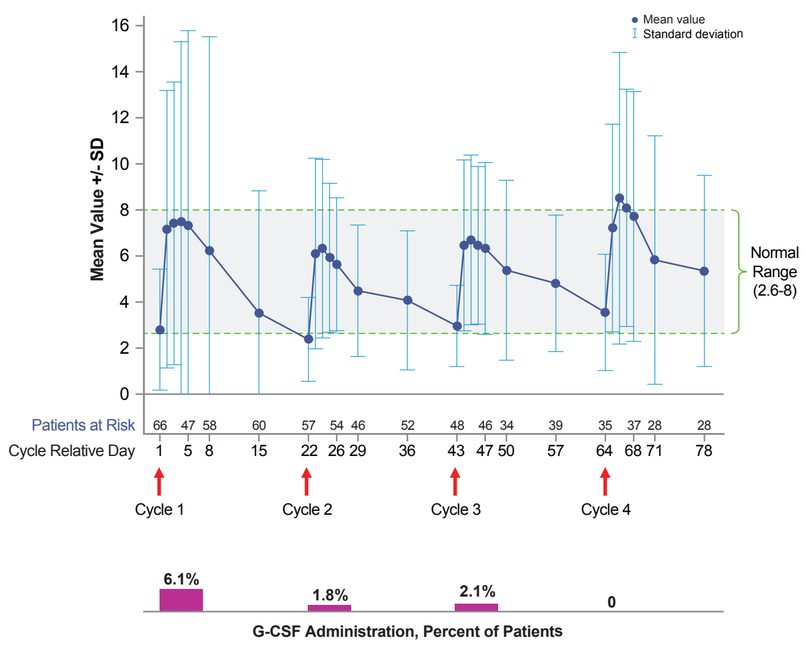


Figure 2A. Platelets Over TAG Cycles 1-4: Overall Population

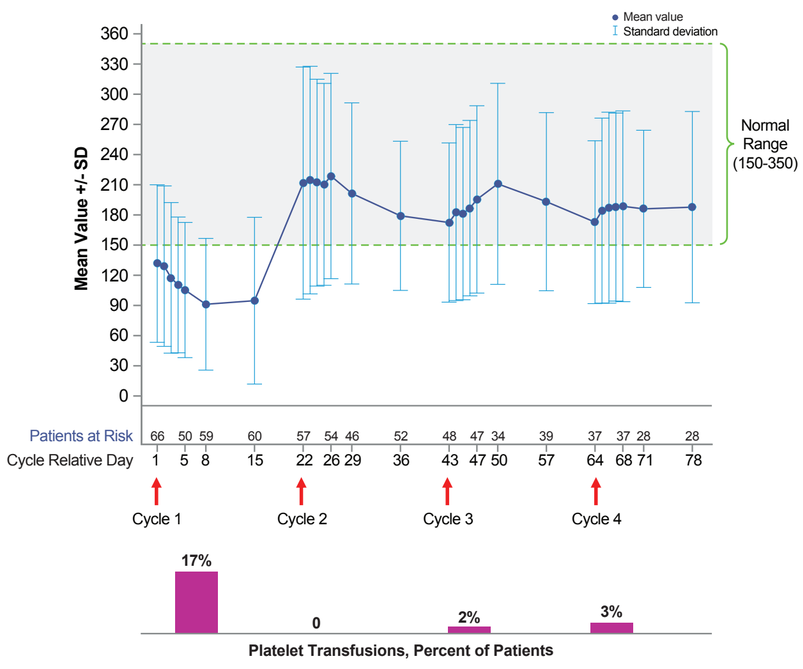
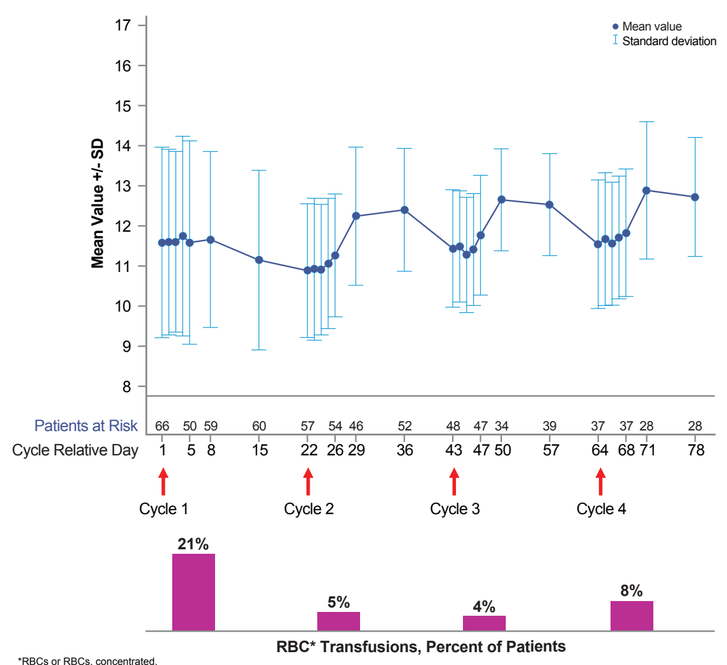


Figure 3A. Hemoglobin Over TAG Cycles 1-4: Overall Population



*RBCs or RBCs, concentrated.
Normal Hb range is 14-17 g/dL for men and 12-15 g/dL for women.

Figure 1B. Disease-Related Neutropenia at Baseline and All Grade Neutropenia by Cycle

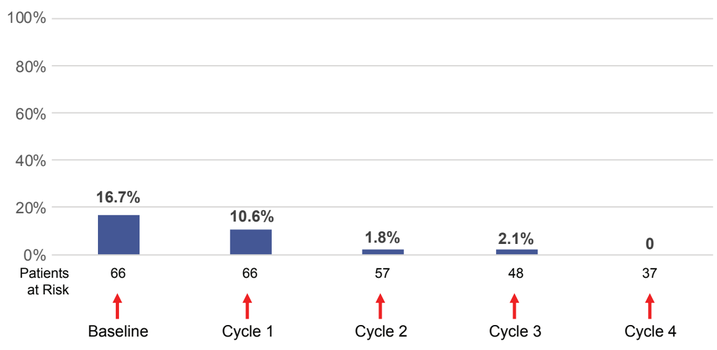


Figure 2B. Disease-Related Thrombocytopenia at Baseline and All Grade Thrombocytopenia by Cycle

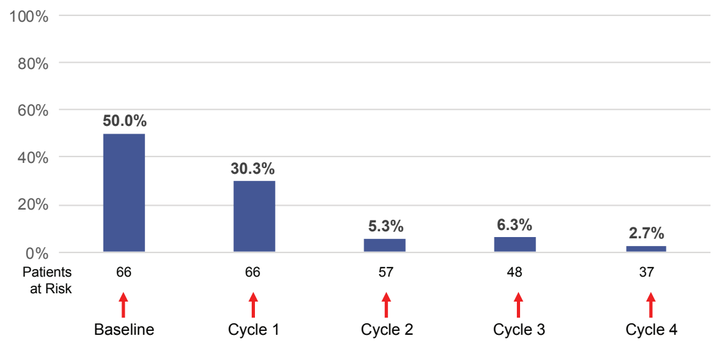
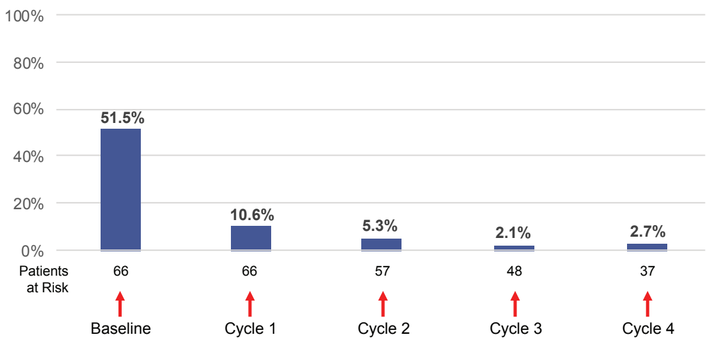


Figure 3B. Disease-Related Anemia at Baseline and All Grade Anemia by Cycle



Peripheral Blasts — *Overall, peripheral blasts clearance was observed in all patients by cycle 2 of TAG treatment* (**Figure 4**).

- Patients with BM disease had a notably higher baseline leukemic/peripheral blast count compared with patients without BM disease.
- A steep decline and full eradication of blasts were seen in both BM disease subgroups with clearance of peripheral blasts observed in all patients by cycle 2 of TAG treatment.

Figure 4. Peripheral Blast Clearance Over TAG Cycles 1-4: Overall Population

Additional Hematologic Adverse Events

- Hematologic TRAEs reported in ≥5% of patients during the study were thrombocytopenia in 31.8% of patients, anemia in 13.6%, neutropenia in 10.6%, and leukopenia in 7.6%.
- No grade 5 hematologic TRAEs occurred.

CONCLUSIONS

- TAG demonstrated stabilization of hematologic parameters over time and with each subsequent cycle in treatment-naïve patients with BPDCN.
  - Cumulative myelosuppression was not observed.
  - Baseline hematologic abnormalities showed improvement beginning with cycle 1 of TAG.
  - Normal hematopoiesis was restored.
- Bone marrow disease at baseline did not impact outcome. In patients with BM disease, the stabilization of hematologic parameters, G-CSF use, platelet transfusions, red blood cell transfusions, and observed hematologic TRAEs were consistent with the stabilization observed in the overall population.
  - Notably, 28% of patients with BM disease had platelet transfusions in cycle 1, which decreased to <6% in subsequent cycles.
- In both populations, hematologic TRAEs occurred primarily in cycle 1 and resolved quickly; no grade 5 events occurred.
- Previously demonstrated rapid (median 39 days) and durable (median duration of response of 24.9 months) responses (ORR 75%, 57% CR/CRc in all patients, and 53% CR/CRc in patients with BM disease) with TAG coupled with its safety profile, lack of cumulative myelosuppression, and restoration of normal hematopoiesis support TAG as monotherapy for patients with treatment-naïve BPDCN.[6]
- The on-target effect and unique bone marrow-sparing profile of TAG is paramount when treating myelosuppressive CD123+ hematologic disease. Given this lack of cumulative myelosuppression, TAG is a safe and promising combination partner for treatment of other CD123+ hematologic malignancies for which the disease itself and most other available combination partners are myelosuppressive.

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ABBREVIATIONS: AE, adverse event; BM, bone marrow; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete response; CRc, clinical complete response; CSF, colony-stimulating factor; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; IV, intravenously; mo, month; no., number; ORR, objective response rate; PS, performance status; RBC, red blood cell; TAG, tagraxofusp; TRAE, treatment-related adverse event.

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