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First-line tagraxofusp leads to durable responses and prolonged survival in adults with blastic plasmacytoid dendritic cell neoplasm regardless of fitness level

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Running head: Fitness subgroup analysis of tagraxofusp in BPDCN

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NP, MH, and MZ contributed to the conception and design of this ad hoc analysis; all authors acquired the data; all authors analyzed the data; and all authors contributed to data interpretation, manuscript writing, editing, and content review, and approved the final draft of the manuscript.

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN), an aggressive, orphan hematologic neoplasm that expresses CD123 and other markers, presents primarily in skin, bone marrow, and blood.[1] While BPDCN impacts all ages, the median age of adults with BPDCN is 67 years.[2] The goal of first-line induction therapy is to attain a durable remission with limited side effects. For eligible patients who successfully achieve a rapid and durable complete response (CR) without cumulative non-hematologic or hematologic toxicities, hematopoietic cell transplantation (HCT) offers a potentially curative option.[1]

The first-in-class CD123-directed agent tagraxofusp is the only approved treatment for BPDCN,[3,4] with a well-characterized and manageable safety profile without cumulative myelosuppression. Regulatory approvals were based on results from a prospective, multicenter phase 2 study (NCT02113982) that employed prespecified, multisystem response criteria and endpoints.[5,6] In this pivotal study,[5,6] the overall response rate (ORR) was 75% in 65 first-line patients (median age 68 years) treated with tagraxofusp (12 μg/kg once daily during the first 5 days of a 21-day cycle). Moreover, 57% achieved a complete response (CR) or clinical CR (CRc: CR with residual skin abnormalities not indicative of active disease) with a median duration of 24.9 months. Half (51%) of these patients were successfully bridged to HCT and reached a median overall survival (OS) of 38.4 months.[6] Real world data confirm these results.[7]

While not approved for BPDCN, intensive multi-agent chemotherapy (IC) prior to HCT has been used, despite short- and long-term toxicities, including myelosuppression, and short duration of response (DOR). Because of age and comorbidities, many patients with BPDCN are ineligible for IC prior to consideration for HCT, and use is restricted to young/fit patients.[8] Overall, these patients from all age groups could benefit from a safe and effective targeted first-line treatment with tagraxofusp to achieve rapid and durable CR to increase HCT eligibility, without risk of long-term toxicities.

Given the heterogeneity in patient fitness, an important clinical question is whether baseline fitness affects tagraxofusp treatment outcomes and safety. The HCT-specific comorbidity index (HCT-CI), a risk-stratification model developed to predict overall and non-relapse mortality after allogeneic-HCT, has been well validated in various hematologic malignancies and is useful for assessing fitness/frailty level.[9-11] HCT-CI includes categories of comorbidities/organ dysfunction assigned a weight of 0 (low-risk), 1-2 (intermediate-risk), or ≥3 (high-risk) based on a patient's past medical history or abnormal laboratory values immediately prior to conditioning treatment. We, therefore, utilized the HCT-CI[12] in a post-hoc analysis of the pivotal trial to assess tagraxofusp safety and efficacy across different baseline fitness levels.

Study methods and results have been previously published.[5,6] The study was approved by the institutional review board at each participating center and conducted in accordance with the principles of the Declaration of Helsinki and applicable clinical practice guidelines. All study participants provided written informed consent. This post-hoc analysis categorized 65 treatment-naïve patients based on available medical history, concomitant medications, and laboratory values into previously validated HCT-CI low-risk (HCT-CI 0), intermediate-risk (HCT-CI 1-2), or high-risk (HCT-CI ≥3) groups.[9-11] Efficacy and safety data for each HCT-CI risk group were analyzed by descriptive statistics only.

Of the 65 patients analyzed, 15 (23%) patients had a low-risk score, 22 (34%) an intermediate-risk score, and 28 (43%) a high-risk score (**Table 1**). Prevalence of the HCT-CI comorbidities is shown in **Supplemental Table 1**. The proportion of patients with a normal Eastern Cooperative Oncology Group performance status decreased with increasing HCT-CI risk score (67%, 50% and 36%, respectively).

The median duration of follow-up was 27.7 months (range, 2.6-51.7) for the low-risk group, 36.6 months (range, 0.2-58.1) for intermediate-risk, and 36.3 months (range, 3.9-54.0) for high-risk. The three groups had a similar median duration of exposure: 72 days (range, 37-545) for low-risk, 71 days (range, 2-159) for intermediate-risk, and 68 days (range, 1-1622) for high-risk. Patients in all groups started a median of 4 cycles and, in cycle 1, received a median of 4 doses for low-risk, 5 doses for intermediate-risk, and 4 doses for high-risk. Reasons for study discontinuation are shown in **Supplemental Table 2**.

The ORR was high in all groups: 80% (low-risk), 68% (intermediate-risk), and 79% (high-risk)(**Figure 1A**). Median time to response was rapid and similar: 24 days (range, 20-49) for low-risk, 22 days (range, 14-53) for intermediate-risk, and 25 days (range, 14-97) for high-risk. Median time to CR was numerically longer in the low-risk (45 days; range, 20-131) and high-risk (43 days; range 22-107) groups than in the intermediate-risk group (24 days; range, 14-53). The median DOR was numerically longer in the low- (24.9 months; range, 1.0-51.1) and intermediate-risk (not reached [NR]; range, 0.9-57.4 months) groups than in the high-risk group (3.9 months; range, 0.7-52.3).

Twenty-one patients were bridged to HCT (5 low-risk, 10 intermediate-risk, 6 high-risk). The three groups of bridged patients had received a median of 4 cycles from start of tagraxofusp to HCT, and had a similar median time from diagnosis to HCT and a similar median time from the first dose of tagraxofusp to HCT (**Supplemental Table 3**). Pre-transplant CR/CRc rates were high in all three risk groups (100% low-risk, 90% intermediate-risk, 83% high-risk; **Figure 1B**).

Transplanted patients in the low- and intermediate-risk groups had numerically shorter median times to overall response (21 days, range, 20-49; and 23 days, range, 14-53, respectively) than patients in the high-risk group (41 days, range, 23-57). The median DOR for transplanted patients was NR in any group.

The median OS in the overall population was 38.4 months (95% CI 8.6, not estimable [NE]) in the low-risk group, 15.8 months (95% CI 9.0, NE) in the intermediate-risk group, and 11.8 months (95% CI 6.2, 18.9) in the high-risk group (**Figure 1C**). Notably, in the transplanted population, median OS was 38.4 months (95% CI 27.7, NE) in the low-risk group and NR (95% CI 3.4, NE and 4.1, NE) in both intermediate- and high-risk groups (**Figure 1D**).

The safety profile of tagraxofusp was consistent across HCT-CI risk groups and with the overall trial population. **Table 2** summarizes treatment emergent AEs leading to dose reduction, dose interruption, and the most common hematologic and non-hematologic any-grade treatment-related adverse events (TRAEs). Most hematologic and non-hematologic TRAEs occurred during cycle 1 and were transient. Grade 3-4 TRAEs occurred in 60% (low-risk), 46% (intermediate-risk), and 64% (high-risk) of patients. Common grade 3-4 TRAEs included increased ALT/AST (40%, 14%, and 29%, respectively) and, to a lesser extent, thrombocytopenia (33%, 14%, and 14%, respectively) and neutropenia (7%, 5%, and 11%, respectively). Capillary leak syndrome (CLS) was observed in 7% (low-risk), 23% (intermediate-risk), and 21% (high-risk) of patients. CLS events were predominantly grade 1-2, occurred in cycle 1, and resolved at a median of 4-6 days across all risk groups (**Supplemental Table 4**). Deaths due to TRAEs were 2 (9%) patients with CLS and 1 (5%) patient with myocardial infarction in the intermediate-risk group. There were no deaths due to TRAEs in the low-risk or high-risk groups.

This analysis represents the first reported use of a pretreatment HCT-CI score to evaluate treatment outcomes in patients with BPDCN, demonstrating how tagraxofusp performs across varying levels of comorbidities and (chemotherapy) fitness. Tagraxofusp demonstrated uniformly high response rates irrespective of HCT-CI fitness risk level, with an 80% ORR for low-risk, 68% for intermediate-risk, and 79% for high-risk groups. Responses were durable, and importantly, patients across all fitness groups successfully bridged to transplant. Overall, OS was prolonged in the transplanted population, with median OS not reached in intermediate- and high-risk patients bridged to HCT. Tagraxofusp's safety profile remained consistent across all HCT-CI risk groups, mirroring previously reported data for the overall population.[5,6]

The HCT-CI, specifically developed and validated for patients undergoing HCT for hematologic malignancies, offers superior sensitivity and predictive accuracy over more general comorbidity indices (eg, Charlson Comorbidity Index), by incorporating transplant-relevant comorbidities.[12] Unlike with IC where high-risk HCT-CI subgroups in acute myeloid leukemia have shown significant early mortality (29% within 28 days),[13] thus limiting treatment options, the current analysis establishes tagraxofusp as a safe and efficacious treatment for BPDCN across all HCT-CI subgroups. While acknowledging the post-hoc nature of this analysis, the patient population's distribution across low-, intermediate-, and high-risk HCT-CI categories (23%, 34%, and 43% respectively) closely aligns with a large BPDCN cohort from the Center for International Blood and Marrow Transplant registry (26%, 31%, and 42% respectively).[14] This robust comparability strengthens the validity of our stratification methodology. Notably, the high-risk group included older patients who had more BPDCN organ involvement, which aligns with previous reports showing number of comorbidities and BPDCN disease sites are associated with older age.[15] Similarly, the distribution of patients with ≥5% bone marrow blasts at baseline was highest in the high-risk group.

In conclusion, results from this post-hoc analysis show that tagraxofusp induced durable responses without the prolonged myelosuppression and cumulative toxicities associated with IC. Critically, tagraxofusp also enabled bridging to HCT for eligible patients across the entire spectrum of fitness, including those high-risk individuals potentially deemed ineligible for intensive cytotoxic upfront regimens. These results affirm tagraxofusp as the standard of care first-line treatment for all eligible patients with BPDCN irrespective of baseline fitness level.

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Table 1. Baseline characteristics by HCT-CI risk groups of all patients treated with first-line tagraxofusp.

	Low risk (n=15)	Intermediate risk (n=22)	High risk (n=28)
Age, median years (range)	61 (22-79)	68 (22-84)	70 (23-84)
Gender, n (%)			
Male	14 (93)	14 (64)	24 (86)
Race, n (%)			
American Indian or Alaska Native	1 (7)	0	0
Asian	0	2 (9)	0
Black or African American	2 (13)	0	0
White	11 (73)	19 (86)	27 (96)
Other	1 (7)	1 (5)	1 (4)
Ethnicity, n (%)			
Not Hispanic or Latino	13 (87)	20 (91)	26 (93)
ECOG performance status, n (%)			
0	10 (67)	11 (50)	10 (36)
1	4 (27)	11 (50)	16 (57)
2	0	0	2 (7)
Missing	1 (7)	0	0
BMI, median kg/m^2 (range)	28 (23-35)	29 (22-48)	31 (21-40)
Time since BPDCN diagnosis, median months (range)	1.4 (0-2.9)	1.1 (0-4.8)	0.9 (0-3.2)
Disease involvement at baseline, n (%)			
Bone marrow	5 (33)	6 (27)	21 (75)
Lymph node	7 (47)	8 (36)	18 (64)
Peripheral blood	2 (13)	3 (14)	12 (43)
Skin	13 (87)	22 (100)	25 (89)
Visceral	3 (20)	0	6 (21)
≥2 disease sites	9 (60)	11 (50)	25 (89)
≥5% bone marrow blasts	6 (40)	6 (27)	21 (75)

BMI, body mass index; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CI, comorbidity index; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation.

Table 2. Adverse events in 4 or more patients in any HCT-CI risk group treated with first-line tagraxofusp.

Any-grade AE, n (%)	**Low risk (n=15)**	**Intermediate risk (n=22)**	**High risk (n=28)**
Any TEAE leading to dose reduction	1 (7)	0	1 (4)
Any TEAE leading to dose interruption	13 (87)	15 (68)	19 (68)
TEAE leading to dose interruption			
ALT increased	5 (33)	1 (5)	4 (14)
AST increased	5 (33)	1 (5)	5 (18)
Hypoalbuminemia	3 (20)	3 (14)	5 (18)
Pyrexia	1 (7)	4 (18)	2 (7)
Weight increased	5 (33)	9 (41)	6 (21)
Hematologic TRAE			
Anemia	0	5 (23)	4 (14)
Neutropenia	1 (7)	2 (9)	4 (14)
Thrombocytopenia	7 (47)	6 (27)	7 (25)
Non-hematologic TRAE			
ALT increased	10 (67)	10 (46)	14 (50)
AST increased	9 (60)	9 (41)	15 (54)
Back pain	1 (7)	1 (5)	4 (14)
Chills	6 (40)	3 (14)	2 (7)
CLS	1 (7)	5 (23)	6 (21)
Decreased appetite	1 (7)	1 (5)	4 (14)
Fatigue	2 (13)	5 (23)	4 (14)

Hypoalbuminemia	4 (27)	10 (46)	11 (39)
Hypotension	2 (13)	4 (18)	6 (21)
Nausea	5 (33)	3 (14)	7 (25)
Peripheral edema	0	3 (14)	5 (18)
Pyrexia	6 (40)	6 (27)	6 (21)
Tachycardia	3 (20)	0	2 (7)
Vision blurred	3 (20)	0	0
Weight increased	3 (20)	6 (27)	9 (32)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, comorbidity index; CLS, capillary leak syndrome; HCT, hematopoietic cell transplantation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Figure 1. Efficacy Outcomes by HCT-CI risk groups. (A) Objective responses in all patients.[a] (B) Objective responses in patients bridged to transplant. (C) Kaplan-Meier overall survival curves in all patients. (D) Kaplan-Meier overall survival curves in patients bridged to transplant. BPDCN, blastic plasmacytoid dendritic cell neoplasm; CI, comorbidity index; CR, complete response; CRc, CR with residual skin abnormalities not indicative of active BPDCN; HCT, hematopoietic cell transplantation; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response. [a]Four patients in the intermediate-risk group were not evaluable.

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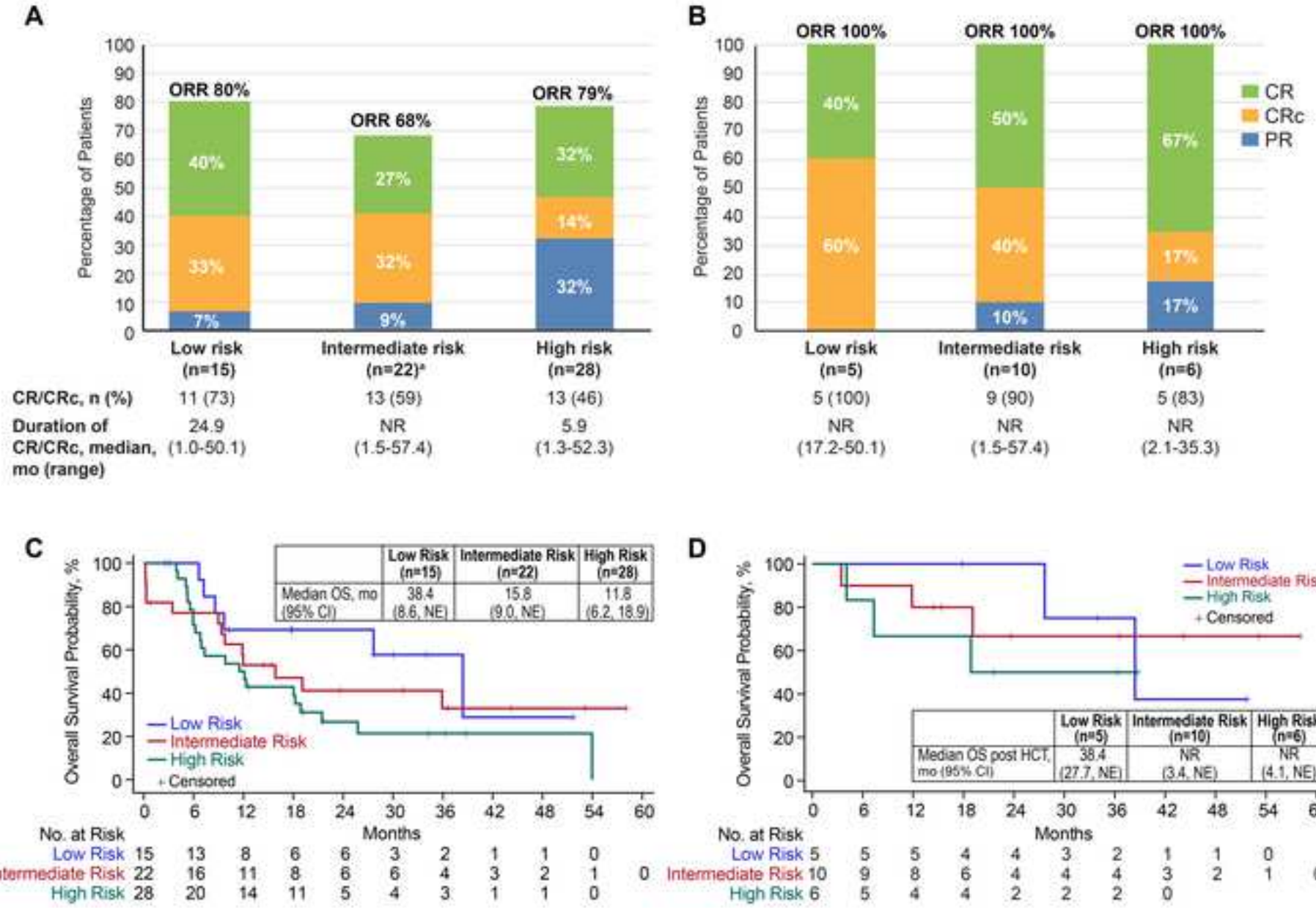

Supplemental Material

Supplemental Table 1. Baseline distribution of HCT-CI criteria in patients treated with first-line tagraxofusp. Anonymized data from treatment-naïve adults with BPDCN prospectively treated with tagraxofusp 12 µg/kg/day on days 1-5 of each 21-day cycle were used. Available medical history, concomitant medications, and laboratory values were used to determine the HCT-CI scores by assigning points for 16 HCT-CI criteria. It was not possible to assess the "severe pulmonary disease" HCT-CI criterion since these patients were excluded from the study, and lung function tests were not collected to determine this post hoc.

Criterion, n (%)	Score value	(N=65)
Arrhythmia	1	13 (20)
Cardiac disease	1	8 (12)
Inflammatory bowel disease	1	0
Diabetes	1	15 (23)
Cerebrovascular disease	1	3 (5)
Psychiatric disturbance	1	13 (20)
Hepatic, mild	1	4 (6)
Obesity	1	13 (20)
Infection	1	5 (8)
Rheumatologic disease	2	4 (6)
Peptic ulcer	2	1 (2)
Moderate/severe renal disease	2	5 (8)
Moderate pulmonary disease	2	8 (12)
Prior solid tumor	3	9 (14)
Heart valve disease	3	5 (8)
Moderate/severe hepatic disease	3	1 (2)

CI, comorbidity index; HCT, hematopoietic cell transplantation.

Supplemental Table 2. Primary Reasons for Study Discontinuation

	Low risk (n=15)	**Intermediate risk (n=22)**	**High risk (n=28)**
Disease recurrence/progression	6 (40)	5 (23)	13 (46)
Physician decision	4 (27)	1 (5)	6 (21)
Lost to follow-up	3 (20)	11 (50)	6 (21)
Withdrawal of consent	2 (13)	1 (5)	1 (4)
Adverse event	0	4 (18)	2 (7)
Other	3 (20)	11 (50)	6 (21)

Supplemental Table 3. Baseline and treatment characteristics by HCT-CI risk groups of patients bridged to transplant after treatment with first-line tagraxofusp.

	Low risk (n=5)	**Intermediate risk (n=10)**	**High risk (n=6)**
Age, median years (range)	40 (22-69)	58 (22-75)	69 (57-78)
Gender, n (%)			
Male	4 (80)	5 (50)	6 (100)
Race, n (%)			
White	5 (100)	10 (100)	6 (100)
Ethnicity, n (%)			
Not Hispanic or Latino	4 (80)	9 (90)	6 (100)
ECOG performance status, n (%)			
0	4 (80)	6 (60)	4 (67)
1	1 (20)	4 (40)	2 (33)
BMI, median kg/m^2 (range)	28 (24-35)	30 (22-48)	32 (26-38)
Time since BPDCN diagnosis, median months (range)	1.4 (0-2.9)	0.8 (0-3.2)	0.7 (0.4-2.9)
Disease involvement at baseline, n (%)			
Bone marrow	0	3 (30)	4 (67)
Lymph node	2 (40)	4 (40)	5 (83)
Peripheral blood	0	2 (20)	3 (50)
Skin	5 (100)	10 (100)	6 (100)
Visceral	0	0	2 (33)
≥2 disease sites	2 (40)	5 (50)	6 (100)
Median number of cycles from start of tagraxofusp to HCT, mo (range)	4 (3-7)	4 (2-7)	4 (2-8)
Median time from diagnosis to HCT, mo (range)	5.4 (4.2-7.7)	5.8 (2.8-8.4)	5.4 (3.6-8.0)
Median time from first dose of tagraxofusp to HCT, mo (range)	3.9 (3.0-5.5)	3.5 (2.4-6.5)	4.1 (2.5-6.7)

BMI, body mass index; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CI, comorbidity index; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation.

Supplemental Table 4. Capillary leak syndrome by HCT-CI risk groups in patients treated with first-line tagraxofusp.

	Low risk (n=15)	**Intermediate risk (n=22)**	**High risk (n=28)**
CLS TRAE, (n %)	1 (7)	5 (23)	6 (21)
Grade 1-2	1 (7)	1 (5)	5 (18)
Grade 3-4	0	2 (9)	1 (4)
Gade 5	0	2 (9)	0
CLS leading to dose interruption, n (%)	1 (7)	1 (5)	2 (7)
Resolution of CLS TRAE, n (%)[a]	1 (100)	3 (60)	6 (100)
Time to resolution of resolved CLS TRAE, median days (range)	4 (4-4)	5 (2-9)	6 (3-69)

[a]The percentage of patients with a resolved CLS TRAE was calculated using as the denominator the total number of patients with that TRAE.

CI, comorbidity index; CLS, capillary leak syndrome; HCT, hematopoietic cell transplantation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.