Favorable outcomes including post-transplant survival are seen independent of baseline skin burden in treatment-naïve patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN) treated with tagraxofusp (TAG): Subgroup analysis of a pivotal trial

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BACKGROUND

- BPDCN is an aggressive orphan malignancy that expresses CD123 and presents in the skin, bone marrow (BM), blood, and viscera.[1,2]
- Tagraxofusp (TAG), a first-in-class CD123-targeted therapy, is the first drug approved for adults or pediatric patients aged ≥2 years with treatment-naïve (1L) or relapsed/refractory BPDCN in the United States, or for adults with treatment-naïve BPDCN in Europe.[3,4]
- In a phase 1/2 trial with prespecified and multisystem response criteria/endpoints (NCT02113982), 1L TAG was associated with high rates of rapid and durable responses—75% objective response rate (ORR), 57% complete response (CR)/clinical CR (CRc; CR with residual skin abnormalities not indicative of active BPDCN) rate, 39 days median time to CR/CRc, and 24.9 months median duration of CR/CRc—with 51% of CR/CRc patients bridging to hematopoietic cell transplantation (HCT).[5]
- Results of a real-world study of TAG for 1L BPDCN also demonstrated rapid and durable responses—90% ORR, median time to response 23.5 days, median duration of response (DOR) 10.3 months, and median overall survival (OS) 20.2 months—with 55% of response-evaluable patients bridging to HCT.[6]
- TAG has a well-characterized and manageable safety profile with transient adverse events (AEs) mostly occurring in cycle 1, no cumulative long-term toxicity or myelosuppression, and early restoration of normal hematopoiesis for most patients, facilitating bridge to HCT.[7]
- The impact of baseline skin disease burden, the most common site of BPDCN, on clinical outcomes remains unclear and has not been previously studied.

OBJECTIVE

- To evaluate the impact of baseline skin disease burden, assessed using the Modified Severity-Weighted Assessment Tool (mSWAT), on clinical outcomes in patients with BPDCN treated with 1L TAG in the pivotal trial (NCT02113982).

METHODS

- Subgroup, descriptive analysis of outcomes following 1L TAG (12 µg/kg intravenously on days 1-5 of a 21-day cycle) in 62 efficacy-evaluable patients with available baseline mSWAT scores.
- Baseline patient data were used to assess total BPDCN skin involvement using the mSWAT to calculate a score accounting for the percentage body surface area affected by each type of lesion and weighting factors for plaque and tumor lesions. The median mSWAT score was determined to be 6.85 (range, 0-102).
- Patients were stratified into "low" (<6.85) and "high" (≥6.85) mSWAT groups based on scores relative to the median.
- Outcomes assessed in this analysis included best overall response, CR/CRc, progression-free survival (PFS), OS, rate of bridging to HCT, treatment-related AEs (TRAEs), and incidence of capillary leak syndrome (CLS).

RESULTS

Patient demographics, baseline characteristics, and treatment characteristics

- Patients in the high (n=31) and low (n=31) mSWAT groups had similar baseline demographic characteristics (**Table 1**).
- The high mSWAT group had numerically higher rates of BM involvement (61% vs 32%) and ≥2 disease sites (87% vs 52%) than the low mSWAT group.
- Two (7%) patients in the high mSWAT group and 5 (16%) in the low mSWAT group had a prior or concomitant hematologic malignancy (PCHM).

Table 1. Patient characteristics

Characteristic	High mSWAT (n=31)	Low mSWAT (n=31)
Age (years), median (range)	68 (22-79)	69 (23-84)
Gender, no. (%)		
Male	24 (77)	25 (81)
Race, no. (%)		
White	28 (90)	27 (87)
Time since BPDCN diagnosis (months), median (range)	0.8 (0-2.9)	1.2 (0-4.8)
Disease involvement at baseline, no. (%)		
Skin	31 (100)	28 (90)
Bone marrow	19 (61)	10 (32)
Peripheral blood	10 (32)	5 (16)
Lymph node	20 (65)	12 (39)
Visceral	6 (19)	2 (6)
≥2 disease sites	27 (87)	16 (52)
HCT-Specific Comorbidity Index,[a] no. (%)		
Low	6 (19)	8 (26)
Intermediate	10 (32)	12 (39)
High	15 (48)	11 (36)
PCHM, no. (%)	2 (7)[b]	5 (16)[c]

[a]HCT-CI is a risk-stratification model based on combined comorbidity scores.[8]
[b]Includes Hodgkin disease (n=1) and lymphoma (n=1).
[c]Includes MDS (n=3), MDS/CMML (n=1), and multiple myeloma (n=1).

RESULTS (CONTINUED)

Median follow-up time was 34.3 months in the high mSWAT group and 30.0 months in the low mSWAT group (Table 2).

- Patients in both groups received a median of 4 (range, 1-5) doses in cycle 1.
- A substantial proportion of patients were successfully bridged to HCT immediately after TAG treatment: 35% of patients in the high mSWAT group and 32% of patients in the low mSWAT group.
- For patients that received HCT at any time post-TAG, the high mSWAT group had a numerically higher rate of post-TAG HCT than the low mSWAT group (58% vs 45%).

Table 2. Patient disposition

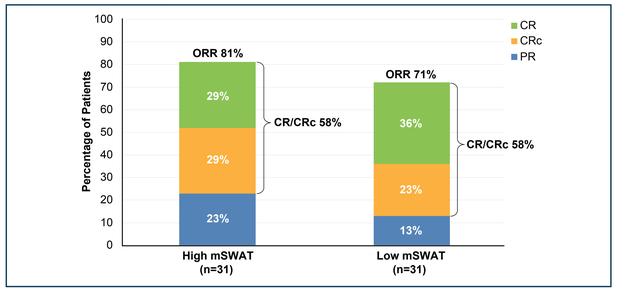
	High mSWAT (n=31)	Low mSWAT (n=31)
Follow-up (months), median (range)	34.3 (0.4-51.7)	30.0 (0.2-58.1)
Exposure (days), median (range)	75 (5-545)	68 (1-1622)
No. of doses in cycle 1, median (range)	4 (1-5)	4 (1-5)
Received HCT anytime post-TAG,[a] no. (%)	18 (58)	14 (45)
Autologous	2 (7)	5 (16)
Allogeneic	14 (45)	7 (23)
Reduced intensity conditioning allogeneic	1 (3)	1 (3)
Other[b]	1 (3)	1 (3)
Bridged to HCT immediately post TAG, no. (%)	11 (35)	10 (32)

[a]Includes patients with any HCT following treatment with TAG (ie, patients bridged to HCT and those who had progression on study and received subsequent HCT).
[b]Includes 1 haploidentical and 1 cord blood stem cell transplant.

High overall response rates were achieved regardless of mSWAT group

- ORR was 81% in the high mSWAT group and 71% in the low mSWAT group; a 58% CR/CRc rate was reported in both groups (**Figure 1**).
- Median time to response was similar between groups:
  - High mSWAT: 23.0 days (range, 14-57)
  - Low mSWAT: 24.0 days (range, 17-97)
- Median time to CR/CRc was longer in the high mSWAT group:
  - High mSWAT: 44 days (range, 14-131)
  - Low mSWAT: 23.5 days (range, 17-88)
- Median DOR was longer in the high mSWAT group vs the low group:
  - High mSWAT: 9.1 months (range, 0.7-51.1)
  - Low mSWAT: 4.6 months (range, 0.7-57.4)
- In patients with CR/CRc, median DOR was not reached (NR; range, 1.3-50.1) in the high mSWAT group and 24.9 months (range, 1.0-57.4) in the low mSWAT group.

Figure 1. Overall response rates



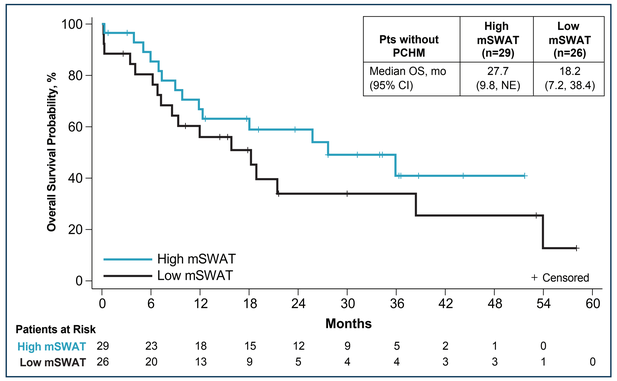
PFS and OS were prolonged in the high mSWAT group

- Median PFS in the overall population:
  - High mSWAT: 7.3 months (95% CI, 3.1-27.7)
  - Low mSWAT: 4.1 months (95% CI, 2.8-5.8)
- Median OS in the overall population:
  - High mSWAT: 25.8 months (95% CI, 11.9-not estimable [NE])
  - Low mSWAT: 12.0 months (95% CI, 6.6-21.5)

Excluding patients with PCHM, median OS remained stable in the high mSWAT group and improved in the low mSWAT group (who had more PCHM)

- Median OS for patients without PCHM (**Figure 2**):
  - High mSWAT (n=29): 27.7 months (95% CI, 9.8-NE)
  - Low mSWAT (n=26): 18.2 months (95% CI, 7.2-38.4)

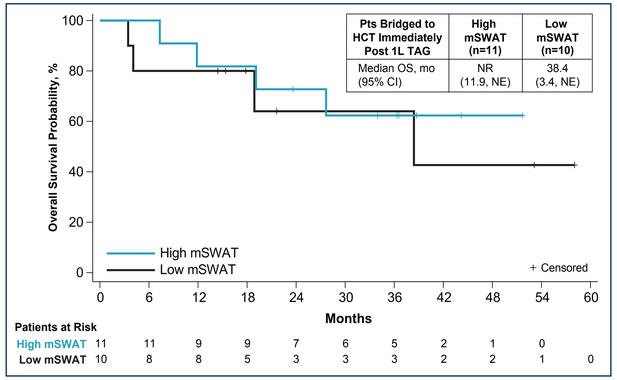
Figure 2. Overall survival in patients without PCHM



Durable survival outcomes observed in patients who bridged to transplant in both mSWAT groups

- Similar numbers of patients in the high (n=11; 35%) and low (n=10; 32%) mSWAT groups successfully underwent HCT immediately after 1L TAG.
- Median PFS in patients bridged to HCT immediately after 1L TAG:
  - High mSWAT: NR (95% CI, 9.7-NE)
  - Low mSWAT: 25.5 months (95% CI, 3.4-NE)
- Median OS in patients bridged to HCT immediately after 1L TAG (**Figure 3**):
  - High mSWAT: NR (95% CI, 11.9-NE)
  - Low mSWAT: 38.4 months (95% CI, 3.4-NE)
- More patients in the high mSWAT group (n=18; 58%) had HCT at any time than patients in the low mSWAT group (n=14; 45%).

Figure 3. Overall survival for patients bridged to transplant immediately post 1L TAG



Rates of CLS were similar in both mSWAT groups, with no grade 3-4 CLS events reported in the high mSWAT group

- Similar rates of any-grade CLS were observed in both mSWAT groups, although the high mSWAT group had a lower rate of grade ≥3 events and faster time to resolution (**Table 3**):
  - High mSWAT: No grade 3-4 CLS events, 1 (3%) patient with grade 5 CLS
  - Low mSWAT: Two (7%) patients with grade 3 CLS, 1 (3%) grade 4, and 1 (3%) grade 5
- All CLS events occurred in cycle 1 and none recurred.

Table 3. CLS

	High mSWAT (n=31)	Low mSWAT (n=31)
Patients with ≥1 CLS event, no. (%)		
Any grade	5 (16)	6 (19)
Grade 3	0	2 (7)
Grade 4	0	1 (3)
Grade 5	1 (3)	1 (3)
Any recurring CLS event, no. (%)	0	0
Time to any CLS event (days), median (range)	6.0 (3-8)	6.5 (4-12)
Time to resolution of grade 1-4 CLS (days), median (range)	4.5 (3-7)	14.0 (5-69)

TRAEs were comparable across groups

- In both groups, the most frequently reported any-grade TRAEs were ALT increased, AST increased, and hypoalbuminemia (**Table 4**).
- Hematologic TRAEs were more common in the high mSWAT group compared to the low mSWAT group, which may be reflective of more baseline BM involvement in patients with high mSWAT.
- Grade 3-4 TRAEs reported in >3 (10%) patients:
  - High mSWAT: Thrombocytopenia (8; 26%), ALT increased (4; 13%), AST increased (4; 13%), and neutropenia (4; 13%)
  - Low mSWAT: ALT increased (12; 39%) and AST increased (12; 39%)
- One (3%) patient in the high mSWAT group and 2 (7%) in the low mSWAT group had a treatment-related death.
- Twenty-two (71%) patients in the high mSWAT group and 24 (77%) in the low mSWAT group had TEAEs leading to dose interruption.
- Most common TEAEs leading to dose interruptions (reported in >15% of patients) were pyrexia, ALT increased, AST increased, weight increased, and hypoalbuminemia.

Table 4. Most common TRAEs

	High mSWAT (n=31)	Low mSWAT (n=31)
Any-grade hematologic TRAEs reported in >15% of patients, no. (%)		
Thrombocytopenia	13 (42)	6 (19)
Neutropenia	6 (19)	1 (3)
Any-grade nonhematologic TRAEs reported in >20% of patients, no. (%)		
ALT increased	15 (48)	18 (58)
AST increased	15 (48)	17 (55)
Hypoalbuminemia	13 (42)	12 (39)
Pyrexia	12 (39)	6 (19)
Weight increased	6 (19)	12 (39)
Nausea	10 (32)	3 (10)
Chills	7 (23)	3 (10)
Hypotension	7 (23)	5 (16)

CONCLUSIONS

- First-line treatment with tagraxofusp induced CR/CRc in patients with BPDCN and enabled successful bridging to hematopoietic cell transplantation, independent of baseline skin disease involvement.
- Despite a higher baseline disease burden (87% with ≥2 disease sites; 61% with bone marrow involvement), patients in the high mSWAT group achieved a clinically meaningful benefit, with a median overall survival (OS) of 25.8 months.
- Among patients achieving a TAG-induced remission and proceeding immediately to HCT, survival outcomes were prolonged across mSWAT subgroups (high mSWAT: median OS not reached; low mSWAT: median OS 38.4 months), highlighting the role of TAG in enabling this potentially curative intervention.
- Patients with high mSWAT scores experienced a longer time to CR/CRc relative to low mSWAT patients, emphasizing the importance of continuing therapy to allow for an optimal response to be achieved.
- The safety profile of TAG was consistent across groups, with a reduced incidence of grade 3-4 capillary leak syndrome observed in patients with higher mSWAT scores.
- Collectively, these findings support tagraxofusp as an effective first-line therapy for BPDCN irrespective of disease burden or clinical presentation and reinforce its role as the standard of care in eligible patients.

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ABBREVIATIONS:

1L, first-line; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BM, bone marrow; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CI, confidence interval; CLS, capillary leak syndrome; CMML, chronic myelomonocytic leukemia; CR, complete response; CRc, clinical complete response; DOR, duration of response; HCT, hematopoietic cell transplantation; HCT-CI, HCT-Specific Comorbidity Index; MDS, myelodysplastic syndrome; mo, month; mSWAT, Modified Severity-Weighted Assessment Tool; NE, not estimable; no., number; NR, not reached; ORR, overall response rate; OS, overall survival; PCHM, prior or concomitant hematologic malignancy; PFS, progression-free survival; PR, partial response; pts, patients; TAG, tagraxofusp; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.