Tagraxofusp, an Anti-CD123 Therapy, in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm: Subanalyses of a Pivotal Trial by Age and Baseline Disease Involvement

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BPDCN

- BPDCN is a highly aggressive, rare hematologic malignancy associated with a very poor prognosis
  - Conventional combination chemotherapy regimens are associated with high toxicity, early death, and high rates of relapse
- Median age at diagnosis is 60–70 years, with clinical presentation marked by skin and BM involvement
  - Secondary sites include peripheral blood, lymph nodes, viscera, and CNS involvement
- BPDCN is derived from the precursors of pDCs that highly overexpress CD123

Pagano L, et al. *Br J Haematol.* 2016;174:188-202.

Tagraxofusp

- Tagraxofusp (TAG) is a first-in-class CD123-targeted therapy that consists of human IL-3 fused to a truncated diphtheria toxin payload

- TAG is the only FDA- and EMA-approved treatment for BPDCN
- TAG 0114 trial (NCT02113982) in BPDCN: Largest prospective trial to date
  - High response rates in 1L patients (ORR=75%; CR/CRc [CR with residual skin abnormality not indicative of active disease] =57%), with median duration of CR/CRc of 24.9 months
  - Fifty-one percent of patients who achieved CR/CRc successfully bridged to HSCT
  - Predictable and manageable safety profile

Aim: To determine whether age or extent of baseline disease involvement impact outcomes following TAG treatment in 1L patients with BPDCN

Pemmaraju N, et al. *N Engl J Med.* 2019;380:1628-1637.

Study Design

- Multicenter, 4-stage, single-arm, phase 1/2 trial evaluating TAG monotherapy in patients with 1L or R/R BPDCN

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			

Key Eligibility Criteria
• Albumin ≥3.2 g/dL

Main Outcome Measures
• CR (defined as CR + CRc), ORR, OS, safety

CRc = CR with residual skin abnormality not indicative of active disease

Demographics and Baseline Characteristics

- 65 1L patients received TAG at 12 mcg/kg

	Age Subgroup				*Baseline Disease Involvement**		
Parameter	**<60 years (n=17)**	**≥60 to <65 years (n=9)**	**≥65 to <75 years (n=28)**	**≥75 years (n=11)**	**Skin-only (n=18)**	**Systemic-only** (n=4)**	**Skin + systemic (n=42)**
Gender, n (%)							
Male	12 (70.6)	6 (66.7)	24 (85.7)	10 (90.9)	13 (72.2)	4 (100)	34 (81.0)
Female	5 (29.4)	3 (33.3)	4 (14.3)	1 (9.1)	5 (27.8)	0	8 (19.0)
Median age, years (range)	41.0 (22–59)	62.0 (61–64)	70.5 (65–74)	78.0 (75–84)	67.0 (28–84)	65.0 (57–72)	68.5 (22–84)
ECOG PS, n (%)							
0	11 (64.7)	4 (44.4)	13 (46.4)	3 (27.3)	12 (66.7)	1 (25.0)	17 (40.5)
1	5 (29.4)	4 (44.4)	15 (53.6)	7 (63.6)	6 (33.3)	3 (75.0)	22 (52.4)
2	0	1 (11.1)	0	1 (9.1)	0	0	2 (4.8)
Missing	1 (5.9)	0	0	0	0	0	1 (2.4)

*One patient was excluded from baseline analysis as not meeting criteria for systemic disease – pretreatment BM biopsy confirmed 3% blast count; **Patients with active or suspected CNS leukemia were excluded.

Efficacy Outcomes Stratified by Age

Parameter	Age Subgroup			
	<60 years (n=17)	≥60 to <65 years (n=9)	≥65 to <75 years (n=28)	≥75 years (n=11)
Response rate, n (%)				
ORR	13 (76.5)	5 (55.6)	22 (78.6)	9 (81.8)
CR/CRc	10 (58.5)	5 (55.6)	16 (57.1)	6 (54.5)
DOR, months (95% CI)	NR (4.6, NR)	1.5 (1.0, NR)	3.9 (2.2, 7.3)	3.8 (0.7, NR)
Bridged to HSCT, %	58.8	11.1	28.6	18.2

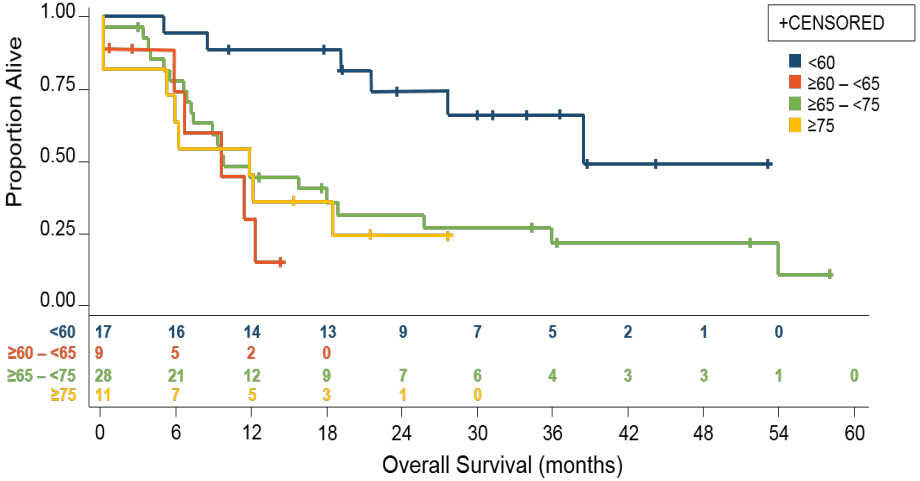
- Similar rates of CR/CRc and ORR were seen across the age cohorts
- Highest number of patients bridging to HSCT were in the <60 years age group (n=10; 59%)

NR, not reached.

Overall Survival Stratified by Age

Age Subgroup				
Parameter	**<60 years (n=17)**	**≥60 to <65 years (n=9)**	**≥65 to <75 years (n=28)**	**≥75 years (n=11)**
Median OS, months (95% CI)	38.4 (38.4, NR)	9.7 (0.2, 12.3)	9.8 (6.9, 25.8)	12.0 (0.3, 18.2)
Survival probability, %				
12 months	87.5	19.8	40.9	43.6
18 months	87.5	25.0	40.9	32.7
24 months	87.5	25.0	31.8	16.4

- Greatest survival benefit (median OS, 38.4 months) was seen in patients <60 years, with similar outcomes across all other age cohorts



NR, not reached.

Efficacy Outcomes Stratified by Baseline Disease Involvement

Parameter	*Baseline Disease Involvement**		
	Skin only (n=18)	Systemic only** (n=4)	Skin + systemic (n=42)
Response rate, n (%)			
ORR	13 (72.2)	3 (75.0)	32 (76.2)
CR/CRc	13 (72.2)	2 (50.0)	21 (50.0)
DOR, months (95% CI)	24.9 (2.5, NR)	NR (3.0, NR)	NR (2.3, NR)
Bridged to HSCT, %	44.4	0	31.0

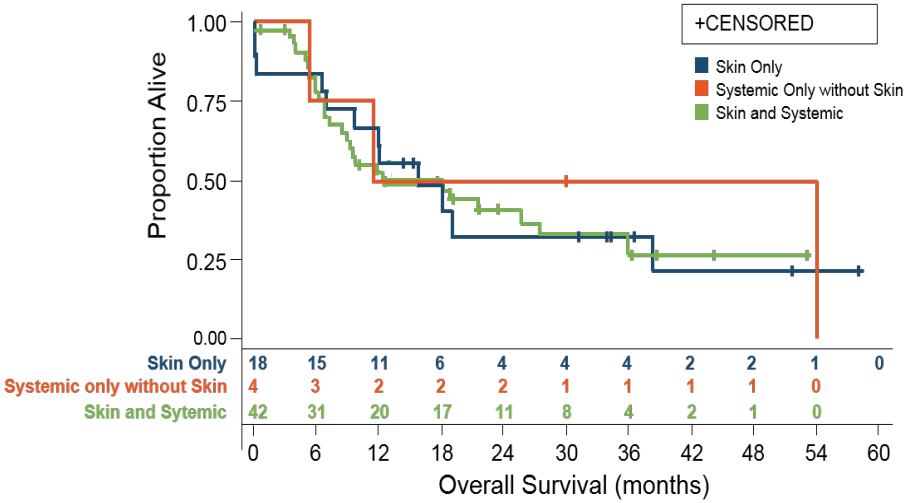
- Similar response rates were observed across the cohorts stratified by baseline disease involvement
- Highest proportion of patients bridging to HSCT were those with baseline skin-only disease (n=8; 44%)

*One patient was excluded from baseline analysis as not meeting criteria for systemic disease – pretreatment BM biopsy confirmed 3% blast count; **Patients with active or suspected CNS leukemia were excluded.

NR, not reached.

Overall Survival Stratified by Baseline Disease Involvement

Baseline Disease Involvement			
Parameter	**Skin only (n=18)**	**Systemic only (n=4)**	**Skin + systemic (n=42)**
Median OS, months (95% CI)	18.2 (7.2, NR)	NR (5.3, NR)	11.9 (7.3, 35.9)
Survival probability, %			
12 months	58.4	50.0	49.5
18 months	50.0	50.0	46.6
24 months	40.0	50.0	39.5



NR, not reached.

Overall Efficacy Outcomes for Patients Who Bridged to HSCT

	CR in 1L Patients and Those Who Bridged to HSCT, n (%)		
Parameter	Baseline (N=65)	Complete remission	HSCT after CR
Age			
≥65 years	39 (60)	22/39 (56)	9/22 (41)
<65 years	26 (40)	15/26 (58)	10/15 (67)
Cardiac history*			
Yes	17 (26)	10/17 (59)	4/10 (40)
No	48 (74)	27/48 (56)	15/27 (56)
BM blasts ≥5%			
Yes	32 (49)	17/32 (53)	7/17 (41)
No	33 (51)	20/33 (61)	12/20 (60)
≥2 disease sites			
Yes	45 (69)	23/45 (51)	11/23 (48)
No	20 (31)	14/20 (70)	8/14 (57)

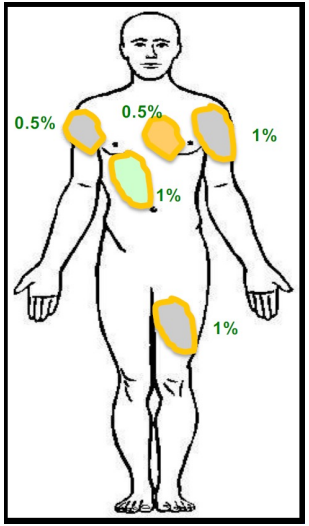
- Nineteen of 37 (51%) patients achieving CR/CRc bridged to HSCT (autologous, n=6; allogenic, n=13)
  - Median age 63 years, range 22–75
  - Forty percent were <65 years of age, 49% had BM blasts ≥5% at baseline, and 69% had baseline disease at ≥2 sites

	Survival Probability
12 months	79%
24 months	66%

*Cardiac history is defined as having at least 1 of the following: CAD, CHF (controlled; non-Class III or IV), MI (>6 months prior to study start), controlled atrial fibrillation, atrial flutter, sick sinus syndrome, or ventricular fibrillation

Skin Assessment and Scoring: Modified Severity-Weighted Assessment Tool (mSWAT)

- mSWAT is the most widely used method for skin scoring
- In BPDCN, the tool is used to capture the physical characteristics of lesions (flat vs raised). The calculation is felt to be more accurate than measurement of total percentage body surface area (BSA) involved alone
- mSWAT requires
  - Direct assessment of percentage of total BSA involved by patches, plaques, and tumor
  - The percentage of involved BSA for each type of lesion is then multiplied by a weighting factor (patch = 1, plaque = 2, tumor = 4), and scores are summed together
- mSWAT is used to measure skin response in clinical trials
  - Complete response: 100% clearance of skin lesions; no new lesions in patients without lesions at baseline
  - Partial response: 50%–99% clearance of skin disease from baseline without any new lesions

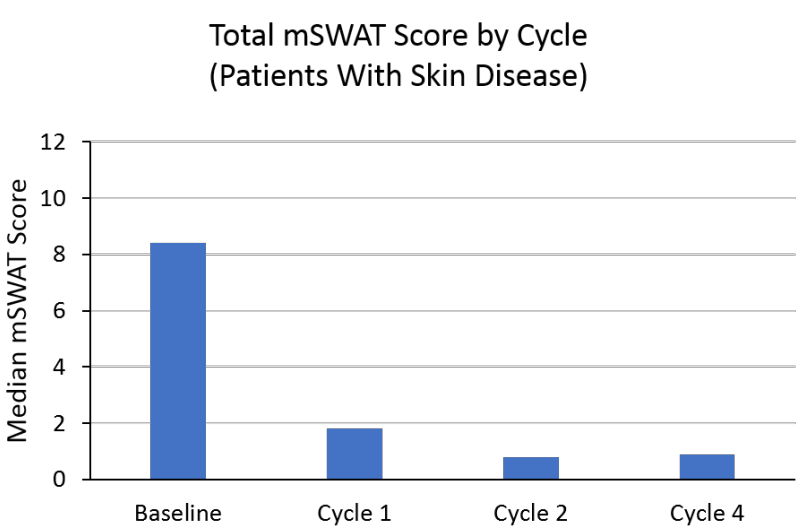


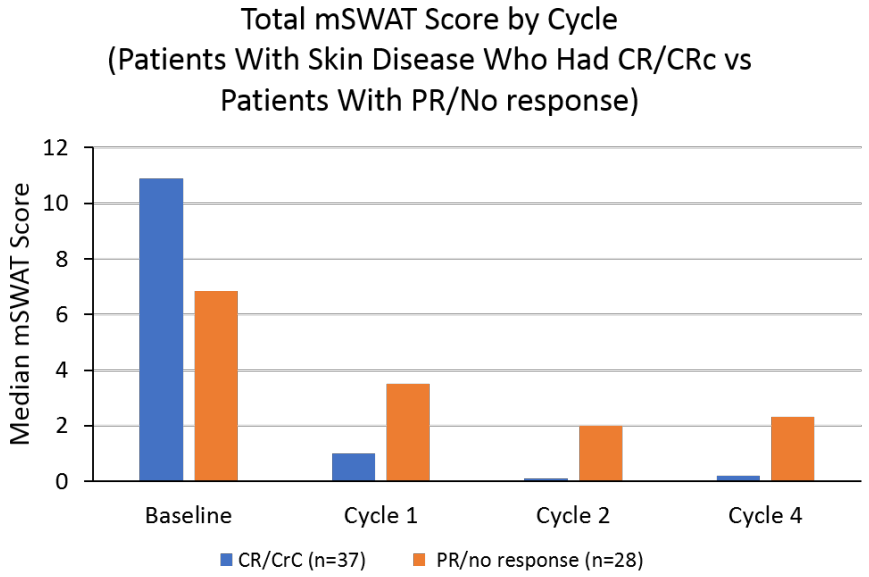
Patch: 2.5% × 1 = 2.5%
Plaque: 1.0% × 2 = 2.0%
Tumor: 0.5% × 4 = 2.0%
Total = 6.5%

Stevens SR, et al. *Arch Dermatol*. 2002;138:42-48.

mSWAT Analysis

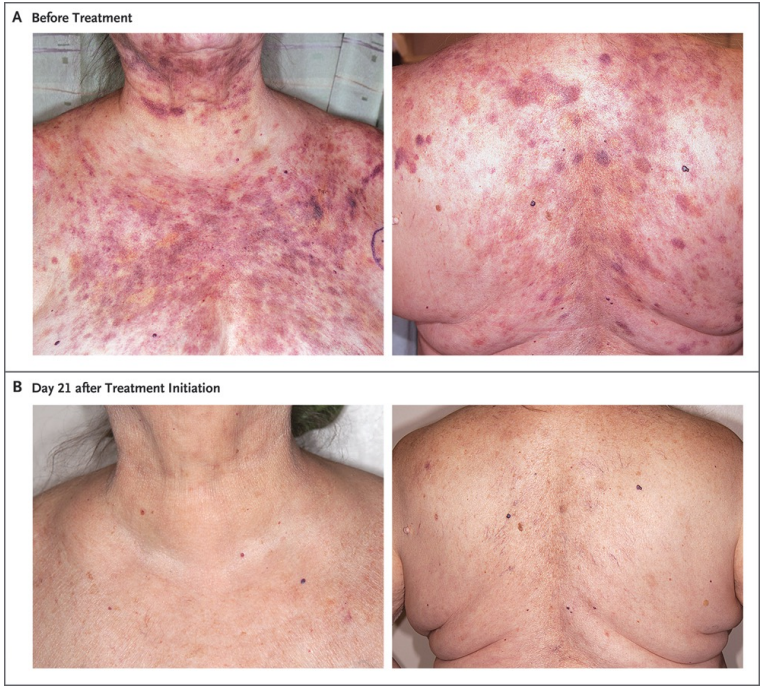
- TAG has pronounced and rapid effects on skin disease as measured by mSWAT





Example of a Dermatologic Response to TAG

- Photographs of chest and back of a 71-year-old female patient participating in clinical trial
- 1L patient with extensive skin and bone BM involvement
- Received 6 cycles of TAG 12 mcg/kg
- Panel A (baseline): Extensive skin and BM involvement
  - BM blasts: 14%
  - mSWAT: 11.3%
- Panel B (day 21): Skin and BM responses
  - BM blasts: 3%
  - mSWAT: 0%
- Bridged to HSCT after achieving CR and 6 cycles of TAG



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Pemmaraju N, et al. *N Engl J Med.* 2019;380:1628-1637.

Safety Outcomes Stratified by Age

Most common TEAEs	Age Subgroup, n (%)			
	<60 years (n=17)	≥60 to <65 years (n=9)	≥65 to <75 years (n=29)	≥75 years (n=11)
Increased ALT	14 (82)	7 (78)	17 (59)	6 (55)
Increased AST	12 (71)	7 (78)	15 (52)	6 (55)
Pyrexia	10 (59)	3 (33)	8 (28)	6 (55)
Thrombocytopenia	10 (59)	2 (22)	13 (45)	1 (9)
Fatigue	9 (53)	3 (33)	13 (45)	3 (27)
Nausea	7 (41)	4 (44)	13 (45)	4 (36)
Headache	7 (41)	1 (11)	10 (35)	2 (18)
Hypoalbuminemia	6 (35)	1 (11)	17 (59)	4 (36)
Increased weight	6 (35)	4 (44)	10 (35)	5 (46)
Hyperglycemia	4 (24)	4 (44)	8 (28)	4 (36)
Edema peripheral	3 (18)	1 (11)	11 (38)	5 (46)
Capillary leak syndrome	1 (6)	3 (33)	5 (17)	2 (18)

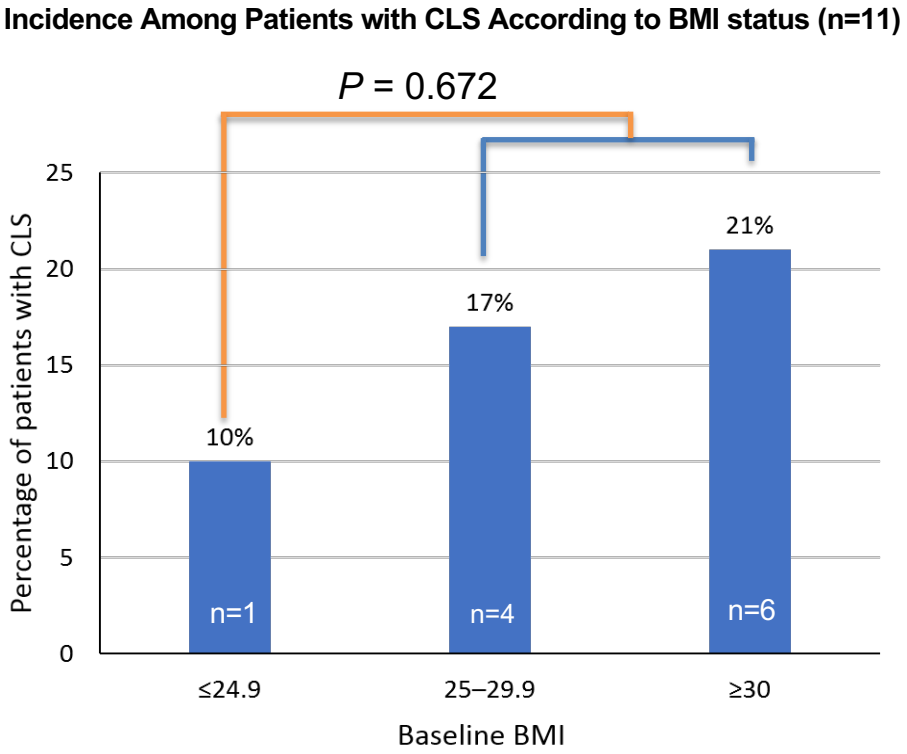
- Safety profile was similar across the age groups
- 11 patients experienced CLS, with the highest incidence occurring in patients ≥65 to <75 years
  - The highest incidence by percentage was in the ≥60 to <65 age group (33% vs 17% in patients aged ≥65 to <75
  - Majority were grade ≤2

Safety Outcomes Stratified by Baseline Disease Involvement

	Baseline Disease Involvement, n (%)		
Most common TEAEs	**Skin-only (n=18)**	**Systemic-only (n=4)**	**Skin + systemic (n=42)**
Increased ALT	10 (53)	3 (75)	30 (71)
Pyrexia	10 (53)	1 (25)	16 (38)
Increased AST	9 (47)	3 (75)	27 (64)
Fatigue	9 (47)	3 (75)	15 (36)
Hypoalbuminemia	9 (47)	1 (25)	18 (43)
Increased weight	9 (47)	0	15 (36)
Nausea	7 (37)	3 (75)	18 (43)
Thrombocytopenia	6 (32)	1 (25)	19 (45)
Hyperglycemia	6 (32)	2 (50)	12 (29)
Edema peripheral	6 (32)	2 (50)	12 (29)
Constipation	6 (32)	2 (50)	11 (26)
Hyperkalemia	2 (11)	2 (50)	5 (12)
Capillary leak syndrome	4 (21)	0	7 (17)

- Site of baseline disease did not predispose patients to different TEAEs

Incidence of CLS and Efficacy Outcomes in 1L Patients - Stratified by BMI



Conclusion

- This trial with TAG is the largest prospective trial to date in BPDCN
- High response rates in 1L patients (ORR=75%; CR/CRc=57%), with median duration of CR/CRc of 24.9 months
  - High rates of durable CRs enabled over half of the patients in CR to be bridged to HSCT, including older adults and patients with extensive baseline disease
- Efficacious across all age cohorts, including older patients and those with significant baseline disease
  - Adverse events were manageable, and the safety profile was similar between older and younger patients
  - Site of baseline disease did not predispose patients to different TEAEs
- TAG is the first-in-class CD123-targeted therapy and the first approved treatment for BPDCN in both the US and EU

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