INTERIM ANALYSIS OF A REGISTRATION-ENABLING STUDY OF PIVEKIMAB SUNIRINE (PVEK, IMGN632) A CD123-TARGETING ANTIBODY-DRUG CONJUGATE, IN PATIENTS WITH BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN)

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Background

- Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare, aggressive hematologic malignancy derived from myeloid dendritic cell precursors with skin, lymph node, blood, CNS, and bone marrow involvement
  - BPDCN may arise de-novo or in the context of a prior or concomitant hematologic malignancy (PCHM)

- CD123 (IL-3Rα) is ubiquitously expressed in BPDCN blasts but has limited expression on normal tissues[1,2]

- Based on the favorable safety and clinical activity of pivekimab sunirine (IMGN632, PVEK) in patients with relapsed or refractory (R/R) BPDCN, PVEK was granted FDA Breakthrough Therapy Designation in October 2020[3]

- Here we report an interim analysis of safety and anti-BPDCN activity data from a phase 2 study in adult patients with frontline or R/R BPDCN

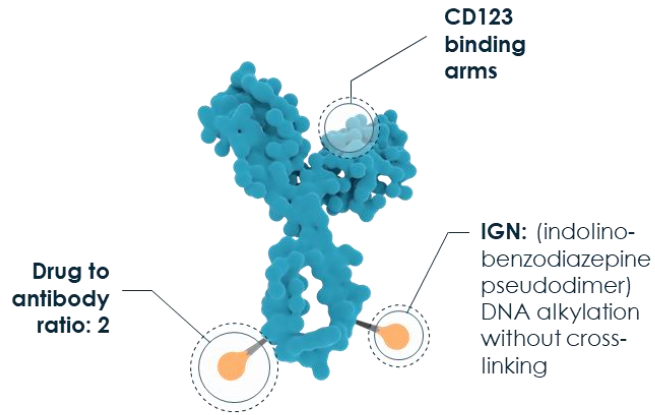
CNS, central nervous system

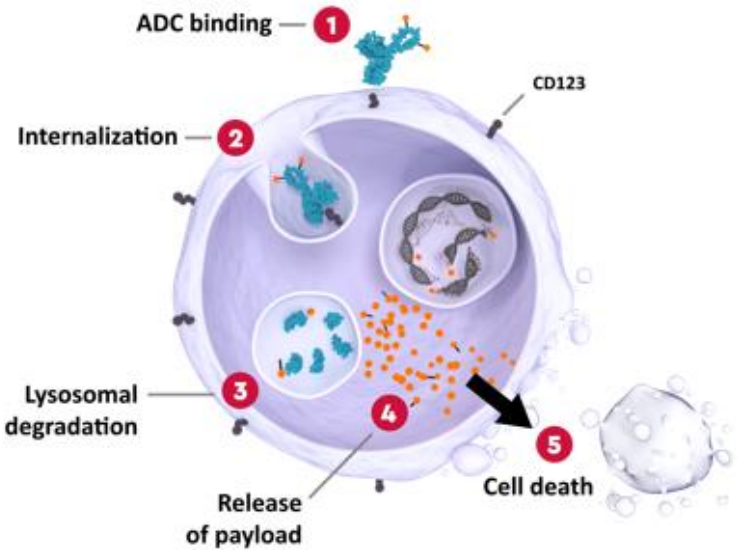
1. Jordan CT, et al. *Leukemia* 2000;14:1777-84. 2. Han L, et al. *Cytometry A* 2015;87:346-56. 3. Pemmaraju N, et al. *Blood.* 2019; 134 (Supplement_1): 167.

Pivekimab Sunirine (PVEK) Mechanism of Action

- PVEK is a first-in-class antibody-drug conjugate (ADC) comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer (IGN) payload

- The IGN payload alkylates DNA and causes single strand breaks without crosslinking. IGNs are designed to have high potency against tumor cells, while demonstrating less toxicity to normal marrow progenitors than other DNA-targeting payloads[1]





1. Kovtun Y,et al. *Blood Adv*. 2018; 2(8):848-858.

Study Design and Objectives

CADENZA (IMGN632-801): Open-label, multicenter, phase 2 study (NCT03386513)

Patients with R/R BPDCN who have received 1-3 prior systemic therapies

Patients with frontline BPDCN who have not received prior systemic therapy

0.045 mg/kg PVEK IV on Day 1 of a 21-day cycle as a <30-minute outpatient infusion

CNS prophylaxis recommended
Patients may receive HSCT as consolidation

Key Inclusion Criteria

- Patients ≥18 years old
- Frontline or R/R BPDCN
- Any CD123 positivity on flow cytometry or IHC
- Frontline patients may have received local therapy (radiotherapy, surgical excision, photodynamic therapy)

Key Exclusion Criteria

- Patients with history of veno-occlusive disease
- Active CNS involvement; R/R patients with history of CNS must have been treated locally and have at least 1 lumbar puncture with no evidence of CNS disease

Primary Endpoint

- CR +CRc rate

Key Secondary Endpoints

- Duration of complete response (CR+CRc)
- Overall response rate (ORR)

BPDCN, blastic plasmacytoid dendritic cell neoplasm; CD, cluster of differentiation; CNS, central nervous system; CR, complete response; CRc, clinical complete response; HSCT, hematopoietic stem cell transplant; IHC, immunohistochemistry; IV, intravenous; PVEK, pivekimab sunirine; R/R, relapsed or refractory.

Patient Characteristics

		Frontline BPDCN N=30	R/R BPDCN N=49
Age, %	Median (range), y ≥ 65y	74 (48-84) **90**	69 (19-82) 59
Gender, %	Male Female	80 20	82 18
Disease, %[a]	Skin Bone marrow Nodal disease (PET/CT scan)	93 43 47	65 47 41
Baseline status, %	Primary refractory First relapse Second or greater relapse	- - -	**43** 33 25
Prior therapy, %[b]	Non-intense (e.g., VEN+/-HMA, CVP, steroids) Tagraxofusp Intense (e.g., HyperCVAD, FLAG, CHOP) Stem cell transplant (14 allo, 2 auto) Local radiotherapy	- - - - 7	74 **43** **55** **33** 18
Number of prior lines of treatment	1 2 3+	- - -	53 **27** **18**

[a]Patients can have multiple sites of disease involvement
[b]Prior therapy types are not mutually exclusive
CT, computerized tomography; CVP, cyclophosphamide/vincristine/prednisone; HMA, hypomethylating agent; PET, positron emission tomography; R/R, relapsed or refractory; VEN, venetoclax; y, years.

Safety Overview

All Frontline and R/R BPDCN Patients (N=79)					
Treatment Emergent Adverse Events (TEAEs)*	All Grades ≥ 15%	≥ 3 Grade	Treatment Emergent Adverse Events (TEAEs)*	All Grades ≥ 15%	≥ 3 Grade
Peripheral edema	46%	10%	Headache	19%	4%
Thrombocytopenia	27%	19%	Neutropenia	18%	17%
Fatigue	25%	4%	Diarrhea	17%	0%
Infusion-related reactions (IRRs)	25%	4%	Hypokalemia	17%	3%
Constipation	23%	0%	Dyspnea	15%	1%
Nausea	22%	0%	Hyperglycemia	15%	6%
Anemia	20%	8%	Pyrexia	15%	1%

*Regardless of attribution to PVEK

BPDCN, blastic plasmacytoid dendritic cell neoplasm; R/R, relapsed or refractory.

Safety Overview

Pertinent Less Frequent AEs

- Liver-related AEs:
  - ALT/AST/TBILI laboratory elevations grade 3 in 3%/3%/1%; no grade 4 or 5 events
  - 1 DLT (Grade 3 ALT, duration 7 days)
  - Reversible VOD all grades 4% (3/79); grade 3 in 1% (n=1); no grade 4 or 5 events
    - 1 patient proceeded to transplant without hepatic complications
- Hypoalbuminemia all grade 13%; grade 3 in 3% (n=2); no grade 4 or 5 events
- No capillary leak syndrome (CLS) events were reported

- Discontinuations due to PVEK related AEs: 3%
- 30-day mortality rate:
  - Frontline patients: 0%
  - R/R patients: 4% (2 deaths due to disease progression)

AEs, adverse events; ALT, alanine transaminase; AST, aspartate aminotransferase; DLT, dose limiting toxicity; R/R, relapsed or refractory; TBILI, total bilirubin; VOD, veno-occlusive disease.

Response Data in Frontline BPDCN

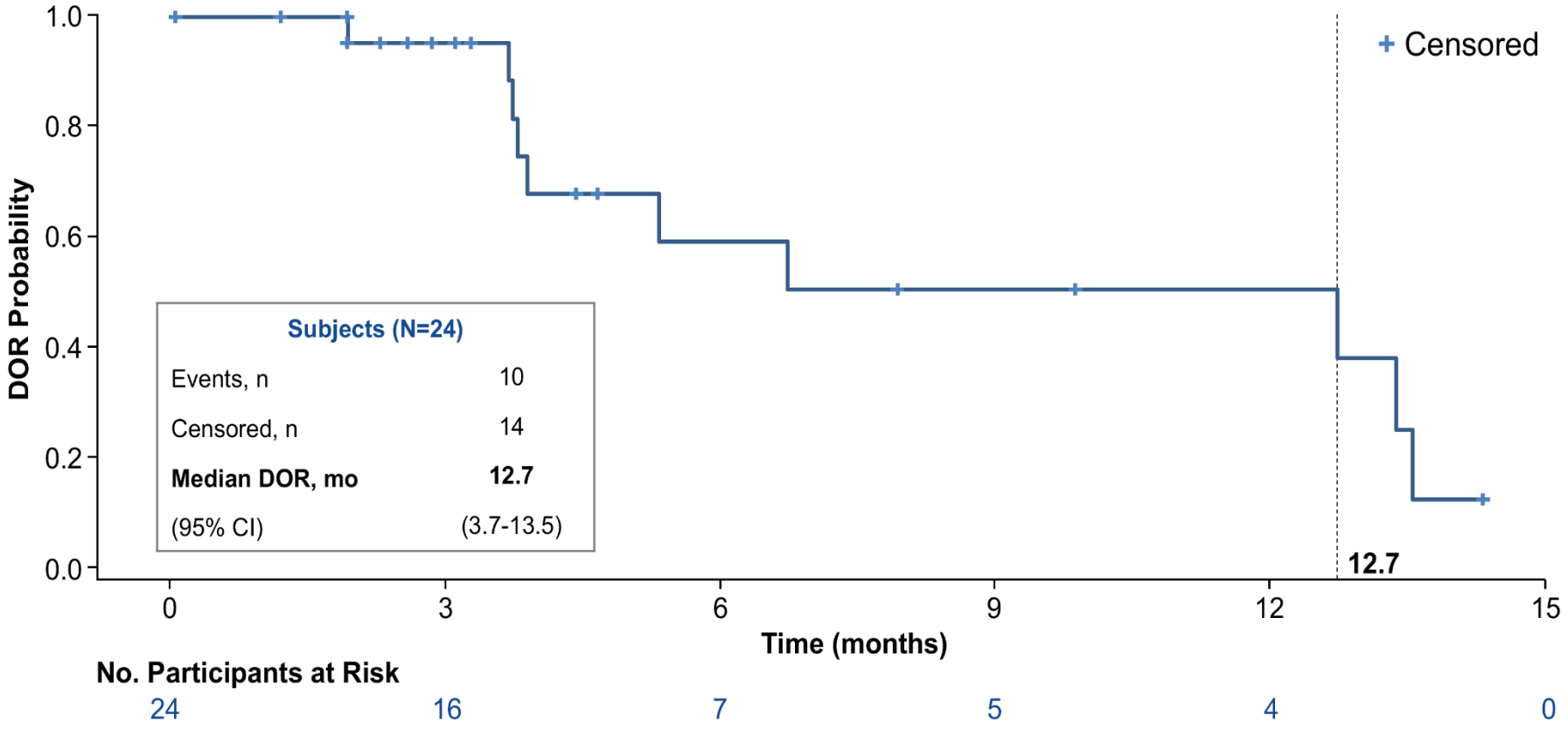
ORR= CR+CRc+CRh+CRi+PR
Composite CR=CR+CRc+CRh+CRi

Frontline patients (N=30)		
	ORR	**Composite CR**
Response rate	**80% (24/30)**	**73% (22/30)**
Time to first response		
Median (range), months	1.3 (0.5-3.5)	1.5 (0.5-4.6)

- 9 patients (30%) were bridged to allogeneic stem cell transplant

BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete remission/response; ORR, overall response rate.

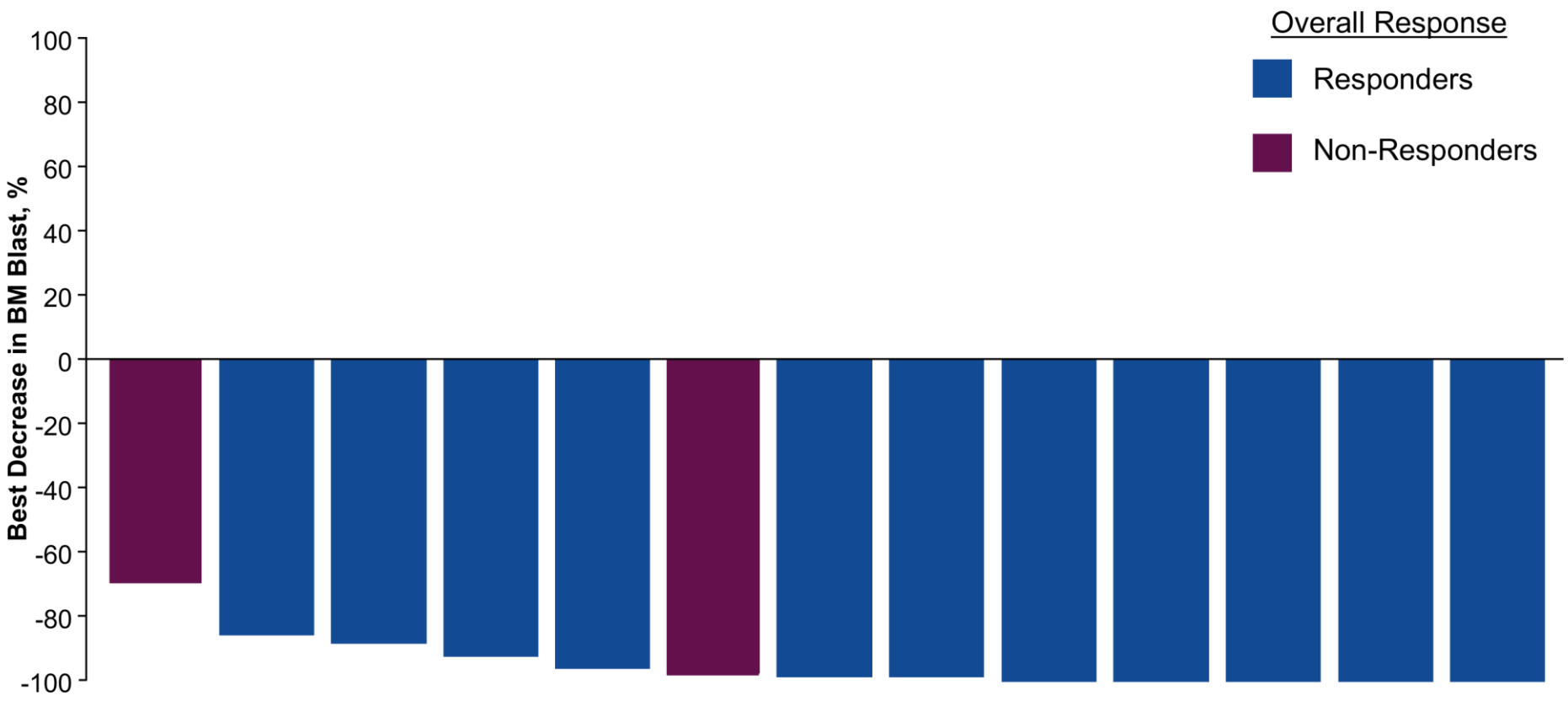
Duration of Response in Frontline BPDCN



- Due to early censoring events, the current duration of response (DOR) and duration of composite complete remission (DOCR) estimates are immature
- Median DOR was 12.7 months (95% CI 3.7-13.5) (including post-transplant durability)
- Median DOCR was 10.3 months (95% CI 3.7-12.9) (including post-transplant durability)

BPDCN, blastic plasmacytoid dendritic cell neoplasm.

Best Decrease in Bone Marrow Blasts (%) in Frontline Patients[a]



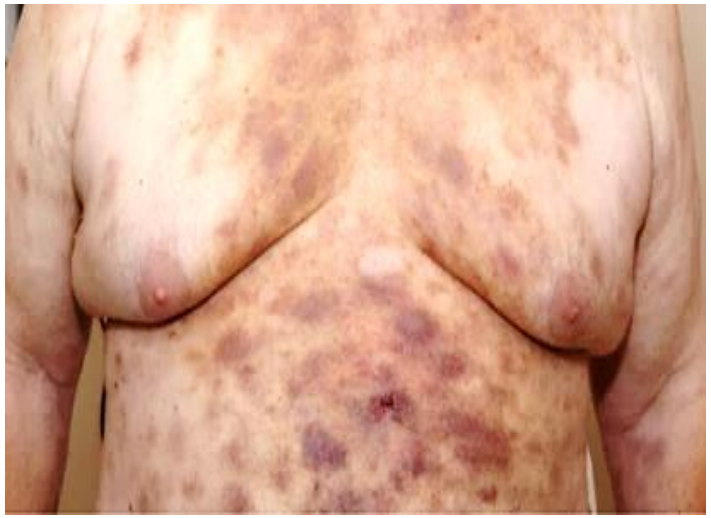
- In patients with bone marrow involvement at baseline, 100% (13/13) of patients achieved bone marrow remission (< 5% blasts)
- Of these 11 of 13 patients achieved an overall response (composite CR+PR)

[a]Patients with >5% bone marrow blasts at baseline only

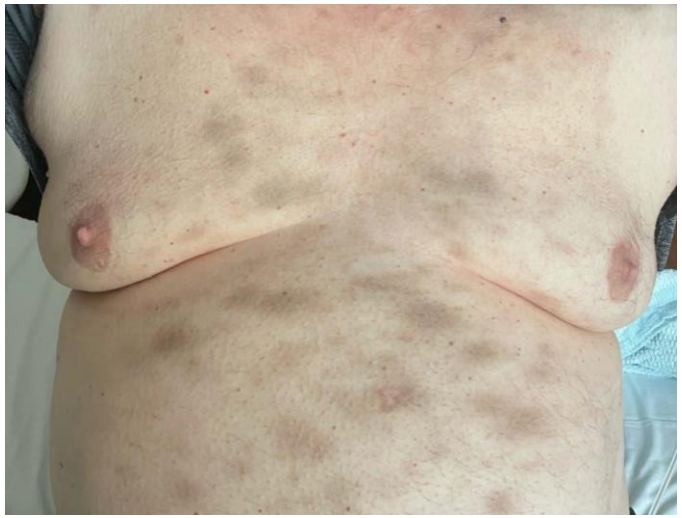
CR, complete remission/response; PR, partial response.

Response Seen in Frontline Patient

Screening Visit



End of Cycle 3 (EOC3)



- 66-year-old male
- Skin mSWAT 88.5 to 0 (EOC3), residual non-BPDCN hyperpigmentation
- Bone marrow 62% to 5% (EOC3), negative for BPDCN

- Achieved a CRc and bridged to SCT

Informed consent was obtained from the patient for use of these images.

BPDCN, blastic plasmacytoid dendritic cell neoplasm; CCR, composite complete response; EOC3, end of cycle 3; mSWAT, modified severity-weighted assessment tool; SCT, stem cell therapy.

Response Data in R/R BPDCN

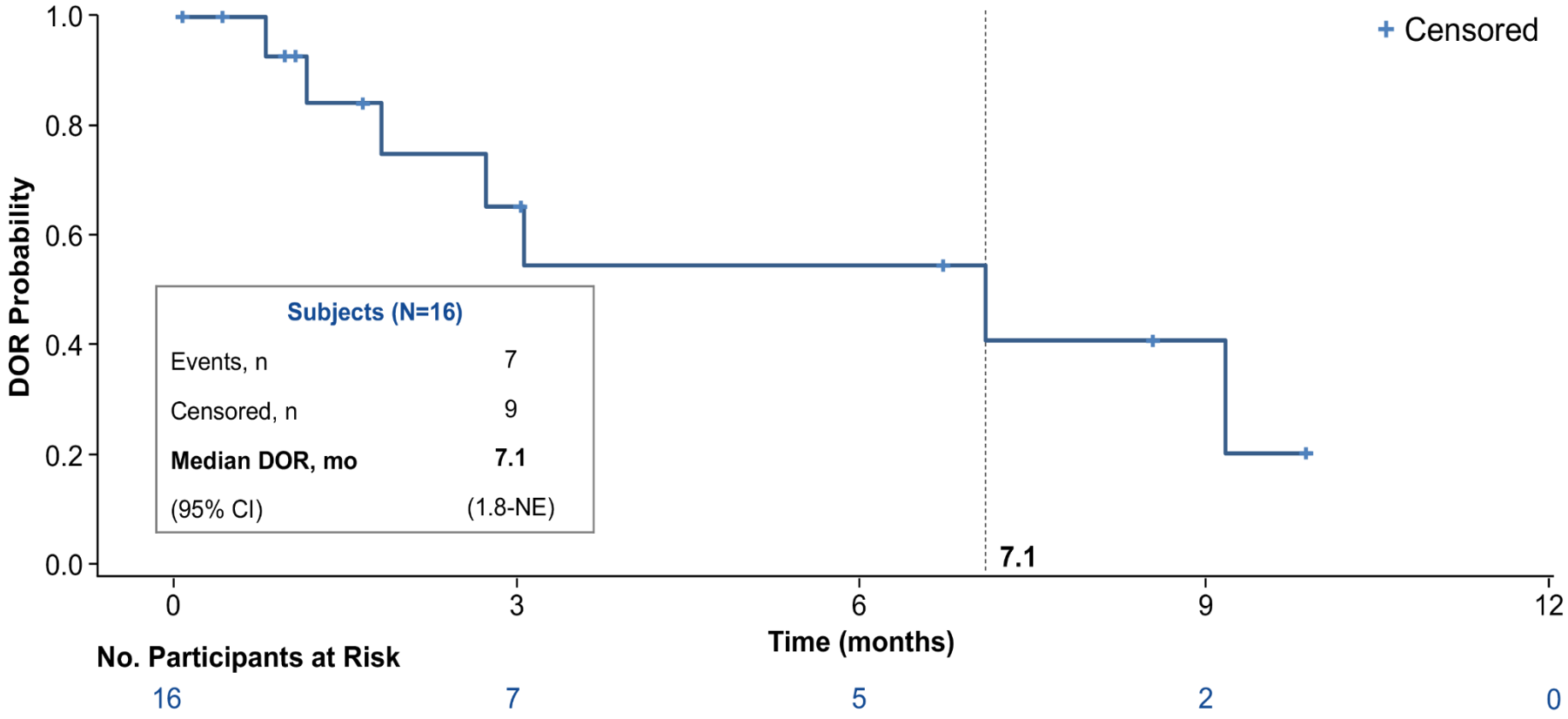
ORR= CR+CRc+CRh+CRi+PR
Composite CR=CR+CRc+CRh+CRi

R/R patients (N=49)		
	ORR	**Composite CR**
All R/R patients	**33% (16/49)**	**20% (10/49)**
Patients who received prior tagraxofusp (n=21)	**33% (7/21)**	**19% (4/21)**
Patients who had prior SCT (n=16)	**50% (8/16)**	**31% (5/16)**
Time to first response in all R/R patients		
Median (range), months	1.3 (0.6-3.7)	1.4 (0.7-1.9)

- 4 patients (8%) were bridged to allogeneic stem cell transplant
- In the 10 patients who did not respond to prior tagraxofusp, 3 of the 10 had a response to PVEK

BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete remission/response; ORR, overall response rate; R/R, relapsed or refractory; SCT, stem cell transplant.

Duration of Response in R/R BPDCN



- Due to early censoring events, the current duration of overall response (DOR) and composite complete remission (DOCR) estimates are immature
- Median DOR was 7.1 months (95% CI 1.8-NE) (including post-transplant durability)
- Median DOCR was 9.2 months (95% CI 0.8-NE) (including post-transplant durability)

BPDCN, blastic plasmacytoid dendritic cell neoplasm; R/R, relapsed or refractory

Conclusions

- PVEK demonstrates compelling clinical activity and tolerable safety in frontline and R/R BPDCN
  - The safety profile was manageable with mostly low-grade peripheral edema and infusion-related reactions
  - PVEK monotherapy leads to high composite CR rates (73%) in frontline BPDCN, as well as durable responses in R/R patients (DOR 7.1 months), including those treated with prior tagraxofusp

- Enrollment continues in the pivotal frontline BPDCN patient cohort (NCT03386513)

BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete remission/response; R/R, relapsed or refractory.

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