Pivekimab Sunirine in Blastic Plasmacytoid Dendritic Cell Neoplasm

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ABSTRACT

PURPOSE Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a unique myeloid malignancy with CD123 interleukin-3 receptor-α overexpression and poor prognosis.

METHODS This phase I/II, open-label, multicenter study evaluated pivekimab sunirine (PVEK), a novel CD123 antibody-drug conjugate, 0.045 mg/kg once every 3 weeks, in adults with frontline (no previous systemic therapy and de novo BPDCN or coexisting hematologic malignancy) or relapsed/refractory BPDCN (ClinicalTrials.gov identifier: NCT03386513) The primary end point in the primary analysis population (PAP; frontline de novo) was composite complete response (CCR; CR+ clinical CR) rate.

RESULTS Of 84 patients, 33 had frontline BPDCN (22 de novo [20 in PAP]; 11 with previous or concomitant malignancy) and 51 had relapsed/refractory disease. The median (range) age was 72 (63-76) years. In the PAP (n = 20), the CCR rate was 75% (95% CI, 51 to 91; n = 15; median duration: 10.6 [95% CI, 3.8 to not reached] months) and the median overall survival (OS) was 16.6 (95% CI, 7.2 to not reached) months. Eight of these 15 (53%) patients proceeded to stem-cell transplant (SCT). The corresponding rate for relapsed/refractory disease was 14% (95% CI, 6 to 26; n = 7; median duration: 9.2 [95% CI, 2.4 to not reached] months), and the median OS was 5.8 (95% CI, 3.9 to 8.4) months. Adverse events (AEs) included peripheral edema (54%), fatigue (26%), and infusion-related reactions (26%). Grade ≥3 events included neutropenia (16%), thrombocytopenia (14%), and peripheral edema (12%). Serious AEs included pneumonia (6%) and febrile neutropenia (5%). Two on-treatment cases of reversible veno-occlusive disease (VOD) occurred. Of the total 19 patients who proceeded to SCT, VOD was reported in five patients (four with relapsed/refractory BPDCN).

CONCLUSION PVEK, with convenient dosing, led to high, durable responses, especially in frontline BPDCN, and a manageable safety profile.

ACCOMPANYING CONTENT

Appendix
Data Sharing Statement
Data Supplement
Protocol

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INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a unique (0.05 cases per 100,000), aggressive, hematologic neoplasm, involving skin, bone marrow, blood, lymph nodes, and CNS.[1-3] The median age at diagnosis is approximately 65 years, with men affected approximately 3:1 compared with women.[1,2] Approximately 20% of patients with BPDCN might have a prior or concomitant hematologic malignancy (PCHM), which may alter disease biology and affect clinical outcomes (eg, lower overall survival [OS]).[4,5] Patients often harbor multiple somatic mutations (eg, *TET2*, *MYB* fusions) contributing to disease heterogeneity.[6-9]

Treatment options for BPDCN are limited, historically including chemotherapy regimens adopted from acute leukemias.[1] However, poor outcomes, relapse, and chemotherapy-related toxicity are frequent limiting factors.[10] Furthermore, patients with BPDCN are often older and may be ineligible for, or poorly tolerate, intensive chemotherapy before stem-cell transplant (SCT), the only potentially curative therapy.[10] There is increased interest in

CONTEXT

Key Objective

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic neoplasm, in which CD123 is overexpressed. Here, we present the primary efficacy and safety of monotherapy with pivekimab sunirine (PVEK), a first-in-class, novel CD123-targeted antibody drug conjugate.

Knowledge Generated

Our findings demonstrated durable and high response rates (composite complete response of 75%) in an older population of patients with frontline or relapsed/refractory BPDCN, with successful bridging of treated patients to stem-cell therapy. PVEK also had a manageable safety profile in this patient population.

Relevance *(C. Craddock)*

These results have the potential to expand treatment options for patients with BPDCN and highlight Pivekimab's potential as a novel agent in the management of AML.*

*Relevance section written by *JCO* Associate Editor Charles Craddock, MD.

immunotherapeutics to improve outcomes and facilitate transition to SCT. Interleukin-3 receptor-α (CD123) is an attractive target, given its overexpression on all BPDCN blasts.[11,12] Tagraxofusp, a CD123-directed cytotoxin, is currently the only agent approved for BPDCN.[1,13]

Pivekimab sunirine (PVEK), a promising investigational therapy for BPDCN, is a first-in-class antibody-drug conjugate comprising a high-affinity anti-CD123 antibody, a cleavable linker, and an indolinobenzodiazepine pseudodimer payload that alkylates DNA and causes single-strand DNA breaks without crosslinking.[14,15] It was designed to have high potency against tumor cells, with less toxicity to normal bone marrow progenitors than other DNA-targeting payloads, potentially because of single- rather than double-stranded DNA breakage.[14] Here, we report the primary efficacy and safety analysis from CADENZA (ClinicalTrials.gov identifier: NCT03386513), a phase I/II, open-label, study evaluating PVEK in adults with BPDCN.

METHODS

Patients and Study Design

From 2018 to 2023, patients 18 years and older with BPDCN and CD123 positivity by flow cytometry or immunohistochemistry were enrolled. Two separate groups were prospectively recruited (cohorts 1 and 6): (1) patients with de novo BPDCN or with PCHM who have not received systemic therapy (frontline) and (2) patients with relapsed/refractory BPDCN who received 1-3 previous systemic therapies, including tagraxofusp, regardless of exposure duration (Fig 1). Full eligibility criteria are provided in the Data Supplement (Table S1, online only). Inclusion criteria required an Eastern Cooperative Oncology Group performance status score of ≤1 and adequate organ function. Patients with a history of hepatic veno-occlusive disease (VOD), grade 4 capillary leak syndrome (CLS), or noncardiac grade 4 edema, related to previous tagraxofusp or other etiology, were excluded. Frontline patients with active CNS involvement (confirmed by cerebrospinal fluid analysis) were prohibited from enrollment. Patients with relapsed/refractory disease with CNS disease could be included if treated and had no evidence of CNS disease before first treatment dose.

This was an international phase I/II, open-label, nonrandomized and, to our knowledge, first-in-human study of PVEK including a dose-escalation and dose-expansion phase. As previously described, the dose-escalation phase used a standard 3 + 3 design and enrolled patients with CD123+ relapsed/refractory AML or BPDCN.[16] Briefly, dose escalation evaluated two dosing schedules (once every 3 weeks [schedule A] and fractionated [schedule B]); given similar safety and antileukemia activity, schedule B was not further evaluated.[16] In the subsequent dose-expansion phase, two doses of PVEK on schedule A (0.045 mg/kg and 0.090 mg/kg once every 3 weeks) were evaluated in predetermined groups (cohorts 2 and 5) with relapsed/refractory AML to optimize selection of the recommended phase 2 dose (RP2D)[16]; additional dose-expansion groups included relapsed/refractory acute leukemias (cohort 3), other CD123+ relapsed/refractory hematologic malignancies (cohort 4), frontline BPDCN (cohort 6; two further cohorts: de novo or with PCHM), or relapsed/refractory BPDCN (cohort 1; Fig 1). Within the frontline BPDCN group, the primary analysis population (PAP) was patients enrolled following a protocol amendment to define the de novo population, who met eligibility criteria and received ≥1 dose of PVEK. Patients enrolled before the amendment were excluded from the PAP but included in the overall de novo cohort; no other cohorts were affected.

The study was approved by the institutional review board of each participating site and conducted in accordance with the

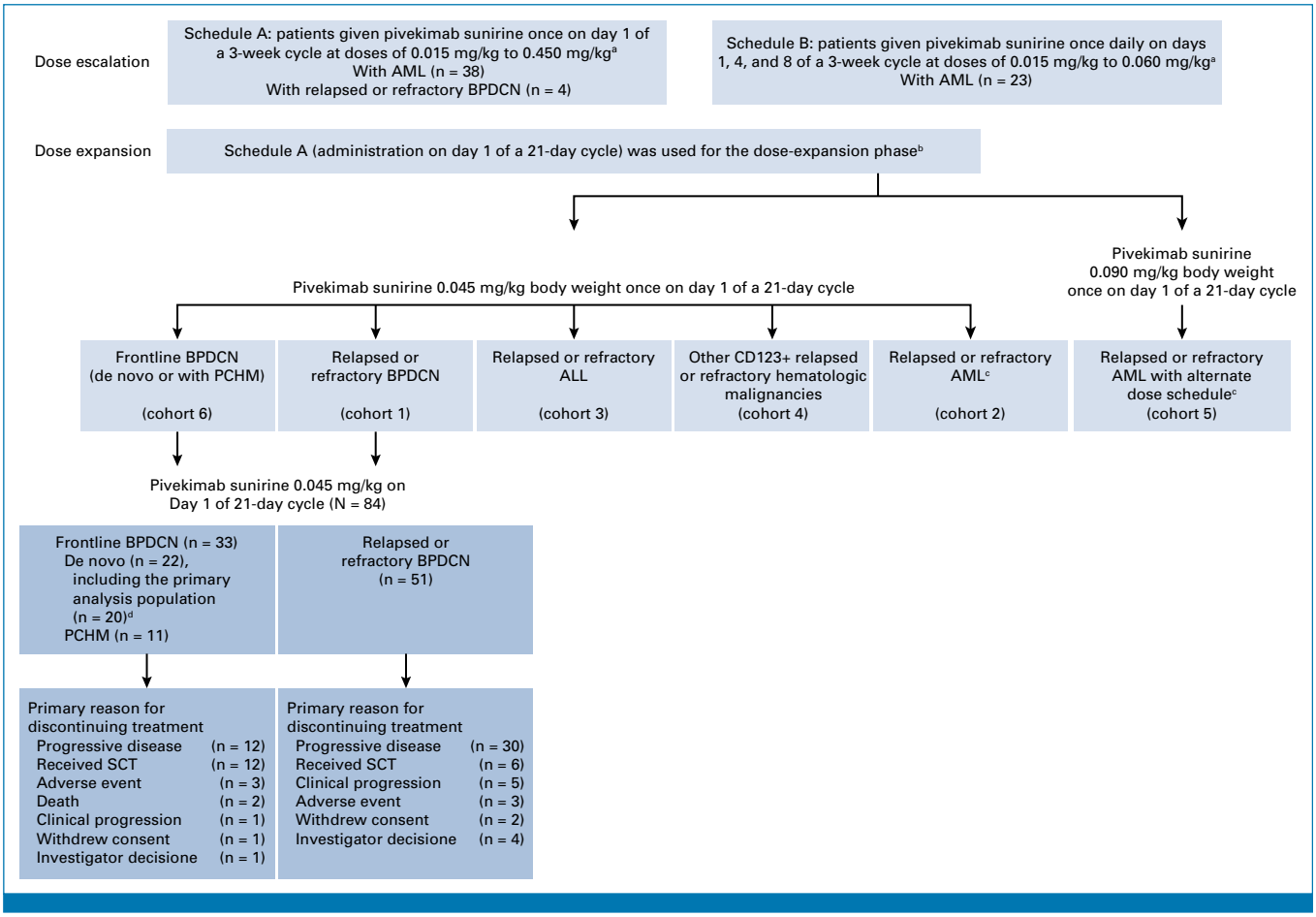

FIG 1. Patient disposition. Pivekimab sunirine dose-expansion phase. [a]Study details previously reported for the phase I dose-escalation portion of the study, including full attrition; the schedule A starting dose was 0.015 mg/kg on day 1 of a 3-week cycle, with dose escalation following a modified Fibonacci schema. Schedule A was further evaluated in dose expansion, whereas schedule B was not further evaluated given the comparative efficacy and safety with schedule A.[16] [b]Based on the totality of data from the dose-escalation phase, two doses for schedule A (administration on day 1 of a 21-day cycle) were used for the dose-expansion phase. Study details previously reported for dose-expansion cohorts 2 and 5, findings from which were used to optimize selection of the recommended phase 2 dose.[16] Additional dose-expansion cohorts are also shown. [c]Study details previously reported for cohorts 2 (n = 20) and 5 (n = 10); 20 patients discontinued cohort 2 (11 because of progression, 3 because of death, three because of investigator decision, three withdrew consent), and 10 patients discontinued cohort 5 (one because of adverse event, six because of progression, two because of death, one withdrew consent).[16] [d]The primary analysis population included frontline patients with no prior or concomitant hematologic malignancy, who met eligibility criteria and enrolled following the protocol amendment to define the de novo population, and received at least one dose of pivekimab sunirine. These patients were a subset of the frontline BPDCN group. Two patients with de novo BPDCN enrolled before the protocol amendment and were included in the broader frontline BPDCN group. No other cohorts were affected by the protocol amendment. [e]Not related to an adverse event. BPDCN, blastic plasmacytoid dendritic cell neoplasm; PCHM, prior or concomitant hematologic malignancy; SCT, stem-cell transplant.

principles of the Declaration of Helsinki and all clinical practice guidelines. All patients provided written informed consent.

Procedures

This report describes outcomes from patients with BPDCN (data cutoff of October 2, 2024), who received the RP2D of 0.045 mg/kg PVEK, once every 3 weeks, on day 1 of a 21-day cycle as a <30-minute infusion.

Outcomes

Primary end point was defined as rate of composite complete response (complete response [CR] and clinical complete response [CRc]; CR + CRc) per investigator assessment in the PAP. CR required normalization of blast percentage and neutrophil and platelet counts, the absence of circulating leukemic blasts, complete clearance of skin lesions and no new lesions in patients without lesions at baseline, regression of nodal masses to normal size on computed tomography, and no splenic or hepatic nodules; CRc permitted minimal residual skin abnormality. Response criteria defined in the Data Supplement (Table S2) were based on those validated by the tagraxofusp trial,[11] with addition of CR with partial hematologic recovery (CRh).[17,18] The key secondary end point was duration of CR + CRc in patients with frontline de novo BPDCN. Additional end points, including secondary, exploratory, and post hoc, are described in the Data Supplement (Table S3).

Statistical Analysis

All efficacy analyses were assessed in the modified intent-to-treat group, defined as all eligible patients who received at least one PVEK dose. Patients without any response assessments were included as nonresponders.

The sample size of 20 patients with frontline de novo BPDCN was determined based on the lower bound of a two-sided 95% CI of CR + CRc rate to rule out the reference rate of 10%. CR + CRc rate with 95% CI based on the Clopper-Pearson method was calculated with 10% for comparison. Interim analyses were not conducted because of small sample size to allow for more enrolled patients with longer follow-up. Prespecified subgroup analyses for the primary end point were performed by age, race, ethnicity, baseline renal and hepatic status, progression to SCT, and previous tagraxofusp treatment. A sample size of 50 patients with relapsed/refractory BPDCN was determined based on the lower bound of a two-sided 95% CI of CR + CRc to rule out the reference rate of 5%. CR + CRc rate with 95% CI based on the Clopper-Pearson method was calculated with 5% for comparison.

Overall duration of response and survival were estimated using the Kaplan-Meier methodology. In the duration-of-response (DoR) analysis, patients without relapse or death were censored at time of last response assessment, whereas patients who had relapsed or died after two or more consecutive missed disease assessments were censored at the date of last assessment. In the OS analysis, patients who were not confirmed to have died at time of analysis were censored on the last known alive date. For time-to-event analyses, post-treatment SCT was not considered as a censoring event. OS analysis stratified by subgroup analyses is exploratory and descriptive in nature.

Two-sided 95% exact binomial (Clopper-Pearson) CIs without multiplicity adjustment are presented and should not be used for hypothesis testing. All statistical analyses were performed using SAS (Cary, NC) version 9.4 or higher.

Role of Funding Source

The previous sponsor, ImmunoGen, Inc (now part of AbbVie, Inc), designed the study, performed the data collection and statistical analysis, and study monitoring, with the medical monitor and principal investigators providing medical expertise to inform decisions pertaining to study conduct. All authors confirmed the accuracy of the reported data and adherence to the protocol. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing was funded by AbbVie, Inc.

RESULTS

Considering the totality of data from the previously published dose-escalation phase, two doses on Schedule A were chosen for the dose-expansion phase: 0.045 mg/kg (cohort 2) and 0.090 mg/kg (cohort 5) administered once on day 1 of a 21-day cycle to further optimize RP2D selection (Summary of AML data in the Data Supplement, Fig S1).[16] There were four patients with relapsed/refractory BPDCN (no de novo) treated in phase I (escalation part).

Patients—BPDCN Dose-Expansion Groups

The overall frontline group (cohort 6) included 33 patients (20 de novo patients in the PAP plus two patients who enrolled before the protocol amendment to define the de novo population and 11 with PCHM; Fig 1). The median (range) age was 73 (48-84) years, and importantly, 91% was 65 years and older. Most (82%) were male. At baseline, 94% had cutaneous involvement and 49% had bone marrow involvement (Table 1).

In patients with relapsed/refractory BPDCN (cohort 1; n = 51), the median (range) age was 69 (19-85) years, with 59% 65 years and older, and 82% was male. In this group, 57% had received one line of therapy and 42% had received two or more lines. In this heavily pretreated group, 49% had previous intensive chemotherapy, 57% had previous tagraxofusp, and 31% had previous hematopoietic SCT. At baseline, 67% had cutaneous involvement and 47% had bone marrow involvement. No patients had CNS disease at baseline (Table 1).

Representativeness with the overall BPDCN population is detailed in the Data Supplement (Table S4).

Clinical Activity

The CR + CRc rate in the PAP of 20 frontline de novo patients was 75% (95% CI, 51 to 91; n = 15), with overall response achieved by 80% (95% CI, 56 to 94; n = 16) and CR achieved by 65% (95% CI, 41 to 85; n = 13; Table 2; Data Supplement, Fig S1). The median duration of CR + CRc was 10.6 (95% CI, 3.8 to not reached [NR]) months, and the median time to response was 1.4 (IQR, 1-3) months. With a median follow-up of 21.5 (range, 4.2-25.4) months, the median OS was 16.6 (95% CI, 7.2 to NR) months (Fig 2). Of patients who achieved CR + CRc, 53% (8 of 15) received SCT. Median OS by SCT status is reported in the Data Supplement (Fig S2).

For all 33 frontline patients, the CR + CRc rate was 70% (95% CI, 51 to 84; n = 23) and the overall response rate was 85% (95% CI, 68 to 95; n = 28; Table 2). CR was achieved by 55% (95% CI, 36 to 72; n = 18). The median duration of CR + CRc was 9.8 (95% CI, 4.6 to NR) months, and the median time (IQR) to said response was 1.5 (1-3) months. The median (range) duration of follow-up was 21.5 (18.4-24.8) months, with a median OS of 16.6 (11.4-NR) months (Fig 2). Median OS did not notably differ between patients with PCHM and the overall frontline group (Data Supplement, Fig S3). Twelve of 23 patients (52%) who achieved CR + CRc received

TABLE 1. Demographic and Clinical Characteristics of the Patients at Baseline

Characteristic	Frontline De Novo BPDCN[a] (n = 20)	Frontline (de novo and PCHM) BPDCN[b] (n = 33)	Relapsed/Refractory BPDCN (n = 51)	Total (N = 84)
Age, years, median (range)	74 (48-84)	73 (48-84)	69 (19-85)	72 (19-85)
Age ≥65 years, No. (%)	17 (85)	30 (91)	30 (59)	60 (71)
Male, No. (%)	17 (85)	27 (82)	42 (82)	69 (82)
Race, No. (%)				
White	15 (75)	27 (82)	42 (82)	69 (82)
Black	1 (5)	1 (3)	2 (4)	3 (4)
Asian	0 (0)	0 (0)	1 (2)	1 (1)
Not reported	4 (20)	5 (15)	6 (12)	11 (13)
Ethnicity, No. (%)				
Hispanic or Latino	3 (15)	4 (12)	8 (16)	12 (14)
Not Hispanic or Latino	17 (85)	28 (85)	38 (75)	66 (79)
Missing	0 (0)	1 (3)	5 (10)	6 (7)
ECOG performance status, No. (%)				
0	7 (35)	12 (36)	18 (35)	30 (36)
1	13 (65)	21 (64)	30 (59)	51 (61)
2	0 (0)	0 (0)	2 (4)	2 (2)
3	0 (0)	0 (0)	1 (2)	1 (1)
Disease involvement, No. (%)				
Skin	18 (90)	31 (94)	34 (67)	65 (77)
Bone marrow	9 (45)	16 (49)	24 (47)	40 (48)
Peripheral blood	1 (5)	3 (9)	10 (20)	13 (16)
Lymph nodes	6 (30)	12 (36)	18 (35)	30 (36)
Viscera	0 (0)	0 (0)	3 (6)	3 (4)
Bone marrow blasts				
No.	20	33	48	81
No., median (range)	5 (0-89)	5 (0-89)	6 (0-99)	5 (0-99)
Hepatic function, No. (%)				
Normal	16 (80)	27 (82)	43 (84)	70 (83)
Mild impairment	3 (15)	4 (12)	6 (12)	10 (12)
Moderate impairment	1 (5)	2 (6)	2 (4)	4 (5)
Renal function, No. (%)				
Normal	8 (40)	13 (39)	26 (51)	39 (46)
Mild impairment	12 (60)	18 (55)	20 (39)	38 (45)
Moderate impairment	0 (0)	2 (6)	5 (10)	7 (8)
Disease history/type, No. (%)				
De novo	20 (100)	22 (67)	42 (82)	64 (76)
Secondary	0 (0)	11 (33)	9 (18)	20 (24)
Status at baseline, No. (%)				
Frontline	20 (100)	33 (100)	0	33 (39)
First relapse	0	0	15 (29)	15 (18)
Primary refractory	0	0	25 (49)	25 (30)
Relapsed/refractory	0	0	11 (22)	11 (13)
Previous therapies, No. (%)				
Nonintensive chemotherapy	NR	NR	32 (63)	32 (38)
Tagraxofusp	0	0	29 (57)	29 (35)
Intensive chemotherapy	NR	NR	25 (49)	25 (30)
Previous HSCT	0	0	16 (31)	16 (19)
Radiotherapy	0	2 (6)	9 (18)	11 (13)

(continued on following page)

TABLE 1. Demographic and Clinical Characteristics of the Patients at Baseline (continued)

Characteristic	Frontline De Novo BPDCN[a] (n = 20)	Frontline (de novo and PCHM) BPDCN[b] (n = 33)	Relapsed/Refractory BPDCN (n = 51)	Total (N = 84)
No. of previous lines of therapy, No. (%)				
1	0	0	29 (57)	29 (35)
2	0	0	12 (24)	12 (14)
≥3	0	0	9 (18)	9 (11)
Missing	0	0	1 (2)	1 (1)

Abbreviations: BPDCN, blastic plasmacytoid dendritic cell neoplasm; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem-cell transplant; NR, not reported; PCHM, prior or concomitant hematologic malignancy.

[a]Primary analysis population including patients who met eligibility criteria, prospectively enrolled, and received at least one dose of pivekimab sunirine. These patients were a subset of the frontline BPDCN group.

[b]Includes 22 patients with de novo BPDCN (20 patients in the primary analysis plus two patients who enrolled before the protocol amendment) and 11 patients with prior or concomitant hematologic malignancy.

SCT. Median OS by post-treatment SCT status in all frontline patients is shown in the Data Supplement (Fig S2).

In 51 patients with relapsed/refractory BPDCN, the CR + CRc rate was 14% (95% CI, 6 to 26; n = 7) and the overall response was 35% (95% CI, 22 to 50; n = 18; Table 2). CR was achieved by 14% (95% CI, 6 to 26; n = 7). The median duration of CR + CRc was 9.2 (95% CI, 2.4 to NR) months, with a median time (IQR) to response of 1.4 (1-2) months. The median (range) follow-up was 24.1 (13.8-26.7) months, with a median OS of 5.8 (95% CI, 3.9 to 8.4) months (Fig 2). Two (29%) of seven patients who achieved CR + CRc progressed to SCT (Table 2). OS by SCT status is shown in the Data Supplement (Fig S2). Analyses of patients with and without previous tagraxofusp exposure showed similar response rates (Data Supplement, Table S5).

Results from the PAP (20 de novo BPDCN patients from cohort 6) rejected the null hypothesis of 10%, and results from the 51 patients with relapsed/refractory BPDCN from cohort 1 rejected the null hypothesis of 5%, with both groups meeting the primary objectives for these cohorts.

In each group, clinical responses were observed independent of CD123 expression levels (Data Supplement, Fig S4). Furthermore, rates of CR + CRc were generally similar across prespecified subgroups in the frontline group, except for post-SCT status, in which higher rates were observed in patients with post-SCT (Data Supplement, Table S6).

Safety

Safety in patients with AML was previously reported (Data Supplement). For the BPDCN PAP (n = 20), the median (range) duration of PVEK exposure was 15.4 (6.3-86.0) weeks and patients received a median (range) of 5 (2-23) cycles. In the total frontline group (n = 33), the median (range) duration of exposure was 16.4 (6.3-86.0) weeks and patients received a median (range) of 5 (2-23) cycles. The median (range) duration of exposure in those with relapsed/refractory BPDCN (n = 51) was 9.0 (1.0-128.9) weeks and a median (range) of 3 (1-34) cycles were administered.

Safety was assessed in all 84 treated patients. Adverse events (AEs) leading to PVEK dose delay, dose reduction, and discontinuation occurred in 25%, 5%, and 13% of patients, respectively (Table 3; in the Data Supplement, Table S7). The most common AEs in ≥20% of patients were peripheral edema, fatigue, infusion-related reactions, nausea, and hypokalemia (Table 3). Grade ≥3 AEs were reported in 79% of patients, and those reported in ≥5% of patients included neutropenia (16%), thrombocytopenia/decreased platelet count (24%), leukopenia/white blood cell count decrease (14%), peripheral edema (12%), anemia (8%), pneumonia (7%), and febrile neutropenia and lymphocyte count decrease (6% each; Data Supplement, Table S8).

Among patients with peripheral edema, most events (59%) initially occurred in cycle 3, with the median (range) time to onset being 55.0 (0-217) days. Events were manageable; 70% of patients received diuretic treatment, 56% of cases resolved, and only 1% discontinued treatment. Most infusion-related reaction events were mild to moderate in severity (4% at maximum grade 3), of short duration (resolving in a median [range] of 1 [1-22] day), preventable with prophylactic corticosteroids, and managed with supportive care and did not lead to treatment discontinuation. During treatment, VOD was reported in two patients. Both events resolved but led to treatment discontinuation. Of 19 patients who received post-treatment SCT, VOD was reported in five patients and four received PVEK for relapsed/refractory BPDCN (Data Supplement, Table S9). All patients had one or more other risk factors for VOD, including relapsed/refractory disease, previous SCT, concomitant and pre-existing liver-related conditions, and busulfan-based conditioning with or without sirolimus exposure. Importantly, no CLS events were reported. The median (IQR) time from the last dose of PVEK until SCT was 46 (35-56) days and 52

TABLE 2. Primary Response Assessment and Other Secondary Efficacy End Points (modified ITT population)

End Point	Frontline De Novo BPDCN[a] (n = 20)	Frontline (de novo and PCHM) BPDCN (n = 33)[b]	Relapsed/Refractory BPDCN (n = 51)
Best overall response rate,[c] No. (%; 95% CI)			
CCR (CR + CRc)	15 (75; 51 to 91)	23 (70; 51 to 84)	7 (14; 6 to 26)
CR + CRc + CRh	15 (75; 51 to 91)	27 (82; 65 to 93)	9 (18; 8 to 31)
ORR (CR + CRc + CRh + CRi + PR)	16 (80; 56 to 94)	28 (85; 68 to 95)	18 (35; 22 to 50)
Duration of response,[c,d] months, median (95% CI)			
CCR (CR + CRc)	10.6 (3.8 to not reached)	9.8 (4.6 to not reached)	9.2 (2.4 to not reached)
CR + CRc + CRh	10.6 (3.8 to not reached)	9.2 (4.4 to 12.9)	9.2 (0.8 to not reached)
ORR (CR + CRc + CRh + CRi + PR)	13.2 (5.3 to not reached)	11.1 (5.3 to 13.5)	4.1 (1.8 to not reached)
Time to response, months, median (IQR)			
CCR (CR + CRc)	1.4 (1-3)	1.5 (1-3)	1.4 (1-2)
CR + CRc + CRh	1.4 (1-3)	1.6 (1-3)	1.4 (1-2)
ORR (CR + CRc + CRh + CRi + PR)	0.8 (1-1)	1.3 (1-2)	1.4 (1-2)
Overall survival[c,d,e]			
Months, median (95% CI)	16.6 (7.2 to not reached)	16.6 (11.4 to not reached)	5.8 (3.9 to 8.4)
Rate at 12 months, % (95% CI)	60 (35.7 to 77.6)	64 (44.9 to 77.5)	31 (18.2 to 44.1)
Rate at 18 months, % (95% CI)	49 (26.0 to 68.6)	44 (26.7 to 60.3)	19 (8.9 to 32.7)
Bridge to HSCT among patients who achieved CCR			
Rate, % (No./n)	53 (8/15)	52 (12/23)	29 (2/7)
Duration of response, months, median (95% CI)	Not estimated (4.4 to not reached)	Not estimated (4.4 to not reached)	Not estimated (4.1 to not reached)
Time to response, months, median (IQR)	1.4 (1-2)	1.5 (1-2)	2.7 (2-4)
Bridge to HSCT among all patients			
Rate, % (No./n)	40 (8/20)	39 (13/33)	12 (6/51)

Abbreviations: BPDCN, blastic plasmacytoid dendritic cell neoplasm; CCR, composite complete response; CR, complete remission; CRc, clinical complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete recovery; HSCT, hematopoietic stem-cell transplantation; ITT, intent-to-treat; ORR, overall response rate; PCHM, prior or concomitant hematologic malignancy; PR, partial response; SCT, stem-cell transplant.

[a]Primary analysis population in which the primary end point of composite complete response and key secondary end point of duration of composite complete response were evaluated.

[b]Includes 22 patients with de novo BPDCN (20 patients in the primary analysis plus two patients who enrolled before the protocol amendment) and 11 patients with prior or concomitant hematologic malignancy.

[c]95% CIs were calculated using the Clopper-Pearson method. The two-sided CIs do not have multiplicity adjustment and should not be used for hypothesis testing.

[d]Duration of response and estimated probabilities of survival, which were estimated using the Kaplan-Meier method.

[e]The median (range) follow-up time was 21.5 (18.4-24.8) months for frontline patients and 24.1 (13.8-26.7) months for those with relapsed/refractory BPDCN.

(29-63) days for frontline and relapsed/refractory patients, respectively.

DISCUSSION

BPDCN is a difficult-to-diagnose malignancy due in part to its relative rarity, heterogenous presentation, potential for PCHM, and evolving nomenclature and classification.[19] Present treatment is complex and must be individualized to some extent, with limited clear consensus in approach.[20] Outcomes are traditionally poor, and while improvements in progression-free survival have been observed after intensive chemotherapy regimens and SCT, older patients who comprise a large proportion of the disease population may be ineligible for such therapies.[20]

In this clinical study, frontline therapy with PVEK, a newly designed anti-CD123 antibody-drug conjugate, was associated with high and durable response rates (CR + CRc of 75%) in the PAP of older patients with de novo BPDCN. Inclusion of patients with PCHM in the analysis of the overall frontline group did not notably affect response rates (CR + CRc of 70%) or OS, representing meaningful outcomes for this understudied group of patients.[21] Importantly, PVEK might have enabled some patients (n = 19) to receive SCT, the majority of which were allogenic, in both frontline and relapsed/refractory patients, most of whom were older and might have otherwise been ineligible.[20] The exploratory analysis of OS by SCT status has limitations because of the small sample size. These findings expand on those previously published with PVEK in AML, in which no

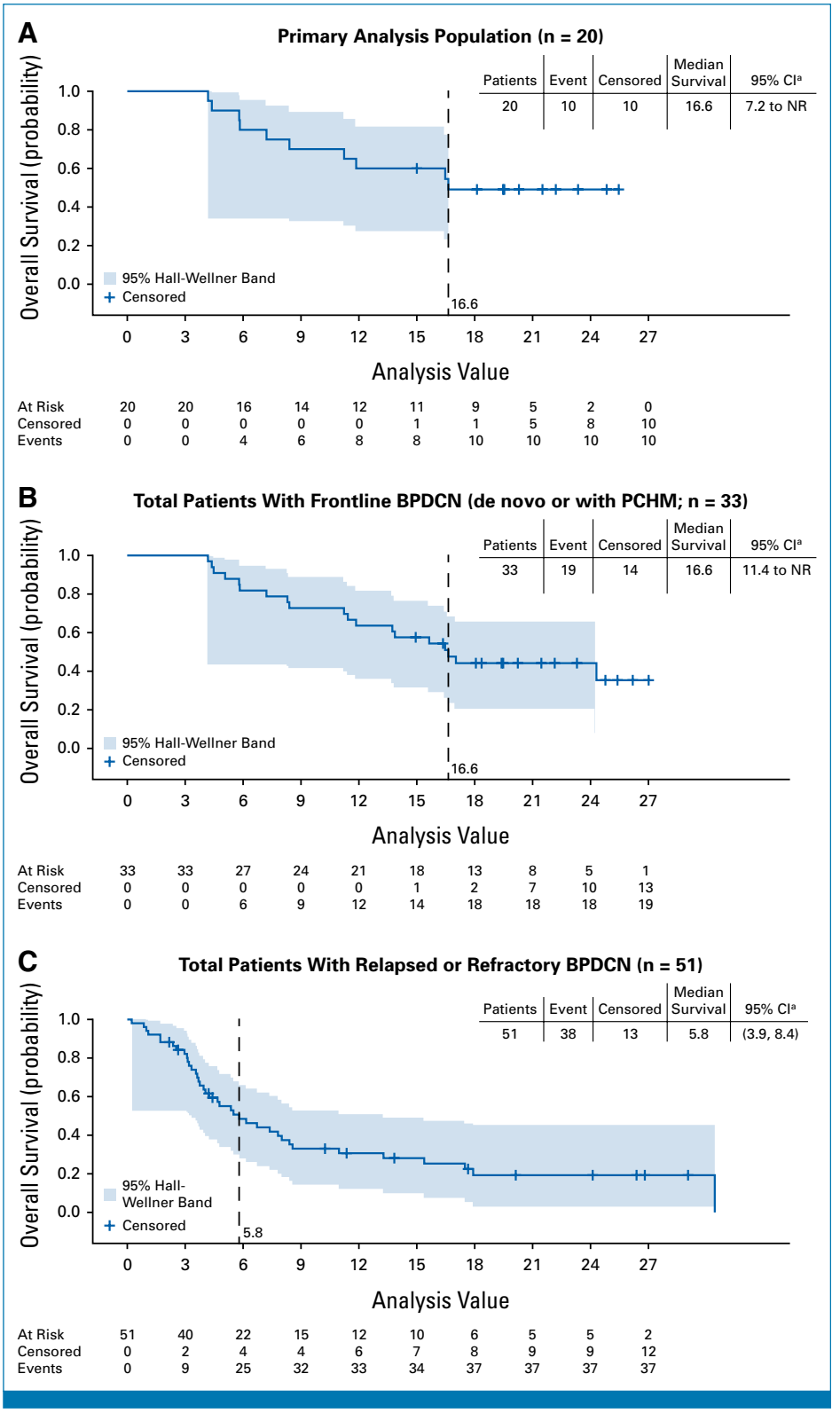

FIG 2. Kaplan-Meier[a] estimate for overall survival in months in the (A) primary analysis population, (B) overall frontline group, and (C) relapsed/refractory group. [a]The two-sided CIs do not have multiplicity adjustment and should not be used for hypothesis testing. BPDCN, blastic plasmacytoid dendritic cell neoplasm; NR, not reached; PCHM, prior or concomitant hematologic malignancy.

TABLE 3. AEs (safety population)

AE[a]	Frontline De Novo BPDCN (n = 20), No. (%)	All Frontline BPDCN (n = 33), No. (%)	Relapsed/Refractory BPDCN (n = 51), No. (%)	Total (N = 84), No. (%)
Any AE	20 (100)	33 (100)	50 (98)	83 (99)
Drug-related AE[b]	18 (90)	29 (88)	32 (63)	61 (73)
Any grade ≥3 AE[c]	16 (80)	28 (85)	38 (75)	66 (79)
Drug-related AE[b]	7 (35)	14 (42)	16 (31)	30 (36)
Any serious AE	14 (70)	23 (70)	20 (39)	43 (51)
Drug-related serious AE[b]	7 (35)	13 (39)	7 (14)	20 (24)
Serious AE in ≥3% of all patients				
Pneumonia[d]	1 (5)	1 (3)	4 (8)	5 (6)
Sepsis	0	0	3 (6)	3 (4)
COVID-19 disease[d]	2 (10)	2 (6)	1 (2)	3 (4)
Febrile neutropenia	1 (5)	1 (3)	3 (6)	4 (5)
Generalized edema	2 (10)	3 (9)	0	3 (4)
Peripheral edema	1 (5)	3 (9)	0	3 (4)
Pneumonitis	3 (15)	3 (9)	0	3 (4)
Any AE leading to				
Dose delay	7 (35)	14 (42)	7 (14)	21 (25)
Dose reduction	2 (10)	3 (9)	1 (2)	4 (5)
Drug discontinuation	3 (15)	6 (18)	5 (10)	11 (13)
Death	0	1 (3)	1 (2)	2 (2)
Any AE occurring in ≥15% of patients				
Peripheral edema	13 (65)	24 (73)	21 (41)	45 (54)
Fatigue	5 (25)	10 (30)	12 (24)	22 (26)
Infusion-related reaction	2 (10)	3 (9)	19 (37)	22 (26)
Nausea	3 (15)	7 (21)	10 (20)	17 (20)
Hypokalemia	3 (15)	10 (30)	7 (14)	17 (20)
Constipation	4 (20)	6 (18)	10 (20)	16 (19)
Anemia	3 (15)	9 (27)	7 (14)	16 (19)
Thrombocytopenia	1 (5)	4 (12)	12 (24)	16 (19)
Diarrhea	5 (25)	7 (21)	8 (16)	15 (18)
Headache	8 (40)	9 (27)	5 (10)	14 (17)
Neutropenia[e]	0	5 (15)	9 (18)	14 (17)
Fall	4 (20)	6 (18)	7 (14)	13 (16)
Insomnia	5 (25)	9 (27)	4 (8)	13 (16)
Hypoalbuminemia	3 (15)	7 (21)	6 (12)	13 (16)
Decreased appetite	2 (10)	4 (12)	8 (16)	12 (14)
Asthenia	2 (10)	4 (12)	8 (16)	12 (14)
Pyrexia	1 (5)	3 (9)	8 (16)	11 (13)
Dyspnea	6 (30)	7 (21)	4 (8)	11 (13)
Cough	4 (20)	5 (15)	5 (10)	10 (12)
Hypophosphatemia	4 (20)	6 (18)	3 (6)	9 (11)
AST increased	3 (15)	6 (18)	3 (6)	9 (11)
Dizziness	3 (15)	5 (15)	3 (6)	8 (10)
ALT increased	3 (15)	6 (18)	2 (4)	8 (10)
Blood bilirubin increased	3 (15)	6 (18)	2 (4)	8 (10)
Hyperuricemia	3 (15)	6 (18)	1 (2)	7 (8)
Hypoxia	4 (20)	5 (15)	1 (2)	6 (7)
Decreased platelet count	3 (15)	8 (24)	4 (8)	12 (14)
Pneumonitis[f]	3 (15)	4 (12)	1 (2)	5 (6)
Hypoesthesia	3 (15)	3 (9)	0	3 (4)

(continued on following page)

TABLE 3. AEs (safety population) (continued)

AE[a]	Frontline De Novo BPDCN (n = 20), No. (%)	All Frontline BPDCN (n = 33), No. (%)	Relapsed/Refractory BPDCN (n = 51), No. (%)	Total (N = 84), No. (%)
Paresthesia	3 (15)	3 (9)	2 (4)	5 (6)
Contusion	3 (15)	4 (12)	2 (4)	6 (7)
Hypertension	3 (15)	3 (9)	2 (4)	5 (6)
Anxiety	3 (15)	4 (12)	3 (6)	7 (8)
Arthralgia	3 (15)	4 (12)	5 (10)	9 (11)
Muscular weakness	4 (20)	4 (12)	2 (4)	6 (7)

Abbreviations: AE, adverse event; BPDCN, blastic plasmacytoid dendritic cell neoplasm.
NOTE. For the primary analysis group, patients received a median (range) of 5 (2-23) cycles. Most patients (15 of 20) received ≤7 cycles; four patients received 10-14 cycles and one patient received 23 cycles. In the total frontline group, patients received a median (range) of 5 (2-23) cycles; 23 patients received ≤7 treatment cycles, seven received 8-14 cycles, and three received up to 23 cycles. In patients with relapsed or refractory BPDCN, a median (range) of 3 (1-34) cycles was administered. In these patients, most (46 of 51) patients received ≤7 cycles, four patients received 8-15 cycles, and one patient received 34 cycles.
[a]Events include preferred terms defined with the use of the *Medical Dictionary of Regulatory Activities*, version 27.1.
[b]AEs that are definitely, probably, or possibly related to the study drug are considered as related to the study drug. AEs with missing or unknown relationship to the study drug are considered as related to the study drug. AEs with the closest relatedness to the study drug are used for summaries.
[c]AE severity is assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
[d]The clinical trial was conducted during the COVID-19 pandemic.
[e]Granulocyte colony-stimulating factor was administered to one patient in the frontline group with prior or concomitant hematologic malignancy.
[f]Grade of pneumonitis included n = 1 at grade 1, n = 2 at grade 2, and n = 2 at grade 3; four events occurred in patients 65 years and older. Two events led to treatment discontinuation (1 grade 2 and 1 grade 3).

maximum tolerated dose was defined related to toxicities, and the RP2D of 0.045 mg/kg once every 3 weeks was chosen based on antileukemic activity in heavily pretreated patients with poor risk characteristics.[16]

Currently, only one targeted treatment, tagraxofusp, is approved for BPDCN. In the pivotal study of tagraxofusp 12 μg/kg given on days 1 to 5 of each 21-day cycle, 72% of frontline patients with BPDCN (n = 29; median age 67 years) achieved a CR + CRc and 90% achieved a partial response or better.[11] In a subgroup analysis of the tagraxofusp study, rates of CR + CRc and overall response were generally similar between frontline patients with or without PCHM,[5] consistent with the findings of this study. In an extended analysis of tagraxofusp (median follow-up of 34 months), the CR + CRc was 57% with an overall response rate of 75%.[22] CLS was the most important identified risk with tagraxofusp, occurring in 21% of patients in long-term follow-up.[11,22] An important strength of our study was the inclusion of patients with previous tagraxofusp exposure in the relapsed/refractory BPDCN group (57% [29 of 51 patients]), in which the tolerability profile was similar between patients with and without previous tagraxofusp exposure (Data Supplement, Table S10), and clinical responses and OS with PVEK can be considered clinically meaningful. Preclinical data indicate that tagraxofusp resistance may be due to acquired impairments in the diphthamide synthesis pathway and insensitivity to diphtheria toxin in BPDCN cells, rather than loss of CD123 expression.[23] These findings help provide rationale as to why CD123-directed activity with PVEK may elicit clinical responses in patients with previous tagraxofusp resistance. Further in our study, CD123 expression was not correlated with treatment efficacy, suggesting that the potential resistance mechanism is likely due to the payload.

In the current study, treatment was associated with a manageable safety profile in patients with a varied range of exposure and no cases of CLS were reported. Patients with previous, resolved CLS (excluding grade 4) could be enrolled in the study. Three patients had previous CLS (maximum grade 2) that was resolved at time of study entry (two had previous tagraxofusp exposure). Peripheral edema and infusion-related reactions were among the most common AEs, predominantly grade 1 or 2, and were mostly reversible with diuretics and corticosteroid premedication, respectively. The frequency of all-grade peripheral edema and infusion-related reactions at the RP2D in patients with AML was 3% and 17%, respectively.[16] Higher rates of these events in the current study (54% and 26%, respectively) may reflect the difference in treatment duration in patients with BPDCN (median of 11 [IQR, 6-20] weeks) compared with those with AML (median of 9 [range, 6-12] weeks).[16]

Reversible VOD was previously reported as a dose-limiting toxicity during the dose-escalation phase in two patients with AML (Data Supplement, Table S11)[16]; both events occurred at doses 6-10 times higher than the RP2D. At the RP2D, two VOD events (one grade 2 and one grade 3) occurred during PVEK treatment (both with frontline de novo BPDCN) and resolved but led to treatment discontinuation. VOD is a known risk of DNA-damaging antibody-drug conjugates, such as gemtuzumab ozogamicin and

inotuzumab ozogamicin, in which higher on-treatment rates of 4.6% and 14.0% have been reported, respectively.[24,25] In CADENZA, post–SCT VOD was also observed in five of 19 patients after discontinuing treatment, including in four patients with relapsed/refractory BPDCN. All five patients had one or more known risk factors for VOD in the setting of SCT, reflecting the difficulty in attributing risk for occurrence of the event during this procedure.[26,27] Given the well-established benefit of SCT on survival in patients with BPDCN,[28,29] identifying patients with additional known risks and attempting to mitigate them are important future needs.[26,27]

For ultrarare cancers such as BPDCN, where limited treatment options exist, novel drug development maximizes expedited pathways to bring promising treatment options to patients as soon as possible. Furthermore, the inherent challenges of small sample sizes and heterogeneous patient populations in rare diseases preclude the feasibility of randomized trials. The findings from this phase I/II, open-label study demonstrate that PVEK is a promising therapy for BPDCN, with high rates of response, and enables bridge to SCT in both frontline and relapsed/refractory patients, with a manageable safety profile. PVEK can help address unmet needs for this often-older population that might have comorbid conditions, have high risk for complications with available therapies, and be ineligible for intensive chemotherapy or SCT. Administered as a convenient 30-minute infusion once every 3 weeks, with no requirement for inpatient hospitalization, monitoring, and no concern for CLS, PVEK will help evolve clinical practice for BPDCN and, given these points, this ultimately represents a potentially practice-changing paradigm for the treatment approach for patients with BPDCN.

The findings from our study support submission to health authorities for PVEK treatment of BPDCN. In addition, PVEK treatment is being investigated in a frontline triplet regimen in unfit patients with CD123-positive newly diagnosed AML (ClinicalTrials.gov identifier: NCT04086264).[30]

Additional future investigations can include long-term follow-up after consolidative SCT as well as potential combination approaches and assessment in CD123-expressing neoplasms beyond BPDCN.[16,31]

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DISCLAIMER

The previous sponsor, ImmunoGen, Inc (now part of AbbVie, Inc), designed the study, performed the data collection and statistical analysis, and study monitoring, with the medical monitor and principal investigators providing medical expertise to inform decisions pertaining to study conduct. AbbVie, Inc participated in the analysis, data collection, and interpretation of data, as well as review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

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N.P. and N.G.D. contributed equally to this work.

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Pivekimab Sunirine in Blastic Plasmacytoid Dendritic Cell Neoplasm

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Research Funding: Jazz Pharmaceuticals, Aprea Therapeutics (Inst)

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Travel, Accommodations, Expenses: Miltenyi Biotec

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Research Funding: AbbVie, Actinium Pharmaceuticals, Actuate Therapeutics, Arog, Astellas Pharma, Bristol Myers Squibb/Celgene, Celator, Constellation Pharmaceuticals, Daiichi Sankyo, Deciphera, Delta-Fly Pharma, FORMA Therapeutics, Fujifilm, Gamida Cell, Genentech/Roche, Geron, Incyte, Karyopharm Therapeutics, Kite, a Gilead company, Mateon Therapeutics, Onconova Therapeutics, Pfizer, PrECOG, REGiMMUNE, Samus Therapeutics, Sangamo Bioscience, Sellas Life Sciences, Stemline Therapeutics, Takeda, Tolero Pharmaceuticals, Trovagene, Agios, Amgen, Jazz Pharmaceuticals, ElevateBio, Ono Pharmaceutical, Novartis, Sanofi, AVM Biotechnology, Syros Pharmaceuticals, glycomimetics, Aptevo Therapeutics, Biomea Fusion, Bio-Path Holdings, Biosight, Cellectis, Celularity, Cogent Biosciences, Cullinan Oncology, Fate therapuetics, Immune-Onc Therapeutics, Kronos Bio, Kura Oncology, Loxo, Marker Therapeutics, REGiMMUNE, Syros Pharmaceuticals

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Speakers' Bureau: Agios, Incyte, Jazz Pharmaceuticals, Novartis, Bristol Myers Squibb Foundation, AbbVie, SERVIER, Syndax
Research Funding: AbbVie (Inst), Agios (Inst), Amgen (Inst), Daiichi Sankyo (Inst), FORMA Therapeutics (Inst), Gilead/Forty Seven (Inst), Immunogen (Inst), Jazz Pharmaceuticals (Inst), Macrogenics (Inst),

Novartis (Inst), PTC Therapeutics (Inst), AbbVie (Inst), Glycomimetics (Inst), ALX Oncology (Inst), SERVIER (Inst), Aptose Biosciences (Inst), Sumitomo Dainippon Pharma Oncology (Inst), Ascentage Pharma (Inst), Kura Oncology (Inst), Oryzon Genomics (Inst), Taiho Oncology (Inst)
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Research Funding: Novartis (Inst), AbbVie (Inst), glycomimetics (Inst), Blueprint Medicines (Inst)

Enrico Derenzini
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Research Funding: TG Therapeutics, ADC Therapeutics, Takeda, Incyte
Travel, Accommodations, Expenses: AbbVie, AstraZeneca

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Stock and Other Ownership Interests: AbbVie, Incyte (I)

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Research Funding: Bristol Myers Squibb (Inst), Pfizer (Inst), Immunogen (Inst), Genentech (Inst), AbbVie (Inst), Astellas Pharma (Inst), Servier (Inst), Daiichi Sankyo (Inst), Gilead Sciences (Inst), Amgen (Inst), Trillium Therapeutics (Inst), Hanmi (Inst), Trovagene (Inst), FATE Therapeutics (Inst), Novimmune (Inst), Glycomimetics (Inst), Kite, a Gilead company (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of Investigators for Pivekimab Sunirine in Blastic Plasmacytoid Dendritic Cell Neoplasm

Investigator	Institution
Navel Daver Naveen Pemmaraju	The University of Texas MD Anderson Cancer Center, Houston, TX
Eunice Wang	Roswell Park Comprehensive Cancer Center, Buffalo, NY
Daniel DeAngelo Andrew Lane	Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
Harry Erba	Duke Cancer Institute, Durham, NC
David Sallman	Moffitt Cancer Center, Tampa, FL
Roland Walter	Fred Hutchinson Cancer Center, Seattle, WA
Ahmed Aribi	City of Hope National Medical Center, Duarte, CA
Matthew Ulrickson	Banner MD Anderson Cancer Center, Gilbert, AZ
Gary Schiller	David Geffen School of Medicine, Los Angeles, CA
Pau Montesinos	Hospital Universitari i Politècnic La Fe, Valencia, Spain
Enrico Derenzini Luca Mazzella	IRCCS IEO – Istituto Europeo di Oncologia, Milan, Italy
Maria Benedetta Giannini Giovanni Martinelli Giovanni Marconi	Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"—IRST S.r.l. Istituto di Ricovero e Cura a Carattere Scientifico, Meldola (FC), Italy
Eric Deconinck	CHU Besançon, France
Ollivier Legrand	Sorbonne Université, Paris, France
Delphine Lebon	Centre Hospitalier Universitaire d'Amiens, Amiens, France
Valerio Maisano	Aix-Marseille University, Marseille, France