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Real-world outcomes of venetoclax plus hypomethylating agents in BPDCN across treatment lines

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Authorship Contributions
E.N.L. performed the data analysis and wrote the manuscript. J.T., A.A.L., and S.S. provided guidance on study design and contributed to manuscript writing. S.M. performed the chart review. All authors reviewed and approved the final manuscript.

Disclosure of Conflicts of Interest
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Data Availability
De-identified clinical, treatment, and genomic data supporting the findings of this study are available from the corresponding author upon reasonable request. Requests will be considered in accordance with IRB approvals and applicable patient privacy regulations

To the Editor:

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive malignancy with limited therapeutic options(1-3). Preclinical data demonstrate BCL-2 dependence in BPDCN blasts, providing rationale for venetoclax-based therapy(4), which has demonstrated efficacy in combination with hypomethylating agents in acute myeloid leukemia(5). While a recent prospective trial established activity of venetoclax plus hypomethylating agents (Ven+HMA) in relapsed/refractory (R/R) BPDCN(6), real-world outcomes across treatment lines remain poorly characterized. We conducted a multi-institutional retrospective study of 14 BPDCN patients treated with Ven+HMA. Although clinically meaningful responses were observed in both frontline (3/4 complete remission (CR)) and R/R (5/10 CR) settings, durable disease control was uncommon. Median duration of response (DOR) was 263 days, and 13 of 14 patients ultimately experienced disease progression or relapse, frequently involving the central nervous system (CNS) or extramedullary sites, underscoring the need for vigilant monitoring, CNS prophylaxis, and novel therapeutic strategies.

We retrospectively identified BPDCN patients treated with Ven+HMA at Dana-Farber Cancer Institute and the University of Miami Sylvester Comprehensive Cancer Center between 2009 and 2024. Diagnosis was confirmed by morphology and immunophenotyping (CD123, CD4, CD56) according to WHO criteria. Venetoclax was administered with azacitidine or decitabine per treating physician discretion. Molecular profiling was performed using institutional next-generation sequencing panels (Neogenomics Myeloid Panel at UM; Rapid Heme Panel at DFCI). Responses were assessed using consensus BPDCN criteria as described by Pemmaraju et al.(7) CR required normalization of peripheral blood counts, resolution of skin lesions and all measurable disease, and <5% bone marrow blasts. Time-to-event analyses were performed using Kaplan-Meier methods. Fisher's exact test was used to compare CR rates. This study was approved by the University of Miami IRB with a data-sharing agreement with Dana-Farber Cancer Institute.

The median age at diagnosis was 64 years (range, 14–84), and 13/14 (93%) of patients were male. Two patients (14%) had concurrent myelodysplastic syndrome. All patients had ECOG performance status 0–2. Skin involvement was present in 11/14 (79%) at diagnosis, and bone marrow was involved in 10/14 (71%). Baseline hematologic parameters showed a median hemoglobin of 14.1 g/dL, platelet count of 106 $\times 10^9$/L, and WBC of 4.06 $\times 10^9$/L. Peripheral blasts were typically absent (median 0%), whereas bone marrow blasts ranged from 0–95% **(Table 1)**.

Patients received various initial therapies, including tagraxofusp in 7/14 (50%), acute leukemia–based chemotherapy, or Ven+HMA. The overall initial treatment CR rate, across all therapies (not limited to Ven+HMA) was 64%, with a median time to initial response of 46 days (range, 13–159) and median time to relapse of 187 days (range,

2–1218). Venetoclax-based therapy was administered frontline in 4 patients (29%) and in R/R settings in 10. Seven patients underwent allo-HSCT during their disease course. Two patients underwent transplantation following Ven+HMA, whereas five had previously undergone transplantation before receiving Ven+HMA for relapsed disease. Both patients transplanted after Ven+HMA subsequently relapsed approximately 2 and 3 months after transplantation (8, 9).

Among 10 patients with sequencing data, mutations were observed in TET2 (6/10, 60%), ASXL1 (3/10, 30%), JAK2 and NRAS (2/10, 20% each), and IKZF1 and ZRSR2 (2/10, 20% each) **(Figure 1A).** Additional low-frequency alterations in DNMT3A and CBL (1/10, 10% each) were also identified. These mutational patterns mirror those seen in myeloid neoplasms, supporting the biologic rationale for venetoclax in this genetic context. Immunophenotyping confirmed diagnostic CD123/CD4/CD56 co-expression in all 13 patients tested **(Figure 1B)**.

Among patients treated with frontline Ven+HMA, 3/4 achieved CR, whereas 5/10 patients treated in the relapsed/refractory setting achieved CR (**Figure 2A**). Fisher's exact test did not demonstrate a statistically significant difference between groups ($p = 0.58$). However, given the limited sample size, these results are descriptive and should not be interpreted as evidence of comparable efficacy. Across all lines of Ven+HMA, the median time to response was 59 days (range, 10–159), and the median DOR was 263 days (range, 126–760) (Figure 2C). Disease progression or relapse following Ven+HMA occurred in 13/14 patients. The only patient who did not experience post-Ven+HMA relapse achieved CR with sixth-line venetoclax plus azacitidine and died from causes unrelated to BPDCN progression. Notably, four patients experienced CNS relapse, while four experienced extramedullary relapse, including two isolated extramedullary relapses and two involving both bone marrow and extramedullary disease. No patient experienced concurrent CNS and extramedullary relapse. Median overall survival (OS) was 27 months (range, 3–129), with 1-, 2-, and 5-year OS rates of 77%, 50%, and 14%; median OS for R/R patients was 10.5 months **(Figure 2B).**

Our multi-institutional cohort provides detailed patient-level data complementing both the prospective trial by Pemmaraju et al.(6) and population-level database analyses by Lee et al(10). Descriptively, responses were observed in both frontline and relapsed/refractory settings, although interpretation is limited by the small cohort size and treatment heterogeneity. However, these observations suggest flexibility in treatment sequencing, which remains an area of uncertainty in BPDCN management. Our findings are also consistent with prior retrospective reports demonstrating activity of venetoclax-based regimens in BPDCN(11). The high frequency of TET2, ASXL1, and JAK2 mutations reinforces the myeloid genetic continuum of BPDCN and the biologic rationale for venetoclax therapy (4, 12).Additionally, a principal finding of this study is that although Ven+HMA induced remissions in both frontline and relapsed/refractory

BPDCN, durable disease control remained uncommon, with 13/14 patients ultimately experiencing disease progression or relapse. The near-universal relapse rate (93%), with frequent CNS and extramedullary involvement, highlights the critical importance of disease surveillance and CNS-directed strategies(13, 14).

This study has limitations inherent to its retrospective design and small sample size, reflecting the rarity of BPDCN. Treatment heterogeneity across institutions may influence outcomes. Nonetheless, these findings support Ven+HMA as a viable treatment option across multiple lines of therapy, particularly for patients ineligible for or relapsing after tagraxofusp(7, 15). Continued integration of prospective, real-world, and translational datasets will be essential to refine treatment sequencing and improve outcomes in this rare malignancy(3).

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Table

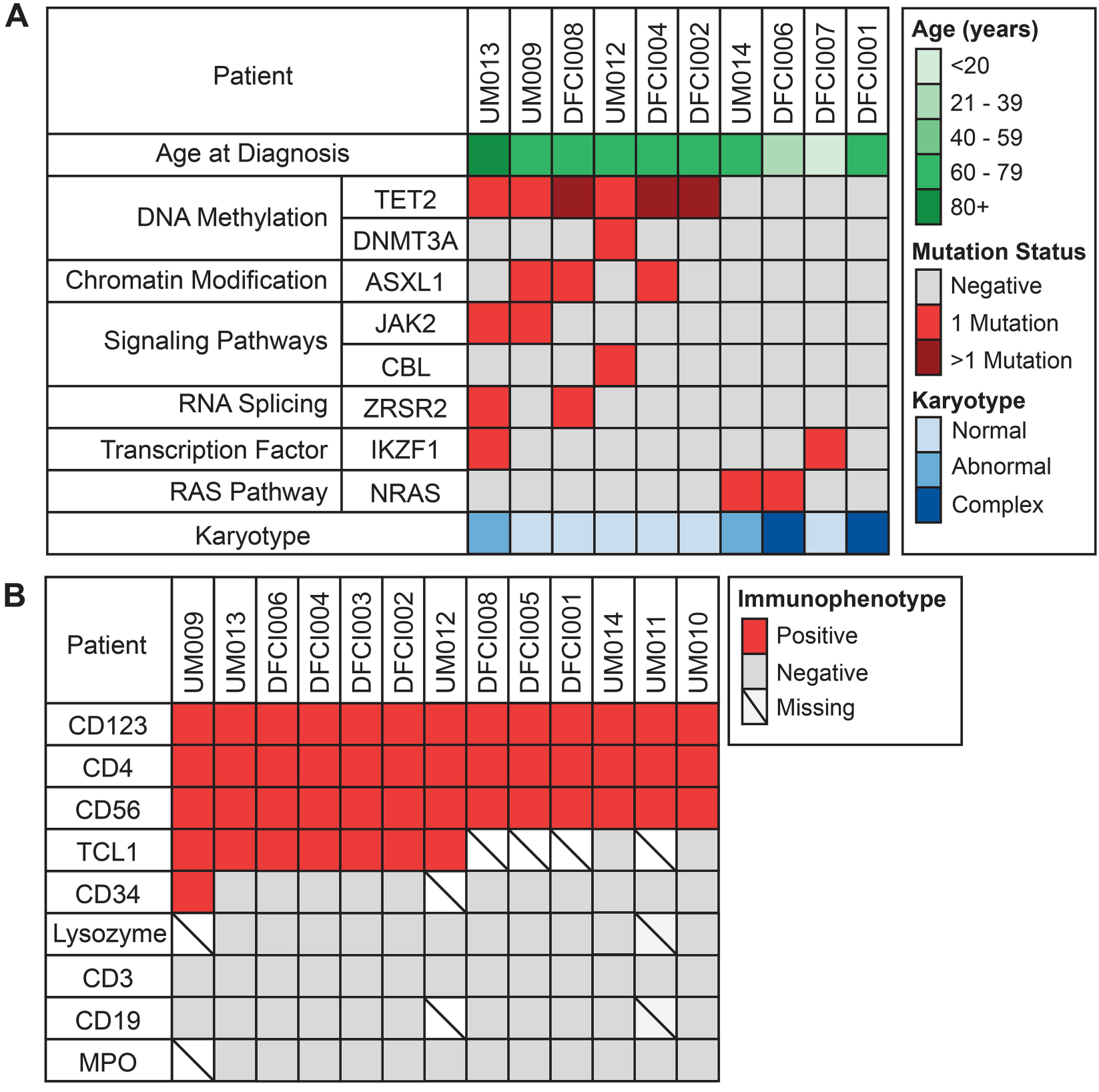
Patient Demographics and Disease Characteristics				
Age at Diagnosis, Median (Range)	64 years (14–84)			
Sex	Male: 92.86% (13/14) Female: 7.14% (1/14)			
Concurrent Myeloid Disease	No: 85.71% (12/14) MDS: 14.29% (2/14)			
ECOG at Diagnosis	0: 71.43% (10/14) 1: 21.43% (3/14) 2: 7.14% (1/14) 3–5: 0% (0/14)			
Biopsy Sites at Diagnosis	Skin: 50% (7/14) Bone Marrow: 71.43% (10/14) LAD: 7.14% (1/14)			
Extramedullary Disease (except skin)	15.38% (2/13) - LAD, Splenomegaly			
Skin Involvement at Diagnosis	78.57% (11/14)			
Hematologic Parameters at Diagnosis				
	Median	**Mean (SD)**	**Range**	**n**
Hgb (g/dL)	14.10	13.35 (2.48)	9.00 - 16.00	11
WBC (x10⁹/L)	4.06	8.20 (12.14)	2.33 - 44.30	11
Plt (x10⁹/L)	106	112.27 (56.76)	38.00 - 238.00	11
Blasts (%)	0.00	6.57 (16.52)	0.00 - 44.00	7
Bone Marrow Blasts (%)	2.00	34.49 (43.17)	0.00 – 95.00	11
Initial Treatment				
SL-401 Included in Initial Treatment	50% (7/14)			
Initial Treatment Regimens (all patients)	SL401 (7), Venetoclax + Azacitidine (2), Venetoclax alone (1), 7+3 (1), 7+3 + Etoposide (1), CLAG (1), EPOCH (1), HyperCVAD + Venetoclax + SL401 (1)			
Initial Treatment Response	CR: 64.29% (9/14) PR: 21.43% (3/14) PD: 14.29% (2/14)			
Time to Initial Treatment Response	N = 11 Median: 46 days Mean (SD): 57.45 (45.15) Range: 13–159 days			
Time from Response to Relapse	N = 10 Median: 187 days Mean (SD): 262.4 (347.67) Range: 2–1218 days			
VEN+HMA and HSCT				
HSCT Received	50% (7/14)			
HSCT Post-VEN+HMA	14.29% (2/14)			
Line of Treatment Venetoclax Used	1st Line: 28.57% (4/14) 2nd Line: 28.57% (4/14) 3rd Line: 14.29% (2/14) 4th–7th Line: 7.14% (1/14) each			

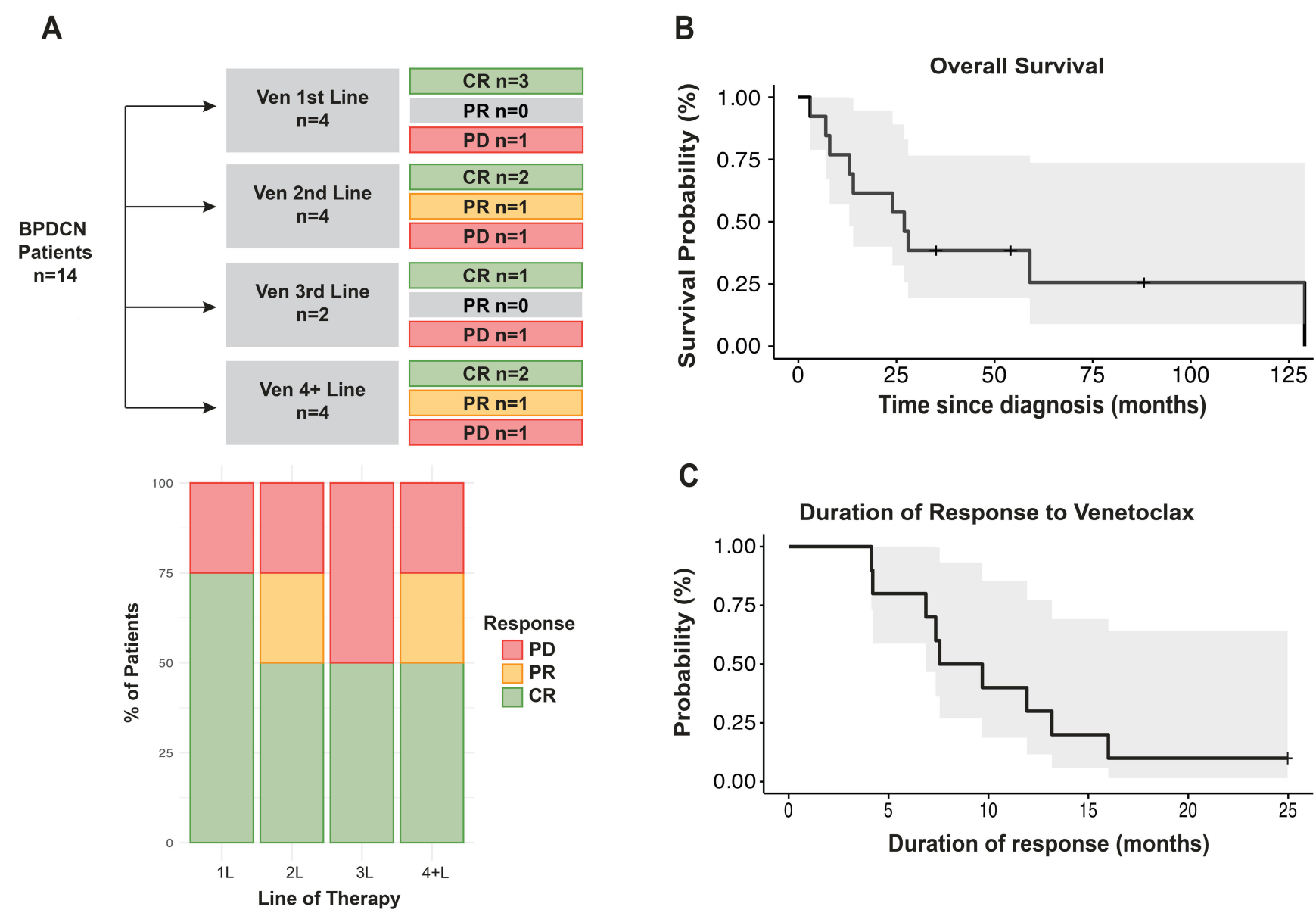
Table 1. Baseline clinical and hematologic characteristics of BPDCN patients receiving venetoclax plus hypomethylating agents (n=14). Data are presented as median (range) or n (%), unless otherwise indicated. Hematologic parameters include hemoglobin (Hgb), white blood cell count (WBC), platelet count (Plt), and blast percentages in peripheral blood and bone marrow. ECOG = Eastern Cooperative Oncology Group performance status; LAD = lymphadenopathy; MDS = myelodysplastic syndrome; CR = complete response; PR = partial response; PD = progressive disease; SL-401 = tagraxofusp.

Figure Legends

Figure 1. Mutation landscape and immunophenotypic characteristics of BPDCN patients. (A) Oncoplot showing molecular alterations and karyotypic abnormalities across 10 BPDCN patients. Patient age at diagnosis is indicated by the color-coded bar at the top (green gradient: <20 years to 80+ years). Mutation status is displayed for key genes involved in DNA methylation (*TET2*, *DNMT3A*), chromatin modification (*ASXL1*), signaling pathways (*JAK2*, *CBL*), RNA splicing (*ZRSR2*), transcription factors (*IKZF1*), and RAS pathway (*NRAS*). Dark red shading indicates multiple pathogenic alterations in the same gene (multi-hit), light red indicates a single pathogenic alteration, and gray indicates no detected alteration/wild-type status. Karyotype status is shown in the bottom row (light blue: normal, medium blue: abnormal, dark blue: complex karyotype). **(B)** Immunophenotypic profile across 13 BPDCN patients showing expression patterns of key surface markers and intracellular proteins. Red squares indicate positive expression, gray squares indicate negative expression, and diagonal lines indicate missing/unavailable data. The panel includes characteristic BPDCN markers (CD123, CD4, CD56, TCL1), stem cell markers (CD34), myeloid markers (lysozyme, MPO), and lymphoid markers (CD3, CD19).

Figure 2. Venetoclax treatment outcomes and survival in BPDCN patients. (A) Response rates to venetoclax across different lines of therapy (n=14). Upper panel shows patient numbers; lower panel shows percentage distribution. CR, complete response; PR, partial response; PD, progressive disease. **(B)** Kaplan-Meier curve of OS from time of diagnosis. **(C)** Kaplan-Meier curve of DOR in patients achieving CR or PR with venetoclax therapy.


A
Patient
UM013
UM009
DFCI008
UM012
DFCI004
DFCI002
UM014
DFCI006
DFCI007
DFCI001
Age at Diagnosis
DNA Methylation
TET2
DNMT3A
Chromatin Modification
ASXL1
Signaling Pathways
JAK2
CBL
RNA Splicing
ZRSR2
Transcription Factor
IKZF1
RAS Pathway
NRAS
Karyotype
Age (years)
<20
21 - 39
40 - 59
60 - 79
80+
Mutation Status
Negative
1 Mutation
>1 Mutation
Karyotype
Normal
Abnormal
Complex
B
Patient
UM009
UM013
DFCI006
DFCI004
DFCI003
DFCI002
UM012
DFCI008
DFCI005
DFCI001
UM014
UM011
UM010
CD123
CD4
CD56
TCL1
CD34
Lysozyme
CD3
CD19
MPO
Immunophenotype
Positive
Negative
Missing


A
BPDCN Patients n=14
Ven 1st Line n=4
CR n=3
PR n=0
PD n=1
Ven 2nd Line n=4
CR n=2
PR n=1
PD n=1
Ven 3rd Line n=2
CR n=1
PR n=0
PD n=1
Ven 4+ Line n=4
CR n=2
PR n=1
PD n=1
100
75
50
25
0
% of Patients
1L
2L
3L
4+L
Line of Therapy
Response
PD
PR
CR
B
Overall Survival
Survival Probability (%)
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Time since diagnosis (months)
C
Duration of Response to Venetoclax
Probability (%)
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Duration of response (months)