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Received: August 10, 2026.

Accepted: September 22, 2026.

Citation: Naseema Gangat, Erica Andres, Buraq Ahmed, Clifford M. Csizmar, Momna Warraich, Kristen McCullough, Aref Al-Kali, Luis Porrata, Hassan Alkhateeb, Kebede Begna, James Foran, William Hogan, Mark R. Litzow, Abhishek A. Mangoankar, Aasiya Matin, Hemant Murthy, Cecilia Arani Yi, Antoine N. Saliba, Mithun Shah, Mehrdad Hefazi Torghabeh, Mrinal M. Patnaik, Mohamed A. Kharfan-Dabaja and Ayalew Tefferi. Allogeneic hematopoietic stem cell transplantation rather than specific front-line therapy is associated with long-term survival in blastic plasmacytoid dendritic cell neoplasm: the Mayo Clinic experience.

Haematologica. 2026 Oct 1. doi: 10.3324/haematol.2026.301790 [Epub ahead of print]

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Running title: Outcomes in BPDCN

Supplemental material: 2 tables.

Data sharing: please email the corresponding author

References: 12

Disclosures: A.K: Consulting/Advisory Role for Novartis. Research funding from Novartis, Celgene, Bristol-Myers Squibb, Astex Pharmaceuticals, Aprea Therapeutics, Hemavant Sciences, ALX Oncology. A.A.M: Research funding from Bristol-Myers Squibb, Incyte, Novartis, Gilead Sciences. A.N.S: Consulting/Advisory Role for Novartis. Research funding from Kura Oncology, Chordia Therapeutics, Daiichi Sankyo/UCB Japan, Gilead Sciences. M.R.L: Honoraria from BeiGene, Amgen. Speaker's Bureau for BeiGene, Amgen. Research funding from Amgen, Astellas, Actinium Pharmaceuticals, Syndax. Travel support from BeiGene, Amgen. M.S: Honoraria from Omeros. Research funding from Celgene/Bristol-Myers Squibb, AbbVie, Kura Oncology, Marker Therapeutics, Astellas. M.M.P: Consulting/Advisory Role for Kura Oncology. Honoraria from GlaxoSmithKline, AstraZeneca, CTI/SOBI. Research funding from Stemline Therapeutics, Epigenetix, Solutherapeutics, Kura Oncology, Polaris.

J.F: Consulting/Advisory Role for Amgen, Takeda, Syndax, Ascentage Pharma. Stock ownership in Aurinia Pharmaceuticals. Research funding from Kura Oncology, Sellas Life Sciences, Celgene/Bristol-Myers Squibb, Chordia Therapeutics, Takeda, Roivant. Travel support from Peerview.

CAY: Consulting/Advisory Role for Blueprint-Sanofi, Cogent Pharmaceuticals, Takeda, Bristol Myers Squibb, Geron, Novartis, Research funding from Blueprint Sanofi, Travel support from Dava Oncology.

MAK-D: Research/grant to institution from Bristol Myers Squibb and Pharmacyclics; Scientific Advisory Board for Incyte Corp.

NG: Advisory Board for Disc Medicine and Agios.

The remaining authors declare no competing financial interests.

Author contributions: NG, EA, CC designed the study, collected data, performed analysis and wrote the paper. BA performed analysis and wrote the paper. MW collected data. KM, AK, LP, HA, KB, JM, WH, MRL, AAM, AM, HM, CA, MMP, ANS, MS, MH, MAK-D, AT contributed patients.

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy arising from plasmacytoid dendritic cell precursors (estimated prevalence 0.04 per 100,000)¹. Despite the 2018 FDA approval of tagraxofusp, a CD123-directed cytotoxin, and the 2026 approval of pivekimab sunirine ², a CD123-directed antibody-drug conjugate³, median overall survival (OS) remains approximately 18-24 months, and durable remission is rarely achieved without consolidative allogeneic hematopoietic stem cell transplantation (allo-HCT)⁴. Current prognostic and treatment data are derived from heterogeneous cohorts, and it remains unclear which frontline treatment regimens most effectively bridge patients with BPDCN to potentially curative allo-HCT, as opposed to simply inducing short-lived remission⁵. In the current study, we analyzed 70 patients with BPDCN treated at the Mayo Clinic to characterize baseline disease features, evaluate frontline treatment patterns in relation to bridging to allo-HCT, and identify clinical and genomic predictors of survival, using landmark and competing-risks methods to address immortal-time bias.

Patients diagnosed with BPDCN at Mayo Clinic (AZ, FL, MN, USA) were identified retrospectively. The study was approved by the Mayo Clinic Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. Next-generation sequencing (NGS) using a clinical 47-gene panel was performed at diagnosis in a subset of patients. Categorical variables were compared with Fisher's exact or chi-squared tests, continuous variables with Mann-Whitney or Kruskal-Wallis tests. Multivariate analysis used a Cox proportional hazards model with allo-HCT modeled as a time-varying covariate, patients with missing karyotype were excluded from the multivariable model (complete-case analysis). As a complementary correction, a pre-specified landmark analysis was performed at 200 days (6.6 months) post-diagnosis, an interval chosen a priori to approximate when most transplants had occurred, restricted to patients alive and event-free at that time. Relapse and non-relapse mortality were analyzed as competing risks (Aalen–Johansen). Three patients who underwent autologous HSCT were excluded from all transplant analyses.

The median age at diagnosis was 69 years (range 19-94), with a male predominance (81%), consistent with previously reported adult BPDCN cohorts^{6,7}. Skin (79%) and bone marrow involvement (74%) were the most common presenting features, followed by lymphadenopathy (49%), splenomegaly (28%), and central nervous system involvement (13%). A concurrent hematologic malignancy, most commonly chronic myelomonocytic leukemia (CMML) or myelodysplastic syndrome (MDS), was identified in 16 (25%) of patients, and abnormal karyotype was present in 12 of 49 (24%) evaluable patients; these were cytogenetically heterogeneous, with a complex karyotype (≥ 3 abnormalities) in 6 of 12, and the adverse survival association was not confined to complex karyotypes⁸. Additional baseline laboratory and treatment characteristics, and transplant details including donor source and conditioning regimens are provided in Table 1.

Treatment information was available in 53 patients and front-line treatment regimens included tagraxofusp ($n=10$; 19%), acute myeloid leukemia (AML) regimen ($n=19$, 36%), acute lymphoblastic leukemia (ALL) regimen ($n=14$; 26%), lymphoma regimen ($n=6$; 11%), or other regimens ($n=4$; 8%). Treatment regimens differed significantly by age ($p<0.001$): younger patients predominantly received ALL-type/Hyper-CVAD regimens (median age 45 years), whereas older patients received AML-type, tagraxofusp, or lymphoma-type regimens. CR rates also differed by regimen type (comparison across the five parental categories; ALL-type, AML-type, tagraxofusp, lymphoma-type, and other; $p=0.013$), being highest with ALL-type regimens; individual sub-regimens were described but not statistically compared (Supplementary Table 1). Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) administered alone ($n=12$) or with venetoclax ($n=2$), achieved a CR rate of 11 of 12 (92%). Among AML-directed therapies, CR was achieved in 8 of 9 (89%) patients treated with intensive chemotherapy and in 5 of 8 (63%) treated with hypomethylating agents plus venetoclax (overall AML-group CR, 14 of 19 [74%]). Tagraxofusp achieved CR in 6 of 10 (60%) (**Supplementary Table 1**). Bridge-to-transplant rates differed by regimen (tagraxofusp 7/10 [70%], ALL 8/13 [62%], AML-type 6/18 [33%], lymphoma-type 1/6 [17%], other 0/4 [0%]; Fisher exact $p=0.04$)². Of 14 Hyper-

CVAD-treated patients, 8 did not proceed to allo-HCT (donor unavailability, lack of caregiver support, patient preference, or infection). Transplant-censored 1-year OS did not differ significantly across regimens ($p=0.15$); however, because censoring at transplantation is informative and differs across regimens, this comparison should be interpreted cautiously and does not establish equivalent antileukemic efficacy.⁷ On multivariate logistic regression, age was an independent predictor of undergoing allo-HCT (OR 0.78 per year, $p=0.009$), while regimen-specific effects were non-significant after adjustment for age (all $p>0.1$).

Among 62 evaluable patients (diagnosed between 2000 and 2025; median follow-up among survivors, 15.3 months), median OS was 14.5 months (95% CI 11.7–20.8). Nineteen (31%) patients underwent allo-HCT, which was associated with improved OS (51 vs 10 months, $p<0.01$). A pre-specified 200-day (6.6-month) landmark analysis confirmed this benefit after accounting for immortal-time bias (log-rank $p=0.037$; Figure 1)^{6,7}.

Among allo-HCT recipients ($n=19$), 8 of 17 evaluable patients were alive at 3 years (6 of 17 alive and relapse-free) and 3 of 15 evaluable patients were alive and relapse-free at 5 years (Kaplan–Meier 3- and 5-year OS from diagnosis, 51% and 28%). Only 2 of 43 evaluable non-allografted patients were alive at 3 years. The four longest survivors (aged 29–67 years; alive approximately 4–9 years post-transplant) had all undergone allo-HCT after CR to 7+3, azacitidine/venetoclax, or Hyper-CVAD, with matched-unrelated, matched-related, or haploidentical donors and predominantly busulfan-based conditioning. Among allo-HCT recipients, TBI-based conditioning (8/19, 42%) was not associated with survival ($p=0.54$).

Achievement of CR/CRi with frontline therapy was associated with superior OS among non-allografted patients (median OS, 13.2 vs 7.9 months; $p=0.02$). Pre-transplant disease status was documented in 17 of 19 allo-HCT recipients, all of whom were in CR at transplantation (including one patient who achieved CR only after second-line therapy); no patient was transplanted with documented active disease, and

because only two recipients had not achieved CR with frontline therapy, OS was not compared by frontline response within the transplanted group. Notably, abnormal karyotype stratified survival among transplanted patients ($p=0.023$) but not among non-transplanted counterparts ($p=0.41$), and front-line treatment regimen showed a non-significant trend among transplanted patients ($p=0.052$) but not among non-transplanted ones ($p=0.54$); however, these subgroup comparisons are underpowered and hypothesis-generating, and do not establish that pre-transplant treatment choice is irrelevant to prognosis.⁸ Among 19 allo-HCT recipients, cumulative incidence of non-relapse mortality (attributed to graft-versus-host disease ($n=4$), sepsis ($n=2$)) was 12% at 12 months and 25% at 24 months, while cumulative incidence of relapse was 6% at 12 months and plateaued at 21% by 24 months, with non-relapse mortality significantly exceeding relapse as a cause of treatment failure ($p<0.01$).

To identify independent predictors of survival, we constructed a multivariable Cox model with time-varying allo-HCT status. Given the number of events, we pre-specified a parsimonious model including allo-HCT together with the two factors most strongly associated with survival in univariate analysis and prior reports—age ≥ 50 years and abnormal karyotype, with autologous recipients excluded (62 time-varying records, 38 events). Allo-HCT was independently associated with improved survival (HR 0.34, 95% CI 0.15–0.76, $p=0.009$), while abnormal karyotype (HR 3.04, 95% CI 1.31–7.07, $p=0.010$) and age ≥ 50 years (HR 3.14, 95% CI 1.02–9.66, $p=0.046$) were independent adverse predictors (Figure 2). Male sex was adverse in univariate analysis (HR 2.9, $p=0.02$) but not after adjustment for allo-HCT and age ($p=0.07$). Among 24 patients with NGS, the median mutation number was 3 (range 0–7); TET2 ($n=18$), ASXL1 ($n=14$), NRAS ($n=7$), and SRSF2 ($n=7$) were most frequent (Supplementary Table 2). *SRSF2* mutation predicted inferior OS in univariate analysis (15 vs 51 months, $p=0.02$), but not after multivariable adjustment for age, karyotype, and allo-HCT; no mutation predicted receipt of allo-HCT or induction response.

Given the association between BPDCN and myeloid neoplasms, we examined the impact of concurrent CMML or MDS ⁴. Concomitant myeloid malignancy was not associated with allo-HCT (25% vs 36%; $p=0.54$) or OS ($p=0.73$).

The current study represents one of the largest contemporary single-institution series of BPDCN and is among the first to evaluate frontline treatment strategies using time-varying Cox regression, landmark, and competing-risk methods. The findings reinforce allo-HCT as central to durable remission in BPDCN ^{5,7,9, 10}. Although tagraxofusp and, more recently, pivekimab sunirine¹¹ have expanded therapeutic options for BPDCN, our data suggest that a principal value of frontline therapy may lie less in achieving remission per se than in safely bridging patients to allo-HCT, which in this cohort was the treatment most consistently associated with durable long-term survival. As previously reported, abnormal karyotype emerged as an independent predictor of inferior survival⁸. Limitations include the retrospective, single-center design; the small subgroup sizes inherent to this rare disease; the absence of systematically recorded race/ethnicity and socioeconomic data; and the susceptibility of transplant comparisons to selection bias and informative censoring, such that the survival benefit associated with allo-HCT is associative rather than proven causal. Our findings support prospective studies evaluating CD123-directed and combination regimens (e.g., azacitidine–venetoclax plus tagraxofusp) by their ability to improve allo-HCT eligibility, reduce relapse, and enhance survival, not response alone¹².

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Table 1. Baseline demographic, clinical, laboratory, and treatment characteristics of 70 patient with BPDCN.

Variable	Units	Value	N	Range / %	Summary
Demographics					
Age	Median (range)	69	70	19 - 94	69 (19 - 94)
Male	Number (%)	57	70	81.4	57 (81%)
Presenting Features					
Skin involvement	Number (%)	54	68	79.4	54 (79%)
Lymphadenopathy		33	68	48.5	33 (49%)
Splenomegaly		18	64	28.1	18 (28%)
Bone marrow involvement		50	68	73.5	50 (74%)
CNS involvement		8	62	12.9	8 (13%)
Myeloid malignancy		16	63	25.4	16 (25%)
Laboratory Parameters					
Hemoglobin, g/dl	Median (range)	12	63	2.8 - 16.9	12 (2.8 - 16.9)
Platelet count x 10 ⁹ /l		116	63	8 - 577	116 (8 - 577)
White blood cell count, x 10 ⁹ /l		4.9	63	0.5 - 291	4.9 (0.5 - 291)
Bone marrow involvement, %		35.5	44	0 - 95	35.5 (0 - 95)
Abnormal karyotype	Number (%)	12	49	24.5	12 (24%)
Frontline Treatment					
AML regimen	Number (%)	19	53	35.8	19 (36%)
ALL regimen		14	53	26.4	14 (26%)
Lymphoma regimen		6	53	11.3	6 (11%)
Tagraxofusp		10	53	18.9	10 (19%)
Other		4	53	7.5	4 (8%)
Transplant characteristics					
Autologous	Number (%)	3	22	13.6	3 (14%)
Allogeneic		19	22	86.4	19 (86%)
MRD		3	18	16.7	3 (17%)
MUD		12	18	66.7	12 (67%)
MMUD		1	18	5.6	1 (6%)
Haplo		2	18	11.1	2 (11%)
HCT Regimen					
BEAM	Number (%)	2	21	9.5	2 (10%)
BuCy		2	21	9.5	2 (10%)
CyTBI		3	21	14.3	3 (14%)
FluBu		6	21	28.6	6 (29%)
FluBuTBI		1	21	4.8	1 (5%)
FluCyTBI		1	21	4.8	1 (5%)
FluMel		2	21	9.5	2 (10%)
FluMelTBI		2	21	9.5	2 (10%)
FluTBI		2	21	9.5	2 (10%)
Outcomes					
GVHD	Number (%)	14	17	82.4	14 (82%)
Capillary leak syndrome (tagraxofusp, any line)		9	12	75.0	9 (75%)
Death		57	70	81.4	57 (81%)

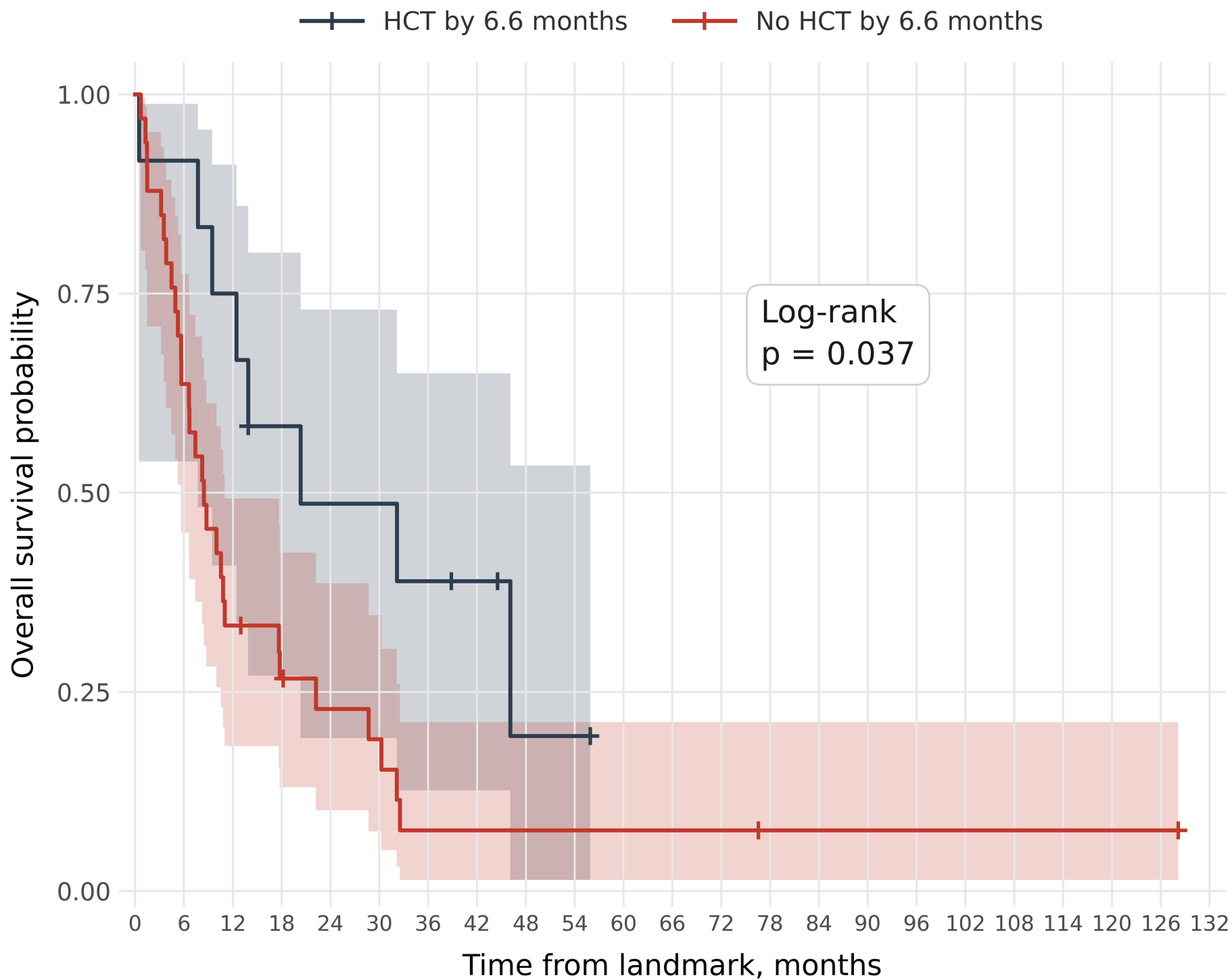
Values are presented as median (range) for continuous variables and n (%) for categorical variables, calculated among evaluable patients for each parameter (denominators vary by variable due to missing data and are shown in the N column). Abnormal karyotype was defined as any cytogenetic abnormality identified on diagnostic bone marrow karyotyping. Myeloid malignancy refers to a concurrent or antecedent diagnosis of chronic myelomonocytic leukemia

(CMML), myelodysplastic syndrome (MDS), or myeloproliferative neoplasm (MPN). HCT type and donor source are reported among patients who underwent hematopoietic cell transplantation (HCT); conditioning regimens are reported among evaluable transplant recipients with documented regimen data. Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ; Haplo, haploidentical donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor BEAM, carmustine, etoposide, cytarabine, melphalan; BM, bone marrow; BuCy, busulfan/cyclophosphamide; CI, confidence interval; CNS, central nervous system; CyTBI, cyclophosphamide/total body irradiation; FluBu, fludarabine/busulfan; FluCyTBI, fludarabine/cyclophosphamide/total body irradiation; FluMel, fludarabine/melphalan; FluTBI, fludarabine/total body irradiation; GVHD, graft-versus-host disease (any grade; reported among 17 allogeneic recipients with available data; acute versus chronic type and grade were not systematically recorded). Capillary leak syndrome is reported among all patients who received tagraxofusp in any line of therapy (n=14: 10 as frontline therapy and 4 in later lines), of whom 12 had evaluable toxicity data; the denominator therefore exceeds the 10 patients listed under frontline treatment. Conditioning regimens are listed individually and were not classified by intensity

Figure legend

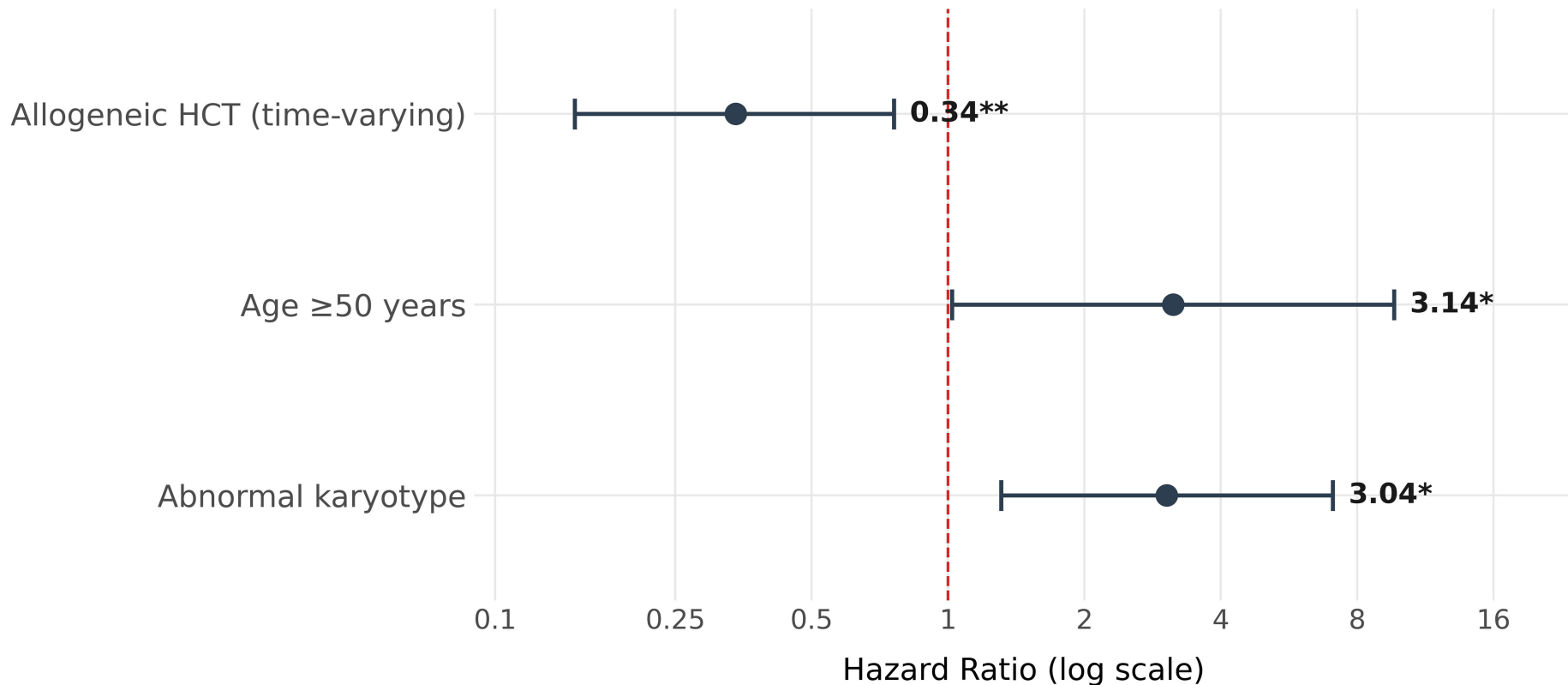
Figure 1. Overall survival by allo-HCT status: pre-specified 200-day landmark analysis. Kaplan-Meier estimates of overall survival among patients alive and event-free at the pre-specified 200-day (6.6-month) landmark, stratified by whether allo-HCT had occurred by the landmark (n=45; 12 with allo-HCT by the landmark, 33 without). Survival is measured from the landmark forward to correct for immortal-time bias inherent in comparing transplant status using time from diagnosis. Patients transplanted by 200 days had significantly improved overall survival (log-rank $p=0.037$). Tick marks indicate censored observations.

Figure 2. Multivariable Cox model: predictors of survival. Forest plot of hazard ratios (log scale) from a pre-specified parsimonious multivariable Cox proportional hazards model with time-varying allo-HCT status (autologous recipients excluded; 62 time-varying records, 38 events), including allo-HCT, age ≥ 50 years, and abnormal karyotype. Squares indicate point estimates; error bars represent 95% confidence intervals; the dashed line indicates HR=1 (no effect).



Multivariable Cox Model: Predictors of Survival

Time-dependent allogeneic HCT status; pre-specified parsimonious model
(autologous recipients excluded), 38 events * p<0.05 ** p<0.01 *** p<0.001



Supplemental material

Supplementary Table 1. BPDCN Treatment Outcomes.

Regimen	N	Age (y)	ANOVA	CR	Chi Sq	HCT	Fisher	1y OS	mOS (mo)	Log-rank
Tagraxofusp	10	68.5 (40-77)	<0.001	6/10 (60%)	0.013	7/10 (70%)	0.04	88%	20.8	0.07
ALL	14	45 (20-72)		11/12 (92%)		8/13 (62%)		74%	50.7	
Hyper-CVAD	14	45 (20-72)		11/12 (92%)		8/13 (62%)		74%	50.7	
AML	19	69 (31-80)		14/19 (74%)		6/18 (33%)		58%	14.2	
Intensive HMA+Venetoclax	9	64 (31-77)		8/9 (89%)		4/8 (50%)		57%	12.4	
Other	8	69 (65-80)		5/8 (63%)		2/8 (25%)		50%	14.0	
	2	73 (72-74)		1/2 (50%)		0/2 (0%)		—	—	
Lymphoma	6	78 (49-85)		2/4 (50%)		1/6 (17%)		67%	17.4	
CHOP	5	78 (49-85)		2/4 (50%)		1/5 (20%)		60%	24.9	
Other/unspecified	1	77		0/0†		0/1 (0%)		—	—	
Other	4	70 (63-94)		0/4 (0%)		0/4 (0%)		25%	10.0	

Age is presented as median (range). CR and HCT are presented as n/N (% of evaluable cases), where N is the number of patients evaluable for that endpoint. ANOVA (age), chi-squared (Chi Sq; CR), Fisher's exact test (HCT), and log-rank (OS) p-values compare the five parental regimen categories only (tagraxofusp, ALL, AML, lymphoma, or other regimen); sub-regimens are shown descriptively and were not independently tested. †Not evaluable for CR (0 of 0 evaluable). Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANOVA, analysis of variance; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; HCT, hematopoietic cell transplantation; HMA, hypomethylating agent; mo, months; mOS, median overall survival; OS, overall survival; y, years; 1y OS, 1-year overall survival.

Supplementary Table 2. Frequency and variant allele fraction of somatic mutations identified by next-generation sequencing (n=23).

<i>Variable</i>	<i>Units</i>	<i>Value</i>	<i>N</i>	<i>Range / %</i>	<i>Summary</i>
<i>Mutation Stats</i>					
<i>Number</i>	<i>Median (range)</i>	3	24	0-7	3 (0-7)
<i>Mutations</i>					
<i>ASXL1</i>	<i>Number (%)</i>	14	23	60.9	14 (61%)
<i>CBL</i>		2	23	8.7	2 (9%)
<i>CEBPA</i>		0	23	0.0	0 (0%)
<i>DAXX</i>		0	23	0.0	0 (0%)
<i>ETV6</i>		2	23	8.7	2 (9%)
<i>EZH2</i>		1	23	4.3	1 (4%)
<i>FLT3</i>		0	23	0.0	0 (0%)
<i>GATA2</i>		0	23	0.0	0 (0%)
<i>IKZF3</i>		0	23	0.0	0 (0%)
<i>JAK2</i>		3	23	13.0	3 (13%)
<i>KIT</i>		0	23	0.0	0 (0%)
<i>KRAS</i>		1	23	4.3	1 (4%)
<i>MPL</i>		0	23	0.0	0 (0%)
<i>NF1</i>		1	23	4.3	1 (4%)
<i>NOTCH1</i>		0	23	0.0	0 (0%)
<i>NRAS</i>		7	23	30.4	7 (30%)
<i>PHF6</i>		1	23	4.3	1 (4%)
<i>PTPN11</i>		1	23	4.3	1 (4%)
<i>RUNX1</i>		1	23	4.3	1 (4%)
<i>SF3B1</i>		1	23	4.3	1 (4%)
<i>SH2B3</i>		0	23	0.0	0 (0%)
<i>SRSF2</i>		7	23	30.4	7 (30%)
<i>TET2</i>		18	23	78.3	18 (78%)
<i>TP53</i>		1	23	4.3	1 (4%)
<i>ZRSR2</i>		4	23	17.4	4 (17%)

Mutation status (number and percentage positive) and variant allele fraction (median, range) for 25 genes assessed by targeted NGS panel at diagnosis. Denominators reflect all NGS-tested patients (n=23) for mutation frequency; VAF summary statistics are calculated only among mutation-positive cases for each gene, and denominators vary accordingly (see N column).