

Review

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Review

Blastic Plasmacytoid Dendritic Cell Neoplasm in the Era of Targeted Therapies

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Abstract

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare myeloid malignancy, characterized by the involvement of multiple organs, including skin, bone marrow and blood, lymph nodes and central nervous system. According to tumor location, the disease is classified as skin only, systemic only and skin and systemic. The cutaneous manifestations of disease are typical and are represented by violaceous single tumors or multiple plaques present in sun-exposed cutaneous areas. BPDCN is issued from the malignant transformation of dendritic cell progenitors and is immunophenotypically diagnosed by the classical immunophenotypes CD123, CD4 and CD56 in addition to specific membrane markers of plasmacytoid dendritic cells. BPDCN is an aggressive disease and is associated with a short survival. Upfront therapies involve either chemotherapy regimens in fit patients and CD123-targeted therapies, including interleukin-3 conjugated with diphtheria toxin (Tagraxofusp, SL-401) or Pivekimab sunirine an anti-IL-3R-drug conjugate, for both fit and unfit patients. Targeted treatments limit the toxicities of chemotherapy and allow the bridging of a consistent proportion of patients to hematopoietic stem cell transplantation, the only treatment associated with potential long-term survival.

Keywords: Blastic Plasmacytoid Dendritic Cell Neoplasm; targeted therapy; Myeloid Neoplasia; interleukin-3 receptor; drug-conjugated peptides; drug-conjugated antibody

1. Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy. Initially it was considered as a form of lymphocyte-derived cutaneous lymphoma and called CD4⁺/CD56⁺ hematodermic tumor and agranular CD4⁺ NK cell leukemia. However, subsequent studies have shown that the disease is originated from plasmacytoid dendritic cells rather from lymphocytes and in 2016 World Health Organization designated BPDCN as a separate category of myeloid malignancies [1].

BPDCN is an aggressive hematologic malignancy with features of cutaneous lymphoma, related to malignant plasmacytoid dendritic cells in blood and bone marrow [2]. At more advanced stages, malignant dendritic cells may infiltrate other tissues, including liver, spleen, lymph nodes, central nervous system and other tissues [2].

BPDCN is a very rare disease representing <1% of all acute leukemias and cutaneous lymphomas. It was estimated an incidence rate of approximately 0.04 to 0.05 cases per 100,000 individuals in the United States; 1,000 to 1,400 new cases are estimated to occur annually in the USA and Europe combined [3]. BPDCN primarily affects older adults, with a median age at diagnosis between 62 and 70 years; there is a significant male predominance, with a male-to-female ratio comprised 3:1 to 5:1 [3]. BPDCN has a bi-modal distribution with one peak affecting children, adolescents and young adults (peaking around 20 years) and a second more frequent peak in older adults (peaking around 65-70 years) [4,5]. Pediatric cases are rare and usually present with a different clinical picture than adult cases [5].

The initial presentation of BPDCN is variable and may be localized only at skin (skin-only) or only systemic (systemic-only) or mixed (systemic plus skin) [6]. The localization at the level of the skin, under form of deep purple tumors or plaques single or disseminated, is very frequent (80-95%) either alone or in association with systemic disease (50% of cases); systemic-only disease is more rare (10-20% of cases) [6].

Recent studies have contributed to a better understanding of the pathogenesis of BPDCN and have shown some improvements in the treatment of this aggressive tumor. Here, these studies are reviewed and critically analyzed.

2. Immunophenotypic Features of BPDCN

BPDCN is characterized by a specific immunophenotype, usually positive for CD4, CD56, CD123, HLA-DR and TCF4. Frequently, it is also positive for TCL1 and lacks lineage-specific markers of T-cells, B-cells or myeloid cells [7]. According the the WHO classification, positive markers for BPDCN are CD123, TCF4, TCL1, CD303, CD304, CD4 and CD56; negative markers are CD3, CD14, CD19, CD34, lysozyme and myeloperoxidase [1].

According to WHO 2022, standard immunophenotypic diagnostic criteria imply: (i) expression of CD123 and of one of these other markers of pDCs (TCF4, TCL1, CD303 or CD304); (ii) expression of any of these three markers and absence of all the expected negative markers [8]. (Table 1)

Table 1. Immunophenotypic diagnostic criteria in BPDCN, according to WHO 2022.

Expected positive expression	Expected negative expression
CD123*	CD3
TCF4*	CD14
TCL1*	CD19
CD303*	CD34
CD304*	Lysozyme
CD4	Myeloperoxidase
CD56	
Immunophenotypic diagnostic criteria:	
- Expression of CD123 and one other pDC marker (*) in addition to CD4 and/or CD56.	
- Expression of 3 pDC markers and lack of expression of all expected negative markers.	
Additional diagnostic criteria can be based also on SOX4/TCF4 and SOX4/CD123 positivity.	

At immunophenotypical level is important to distinguish BPDCN cells from reactive pDCs. An extensive flow cytometric analysis showed that BPDCN can be distinguished from reactive pDCs for CD56 expression, decreased/negative CD38, positive CD7, negative CD2, increased HLA-DR, and decreased CD123 expression [9]. Dual TCF4 and CD123 is highly sensitive and specific BPDCN with 100% of positivity in all cases analyzed [10]. Furthermore, the immunohistochemical combination SOX4/CD123 distinguishes BPDCN, including also cases CD56⁺ BPDCN, from reactive PDCs and other dendritic neoplasms [11]. Thus, the combinations of TCF4/CD123, TCF4/CD56 and SOX4/CD123 are very useful for BPDCN diagnosis and for monitoring minimal residual disease (MRD) [11].

A large retrospective analysis involved 297 BPDCN patients analyzed for their clinical and immunophenotypical features, with an immunohistochemical report in 236 cases; most patients were males (78%), 75% had bone marrow involvement (>5% BPDCN blasts), peripheral blood (62%), skin (82%), lymphadenopathy (49%), CNS (29%) [11]. Immunohistochemistry and flow cytometry analyses showed positivity for CD123, CD4 and CD56 in almost all samples [12].

3. Genetic Alterations in BPDCN

BPDCNs display a consistent number of genetic alterations, resembling at some extent those observed in myeloid malignancies, particularly molecularly defined secondary AMLs [2].

Epigenetic modifiers are frequently mutated in BPDCN and their alterations play a relevant role in the pathogenesis of this malignancy. Genes involved in DNA methylation (*TET2* and *IDH2*), chromatic accessibility (*ARID1A*, *SMARCA1*), histone methylation (*ASXL1*) and histone demethylation (*KMD4D*) are frequently mutated in BPDCN [13]. *TET2* is the gene most frequently mutated in BPDCN (being mutated in >50% of cases) and its mutations play a relevant role in the pathogenesis of this malignancy [14,15]. The molecular characterization of *TET2* mutations occurring in BPDCN patients showed that truncating mutations (stopgain, frameshift or spice) predicted a worse outcome in BPCDN patients compared to missense *TET2* mutations [15].

A fundamental study by Shimony and coworkers evaluated the association between *TET2* and *RAS* mutations with organ involvement in adults with BPDCN [6]. According to organ involvement, 66 BPDCN patients were classified as skin only, systemic plus skin and systemic-only. Patients with skin only BPDCN were more frequently aged ≥75 years, had higher UV exposure, had lower complex karyotypes (0% vs 32%, respectively) and mutated *NRAS* (0% vs 29%) [6]. Conversely, those without skin involvement had lower UV exposure, fewer *TET2* mutations (33% vs 72%) [6]. (Table 2) Median OS was 23.5, 20.4 and 17.5 for skin only, systemic plus skin and systemic only, respectively [6]. Finally, the overt BM involvement (>5% BPDCN cells) was associated with poor OS compared to microscopic BM involvement (<5% BPDCN cells) [6].

Table 2. Age, UV-exposure, chromosome abnormalities and mutational profile in BPDCN patients with different organ involvement.

	Skin-only	Systemic plus skin	Systemic-only
UV-exposure	High	High	Low
Complex karyotype	Absent	Present	Present
<i>TET2</i> mutations	Frequent	Frequent	Rare
<i>NRAS</i> mutations	Absent	Frequent	Frequent
<i>ASXL1</i> mutations	Frequent	Frequent	Frequent
Age ≥75 years	Frequent	Rare	Rare

A key study by Griffin et al. clarified the fundamental role of *TET2* mutations in the pathogenesis of BPCDN skin lesions [16]. A preceding study by Khanlari and coworkers provided evidence that bone marrow clonal hematopoiesis is highly prevalent (65% of cases) in BPDCN and frequently shares a clonal origin as evidenced by 77% of shared *TET2* mutations [17]. In BPDCN, in the bone marrow, clonal progenitors can undergo malignant transformation to acute leukemia or differentiate into immune cells that contribute to disease pathology in peripheral tissues. Outside the marrow, these clones are exposed to a variety of tissue-specific mutational processes. In BPDCN, sun exposure of plasmocytoid dendritic cells and committed precursors causes the development of skin tumors and the acquisition of loss-of-function mutations in *TET2*, the most common premalignant alteration in BPDCN, confers resistance to UV-induced cell death in plasmocytoid dendritic cells, thus pathogenetically contributing to their malignant transformation [16].

It is important to note that *TET2* mutations in BPDCN are biallelic, whose frequencies are higher in BPDCN than in other myeloid malignancies [18]. Frequently, *TET2* mutations are associated with *ASXL1* mutations [18].

IDH1/IDH2 mutations are observed in 5-10% of BPDCN patients and are mutually exclusive with *TET2* mutations; the presence of *IDH* mutations is important for their possible targeting using *IDH* inhibitors.

RAS signaling pathway mutations, including *NRAS*, *KRAS* and *PTPN11*, are frequent in BPDCN and drive rapid cellular proliferation. *RAS* mutations are specific of BPDCN and are usually not observed in preleukemic clonal hematopoiesis [17].

Mutations of RNA splicing factors *SRSF2*, *ZRS2*, *U2AF1* and *SF3B1* are often observed in BPDCN patients. Loss of function mutations of *ZRS2*, an X chromosome gene encoding a splicing factor, are enriched in BPDCN and almost all cases occur in males [19]. BPDCN-associated *ZRS2* mutations impair apoptosis and promote expansion of pDCs and predispose to leukemic transformation of these cells [19].

Mutations in tumor suppressor genes, such as *TP53*, *ATM* and *RB1*, are observed in a minority of BPDCN patients.

Mutations and deletions of transcription factors, such as *IKZF1* (*Ikaros*) and *ETV6* are frequently observed in BPDCN patients. In a series of 10 BPDCN patients, 20% of cases of *IKZF1* gene inactivation through structural rearrangement, focal inactivation or gene fusion were observed [20]. *IKZF1* gene inactivation may favor BPDCN development promoting cell growth [20].

Two types of recurrent chromosomal rearrangements are observed in BPDCN: about one-third of patients harbor a rearrangement of the *MYC* locus at 8p24, most frequently a translocation t(6;8) with 6p21; about 20-30% of patients with BPDCN display rearrangements generating fusions of the transcription factor *MYB* with several recurrent partners. Suzuki et al. analyzed 14 BPDCN patients, 5 pediatric and 9 adult patients: 100% of pediatric patients displayed *MYB* fusions as the unique genetic alteration; 4/9 adult patients showed *MYB* fusions, associated with the typical BPDCN mutations [21]. The most frequent gene fusions observed in these patients were *MYB/PLEKH01*, *MYB/ZFAT*, *MYB/DCPS* [21]. An experimental study in part elucidated the role of BPDCN *MYB* fusions in disease pathogenesis through a shift of *MYB* function from a regulator of CD lineage genes to a regulator of G2/M cell cycle control genes: *MYB* fusions greatly increase the DNA binding at these gene locations resulting in an uncontrolled gene expression and cell growth; furthermore, *MYB* fusions impair DC differentiation [22]. Rearrangements of *MYC* gene locus determine the location of *RUNX2* regulatory regions upstream of *MYC* and drive its high expression promoting, in cooperation with *TET2* gene mutations, dendritic-like leukemia in mice [23].

Cytogenetic abnormalities are commonly observed in BPDCN. Particularly, BPDCN is frequently characterized by the occurrence of major deletions involving chromosome 5q (loss of *CDKN1B* and *ETV6*); chromosomes 13q13-q21 (loss of the *RB1* gene); chromosome 6q23-qTER frequently observed in BPDCN patients. As above underlined, complex karyotype alterations are exclusively observed in BPDCN with systemic tumor location [6].

4. BPDCN with Prior of Concomitant Hematologic Malignancy

A unique feature of BPDCN is that it frequently occurs concurrently with or evolving from another myeloid neoplasm such as chronic myelomonocytic leukemia (CMML) or myelodysplastic syndrome (MDS) and may be diagnosed concurrently or asynchronously. In a group of 87 adult BPDCN patients, Pemmaraju et al. observed that 20 patients (23%) presented as BPDCN with prior or concomitant hematologic malignancy (PCHM): 9 with MDS, 5 with CMML, 3 with myelofibrosis, and 3 with lymphoid/myeloma (1 T-ALL, 1 Hodgkin lymphoma and 1 multiple myeloma) [24]. No significant differences were observed at clinical and genetic level between the group of BPDCN patients with or without PCHM [24].

Some case report studies have displayed separated NGS analysis on BPDCN and CMML samples from patients who developed BPDCN after a prior history of CMML; these reports showed a shared genetic clonal origin and distinct clonal evolution of BPDCN and CMML [25–27]. Interestingly, the analysis of paired samples of a single patient with BPDCN transformation from an underlying CMML showed the common origins of CMML and BPDCN and the biallelic inactivation of the retinoblastoma gene (*RB1*) associated with transformation of CMML to a BPDCN [27]. Interestingly, islands of CD123^{high} cells were commonly observed in the bone marrow of patients with CMML; these cells display *Ras* pathway mutations as well as monocytic leukemic cells [28].

The analysis of patients with concomitant BPDCN and MDS showed that both originated from the same clonal origin known as clonal hematopoiesis, which subsequently evolved to BPDCN by acquiring multiple copy number alterations, including the loss of 13q14 [29].

5. Treatment of BPDCN Patients

The treatment of BPDCN evolved in the time and now in addition to chemotherapy, targeted therapies are also available.

5.1. Chemotherapy-Based Treatments

Two reports of clinical studies from two USA centers showed frequent disease responses in BPDCN patients treated with hyperfractionated Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone (Hyper-CVAD) alternating with Methotrexate and Cytarabine [30,31]. The use of this intensive ALL-type therapy in younger and fit BPDCN patients, particularly in those eligible for hematopoietic stem cell transplantation (HSCT) elicited good results with up to 80% of complete responses (CR) and with an overall survival (OS) around 30 months. Patients who received allo-HSCT had a significantly longer OS compared to those who did not receive transplantation [30].

However, many patients with BPDCN are older and frail and may not be able to tolerate the intensive HCVAD chemotherapy regimen. Thus, intensive chemotherapy regimens are not appropriate for many BPDCN patients with an age over 65 years.

5.2. Targeted Treatments for BPDCN Patients

To bypass this important limitation, a targeted therapy for BPDCN was developed through targeting of CD123, the alpha chain of interleukin-3 receptor (IL-3R α), highly expressed on the membrane of BPDCN cells [32]. To this end, Tagraxofusp (SL-401), a diphtheria toxin (DT) payload fused to recombinant human IL-3, was developed: this agent binds with high affinity to IL-3R and following its binding, the IL-3-DT is internalized and DT is translocated to the cytosol where blocks protein synthesis and induces apoptosis [33].

The DT-IL-3 compound (Tagraxofusp, SL-401) was evaluated in BPDCN patients. Initial phase I/II clinical studies showed an acceptable safety profile of SL-401, with a MTD of 12.5 $\mu\text{g/kg/day}$ and a phase II clinical study showed 84% of ORR, with 59% of CR [34]. In 2019, the results of a phase II clinical study supported the approval of SL-401 for BPDCN patients: 29 patients received SL-401 as first-line treatment and 15 as second-line and third-line of treatment; in untreated patients, 72% achieved a CR and 45% of these patients subsequently underwent HSCT, with a survival rate of 52% at 24 months, while in R/R BPDCN patients the ORR was 67% with an OS of 8 months [35]. The long-term results of this study, extended also to additional patients (65 treatment-naïve and 19 R/R), showed: for treatment-naïve patients, the ORR was 75%, 57% achieved CRc and the median duration of response was 24.9 months; 51% of patients achieving a CR were bridged to allo-HSCT [36].

Post-hoc subgroup analyses of this study helped to better define the impact of SL-401 in BPDCN patients. Of the 65 BPDCN patients treated with first-line SL-401, 21 received HSCT, 17 allo-HSCT and 7 auto-HSCT [37]. For allo-HSCT mOS was 38.4 months and not reached for auto-HSCT [37]. Another post-hoc analysis involved ten patients aged <50 years enrolled in this study; at a median follow-up of 34 months, 2 patients achieved CR, 5 CRc and 1 PR; all these patients were bridged to HSCT (allo-HSCT for 8 and auto-HSCT for 2; 7 of these patients were bridged to HSCT immediately following a SL-401-induced CR and 3 after additional multiagent chemotherapy) [38]. The mOS was 38.4 months for these patients [38]. Findings of this subgroup analysis suggest that SL-401 treatment is safe and effective treatment for younger adults with BPDCN, supporting this drug as the standard of care for all eligible patients with BPDCN [38].

Another post-hoc analysis explored BPDCN patients with different fitness. Responses were observed in patients pertaining to different risk stratification (low-risk, LR; intermediate-risk (IR) and high-risk (HR)): ORR was 80%, 68% and 79%, while CR+CRc was 73%, 59% and 46% among LR, IR and HR, patients, respectively; mOS was 38.4 months, 15.8 months and 11.8 months for LR, IR and HR patients, respectively [39]. 5/15, 10/22 and 6/28 LR, IR and HR patients, respectively were bridged to HSCT and displayed a post-transplant mOS of 38.4 months, NR and NR, respectively [39]. These results showed that SL-401 enabled bridging to HSCT for eligible patients across the entire spectrum

of fitness, including high-risk patients potentially deemed ineligible for intensive cytotoxic upfront regimens [39].

Multiagent intensive chemotherapy regimens used to treat BPDCN carry a high risk of myelosuppression. Thus, a post-hoc analysis evaluated the effect of SL-401 on hematopoiesis [40]. Of the 66 BPDCN patients treated in first line with SL-401, 32 had baseline bone marrow (BM) disease and 34 had no BM disease. Over the course on SL-401 monotherapy treatment hematopoiesis progressively restored to normal values with a restoration of neutrophil levels, a recovery of platelet counts and improvement of hemoglobin levels [40]. By cycle 2 of treatment, all patients displayed peripheral blast clearance regardless of BM status [40].

Real-world results from a European Named Patent Program (ENPP) confirmed the acceptable safety profile and the efficacy of SL-401 in both treatment-naïve and relapsed/refractory BPDCN patients, with a significant rate of patients bridged to HSCT in both groups of patients [41,42].

A recent study evaluated a new agent targeting CD123, Pivekimab sunirine (PVEK), a first-in-class antibody-drug conjugate comprising a high-affinity anti-CD123 antibody with engineered cysteines in the CH3 domain to enable site-specific attachment of an alkylating indolinobenzodiazepine pseudodimer payload (through a cleavable linker) that alkylates DNA and causes single-strand DNA breaks without cross linking [43]. The phase I/II clinical study CADENZA evaluated PVEK in newly diagnosed (ND) and relapsed/refractory (R/R) BPDCN patients [44]. 33 with ND BPDCN: 20 BPDCN alone (de novo) and 13 with BPDCN associated with another myeloid malignancy (de novo and PCHM); 51 with R/R BPDCN [42]. CR+CRc was 75% for de novo BPDCN, 82% for BPDCN + PCHM and 18.8% for R/R BPDCN; mOS was 16.6 months for both de novo BPDCN and de novo BPDCN + PCHM and 5.8 months for R/R BPDCN [44]. Of the total 84 patients, 19 proceeded to HSCT; among patients with CR+CRc the HSCT rate was 52% for de novo BPDCN and de novo BPDCN+PCHM and 29% among R/R BPDCN [44].

Resistance to PVEK, as well as to other antibody-drug conjugates (ADCs) may be related to various mechanisms, such as antigen loss or downregulation, impaired receptor internalization, altered intracellular trafficking and upregulation of drug efflux transporters [45]. A recent study suggested an alternative mechanism of resistance based on the emergence of protective tissue niches capable of sustaining disease persistence after PVEK treatment [46].

5.3. Venetoclax-Based Therapy

A preclinical study based on the evaluation of patient-derived BPDCN xenografts showed a consistent sensitivity to the anti-leukemic activity of the BCL2 inhibitor Venetoclax (VEN) [47]. Furthermore, the treatment of two R/R BPDCN patients showed a significant clinical response [47]. Gangat and coworkers reported a case series of 10 BPDCN patients treated with VEN+hypomethylating agents (HMA), with all patients responding to the treatment (70% CR and 30% PR); however, responses were short-lived and 30% of patients underwent HSCT [48]. Agha and coworkers reported a very remarkable complete and durable response in a patient with large skin and systemic involvement, initially treated with Bortezomib and then treated with VEN [49].

Pemmaraju et al. reported the results on 10 R/R BPDCN patients who received previous chemotherapy or anti-CD123 therapy or both and were treated with VEN-based regimens: 3 with VEN alone; 5 with VEN + Decitabine; 2 with VEN + Azacitidine. The response rate was 60%, including 4 patients who achieved CR/CRc and 2 with partial response; however, the duration of responses was short, ranging from 3 to 6 months [49]. Patients with *TET2* mutations had shorter responses [50].

Two recent studies reported the evaluation of larger sets of BPDCN patients treated with VEN-based regimens. Stein and coworkers reported the results of a retrospective analysis carried out on 47 BPDCN patients treated with SL-401 and 47 BPDCN patients treated with VEN-based regimens (26 with VEN alone and 21 with VEN+HMA) [51]. Median OS was significantly longer in patients treated with SL-401 compared to those treated with VEN regimens (35.3 months vs 10.5 months, respectively); 12-month survival rates were better for SL-401-treated patients than for VEN-treated

patients (72.1% vs 42.8%, respectively) [51]. In patients treated with VEN-based regimens VEN+HMA treatment did not improve responses compared to VEN alone [51].

Lamkin et al. reported the results related to real-world use of VEN+HMA in a group of 14 BPDCN patients (10 with R/R disease) [52]. In R/R patients, ORR was 70%, with a MDS of 10.5 months [52]. Although the response rates in R/R patients were high, many of these patients displayed relapses involving central nervous system or extramedullary disease [52].

Khalife-Hachem et al. retrospectively analyzed data issued from 9 French institutions that treated a total of 12 ND BPDCN patients, not eligible for intensive chemotherapy, with a combination of VEN, Bortezomib and Dexamethasone; the ORR was 100% and all patients achieved a CR or CRc; with a median follow-up of 14.5 months relapse-free survival and overall survival were 8.4 and 9.4 months; at the last follow-up, 50% of patients were still alive, with 4 CR [53].

There is a clear rationale to evaluate the association of SL-401 with VEN-based regimens for the treatment of both AML and BPDCN patients. A phase Ib clinical trial supported the acceptable safety and the efficacy of a triplet regimen based on SL-401, VEN and AZA for the treatment of CD123-positive AML and high-risk MDS [54]. Thus, a recent study reported the results on 27 BPDCN (16 ND and 11 R/R) treated with SL-401, VEN and AZA [55]. Among ND patients 88% of patients achieved CRc and 64% in the R/R cohort; 63% of ND patients went to allo-HSCT and 55% among R/R patients [55]. Median OS was not reached in the ND cohort, with both 1- and 2-year OS of 60%; median progression-free survival in the ND cohort was not reached, with 1- and -year PFS of 58%; in the R/R cohort, median OS was 8.4 months, with 1-year OS of 36% and 2-year OS of 18%; median PFS in the R/R cohort was 6.3 months [55].

6. Conclusions

BPDCN is a rare aggressive myeloid malignancy. Consistent progresses have been achieved in the last three decades concerning the understanding of the cellular and molecular mechanisms underlying BPDCN development and in its treatment.

Some remarkable progresses have been made in the development of targeted treatments of BPDCN, mainly related to the discovery other near-universal overexpression of CD123 in this tumor. Two compounds targeting CD123, Tagraxofusp (SL-401) and Pivekimab sunirine (PVEK) have shown high response rates in the frontline setting, allowing the bridging of a significant proportion of patients to HSCT. Other promising investigational targeted approaches are represented by BCL2 inhibitors and proteasome inhibitors. These new therapeutic strategies may contribute to significantly improve the historically poor outcomes associated with BPDCN.

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