# Blastic Plasmacytoid Dendritic Cell Neoplasm: Emerging Developments and Special Considerations for 2023

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**Abstract:** The field of blastic plasmacytoid dendritic cell neoplasm (BPDCN) is rapidly evolving. Recent clinical developments in this ultra-rare hematologic malignancy have included the emergence of CD123-targeted therapies as the first generation of specific drugs approved for BPDCN. Despite the clinical improvements observed thus far in the CD123-targeted era, many patients still experience relapse and central nervous system (CNS) involvement. In addition, targeted agents for BPDCN are still not widely available around the world, resulting in major unmet medical needs in the BPDCN field. The aim of this review is to describe several emerging clinical concepts and examine special considerations in the field of BPDCN, including: (1) identification of novel markers that aid in clinically distinguishing BPDCN from other related entities; (2) the role of *TET2* mutations in BPDCN; (3) the common occurrence of prior or concomitant hematologic malignancies; (4) the growing recognition of the frequency of CNS involvement in BPDCN and therapeutic strategies for prevention and treatment; (5) the ongoing clinical trials designed to build on the CD123-directed monotherapy backbone by moving the field toward combination therapy with the addition of cytotoxic chemotherapy, hypomethylating agents, BCL2-directed therapies, and central nervous system–directed therapies; and (6) the investigation of newer, second-generation CD123-targeted agents.

Keywords
BCL2, blastic plasmacytoid dendritic cell neoplasm, BPDCN, CD123, CSF, TET2

## Background

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a highly clinically aggressive, ultra-rare hematologic malignancy.[1] The worldwide incidence is largely unknown because of 3 major barriers: (1) the disease is rare, affecting an estimated 500 to 1000 patients per year in the United States; (2) BPDCN has changed names approximately half a dozen times over the past 40 years, further adding to the difficulty in identification and definitive diagnosis; and (3) the diagnostic algorithm and differentiating features between this entity and reactive plasmacytoid dendritic cells (pDCs) or other closely

related malignancies, such as acute myeloid leukemia (AML) with leukemia cutis, have only been recently elucidated.[2,3] One estimate suggests that BPDCN accounts for 0.44% of all hematologic malignancies and roughly 0.7% of cutaneous lymphomas.[4-6] In a recent study according to the Surveillance, Epidemiology, and End Results database, the authors estimated that the US incidence of BPDCN is approximately 0.4 cases per 100,000.[7] Notably, BPDCN is much more common in men than women.[8] After a series of many nomenclature and classification changes,[9,10] most recently in 2022, the World Health Organization has reclassified BPDCN under the category of dendritic cell and histiocytic neoplasms, under the subheading of plasmacytoid dendritic cell neoplasms.[11]

Outcomes in BPDCN historically have been poor around the world, with most groups reporting a median overall survival (OS) of less than 2 years.[4,12] One of the main clinical problems with BPDCN is that regardless of its initial clinical presentation (skin-only, bone marrow, or lymph node) and regardless of therapy, patients have experienced dismal outcomes.[4,5,13] Historically, patients have been treated with multiagent chemotherapy regimens, including AML-based,[14] acute lymphocytic leukemia (ALL)-based,[15] or lymphoma-based approaches.[16] However, the disease can transform to an acute leukemia state or patients can experience multiorgan failure or fatal infections, particularly in an a largely older and frail population with comorbidities, leading to very low rates of survival in the relapsed/refractory (R/R) setting.[12,16,17] Therefore, new research and novel approaches are urgently needed in BPDCN.[5,18] In this review, we aim to describe several emerging newer concepts and special clinical considerations that may have a large effect on patient care and future directions in the BPDCN field.

## Distinguishing Between BPDCN and AML With Leukemia Cutis and Other Related Entities

Several emerging diagnostic tools and newer markers, including flow cytometry and immunohistochemistry, are aiding in the recognition and diagnosis of BPDCN, as well as distinguishing between BPDCN and other related entities.[19] In addition to checking for the traditional markers of CD4, CD56, and CD123, checking for T-cell leukemia/lymphoma protein 1 (TCL1) has added specificity to the diagnosis of BPDCN and helps to differentiate it from AML with skin involvement.[20] Further markers that improve the clinical specificity have been added to the clinical workup, including TCF4[2] and CD303.[21] Newer markers, such as SRY-box transcription factor 4 (SOX4) by immunohistochemistry, have recently demonstrated being able to assist in confirming a diagnosis of BPDCN vs reactive pDCs.[3] Importantly, a novel entity known as pDC-AML has recently been[22] proposed to be distinct from BPDCN and AML. This entity is characterized by frequent occurrence of *RUNX1* mutations, increased incidence of skin lesions compared with standard AML, and worse OS.[23,24] Therefore, it will be critical to work closely with expert pathology teams (both hematopathology and dermatopathology) moving forward to help improve diagnostics and distinguish among the various pDC and CD123-positive entities, including reactive pDC states, chronic myelomonocytic leukemia (CMML) with pDC involvement, BPDCN, AML with leukemia cutis, and pDC-AML.[18,19,25]

## Optimization of Novel Therapies Focused on CD123-Directed Inhibition

Frankel and colleagues[26] and Pemmaraju and colleagues[12] have conducted clinical trials investigating tagraxofusp (Elzonris, Stemline), also known as SL-401 or TAG, specifically for patients with BPDCN. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the dose that the trial by Pemmaraju and colleagues identified as the target dose: 12 μg/kg intravenously daily for 5 days, in December 2018 and January 2021, respectively. Additionally, several important therapeutic monitoring parameters are provided in the package insert as per the clinical trial, including monitoring for capillary leak syndrome (CLS).[27,28] Tagraxofusp represents the first CD123-targeted agent approved in the field of hematology/oncology and the first agent approved specifically for BPDCN.[29]

More recently, the approximately 3-year follow-up data from the 2019 clinical trial by Pemmaraju and colleagues were published.[12,30] In this longer-term follow-up of the original clinical trial, which included a fourth stage of patients, no new or unexpected safety signals were revealed. Among the frontline patients (n=65), the vast majority were male (80%) and 92% had skin involvement. In addition, the complete response (CR)/clinical CR rate was 57%, the overall response rate was 75%, and 32% of patients were bridged to stem cell transplant (SCT) among the 65 frontline-treated patients. The median duration of CR/clinical CR was 24.9 months. The median duration of follow-up was 34 months and the median OS probability at 24 months was 40%.[30]

### *Capillary Leak Syndrome*

The occurrence of CLS remains one of the most clinically important risks for patients and health care providers to be aware of regarding tagraxofusp.[31] CLS has been seen throughout oncology for decades, including in the setting of cytotoxic chemotherapy, SCT, and several other novel agents, including those that include bacterial toxins such

as denileukin diftitox and moxetumomab (Lumoxiti, AstraZeneca).[32-34] CLS is potentially fatal. It occurs at all grades (1-5) in approximately 18% to 20% of patients who receive tagraxofusp, with the majority of cases being low-grade. However, with education, awareness, prevention, monitoring, and treatment, CLS is a better-recognized and better-managed phenomenon.[12,26,28,35] Alfayez and colleagues[28] have published an algorithm for tagraxofusp that can be used along with the package insert. Recently, a successful case was published featuring a young patient treated with a tagraxofusp-based therapy for newly diagnosed BPDCN. In the first cycle, the patient experienced myocardial edema that resulted in shortness of breath and the need for supplemental oxygen. Cardiac magnetic resonance imaging showed such profound cardiac edema that it mimicked an infiltrative process such as cardiac amyloidosis; instead, it was found to be edema in the setting of CLS. The patient received intensive fluid diuresis in the hospital setting and made a full recovery. The patient experienced no permanent cardiac or pulmonary damage and was able to be successfully re-challenged with tagraxofusp. The patient experienced a CR, underwent subsequent allogenic SCT and was alive and well 3 years later. This case illustrates the concept that early identification and early management of CLS can be lifesaving and permit the ability to rechallenge and proceed with curative-intent therapy for patient with BPDCN.[35]

## Targeting CD123 Beyond Tagraxofusp: Pivekimab Sunirine

Several other approaches to targeting the surface marker of CD123 have been investigated.[36,37] One notable agent is the novel CD123-targeting antibody-drug conjugate pivekimab sunirine, also known IMGN632.[38-40] The activity of IMGN632 in R/R BPDCN was established using patient-derived xenograft model systems, which demonstrated that the drug lowered tumor burden in bone marrow and led to increased lifespan in animal models.[34] Daver and colleagues[41] and Pemmaraju and colleagues[42] have presented the results of clinical trials with IMGN632 in both AML and BPDCN at several American Society of Hematology annual meetings between 2020 and 2022.[43] In a study of 29 patients with R/R BPDCN who had a median age of 72 years (range, 19-82 years) and were 76% male, with 45% having prior tagraxofusp exposure and 24% having had a prior SCT, the overall response rate to IMGN632 monotherapy was 29% (31% among patients with prior tagraxofusp treatment).[42] Importantly, there were no cases of CLS, no drug-related discontinuations, and no mortality at 30 days. Toxicities were generally manageable. The most common grade 3 or higher adverse events were hyperglycemia, febrile neutropenia, and thrombocytopenia, each occurring in approximately 10% of patients. There were 2 liver-related events, including a grade 3 elevation in liver function tests that resolved and a grade 3 hyperbilirubinemia that resolved, with the patient going on to SCT. Based on these data, the FDA granted this agent Breakthrough Therapy designation. The frontline clinical trial is active and enrolling patients at both US sites and European sites (NCT03386513).[18]

Additional modalities targeting CD123 and beyond, such as bispecifics, chimeric antigen receptor T-cell therapy, and other immunomodulatory approaches are actively being investigated in both preclinical and early phase clinical trials in the BPDCN field.[21,36,44-48]

### *BCL2 Inhibition in BPDCN: Monotherapy and Combination Approaches*

Targeting BCL2 has been extensively investigated in patients with both myeloid and lymphoid malignancies.[49,50] After the FDA approval of venetoclax in chronic lymphocytic leukemia (CLL) in 2016, investigators explored this agent in combination with other agents in both CLL and AML, demonstrating the clinical feasibility of venetoclax-based combination approaches.[51,52] In a study by Montero and colleagues, BPDCN was found to express high levels of the antiapoptotic protein BCL2 in preclinical models and was dependent on this protein.[53] Furthermore, 2 older patients in this study with R/R BPDCN received venetoclax monotherapy, and both experienced a transient clinical benefit.[53] These efforts led to a formal phase 1 clinical trial, which ultimately led to combination studies of doublets and triplets of venetoclax with both hypomethylating agents and cytotoxic agents combined with CD123-targeted agents.[54]

A retrospective case series was conducted at the MD Anderson Cancer Center and the Mayo Clinic, led by Gangat and colleagues, to investigate venetoclax-based approaches in the nonclinical trial setting.[55] In this case series, 10 unfit BPDCN patients with a median age of 70 years (range, 20-88 years) and multiple comorbidities were treated in an off-protocol setting with various forms of hypomethylating agents plus venetoclax. This included 3 patients treated with azacitidine plus venetoclax; 3 patients treated with decitabine for 5 days plus venetoclax; and 4 patients treated with decitabine for 10 days plus venetoclax. All 10 patients experienced a response, with some responses being transient. The analysis included 2 patients who were ultimately bridged to allogeneic SCT, representing a feasible way to deliver therapy to an older unfit patient population with comorbidities in a community setting, especially in the absence of CD123-based approaches.[55]

Additional venetoclax combinations for BPDCN have included multiagent cytotoxic chemotherapy. A study

**Table.** Selection of Clinical Trials and Investigational Studies in the BPDCN Field

| Study | Identifier |
|---|---|
| Study of venetoclax, a BCL2 antagonist, for patients with BPDCN | NCT03485547 |
| Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) International Registry | NCT05430971 |
| Tagraxofusp in treating patients with BPDCN after SCT | NCT04317781 |
| Venetoclax, SL-401, and chemotherapy in treatment of BPDCN | NCT04216524 |
| SL-401 in combination with azacitidine or azacitidine/venetoclax in AML, MDS, or BPDCN | NCT03113643 |
| Trial to evaluate the safety and efficacy of MB-102 in patients with BPDCN | NCT04109482 |
| Combination chemotherapy in patients with newly diagnosed BPDCN (LpDessai) | NCT03599960 |
| Genetically modified T-cell immunotherapy in treating patients with R/R AML and persistent/recurrent BPDCN | NCT02159495 |
| Study of IMGN632 in patients with untreated BPDCN and R/R BPDCN | NCT03386513 |
| Venetoclax and decitabine in treating participants with R/R AML or relapsed high-risk myelodysplastic syndrome | NCT03404193 |
| Tagraxofusp in patients with CD123+ or with BPDCN-IPh-like AML | NCT04342962 |

Source: ClinicalTrials.gov, accessed March 2023.

AML, acute myeloid leukemia; BPDCN, blastic plasmacytoid dendritic cell neoplasm; IPh, immunophenotype; MDS, myelodysplastic syndrome; R/R, relapsed/refractory; SCT, stem cell transplant.

by Pemmaraju and colleagues showed that in 3 patients treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) plus venetoclax (1 in the frontline setting and 2 in the R/R setting), all were able to achieve a CR with full count recovery and were able to proceed to allogeneic SCT.[56] The feasibility and efficacy of this approach have led to a formal phase 2 clinical trial for a comprehensive treatment program for patients with BPDCN, which includes tagraxofusp in combination with hyper-CVAD (or mini-CVD, which omits the anthracycline) and venetoclax. This trial is open to enrollment at MD Anderson (NCT04216524). Additionally, a clinical trial of the triplet combination of SL-401/azacitidine/venetoclax in both the R/R and frontline settings for patients with BPDCN is open and enrolling patients at MD Anderson, City of Hope, and Dana-Farber Cancer Institute (NCT03113643).[6]

### *CNS Involvement in BPDCN, and CNS-Directed Therapy Approaches*

Martin-Martin and colleagues showed that CNS positivity, generally demonstrated by an asymptomatic occult lumbar puncture positive for malignant BPDCN cells in the cerebrospinal fluid (CSF), is observed with greater frequency in BPDCN than in other myeloid malignancies, such as AML, especially at the time of relapse.[57] This study was conducted before the era of CD123-targeted therapy. Building on these results, Pemmaraju and colleagues examined the incidence of CNS positivity based on CSF in BPDCN during the CD123-targeted therapy era. Among 103 patients with BPDCN at MD Anderson, 22% were CNS-positive based on CSF at any time during their BPDCN disease course. Among these 23 patients, approximately half were receiving frontline treatment. Most CNS-positive cases were occult or asymptomatic, not only at the time of relapse but also at diagnosis or in the initial stages of treatment. Further evaluation of the CNS-positive cohort found statistically significant correlations for patients with the following: (1) lower median baseline hemoglobin anemia levels; (2) higher frequency of *TET2* mutations or variants; and (3) bone marrow involvement (96% of the patients with CNS positivity had bone marrow involvement). According to the high rate of CNS involvement, it is recommended that all patients with BPDCN follow an action plan like that of patients with high-risk ALL. The ALL-based approach calls for the delivery of multiple rounds of prophylactic intrathecal (IT) chemotherapy. Although there are no definitive data yet regarding the timing and frequency, one plan that has been implemented in the clinic is to administer 2 lumbar punctures with IT chemotherapy (using alternating cytarabine and methotrexate) for 4 cycles in either the frontline or R/R setting, regardless of whether the patients is enrolled in a clinical trial, CD123 status, or the cytotoxic chemotherapy approach. This is an important area of research in BPDCN, and several other groups have confirmed the high rate of CNS involvement in BPDCN. Studies are warranted to further investigate the timing, frequency, and type of IT chemotherapy to be used in patients with BPDCN. We recommend that IT

chemoprophylaxis of CNS spread will now be routine for BPDCN patients in the curative intent setting.[58-61] Preclinical and translational studies will further investigate the role of the blood-brain barrier in BPDCN treatment, along with the presence and modulation of neural genes and components upregulated by the nervous system.[62,63]

### *Administration of Multiagent Cytotoxic Chemotherapy in BPDCN*

The onset of CD123-targeted therapies has led to a true practice change in the field of BPDCN. However, CD123-targeted monotherapy, in the absence of SCT or other consolidative strategies, is not curative for the majority of patients.[12,15,64,65] Moving forward, CD123-targeted approaches are expected to serve as the backbone for combination therapy. Some of the most developed multiagent regimens now include combination regimens with cytotoxic agents and BCL2 agents, which may be combined with SCT in younger, fit patients. The median age of BPDCN diagnosis is 70 years in most series, which means that most patients are unable to undergo SCT. Further strategies for these patients include optimizing frontline combinations and selecting appropriate salvage therapies in the second line and beyond.[22,65]

Around the world, particularly in the absence of CD123-targeted therapy, one of the most widely used and successful approaches to BPDCN is ALL-based multiagent lymphoid regimens.[15,66,67] There are several important reasons why ALL-based therapy may be beneficial in patients with BPDCN, including: (1) the frequent presence of *IKZF1* inactivation[68]; (2) successful case reports of the use of vinca alkaloids, dexamethasone corticosteroids, and other ALL-based agents and regimens in the treatment of BPDCN worldwide[69]; (3) the success of CNS-directed therapies, including IT chemotherapy; and (4) the presence of terminal deoxynucleotidyl transferase positivity in 20% to 30% or more[16] of patients with BPDCN and the presence of 8q24/*MYC* gene rearrangement in 10% to 20%[70] of patients with BPDCN. All of these factors suggest the potential for a lymphoid-based angle to this truly hybrid disease.[15,71] Among 100 patients treated with BPDCN in one study, 35 received hyper-CVAD–based frontline regimens that included hyper-CVAD alone, hyper-CVAD with venetoclax, hyper-CVAD with bortezomib, and other hyper-CVAD–based regimens. The CR rate in this study was 80%, and the median OS was 28 months. As mentioned above, most of these patients receive multiple lumbar punctures. The typical regimen was 2 lumbar punctures per cycle, alternating between IT methotrexate and IT cytarabine, for 4 cycles, for a total of up to 8 rounds of IT chemotherapy.[66]

A selection of current clinical trials and active investigational studies in the BPDCN field are listed in the Table.

## The Role of SCT in BPDCN

There remains a role for SCT as a curative therapeutic modality for the treatment of patients with BPDCN who are younger or have a better performance status.[72-75] As demonstrated by several groups worldwide, the preference in the field is to offer allogeneic SCT with myeloablative conditioning in first CR when feasible[15,76,77] Additionally, data exist that have demonstrated the role of autologous SCT in certain subsets of patients with BPDCN; this represents a major area of active investigation.[64,78] Future directions in the field will be to better understand and better define the role of SCT, including the timing, autologous vs allogeneic approaches, and optimal conditioning regimens.

## *TET2* Mutations in BPDCN

*TET2* mutations are the most common molecular mutations/variants seen in BPDCN, followed by mutations in *ASXL1*, *RAS,* splicing factors (eg, *ZRSR2*),[8] and *TP53*.[79-81] One of the earlier studies in this area, by Alayed and colleagues, showed that the *TET2* mutation was present in 80% of BPDCN patients using next-generation sequencing with a 28-gene panel.[82] Furthermore, patients with BPDCN were found to have features similar to myelodysplastic syndrome (MDS) or CMML.[82] Since then, further studies have confirmed that *TET2* mutations are common in BPDCN, even in patients with skin-only disease.[83] One recent study by Beird and colleagues demonstrated that the type of *TET2* mutation in BPDCN appears to correlate with OS in BPDCN.[84] Patients with truncating *TET2* mutations (which included nonsense, frame shift, and splice site mutations) had worse OS than those with either missense or wild-type mutations.[84] Furthermore, Pemmaraju and colleagues showed that CSF positivity for CNS spread correlated with a higher incidence of *TET2* mutations/variants.[58] Additionally, the occurrence of clonal hematopoiesis of indeterminate potential (CHIP) is being studied in BPDCN, especially given that patients are generally older at the time of diagnosis (with a median age of 70 years) and that *TET2* is one of the most commonly implicated mutations in CHIP.[85] Moreover, given that the *TET2* mutation occurs in both BPDCN and CHIP, as well as in patients with concomitant prior concomitant MDS or CMML, further studies are warranted to better understand the therapeutic implications of this finding. These studies should consider the role of hypomethylating agent–based combinations in these settings.[8,55,86-88]

### *Prior or Concomitant Hematologic Malignancies in BPDCN*

Increasingly, it is recognized that BPDCN commonly occurs in the setting of prior or concomitant hematologic

malignancies (PCHMs) in approximately 20% or more of cases.[82] MDS and CMML are the most commonly observed PCHMs in BPDCN,[89] and many other hematologic malignancies have been encountered (either at the time of diagnosis or before the diagnosis), including myeloproliferative neoplasms, multiple myeloma, lymphoma, and AML.[90,91] As described above, there are many intersections in this area of research, including the incidence of CHIP, *TET2* mutations, and shared vs divergent clonal evolution in BPDCN that are active areas of investigation.[85,86] One important goal is to understand more about the etiologies of these PCHMs, and to understand their effect on clinical trial enrollment, assessment of disease response, prognosis, and OS, as well as the need for concomitant vs sequential treatment of BPDCN and PCHMs.

## Summary and Future Clinical Directions

The research field of BPDCN and the clinical treatment landscape are rapidly changing. Current frontline BPDCN approaches include CD123-based regimens, cytotoxic chemotherapy regimens, combinations of hypomethylating agents and venetoclax, and SCT in patients who are young, fit, and therefore eligible for SCT. In terms of future directions in the frontline setting, our group and others are planning to formally investigate triplet combinations. These include CD123/BCL2/chemotherapy in younger, fit patients with BPDCN and CD123/BCL2/hypomethylating agents in older, unfit patients. These approaches are being actively investigated in formal clinical trials.

We have identified several emerging areas that have clinical significance in this field. The recognition of the frequency of *TET2* mutations in BPDCN, and the new observation that the type of *TET2* appears to carry prognostic significance, could lead to a new pathobiologic understanding of the disease. We have also increased our awareness of the CNS-positive rate by CSF testing, which is higher than previously thought in BPDCN and higher than in AML. This finding, which has carried over into the targeted therapy era, demonstrates that CD123-directed therapies likely do not cross the blood-brain barrier, suggesting the need to use IT chemotherapy as prophylaxis against CNS spread in all patients with BPDCN. The frequent occurrence of PCHMs in BPDCN, most commonly MDS or CMML, strengthens the need for full staging of all newly diagnosed patients with BPDCN, including bone marrow examination and assessment of molecular mutational profile. The presence of PCHMs also may have implications for treatment, clinical trial enrollment, and even prognosis, and is an area deserving of more research.

Over the next 5 to 10 years, it will be important to create, maintain, and develop networks and consortia to approach BPDCN at the preclinical, clinical, and translational levels at a larger scale. Several recent calls to action have been published with the goal of galvanizing the worldwide BPDCN research community and bringing together key stakeholders in both laboratory research and clinical trials. In the North American BPDCN Consortium, Pemmaraju and colleagues convened a multidisciplinary, multi-institutional group of experts from the United States, Mexico, and Canada that included hematologists/oncologists focusing on leukemia, SCT providers, hematopathologists, dermatopathologists, dermatologists, and pediatric specialists.[18]

In this paper, the authors call for increased awareness of this ultra-rare disease, more research efforts (including coordinated clinical trial networks), and an increase in grants and specific funding opportunities.[18] To identify unmet clinical needs on a broader global scale, European investigators convened an ad hoc international expert panel led by Pagano and colleagues to review future research directions in BPDCN. Of particular importance is the ability to deliver effective therapy to patients in settings where CD123-directed therapies are not available.[5]

### *Disclosures*

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### *Author Contributions*

*Both authors conceived of, wrote, edited, and approved the final draft of this manuscript.*

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