SPOTLIGHT REVIEW ARTICLE

Tagraxofusp for blastic plasmacytoid dendritic cell neoplasm

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Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy that presents with characteristic dark purple skin papules, plaques, and tumors, but may also involve the bone marrow, blood, lymph nodes, and central nervous system. The disease, which commonly affects older men but can also present in children, is associated with a distinct immunophenotype including universal expression of CD123, the α chain of the interleukin 3 receptor. Recently, tagraxofusp, a CD123-targeting drug consisting of the ligand for CD123, interleukin 3, conjugated to a truncated diphtheria toxin payload was approved for treatment of BPDCN. This was the first agent specifically approved for BPDCN and the first CD123 targeted agent in oncology. Here, we review the development of tagraxofusp, and the key preclinical insights and clinical data that led to approval. Tagraxofusp treatment is associated with a unique toxicity, capillary leak syndrome (CLS), which can be severe but is manageable with proper patient selection and monitoring, early recognition, and directed intervention. We outline our approach to the use of tagraxofusp and discuss open questions in the treatment of BPDCN. Overall, tagraxofusp represents a unique targeted therapy and a step forward in meeting an unmet need for patients with this rare disease.

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an uncommon hematologic malignancy whose rarity (<1% of blood cancers), combined with historical confusion regarding the disease's defining clinical and pathologic criteria, resulted in a disorienting series of changes in name and classification over decades.[1-4] BPDCN is now recognized as a unique disease rather than a subtype of the (relatively) more common acute myeloid leukemia (AML). The diagnosis of BPDCN is made by identifying malignant cells (blasts) that express CD123, with CD4 and/or CD56, and at least one other plasmacytoid dendritic cell (pDC) marker (TCF4, TCL1, CD303, CD304), or that express CD123 with any three pDC markers, without T-cell (CD3), B-cell (CD19), or myeloid/monocytic (lysozyme, myeloperoxidase, or CD14) markers.[3] The approval of tagraxofusp, the first agent approved specifically for BPDCN, has made it imperative that hematologists accurately diagnose the disease.

Beyond its rarity and defining immunophenotype (think "123456" for CD123, CD4, CD56), BPDCN is distinguished by an older (median age 65-70 years) and male (male:female ratio approx. 2-5:1) demographic. It has an aggressive clinical course, and involvement of multiple tissue compartments is common. Patients with BPDCN regularly present to a dermatologist with characteristic, dark purple tumors or plaques involving the skin; initially, these are frequently in sun-exposed areas but they can be found throughout the body (Figure 1). Once identified as likely BPDCN, patients should be referred to a hematologist, and further testing often reveals involvement of blood and marrow, lymph nodes, and central nervous system (CNS). Rarely, a patient does not have skin involvement and the disease is recognized after the patient develops symptomatic cytopenias, adenopathy, or constitutional complaints. An additional challenge in the diagnosis of BPDCN is that it may occur concurrent with, prior to, or subsequent to a diagnosis of another myeloid neoplasm such as chronic myelomonocytic leukemia (CMML),

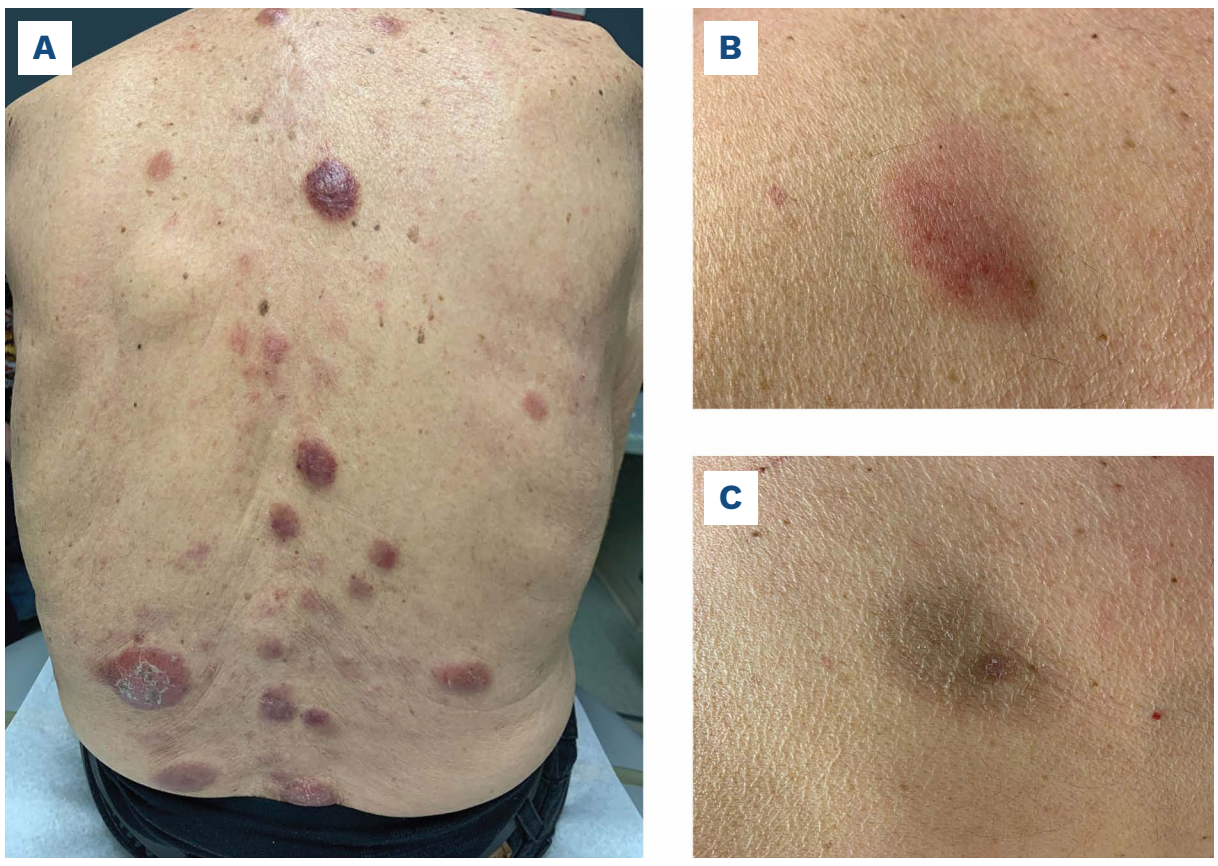

Figure 1. Characteristic blastic plasmacytoid dendritic cell neoplasm lesions and example of a skin lesion achieving complete response with residual skin abnormality not indicative of active disease. (A) Typical skin lesions at the time of diagnosis showing multiple purple bruise-like nodules, plaques, and tumors. (B) Close-up view of a skin lesion prior to treatment. (C) Skin area from panel (B) after two cycles of tagraxofusp, showing a complete response with residual skin abnormality not indicative of active disease. This area of residual hyperpigmentation was biopsied; pathological review showed no overt active disease.

myelodysplastic syndrome (MDS), or AML.[5,6] Co-occurring diagnoses, often confirmed to be clonally related, occur in at least 10% of cases, and may be under-recognized.

Treatment of blastic plasmacytoid dendritic cell neoplasm with chemotherapy

Prior to the approval of tagraxofusp, treatment of BPDCN involved applying a multi-agent chemotherapy regimen developed for AML, acute lymphoblastic leukemia (ALL) or lymphoma.[7-10] Even patients who present with more indolent "skin-only" disease should be offered systemic therapy. In the absence of systemic treatment, the disease invariably advances to a leukemic or lymphomatous phase, although the time to progression is variable.

No chemotherapy regimens have been prospectively compared in patients with BPDCN. However, retrospective studies suggest that acute leukemia regimens, particularly ALL regimens, have superior efficacy.[9-11] Despite this, chemotherapy-treated patients fare poorly due to inherently aggressive, chemo-resistant disease biology combined with an older patient demographic precluding many from receiving optimal treatment intensity. As with older adults treated for AML and ALL, older patients with BPDCN experience high early mortality, modest remission rates (approx. 50%), and a median overall survival (OS) of less than two years due to early treatment failure (refractory disease, early mortality), relapses, and deaths in remission from regimen-related toxicity.[9,12,13] Younger patients who can tolerate intensive conventional chemotherapy regimens may achieve complete remission (CR) more frequently, and are typically offered allogeneic hematopoietic stem cell transplant (allo-HSCT) in first CR (CR1) with long-term remissions regularly demonstrated.[8,9,11,14-19] The role of autologous transplant is not well defined although some series suggest benefit.[20] BPDCN that relapses after any approach is typically refractory and almost never cured.

Given that few patients with BPDCN can benefit from intensive conventional chemotherapy induction approaches and allo-HSCT, BPDCN has long represented a disease with a significant unmet need.

Tagraxofusp: pharmacology and initial experience

The use of diphtheria toxin (DT) as an anti-leukemia immunotoxin has been under investigation since the late 1970s.[21,22] Decades later, in the early 2000s, Frankel *et al*. developed DT-IL-3, a truncated diphtheria toxin fused to recombinant human IL-3 (Figure 2). DT-IL-3 binds with high affinity to the IL-3 receptor (IL-3R), whose α-subunit is also known as CD123, where it is internalized by receptor-mediated endocytosis. The catalytic domain of the DT is cleaved and translocates into the cytosol where it inactivates elongation factor 2 (EF2), which leads to disruption of protein synthesis and apoptotic cell death. This construct was initially investigated in myeloid neoplasms including AML, with the hope that the drug would be effective against leukemia stem cells (LSC), which strongly express CD123.[23,24] In the laboratory, DT-IL-3 efficacy correlated to IL-3R (CD123) density on target cells, but single agent clinical efficacy against MDS

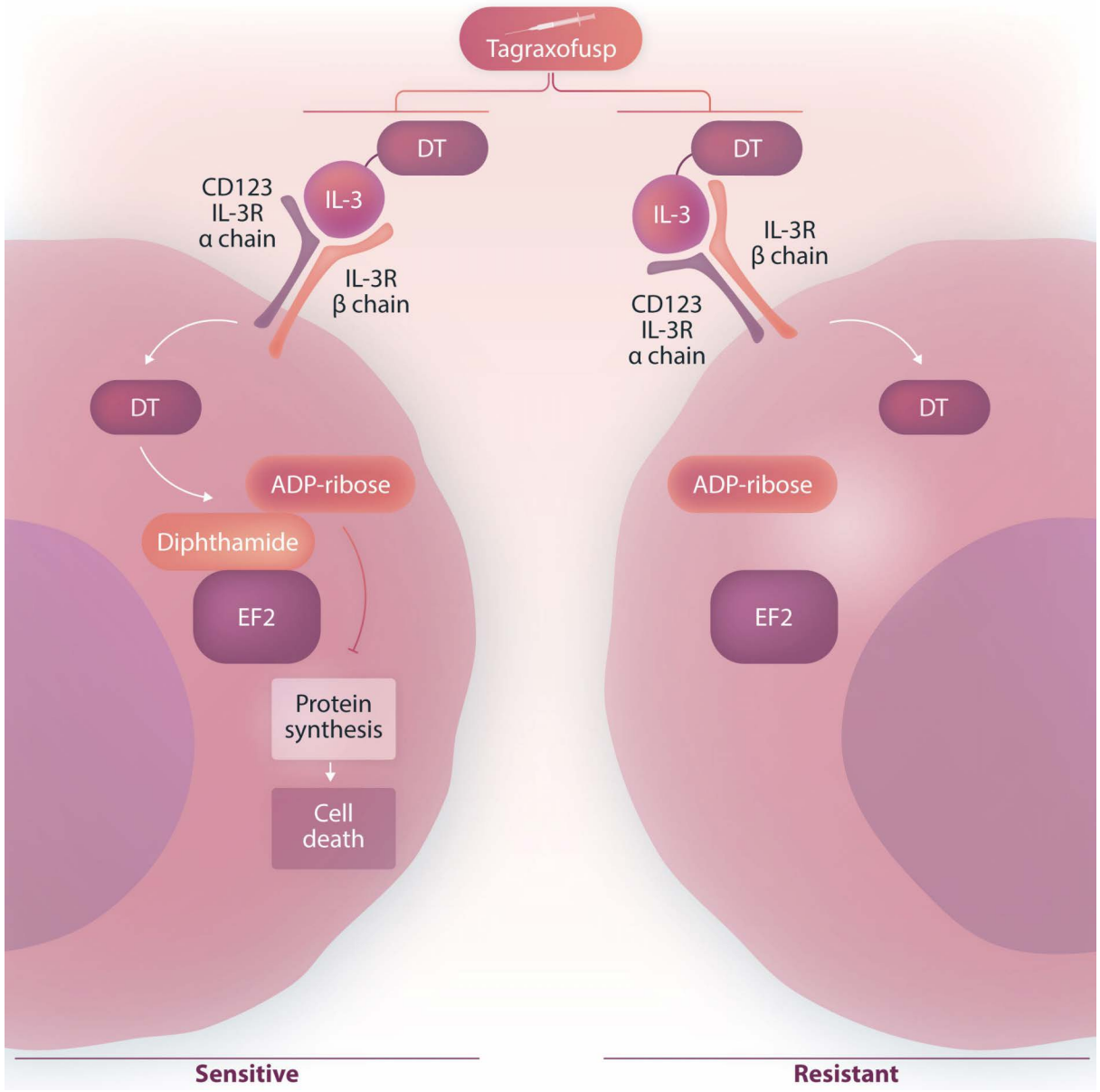

Figure 2. Tagraxofusp mechanism of action and resistance. (Left) Tagraxofusp is a recombinant fusion protein consisting of interleukin 3 (IL3) fused to a truncated diphtheria toxin payload (DT). Tagraxofusp binds to the IL3 receptor, which consists of an α chain (CD123) and a β chain. Upon binding, the drug-receptor complex is internalized, then DT escapes from an endocytic vesicle into the cytoplasm. DT then catalyzes ADP-ribosylation of a modified histidine residue, called diphthamide, on elongation factor 2 (EF2). ADP-ribosylated EF2 inhibits protein synthesis, which causes cell death. (Right) Cells that acquire resistance to tagraxofusp maintain cell surface CD123/IL3R α and β chain expression, drug internalization, and DT cytoplasmic localization. However, due to DNA methylation-mediated silencing of diphthamide synthesis genes, there is no diphthamide target on EF2 in resistant cells. Thus, DT is unable to catalyze ADP-ribosylation of EF2, and cells survive.

and AML was limited.[25-27]

Given that BPDCN cells universally express high levels of CD123, it became an important area of development for DT-IL-3, later re-named SL-401 and then tagraxofusp (TAG).[28] Tagraxofusp had potent *in vitro* and *in vivo* toxicity against BPDCN cell lines, patient-derived BPDCN cells, and mouse models of BPDCN.[23,29] Importantly, in a phase I study of tagraxofusp led by Frankel, 7 of 9 patients with BPDCN (78%) treated with a single course of tagraxofusp at 12.5 μg/kg/day x 5 doses responded (5 achieving CR) with a median duration of response of five months. Although a distinct vascular toxicity, capillary leak syndrome (CLS), occurred in some subjects, the responses and manageable toxicity profile supported further development of tagraxofusp in BPDCN.

Tagraxofusp as a single agent

These pilot data were the basis for the STML-401-0114 multi-stage, multi-center phase I / II clinical trial that administered tagraxofusp in repeating cycles (NCT02113982).[30] Stage 1 was a 3+3 design where escalating doses of tagraxofusp (days 1-5, every 21 days) were administered to patients with both newly diagnosed and relapsed and/or refractory (R/R) disease. No maximum-tolerated dose (MTD) was identified, but 12 μg/kg was tested in the stage 2 expansion phase based on overall review of toxicity and efficacy. Stage 3 was the "pivotal" cohort for untreated patients treated at 12 μg/kg, with the goal of demonstrating sufficient efficacy for registration. Stage 4 provided ongoing access to tagraxofusp in the context of a trial.

Given the risk of CLS, the trial implemented stringent eligibility criteria. Patients were required to be ≥18 years, with Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and have normal hepatic (total bilirubin ≤1.5 mg/dL, ALT/AST ≤2.5x ULN), renal (creatinine ≤1.5 mg/dL), and cardiopulmonary function including normal left ventricular ejection fraction. Notably, a baseline albumin of ≥3.2 g/dL was required for study entry. During stage 1 of the trial, a grade 5 CLS event (death) occurred, which prompted the minimum baseline albumin to be raised from 3.0 to 3.2 g/dL.

Response assessments evaluated all major disease compartments: skin, marrow, lymph nodes, and extramedullary disease. Skin response was evaluated via the modified severity weighted assessment (mSWAT) originally developed for assessment of cutaneous lymphomas, while marrow and lymph node assessment was according to AML and lymphoma criteria.[31-33] Given the frequency of re-

sidual pigment changes with treated skin disease, a new response category called "clinical CR (CRc)" was created to designate patients with persistent skin abnormalities but no clinically significant residual disease (Figure 1B, C). This study did not require assessment of the CNS.

The initial publication reported on 47 patients: 32 without previous treatment (median age 68 years, 81% male) and 15 with previous treatment (median age 72 years, 87% male). The vast majority (94%) had skin disease, with frequent involvement of other compartments: marrow (51%), lymph nodes (45%), blood (17%), and viscera (17%). Among patients with untreated BPDCN who received 12 μg/kg of tagraxofusp (n=29), there was a 90% overall response rate (ORR) and 72% CR/CRc rate (54% CR/CRc rate in the "pivotal" stage 3 cohort), which translated into a 24-month OS of 52% (Table 1). Almost half (45%) of patients proceeded to stem cell transplantation. Responses occurred quickly, after one or two cycles. Responses were less frequent in patients who entered the study with relapsed or refractory disease (ORR 67%).

Long-term follow-up of STML-401-0114, including the stage 4 continued access phase, was recently published, confirming efficacy of tagraxofusp in a larger group of patients (n=84) with longer follow-up (Table 1).[34] Responses were durable (median 24.9 months, 95% CI: 3.9-not reached). The rate of CLS was reported to be 21%, with 7% being grade ≥3. Of note, initial "real-world" clinical practice data from a European expanded access program were recently presented confirming a 67% CR rate (10 out of 15) in previously untreated patients, with a similar safety profile and no deaths related to CLS.[35]

The STML-401-0114 data resulted in US Food and Drug Administration (FDA) approval for tagraxofusp in 2018, for patients aged ≥2 years with newly diagnosed or R/R BPDCN. Tagraxofusp was the first drug approved specifically for BPDCN, as well as the first anti-CD123 drug approved for any indication.[36] The European Medicines Agency followed in 2021 with an approval for first-line treatment in adults. CLS is listed as a "black box warning" on the FDA label.

Key toxicity: capillary leak syndrome

Capillary leak syndrome (CLS) is associated with edema, weight gain, hypoalbuminemia, and cardiovascular instability, and can be rapidly fatal if not recognized and managed properly. Fortunately, with proper patient selection, vigilant monitoring for early identification, and appropriate treatment, CLS has become a manageable toxicity (Table 2).

Patients offered tagraxofusp should meet STML-401-0114 eligibility criteria and demonstrate adequate performance status, organ function, and albumin ≥3.2 g/dL. Interestingly CLS, when it occurs, is an early toxicity occurring almost universally during cycle 1. CLS does not frequently recur. Thus, patients should be admitted to the hospital for administration of the first cycle of therapy to enable increased monitoring and early intervention, while later cycles may be administered in an outpatient setting. The median time to CLS was six days in STML-401-0114, with a median duration of six days. It is prudent to monitor patients in the hospital for 1-2 days after completion of five days of dosing during cycle 1.

Monitoring protocols should include at least daily clinical assessments (including weight), and measurement of albumin and organ function (creatinine, liver function tests) which should be reviewed each day prior to dosing. The expertise of experienced nursing staff is important, and thus safe administration of tagraxofusp requires a multidisciplinary collaboration and training. When there is concern for CLS based on clinical or lab (particularly albumin) parameters, treatment is prompt administration of intravenous (IV) albumin, at least once or twice per day, high-dose IV steroids (methylprednisolone 1-2 mg/kg/day or equivalent), and careful fluid management (often diuresis, but sometimes fluid repletion). If there is any clinically significant CLS, subsequent tagraxofusp doses should be withheld, and likely omitted, in the first cycle. The package insert should be carefully reviewed and followed.

Other common toxicities that typically occur during cycle 1 include transaminitis and mild thrombocytopenia. These

Table 1. Responses for first-line patients with blastic plasmacytoid dendritic cell neoplasm treated with tagraxofusp at 12 μg/kg/day.

	Stages 1-3, N=29	Overall, N=65
CR + CRc	21 (72%)	37 (57%)
Median time to CR + CRc	43 days (range, 14-131)	39 days (range, 14-131)
Bridged to transplant	13 (45%)	21 (32%)
Median duration CR + CRc in months (95% CI) Probability at 24 months, %	NR (5.9-NR) 65	24.9 (3.8-NR) 53
Median OS in months (95% CI) Probability at 12 months, % Probability at 24 months, %	25.8 (9.6-53.9) 62 52	15.8 (9.7-25.8) 55 40

Stage 1-3 is initial dose finding, expansion, and pivotal cohorts.[30] Overall is Stage 1-3 plus a continued access expansion cohort.[34] CR: complete response; CRc: CR with residual skin abnormality not indicative of active disease; CI: confidence interval; OS: overall survival; NR: not reached.

typically resolve quickly and do not recur. Notably, there is no significant myelosuppression or infection risk with tagraxofusp. The reason for tagraxofusp-related toxicity being restricted to cycle 1 is not known.

Resistance to tagraxofusp

Cells that develop acquired resistance to tagraxofusp generally do not lose CD123.[37] Instead, cells develop resistance to diphtheria toxin, which is mediated by DNA methylation-mediated silencing of genes in the diphthamide synthesis pathway (Figure 2). Diphthamide is a modified histidine amino acid on elongation factor 2 (EF2) and is the target for ADP ribosylation by diphtheria toxin. Diphthamide silencing is reversible by azacitidine, and this also reverses tagraxofusp resistance. Furthermore, cells that persist after tagraxofusp treatment have increased apoptotic priming and dependence on the anti-apoptotic protein BCL2. These adaptations promote increased sensitivity to the BCL2 inhibitor venetoclax and to conventional chemotherapy. These data provide a rational basis for ongoing studies that combine tagraxofusp with azacitidine and/or venetoclax (NCT03113643), or with conventional chemotherapy with or without venetoclax (NCT04216524) (Table 3).

Open questions for the use of tagraxofusp in blastic plasmacytoid dendritic cell neoplasm

Much is known about tagraxofusp, its mechanism of action, modes of resistance, toxicity profile, and strategies for proper patient selection and supportive management. However, many questions and challenges still remain regarding the use of this novel therapeutic.

Is tagraxofusp the optimal first-line therapy for blastic plasmacytoid dendritic cell neoplasm?

Although tagraxofusp is the only drug specifically approved for BPDCN, it may not always be the most appropriate first-line therapy. Some patients are not eligible for tagraxofusp due to laboratory derangements (hypoalbuminemia, trans-

Table 2. Tagraxofusp administration: basics.

Patient selection (based on STML-401-0114 eligibility criteria)	Normal hepatic function (Tbili ≤1.5 mg/dL, ALT/AST ≤2.5x ULN) Normal renal function (creatinine ≤1.5 mg/dL) Normal cardiopulmonary function, including normal left ventricular ejection fraction Baseline albumin of ≥3.2 g/dL
Patient age (approval indication)	Adults (US FDA and EMA) Children ≥2 years (US FDA only)
Treatment line	Newly diagnosed (US FDA and EMA) Relapsed, refractory (US FDA only)
Dose and schedule	IV infusion (15 min) 12 μg/kg/day on days 1-5 of a 21-day cycle
Number of cycles	No maximum, continue until progression or transplant
Treatment setting	Cycle 1, inpatient Cycle 2+, outpatient permitted
Pre-medication, for infusion hyper-sensitivity reactions	Corticosteroids, H1 and H2 blockers, and acetaminophen (see package insert)
Monitoring, minimum daily pre-dose	Vital signs, weight (consistent scale), examination (focus on cardiopulmonary status, volume status) Renal function (creatinine), liver function tests (ALT, AST, bilirubin), albumin
Major toxicities	Capillary leak syndrome, transaminitis, thrombocytopenia
Timing of major toxicities	Cycle 1, doses may be delayed up to 10 days for management of toxicities. Omission of subsequent doses recommended in setting of clinically significant CLS
Reasons to withhold drug	ALT, AST >5x ULN (resume when <2.5x ULN) CLS (consider discontinuation until next cycle; see below)
Capillary leak syndrome	
Key features	Edema, weight gain, hypoalbuminemia, cardiovascular instability
Key management tools	IV albumin, to achieve ≥3.5 g/dL or pre-treatment value High-dose IV steroids (at least methylprednisolone 1-2 mg/kg/day or equivalent) Fluid management (often diuresis, but in some cases fluid repletion) Withhold drug, likely for remainder of cycle

STML-401-0114: multi-stage, multi-center phase I / II clinical trial (NCT02113982); Tbili: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: Upper Limit of Normal; US FDA: US Food and Drug Administration; EMA: European Medicines Agency; IV: intravenous; min: minutes; H1/H2: histamine blockers at H1/H2 receptor; CLS: capillary leak syndrome.

Table 3. Select clinical trials in blastic plasmacytoid dendritic cell neoplasm.

Regimen	NCT number (sponsor)
Tagraxofusp combinations	
Tagraxofusp with azacitidine, venetoclax	NCT03113643 (Dana-Farber Cancer Institute)
Tagraxofusp with chemotherapy (hyper-CVAD), venetoclax	NCT04216524 (MD Anderson Cancer Center)
Other CD123 approaches	
IMGN632 (pivekimab sunirine), a CD123 directed antibody-drug conjugate	NCT03386513 (Immunogen)
MB-102, a CD123 auto-CAR T	NCT04109482 (Mustang)

NCT: National Clinical Trial; CVAD: cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride and dexamethasone; auto-CAR T: autologous chimeric antigen receptor T-cell therapy.

aminitis), or tenuous cardiovascular or pulmonary status as a result of high burden, proliferative disease. These patients should receive conventional chemotherapy for urgent disease control. They may be able to receive tagraxofusp later during treatment.

Other patients will never be eligible for tagraxofusp due to baseline, unmodifiable comorbidities such as a low cardiac ejection fraction. These patients may receive less intensive conventional chemotherapy approaches including ALL regimens with dose adjustments or AML-style therapy with a hypomethylating agent (HMA) and venetoclax (VIALE-A regimen).[38] BPDCN cells are uniformly dependent on BCL2 and this translates to high sensitivity to venetoclax.[39]

For patients eligible for either tagraxofusp or conventional chemotherapy, no randomized comparative data exist. Each regimen's toxicities must be considered along with the patient's comorbidities, disease features, and personal preferences, along with the capabilities, preferences, and experience of the treating physician and center. Older patients who may be vulnerable to complications from intensive chemotherapy, particularly myelosuppression, may benefit most from tagraxofusp over other approaches. On the other hand, for younger, fit patients, recent retrospective data generated by investigators at the University of Texas MD Anderson Cancer Center and Moffitt Cancer Center suggest that tagraxofusp and the intensive HCVAD regimen may result in an equivalent CR rate.[8,16] We currently lack clinicopathologic features that predict the likelihood of an excellent response to tagraxofusp *versus* other approaches.

Patients are encouraged to enroll on prospective trials of tagraxofusp, other CD123-directed investigational therapies, chemotherapy, and/or venetoclax (Table 3). The optimal approach may involve combining and/or sequencing multiple active agents to maximize depth and durability of responses. Ideal combination and maintenance therapy might eventually obviate the need for allo-HSCT for cure, although we still recommend prompt transplantation in eligible patients in CR1.

It is important to recognize that tagraxofusp is not approved in all countries or may not be available for other reasons such as expense, lack of infrastructure, or inadequately trained staff for urgent administration. Thus, conventional chemotherapy remains an important treatment for many patients diagnosed with BPDCN even when tagraxofusp might be considered otherwise. Cost and resource barriers to accessing tagraxofusp and other novel treatment approaches will be important considerations in the coming years.

How should the central nervous system be staged and managed in tagraxofusp-treated patients?

It is now recognized that BPDCN, like ALL, commonly involves the CNS at diagnosis and/or at relapse, ultimately affecting up to one-third of patients.[40-42] All patients diagnosed with BPDCN should have CNS assessment and serial intrathecal (IT) chemo-prophylaxis during initial treatment. As tagraxofusp is not known to cross the blood-brain barrier, IT chemotherapy is recommended concurrently with tagraxofusp-based treatment. Although the best approach to management of the CNS in BPDCN has not been established and requires further study, we recommend adopting standards used to prevent and treat CNS disease in patients with high-risk ALL.

How should BPDCN with associated hematologic malignancy be managed?

At least 15-20% of patients with BPDCN have a prior or concurrent diagnosis of MDS, CMML, or AML. As outlined above, the early studies conducted by Frankel suggest that tagraxofusp alone may not be effective treatment for these diagnoses, although this could depend on CD123 expression level or other, yet undetermined, predictive factors. The best approach to these complex situations requires further study. For those with concurrent myeloid neoplasms, HMA and venetoclax-based therapies are attractive in combination with tagraxofusp.

What is the role of measurable residual disease monitoring?

As BPDCN commonly involves multiple compartments (marrow, blood, lymph nodes, skin, and CNS), response assessments must involve imaging (positron emission tomography-computed tomography), bone marrow examinations, cerebrospinal fluid assessments, and detailed skin examinations. An area requiring further study is the clinical rel-

evance and best method to assess measurable residual disease (MRD). Assessing MRD in the skin is particularly challenging as residual pigment changes must be distinguished from active disease (Figure 2B, C). Finally, it is possible that MRD kinetics may be different in patients treated with conventional chemotherapy, tagraxofusp, and combination therapies.

What about CD123-targeted agents under development?

Tagraxofusp was the first drug developed and approved for BPDCN, and the first CD123 targeted agent in oncology. Now, the field is rapidly evolving with other CD123-directed agents under development. The antibody-drug conjugate, IMGN632 (pivekimab sunirine), received US FDA breakthrough therapy designation in 2020 for relapsed or refractory BPDCN based on encouraging early data,[43] and is currently being tested for both newly diagnosed and R/R disease (Table 3). Notably, IMGN632 activity includes patients who previously received tagraxofusp, supporting sequential CD123 therapy and the observation that CD123 expression is often maintained after tagraxofusp. Of note, IMGN632 does not cause CLS, although peripheral edema is reported. As additional CD123-directed agents become available, the relative characteristics of each regarding side-effect profile, route and schedule of administration, cost, ability to combine with other therapeutics, and approved indication, may shift the therapeutic landscape for this disease.

How should tagraxofusp be incorporated into the treatment of children with BPDCN?

The US FDA approval of tagraxofusp includes children ≥2 years, based on activity with no unexpected side-effects in a small series of pediatric patients with relapsed BPDCN.[44] Pediatric BPDCN has similar clinical characteristics at diagnosis as BPDCN in adults, although the genetics differ. Adult BPDCN is characterized by "secondary myeloid-type" mutations (*TET2, ASXL1*, splicing factors), whereas pediatric BPDCN lacks those mutations and instead is enriched for translocations that encode fusions of the transcription factor MYB.[45] Given that pediatric patients with BPDCN respond well to ALL-type chemotherapy,[46] most pediatric oncologists recommend high-risk ALL-type chemotherapy rather than tagraxofusp as initial therapy, and do not recommend allo-HSCT in CR1. The optimal integration of tagraxofusp into treatment of children with BPDCN requires further study.

Summary: how I treat

Blastic plasmacytoid dendritic cell neoplasm is a rare, aggressive leukemia with unique clinical and pathologic features. Most commonly affecting older men, BPDCN can involve the skin, bone marrow, lymph nodes, and CNS. Given the rarity of the diagnosis and unique management considerations, patients should, when possible, be referred to a cancer center with clinical trial availability and with experience in evaluating and managing this disorder. Comprehensive staging and expert hematopathology review are imperative. BPDCN universally expresses CD123, the IL-3 receptor, which is an important therapeutic target. Treatment is systemic, regardless of clinical presentation. In 2023, patients may be treated with tagraxofusp, an IL3-diphtheria toxin conjugate targeting CD123, or a conventional chemotherapy regimen. Novel CD123-directed agents are under development. Consideration of allo-HSCT in CR1 is recommended whenever possible. Treatment selection is dictated by disease features, comorbidities, treatment goals, patient choice, and center expertise. Patients being treated with tagraxofusp require close monitoring for established toxicities including infusion reactions, transaminitis, cytopenias, and particularly for CLS, which all have the highest risk during the first cycle of therapy.

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Contributions

MRL and AAL conceived, wrote, and edited the manuscript.

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