

In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, MD, and sponsored in part by the Charif Souki Cancer Research Fund, we discuss our novel therapeutic approaches for the rare hematologic malignancy, Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN).

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN): Novel Therapeutic Approaches for a Rare Hematologic Malignancy

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) historically has been characterized by poor outcomes. Initial therapy approaches included multi-agent chemotherapy regimens borrowed from acute leukemia or lymphoma. Among these, in our experience, intensive chemotherapy with H-CVAD has shown the best remission rates; however relapses are frequent in the frontline setting and outcomes are poor in the relapsed/refractory setting ([Lee, McCue, Pemmaraju Expert Rev Anticancer Ther. 2020 May 27](#)).

In December 2018, the Food and Drug Administration (FDA) approved tagraxofusp-erzs (formerly DT-IL3, SL-401, Stemline), as the first and only targeted agent for patients with BPDCN ([Hammond D/Pemmaraju N Hematol Oncol Clin North Am. 2020 Jun;34\(3\):565-574](#)). This was also the first approval for a CD123-targeted agent in the field of hematology/oncology. This approval was largely based on the pivotal Phase I/II multi-center clinical trial, which included both frontline and relapsed/refractory patients ([Pemmaraju et al N Engl J Med. 2019 Apr 25; 380\(17\):1628-1637](#)). In this study, tagraxofusp was administered as monotherapy, and the median age of patients was 70 years (range 22-84 years). Among 29 patients treated in the frontline setting, overall response rate was 90%, with 72% of frontline patients achieving complete remission. Forty-five percent of these patients received therapy as a bridge to stem cell transplant. In the relapsed/refractory (R/R) setting (n=15), a 67% overall response rate was observed. Despite these promising results, response duration can be short, thus more therapies and combination approaches are urgently needed ([Pemmaraju N Clin Adv Hematol Oncol. 2019 Apr;17\(4\):207-209](#)).

Another novel approach in the treatment of patients with BPDCN is the oral BCL-2 antagonist, venetoclax, used first as single-agent, and then combined with either hypomethylating agents or chemotherapy. Venetoclax is already FDA approved for patients with chronic lymphocytic leukemia and older patients with acute myeloid leukemia (AML) (in combination with low-dose cytarabine or hypomethylating agents) ([Konopleva et al Cancer Discov. 2016 Oct;6\(10\):1106-1117](#)).

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Our BPDCN Program has several clinical trials and novel therapeutic approaches to build on the initial progress seen in the field.

Frontline BPDCN

1. Tagraxofusp, H-CVAD and Venetoclax: Triple Total Therapy Comprehensive Program for Patients with BPDCN

This new Phase II trial ([NCT04216524](#)) combines tagraxofusp with H-CVAD and venetoclax for untreated/frontline patients with BPDCN. The regimen combines the three most active therapies (intensive chemotherapy plus agents targeting CD123 and BCL-2), previously given individually, in one comprehensive strategy. This trial is now open at MD Anderson and will investigate the safety and efficacy of this combination.

2. IMG632 in Relapsed/Refractory CD123+ Hematologic Malignancies

This Phase I/II trial of IMG632 ([NCT03386513](#)), a conjugated CD123-targeted agent consisting of a novel DNA-alkylating payload, investigates this novel agent in R/R hematologic malignancies, including BPDCN, AML and acute lymphocytic leukemia (ALL) ([Economides, Konopleva, Pemmaraju Ther Adv Hematol. 2019 Sep 23](#)). IMG632 was shown to have activity and prolong survival in AML xenograft models (Adams et al Blood 2016: abstract 2832). Patients with AML and BPDCN are actively being enrolled, and preliminary results presented at the 2018 and 2019 American Society of Hematology meeting established safety and showed an early signal for efficacy (Daver et al ASH 2018, 2019). This trial is open for frontline and R/R patients with BPDCN.

Relapsed/Refractory BPDCN

1. Venetoclax in Combination with Azacitidine for Relapsed/Refractory BPDCN

This Phase I trial of venetoclax for patients with BPDCN ([NCT03485547](#)) is based on pre-clinical and clinical work investigating the role of BCL-2 inhibition in BPDCN ([Montero et al Cancer Discov. 2017 Feb;7\(2\):156-164](#); [DiNardo et al Am J Hematol. 2018 Mar;93\(3\):401-407](#); [Pemmaraju N, Konopleva M, Lane AA, N Engl J Med. 2019 Feb 14;380\(7\):695-6](#)). It is done in partnership with colleagues at Dana-Farber Cancer Center and is specifically dedicated to patients with R/R disease at this time.

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3. MB-102 in Relapsed/Refractory BPDCN

This Phase I/II multicenter trial ([NCT04109482](#)) will assess the safety and efficacy of MB-102 in Patients with R/R BPDCN, AML, and high-risk myelodysplastic syndrome (MDS). It is a novel, autologous chimeric antigen receptor T-cell (CAR-T) construct targeted against CD123. This trial has begun as a Phase I dose-escalation study for patients with R/R BPDCN.

4. Decitabine in Combination with Venetoclax

The combination of 10 days of decitabine and venetoclax has demonstrated safety and efficacy in older patients with AML both in frontline and R/R settings. Based on previously shown clinical activity of both HMAs and venetoclax in older/unfit patients with BPDCN, this trial now includes ability to enroll those patients ([DiNardo et al Am J Hematol. 2018 Mar;93\(3\):401-407](#)).

5. Stem Cell Transplant and Post-SCT Maintenance in BPDCN

Understanding and optimizing the role of stem cell transplant (SCT) in patients with BPDCN is an emerging area of research. At the 2019 European Hematology Association meeting, we reported on outcomes among 24 patients with BPDCN who underwent SCT (n=14 allogeneic, n=10 autologous) with median age of 52 years (range 18-79). Two-year overall survival (OS) was 26% (4% allo, 57% auto) and 56% (24% allo, 80% auto) in auto- and allo-SCT, respectively (p=0.33). In patients transplanted before or after 2015, 2-year progression free survival (PFS) was 13% vs. 54% (p=0.009), respectively, and 2-year OS was 13% and 68% (p=0.017). ([Qazilbash/Pemmaraju et al EHA 2019](#)). Our SCT group has now opened a post-SCT maintenance trial with tagraxofusp focusing on patients with BPDCN.

6. Tagraxofusp (CD123-Directed Therapy) in BPDCN and Beyond

Now that the original SL-401 monotherapy trial for patients with BPDCN is closed to new patient entry, we

continue to follow patients for long-term survival ([Pemmaraju et al ASH 2018](#)). Currently, we use tagraxofusp as standard of care for patients not eligible for clinical trials. They are admitted to the Leukemia inpatient service, with close monitoring of daily weight, creatinine, liver function tests and albumin. It is crucial to monitor these parameters carefully as the most significant toxicity is capillary leak syndrome (CLS), which can be fatal and led to an FDA-mandated “black box” warning. ([Pemmaraju N Clin Adv Hematol Oncol. 2019 Apr; 17\(4\):207-209](#)). Also, tagraxofusp continues to be investigated in several other clinical trials here:

- **AML** ([Togami/Lane et al JCI 2019 Oct 14. pii: 128571. doi: 10.1172/JCI128571](#). [Epub ahead of print]) (tagraxofusp + azacitidine + venetoclax; [NCT03113643](#)).
- **High-risk MDS** (tagraxofusp + azacitidine; [NCT03113643](#)).
- **CMML** (tagraxofusp monotherapy; [NCT02268253](#); Patnaik et al ASCO 2019 and EHA 2019).
- **Myelofibrosis** (tagraxofusp monotherapy; [NCT02268253](#); Pemmaraju et al ASCO 2019, EHA 2019).

7. Importance of Pathology and Molecular Markers in BPDCN

Specialized pathology review – both dermatopathology and hematopathology -- is essential to confirm the diagnosis of BPDCN. Traditionally, we have noted flow cytometry/immunohistochemistry markers that form the backbone of a diagnosis are CD123, CD4 and CD56 (**think “CD123456”**) ([Alayed Am J Hematol. 2013 Dec; 88\(12\):1055-61](#)) ([Pemmaraju and Konopleva, The Hematologist 2018](#)) in combination with additional markers that add specificity: TCL-1, CD303, and now, most recently, TCF4 ([Wang W et al Haematologica. 2020 Apr 2:haematol.2020.247569](#)). There are exceptions, however, as in rare cases that are CD56 negative. The identification of TCF4 with CD123 as a novel dual marker has added further specificity to make the diagnosis ([Sukswai/Khoury J Am J Surg Pathol. 2019 Oct; 43\(10\):1429-1437](#)). Future directions include investigating and understanding other important markers, such as PD-1 and PDL-1 ([Aung PP/Khoury J Cancers \[Basel\]. 2019 May 19; 11\(5\)](#)) and the pre-inflammatory/immune context for development of BPDCN ([Beird et al Blood Cancer J. 2019 Dec 6;9\(12\):99.](#)).

For more information or patient referral for BPDCN, please contact [Naveen Pemmaraju, MD](#) or [Marina Konopleva, MD, PhD](#). Follow Dr. Pemmaraju on Twitter [@doctorpemm](#) and at [#BPDCN](#) for the latest updates.

Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress.

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