

In this month's Leukemia Insights newsletter, written by [Naveen Pemmaraju, M.D.](#), and [Marina Konopleva, M.D., Ph.D.](#), 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). Learn more about our [Leukemia program](#).

## Targeting the p-D-C with C-D-1-2-3 in Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) and p-DC Acute Myeloid Leukemia (AML)

Patients with the rare malignancy blastic plasmacytoid dendritic cell neoplasm (BPDCN) historically has had a poor prognosis with median overall survival (OS) of 8-14 months prior to the era of targeted therapy. Initial therapeutic approaches included multi-agent chemotherapy regimens borrowed from acute leukemia or lymphoma. In our experience, intensive chemotherapy with Hyper-CVAD has shown the best remission rates; however, relapses are frequent in the frontline setting and outcomes poor in the relapsed/refractory setting (R/R) (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 targeted agent for patients with BPDCN ages 2 and older ([Hammond D/Pemmaraju N Hematol Oncol Clin North Am. 2020 Jun;34\(3\):565-574](#)). This approval, the first for a CD123-targeted agent in the field of hematology/oncology, was largely based on the pivotal Phase I/II multi-center trial, which included frontline and R/R 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 frontline patients, overall response rate (ORR) was 90%, with 72% achieving complete remission. Forty-five percent of these patients received therapy as a bridge to stem cell transplant (SCT).

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In the R/R setting (n=15), a 67% ORR 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](#)). Research in targeting CD123 in BPDCN has continued to advance, including most prominently the clinical development of the novel agent IMGN632, which has shown encouraging activity and manageable safety profiles in the R/R setting (Pemmaraju et al ASH 2020).

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](#)).

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

### Frontline BPDCN:

#### **1. IMGN632 in Frontline Therapy**

This Phase I/II trial of IMGN632 ([NCT03386513](#)), a conjugated CD123-targeted agent with a novel DNA-alkylating payload, has now moved into the frontline setting based on promising early results seen in R/R patients. Originally it was open to patients with R/R hematologic malignancies, including BPDCN, AML and acute lymphocytic leukemia (ALL) (Economides, Konopleva, Pemmaraju *Ther Adv Hematol*. 2019 Sep 23). IMGN632 was shown to have activity and prolong survival in AML xenograft models (Adams et al *Blood* 2016: abstract 2832).

Patients with both R/R AML and R/R BPDCN were 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). More recently, Pemmaraju et al reported a 29% overall response rate (ORR) among patients with R/R BPDCN treated with IMGN632 monotherapy, including a 31% ORR among patients who had received prior tagraxofusp (Pemmaraju et al ASH 2020). Based on these promising results, IMGN 632 was given an FDA Breakthrough Therapy Designation (BTD) for R/R BPDCN. It was on this basis that it was opened to frontline patients and is now actively recruiting untreated patients with BPDCN. It remains open for those with R/R disease as well.

#### **2. Tagraxofusp, H-CVAD and Venetoclax: Triple Therapy Comprehensive Program**

This new Phase II trial ([NCT04216524](#)) for frontline patients with BPDCN combines tagraxofusp with Hyper-CVAD and venetoclax. 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 and will investigate the safety and efficacy of this combination.

### Relapsed/Refractory BPDCN:

#### **1. IMGN632 in Relapsed/Refractory CD123+ Hematologic Malignancies**

Details of this Phase I/II trial of IMGN632 ([NCT03386513](#)) are described above. It is open for both frontline and R/R patients with BPDCN.

#### **2. Venetoclax with Azacitidine**

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*

### **3. Tagraxofusp, Venetoclax, Azacitidine**

This phase I/II study of combination of CD123-targeting agent, BCL-2 targeting agent, and hypomethylating agent is now open and enrolling for patients with R/R BPDCN.

### **4. MB-102**

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

### **5. Decitabine with Venetoclax**

The combination of 10 days of decitabine and venetoclax has been shown to be safe and effective in older patients with AML both in the frontline and R/R settings. Based on previous data showing 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).

### **Future Directions and Special Topics in BPDCN:**

#### **Stem Cell Transplant and Post-SCT Maintenance in BPDCN**

Understanding and optimizing the role of SCT in patients with BPDCN is an emerging area of research. At the 2019 European Hematology Association meeting, we reported on outcomes of 24 patients with BPDCN who underwent SCT (n=14 allogeneic, n=10 autologous) with median age of 52 years (range 18-79 years). In patients transplanted before or after 2015 (the beginning of the era of BPDCN targeted therapy), 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 transplant group has now opened a post-SCT maintenance trial with tagraxofusp for patients with BPDCN (NCT04317781).

### **Tagraxofusp in Malignancies that Overexpress CD123**

Now that the original tagraxofusp 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, may in the field use tagraxofusp and tagraxofusp-based regimens as standard of care for patients not eligible for clinical trials. They are admitted to the Leukemia inpatient service, where they are followed closely with a multi-disciplinary group of team members, with rigorous monitoring of daily weight, creatinine, liver function tests and albumin. It is crucial to evaluate these parameters 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 at our center:

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

### **Importance of Expert Pathology Review 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, 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 and have greatly helped in differentiating BPDCN from closely mimicking conditions, such as AML with leukemia cutis (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.).

### **CNS involvement in BPDCN**

Prior to the modern targeted therapy era, Martin-Martin et al demonstrated a high rate of CSF-positive disease in patients with BPDCN, mostly asymptomatic (Martin-Martin L Oncotarget 2016;7(9):10174-10181). As it is yet unknown if the newer targeted agents cross the blood-brain barrier or have CNS penetration, coupled with the fact that patients are living longer with BPCDN, we are starting to observe more cases CSF-positive disease

from lumbar punctures. Consequently, we are investigating the rate of CNS positivity, and have started to incorporate prophylactic intrathecal chemotherapy in all patients, whether frontline or R/R.

### **pDC-AML**

Several groups have recently described an emerging entity known as plasmacytoid dendritic cell acute myeloid leukemia, or pDC-AML. Provisionally viewed as a separate entity with characteristics of both of BPDCN and AML, patients with pDC-AML appear to express CD123, routinely have skin involvement, have markers for both BPDCN and AML, and have a high rate of recurring somatic mutations such as *RUNX1*. (Xiao et al Blood 2021 Mar 11;137(10):1377-1391; Zalmai L et al Haematologica 2020 Oct 13). Importantly, Xiao et al demonstrated in pre-clinical models that treatment with tagraxofusp led to elimination of malignant pDCs and decreased leukemia burden, suggesting the possibility for clinical trials to further investigate (Pemmaraju N Blood 2021 Mar 11; 137(10):1277-1278). Our Phase I/II clinical trial with tagraxofusp, venetoclax, and azactidine has arms for both BPDCN and AML and is actively enrolling ([NCT03113643](https://clinicaltrials.gov/ct2/show/study/NCT03113643)).

**For more information or patient referral for BPDCN, please contact Drs. Naveen Pemmaraju or Marina Konopleva. For the latest updates, follow Dr. Pemmaraju on Twitter [@doctorpemm](https://twitter.com/doctorpemm) and at #BPDCN for the latest updates.**

## Leukemia 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. [View our faculty roster.](#)

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## Announcements

### Leukemia Insights Newsletter

Our Leukemia Insights e-newsletter is now available online. Started in 2007 by [Hagop Kantarjian, M.D.](#), Leukemia Insights focuses on our various therapy options at MD Anderson Cancer Center. [Click here to visit our new website.](#)

### Emil J Freireich Hematology Grand Rounds

The MD Anderson Cancer Center [Emil J Freireich](#) Hematology Grand Rounds now has a virtual format. This series highlights the incredible research taking place at MD Anderson Cancer Center while showcasing leaders from our research community, in an effort to remain engaged and inspired during the COVID-19 pandemic. Hosted by the [Department of Leukemia](#) in collaboration with the [Department of Lymphoma/Myeloma](#), and [Department of Stem Cell Transplantation and Cellular Therapy](#), we aim to strengthen the connections between the scientific and medical community at MD Anderson Cancer Center, our colleagues, patients and friends from around the world. [Click here to visit our new website.](#)