Leukemia insights

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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.

Patients with the rare hematologic malignancy known as blastic plasmacytoid dendritic cell neoplasm (BPDCN) historically have 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 historical experience, intensive chemotherapy with the Hyper-CVAD regimen has shown the best remission rates; however, relapses are still frequent in the frontline setting, and outcomes are poor in the relapsed/refractory (R/R) setting (Pemmaraju N et al Blood Advances 2022 Jan 21).

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, largely was based on the pivotal Phase I/II multi-center trial, which included both 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 (CR)/clinical complete remission (CRc). Forty-five percent of these frontline patients received therapy as a bridge to stem cell transplant (SCT). In the R/R setting (n=15), a 67% ORR was observed. Despite these promising results, response durations can be short; thus, more approaches are urgently needed (Pemmaraju N Clin Adv Hematol Oncol. 2019 Apr;17(4):207-209).

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Research in targeting CD123 in BPDCN has continued to advance, most prominently including the clinical development of the novel agent IMGN632 (CD123-targeting antibody-drug conjugate; pivekimab sunirine; ImmunoGen), which has shown encouraging activity and manageable safety profiles in the R/R setting (Pemmaraju et al ASH 2020) and, more recently, in the frontline setting (Pemmaraju et al ASH 2021).

Another novel approach in the treatment of patients with BPDCN is the oral BCL-2 antagonist venetoclax, used first as a single agent, and then combined with either a hypomethylating agent or chemotherapy (Montero J et al Cancer Discovery 2017 Feb:7(2):156-164; Pemmaraju N et al NEJM 2019 Feb 14;380(7):695-6; Gangat N et al Am J Hematol 2022 Feb 1;97(2):E62-67). 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 a hypomethylating agent) (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

This multi-center 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 for BPDCN, based on promising early results seen in R/R patients. Originally, it was open to patients with R/R hematologic malignancies, including BPDCN and AML (Economides, Konopleva, Pemmaraju Ther Adv Hematol. 2019 Sep 23). IMGN632 was shown to have activity and prolonged 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 meetings 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, IMGN632 was given an FDA Breakthrough Therapy Designation (BTD) for R/R BPDCN.

It was on this basis that it was opened to frontline patients (Pemmaraju et al ASH 2021), and we are now actively recruiting untreated patients. IMGN632 is now known as pivekimab sunirine and the study is open for both frontline R/R BPDCN patients.

2. Tagraxofusp, H-CVAD and Venetoclax: Triple/Total Therapy

This 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 open and will investigate the safety and efficacy of this combination.

3. Decitabine with Venetoclax "DAC10d+VEN"

The combination of decitabine for 10 days plus 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 patients with BPDCN in both frontline and R/R settings (DiNardo et al Am J Hematol. 2018 Mar;93(3):401-407).

Relapsed/Refractory BPDCN:

4. 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.

5. 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 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 open for patients with R/R disease.

6. Tagraxofusp, Venetoclax, Azacitidine

This Phase I//II study of a CD123-targeting agent, BCL-2 targeting agent, and hypomethylating agent is now open for patients with R/R BPDCN. (NCT03113643)

7. MB-102 CD123 CAR-T

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 for patients with R/R BPDCN.

8. 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 (EHA) 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), these results were updated in our recent manuscript (Bashir et al BMT 2022 Jan;57(1):51-56). Our transplant group has now opened a post-SCT maintenance trial with tagraxofusp for patients with BPDCN (NCT04317781).

Tagraxofusp/CD123-Directed Therapy in Malignancies that Overexpress CD123

Thanks to results of the tagraxofusp monotherapy trial for patients with BPDCN, research in CD123-targeted agents (monotherapy or in novel combinations) now is focused on many other hematologic malignancies, including:

- **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, ASH 2021)
- **Myelofibrosis** (tagraxofusp monotherapy; NCT02268253; Pemmaraju et al ASCO 2019, EHA 2019, ASH 2021)

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 has greatly helped in differentiating BPDCN from such mimicking presentations 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 of CSF-positive disease from lumbar punctures (LP). In our recent analysis, we found a high rate of CNS positivity in BPDCN (22%), and have started to incorporate prophylactic intrathecal chemotherapy via LP in all patients with BPDCN, whether frontline or R/R (Pemmaraju N et al Blood 2021 Oct 14;138(15):1373-1377).

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 azacitidine has arms for both BPDCN and AML and is enrolling (NCT03113643).

For more information or patient referrals for BPDCN, please contact Naveen Pemmaraju, M.D., Director of our BPDCN Program. For the latest updates, follow Dr. Pemmaraju on Twitter @doctorpemm and at #BPDCN.

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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