Leukemia insights

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In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, M.D., and Hagop Kantarjian, M.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

Spotlight on rare hematologic malignancies: Development of the Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) Program key updates & insights

Patients with the rare hematologic malignancy 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. Clinically, patients generally present with involvement of one more of the four major compartments: 1) skin 2) bone marrow/blood 3) lymph nodes and 4) central nervous system (CNS). This marks BPDCN as a unique entity, now classified under histiocytic/dendritic cell neoplasms in the 5th edition of the WHO classification of haematolymphoid tumours (Khoury J et al Leukemia 2022 36: 1703-1719).
Initial therapeutic approaches have included multi-agent chemotherapy regimens borrowed most commonly from acute leukemia or lymphoma. In our 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 relapsed/refractory (R/R) disease (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 hematology/oncology, was largely based on the pivotal Phase I/II multi-center trial, which included both frontline

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and R/R patients (Pemmaraju et al N Engl J Med. 2019 Apr 25; 380(17):1628-1637). Tagraxofusp was administered as monotherapy, and the median age of patients was 70 years (range 22-84). Among 29 frontline patients, overall response rate (ORR) was 90%, with 72% achieving complete remission (CR)/clinical complete remission (CRc). Forty-five percent received therapy as a bridge to stem cell transplant (SCT). In the R/R setting (n=15), a 67% ORR was observed. Recently, these data were updated, demonstrating that among 65 frontline patients treated with tagraxofusp monotherapy and with a median follow-up of approximately 3 years, ORR was 75% with a 57% CR/CRc rate (Pemmaraju et al JCO 2022 July 12).

Despite these promising results, median overall survival probability at 24 months remains only 40%; therefore, novel approaches are still urgently needed (Adimora, Wilson, Pemmaraju Cancer 2022 Aug 15;128(16):3019-3026) (Bole-Richard, Pemmaraju et al Cancers 2022 May;14(9):2287). Research in targeting CD123 in BPDCN has continued to advance, most prominently including the ongoing 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 BPDCN field is the use of the oral BCL-2 antagonist venetoclax, used initially 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 continues to expand, with patient referrals from around the world, a robust multidisciplinary team, and novel therapeutic clinical/translational approaches to continue to build on the initial progress seen in the field.

Frontline BPDCN

1. IMGN632 (Pivekimab Sunirine)

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 in R/R AML 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, Kantarjian, Daver 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 and R/R BPDCN patients.

2. Tagraxofusp (SL-401), Hyper-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 with built-in incorporation of LP IT chemotherapy for CNS prophylaxis. 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, as pioneered by Drs. Konopleva and DiNardo in AML, 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).

4. Tagraxofusp (SL-401), 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 both frontline and R/R BPDCN. (NCT03113643)

Relapsed/Refractory BPDCN:

5. 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.

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 both frontline and 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). 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).

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 other hematologic malignancies. We will continue to monitor for short- and long-term toxicities in this field, including capillary leak syndrome (CLS), as we move into various combination therapy regimens and new disease areas (Mouhayar EN, et al JACC CardioOncol 2021 Dec 21).

- **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 dermatopathology and hematopathology review and expert consultation 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 (CSF+) 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%) in the modern treatment era, and have now 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).

Prior or Concomitant Hematologic Malignancies (PCHM)

Patients with BPDCN often exhibit PCHM. We are actively investigating this emerging area.

The occurrence of PCHM appears to be quite common in our series and usually features a concomitant MDS/CMML (Khanlari M, et al Leukemia 2022 May and Yin et al Cancers 2021 Nov 23 and Batta K et al Leukemia 2021 Nov and Pemmaraju et al ASH 2019). Overall survival outcomes appear to be similar in *de novo* BPDCN vs BPDCN-PCHM, and active areas of investigation include rates of CNS involvement, CR1 durations, occurrence of cytopenias, and other key questions.

pDC-AML

Several groups have recently described an entity known as plasmacytoid dendritic cell acute myeloid leukemia, or pDC-AML, including our group's most recent publication (Wang W Cancers 2022 Jul 11:14(14):3375). Provisionally thought of 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 referral for BPDCN, please contact Drs. Naveen Pemmaraju or Hagop Kantarjian. For the latest updates, follow Dr. Pemmaraju on Twitter @doctorpemm and at #BPDCN.

Announcements

MD Anderson Cancer Center Leukemia Fellowship Accepting Applications

The goals of the Leukemia Fellowship Program are to train competent, qualified, caring and empathic physicians who are mindful of the significance of their role in the diagnosis and management of patients with the acute and chronic leukemias as well as myelodysplastic syndromes and myeloproliferative disorders.

The Leukemia Fellowship Program accepts applications for potential positions **August 1 through October 31, 2022**, with the program accepting a limited number of new fellows each year. Initially, a one-year commitment to the Program is required. Fellows in their first year may be considered for an additional year at their request.
The Leukemia Fellowship is non-standard and commences July 1 through June 30 and is recognized by the Texas Medical Board as an approved fellowship program. The program is affiliated with The University of Texas MD Anderson Cancer Center's Hematology/Oncology Fellowship which is accredited by ACGME.

For general inquires, please send an email to leuktrain@mdanderson.org or visit our Leukemia Fellowship page for additional information and requirements.

10th Annual Society of Hematologic Oncology (SOHO) Meeting

The tenth annual meeting of the Society of Hematologic Oncology (SOHO 2021) is scheduled for September 28-October 1, 2022 at the Hilton Americas in Houston, Texas. Hematology/oncology specialists from around the world will gather at the event.
As a hybrid event, SOHO 2022 offers in-person and virtual attendance options. This year, we expect more than 2,500 physicians, nurses and related healthcare specialists to participate in the 3.5-day meeting and participate in several unique educational formats including General Sessions, Meet-the-Professor Sessions, Plenary Lectures, Expert Sessions, Oral Abstract Presentations and other interactive and informal exchanges. Topics will cover the latest advances in the pathophysiology and therapy of: leukemias, lymphomas, myeloma, myelodysplastic syndromes, myeloproliferative neoplasms, related malignancies and exciting developments in cellular therapy.
Click the following link to begin the secure registration process: www.soho.click/2022

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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