Leukemia insights

JUNE 2021

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

In this month's Leukemia Insights newsletter, written by Prithviraj Bose, M.D. and Srdan Verstovsek, 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 malignancies, systemic mastocytosis and myeloid/lymphoid neoplasms with eosinophilia. Learn more about our Leukemia program.

Spotlight on rare, atypical, myeloid neoplasms: systemic mastocytosis and myeloid/lymphoid neoplasms with eosinophilia and FGFR1 rearrangements

Systemic Mastocytosis

Systemic mastocytosis (SM) is a rare myeloid neoplasm driven in approximately 95% of cases by an activating mutation in c-KIT, usually D816V. SM is characterized as indolent, smoldering or advanced, based on the presence and number of so-called B- and C-findings. The latter signify organ damage and are a hallmark of advanced SM (AdvSM). AdvSM, in turn, is typically sub-classified as aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN, the most common subtype) and mast cell leukemia (MCL). Patients with indolent SM (ISM) and smoldering SM (SSM) enjoy much better survival than those with AdvSM, although symptoms in all three subtypes can be severe and debilitating. Imatinib lacks activity against KIT D816V, and is approved for the small minority of patients with ASM in whom this mutation is absent or whose KIT mutational status is unknown. Midostaurin is approved for patients with AdvSM but has only a 28% overall response rate (ORR, comprising complete and partial responses and clinical improvement) by criteria set by the International Working Group for Myeloproliferative Neoplasm Research and Treatment-European Competence Network on Mastocytosis (IWG-MRT-ECNM) (Gotlib, Blood 2013). Furthermore, midostaurin has considerable gastrointestinal toxicity. No targeted agents are approved by the Food and Drug Administration for patients with ISM and SSM. Instead, they are treated with a host of agents aimed at

ABOUT MyMDAnderson

myMDAnderson is a secure, personalized web site helping community physicians expedite patient referrals, as well as improve continuity of care through information access and streamlined communications.

Physicians who have referred patients to MD Anderson or plan to do so, can utilize the HIPAA compliant features of myMDAnderson to:

- Refer a patient
- View your patient's appointments Access patient reports
- Send and receive secure messages

JOIN THE COVERSATION

Connect with us.

JOIN OUR MAILING LIST

If you would like to receive an electronic issue of the MD Anderson Leukemia Insights e-Newsletter on a monthly basis, please email us at Leukemia@mdanderson.org.

It's the easiest way to stay current with information on the latest leukemia news, research, and resources. View archived issues.

CONTACT OUR STAFF

Mary Alma Welch - Editor
Lisa Palacios - Publishing Editor
Leukemia@mdanderson.org

ameliorating symptoms: e.g., anti-histamines, mast cell stabilizers, leukotriene antagonists, corticosteroids, and epinephrine for anaphylactic episodes.

Avapritinib for systemic mastocytosis

Avapritinib (formerly BLU-285) is a highly potent and selective inhibitor of KIT D816V and similar KIT mutants. It has just been approved by the FDA for the treatment of patients with AdvSM without severe thrombocytopenia (i.e., platelets <50 x 109/L). In the Phase 1 EXPLORER trial, avapritinib produced an ORR of 75% by modified IWG-MRT-ECNM criteria among 53 evaluable patients with AdvSM (Gotlib, ASH 2020). In a pre-specified interim analysis of the phase 2 PATHFINDER trial (32 evaluable patients, DeAngelo, AACR 2021, Reiter, EHA 2021), the ORR was also 75%. Responses were rapid, occurring after a median of 8 weeks, and deepened over time, with substantial proportions of patients attaining complete responses with full or partial hematologic recovery (CR/CRh). Avapritinib was well-tolerated overall. In patients without severe thrombocytopenia (<50 x 109/L) at baseline, the incidence of intra-cranial bleeding was very low (≈1%) and similar to that seen in the gastrointestinal stromal tumor (GIST) population (avapritinib is also approved for PDGFRA-mutated advanced GIST). The recommended starting dose of avapritinib in patients with AdvSM is 200 mg daily. In the pivotal Phase 2/3 PIONEER trial, it is also being studied in patients with ISM or SSM who are symptomatic despite 2 or more best supportive care (BSC) medications. In the first part of this study, a starting dose of 25 mg daily was established to be safe and effective (Akin, ASH 2020). This dose of avapritinib will be compared to placebo in the second part of the trial, which will soon open at MD Anderson. Randomization is 2:1 in favor of the avapritinib arm, and all placebo patients cross over to receive avapritinib after the primary endpoint, symptom response, is assessed at 24 weeks.

Myeloid/Lymphoid Neoplasms with Eosinophilia

Myeloid/lymphoid neoplasms with eosinophilia (MLNEo) and rearrangements of PDGFRA, PDGFRB, fibroblast growth factor receptor 1 (FGFR1), or the PCM1-JAK2 fusion represent a rare and unique category within the World Health Organization (WHO) classification of myeloid neoplasms. Although not formally recognized by the WHO, other fusions involving the FLT3, JAK2 and ABL genes, located at 13q12, 9p24 and 22q11, respectively, are also included in this category, and guidelines from the National Comprehensive Cancer Network (NCCN) on the management of these entities have recently been published (Gerds, JNCCN 2020). As the name suggests, these neoplasms can be myeloid or lymphoid; furthermore, they can present in chronic phase or as an acute leukemia. Patients with PDGFRA-rearranged MLNEo are nearly always male. Extramedullary involvement and eosinophilia are common, and the abnormality (an interstitial deletion at 4q12) is usually cytogenetically cryptic (i.e., detected only on fluorescence in situ hybridization [FISH]). The most common partner gene is FIP1L1, and the disease is typically exquisitely sensitive to imatinib. Numerous fusion partners have been described for PDGFRB (located at 5q31-33), and the abnormality is usually, but not always, detected on karyotyping. Response to imatinib is generally excellent, although doses up to 400 mg daily occasionally may be needed (100 mg daily is typically sufficient for PDGFRA-rearranged MLNEo). There are anecdotal reports and case series of responses of FLT3-, JAK2- and ABL-rearranged MLNEo (FISH is required for diagnosis) to FLT3 tyrosine kinase inhibitors, ruxolitinib and BCR-ABL TKIs, respectively.

No currently available therapy has demonstrated significant efficacy against FGFR1-rearranged MLNEo, an aggressive malignancy with a poor prognosis (Strati, Leuk Lymphoma 2018). FGFR1 is located at 8p11, and the most common partners are ZMYM2, located at 13q12, and BCR, located at 22q11. The karyotype is usually abnormal, but the rearrangement must be confirmed by FISH testing. Eosinophilia may not be present, and blast phase disease (both medullary and extra-medullary) is common.

Pemigatinib for myeloid/lymphoid neoplasms with eosinophilia and FGFR1 rearrangement

Pemigatinib is a potent, small-molecule inhibitor of FGFR1/2/3. It is currently approved for the treatment of advanced cholangiocarcinoma bearing an FGFR2 fusion or rearrangement. It is being studied in the pivotal, open-label, FIGHT-203 trial for patients with FGFR1-rearranged myeloid or lymphoid neoplasms. In preliminary results from this trial (13 patients), single-agent pemigatinib yielded an ORR of 85% (Verstovsek, ASH 2018). The trial is open for accrual at MD Anderson.

Announcements

9th Annual Society of Hematologic Oncology (SOHO) Meeting

The ninth annual meeting of the Society of Hematologic Oncology (SOHO 2021) is scheduled for September 8-11, 2021 at the Hilton Americas in Houston, Texas. Hematology/oncology specialists from around the world will gather at the event.

Note that SOHO 2021 is designed as a hybrid event, so all content will be available on the SOHO virtual platform for those unable to travel. In addition, there are virtual options for abstract and poster presenters.

Note that SOHO members receive a significant discount on registration fees. SOHO membership is **FREE** for a limited time. Sign up now to receive a SOHO member discount code to apply towards your annual meeting registration fee. Click the following link to begin the secure registration process: https://www.soho2021.com/soho2021/registration

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.

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.

Clinical Faculty

Kantarjian, Hagop	*Department Chair*	(713) 792-7026
Garcia-Manero, Guillermo	*Deputy Chair, Chief, Section of Translational Research, Chief, Section of Myelodysplastic Syndromes (MDS), and Director, Leukemia Clinical Fellowship Program*	(713) 745-3428
Wierda, William	*Deputy Chair, Chief, Section of Chronic Lymphocytic Leukemia (CLL), and Leukemia Center Medical Director*	(713) 745-0428
Andreeff, Michael	*Chief, Section of Molecular Hematology and Therapy,* Center Medical Director, Bone Marrow Aspiration Clinic	(713) 792-7261
Borthakur, Gautam	*Chief, Section of Developmental Therapeutics*	(713) 563-1586
Daver, Naval	*Director, Leukemia Research Alliance Program*	(713) 794-4392
DiNardo, Courtney D.	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics Leader, Hereditary Hematologic Malignancy Clinic*	(734) 358-1053
Ferrajoli, Alessandra	*Leukemia Center Associate Medical Director*	(713) 792-2063
Issa, Ghayas “Gus"	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-8432
Jabbour, Elias	*Chief, Section of Acute Lymphoblastic Leukemia (ALL)*	(713) 792-4764
Jain, Nitin	Director, Cellular Therapy Program	(713) 745-6080
Kadia, Tapan	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics, Co-Leader, Leukemia Clinical Fellowship Program*	(713) 563-3534
Montalban Bravo, Guillermo	*Director, Chronic Myelomonocytic Leukemia (CMML) Program*	*(713) 792-4956*
Pemmaraju, Naveen	*Director, Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) Program*	*(713) 794-3604*
Ravandi, Farhad	*Chief, Section of Acute Myeloid Leukemia (AML)*	(281) 216-7806
Sasaki, Koji	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-2882
Verstovsek, Srdan	*Chief, Section of Myeloproliferative Neoplasms (MPNs), Director, Clinical Research Center for MPNs*	(713) 745-3429

Leukemia Faculty Contacts

(Continued)

Clinical Faculty

Alvarado, Yesid	(713) 794-4364
Bose, Prithviraj	(713) 792-7747
Burger, Jan	(713) 563-1487
Chien, Kelly	(713) 745-7584
Estrov, Zeev	(713) 794-1675
Kornblau, Steven	(713) 794-1568
Maiti, Abhishek	(346) 725-0901
Masarova, Lucia	(832) 750-4211
Montalban Bravo, Guillermo	(713) 794-3604
Ohanian, Maro	(713) 792-0091
Pemmaraju, Naveen	(713) 792-4956
Short, Nicholas	(713) 563-4485
Takahashi, Koichi	(713) 745-4613
Thompson, Philip	(713) 792-7430
Yilmaz, Musa	(713) 745-9945

Research Faculty

Battula, Venkata	(713) 563-2227
Bhalla, Kapil N.	(713) 563-8619
Burks, Jared K.	(713) 792-7640
Carter, Bing Z.	(713) 794-4014
Chang, Kyung Hee	(713) 792-4694
Colla, Simona	(713) 794-5223
Fiskus, Warren	(713) 563-5901
Gandhi, Varsha V.	(713) 792-2989
Han, Lina	(713) 792-7640
Ishizawa, Jo	(713) 792-7640
Keating, Michael	(713) 745-2376
Piya, Sujan	(713) 792-7305
Plunkett, William	(713) 792-3335
Post, Sean	(713) 794-1458
Pourebrahimabadi, Rasoul	(713) 792-7305
Rytting, Michael E.	(713) 792-4855
Wei, Yue	(713) 792-9854
Zeng, Zhinhong	(713) 792-7640
Zhang, Weiguo	(713) 794-4085