Leukemia insights

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In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, M.D., and Prithviraj Bose, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we outline clinical trials offered for patients with Myelofibrosis (MF). Learn more about our Leukemia program.

Novel Combination Therapies for Patients with Myelofibrosis (MF): A New Era of Clinical Trials in the MPN Field

Background

It has been just over a decade since the approval of the first JAK inhibitor, ruxolitinib, and despite significant progress in the field of myelofibrosis (MF), it remains an area of major unmet medical need (Pemmaraju, Bose, Rampal et al Leuk Lymphoma 2023 Apr). Our focus is now turning to the development of novel agents and combination therapies (Bose P et al Expert Opin Pharmacother 2023 May). Current aims are increased overall survival, better leukemia-free survival and the new goal of improved disease modification (Pemmaraju et al Cancer 2022; Vachhani, Verstovsek, BoseJCO 2022). To those ends, we have a host of clinical trials with novel combinations now open, and they are the focus of this issue.

1. Navitoclax

On the basis of the encouraging results of the REFINE Phase 2 study cohort 1a featuring ruxolitinib (RUXO) "add-on/add-back" approach combined with navitoclax (a novel oral BCL-2/-xL inhibitor) for patients MF and a suboptimal response (Harrison/Pemmaraju JCO 2022), the phase 3 clinical trial of RUXO+navitoclax in the frontline setting is now underway (TRANSFORM-1). Led by Dr. Pemmaraju, our group continues to have interest in targeting BCLxL for patients with MF. A Phase 1b study of ABBV-744 alone or in combination with ruxolitinib or navitoclax, will be opening soon. One arm of this trial will feature a novel-novel combination of BCL-2/-xL inhibition (navitoclax) and BETi (Bromodomain inhibition) with ABBV-744 (NCT04454658).

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CONTACT OUR STAFF

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

2. Azacitidine

Azacitidine (AZA) is a hypomethylating agent used in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) and has been approved for combination therapy with venetoclax in older patients with AML. The closely related agent decitabine has previously been investigated in combination therapy with ruxolitinib for accelerated and blast phase myeloproliferative neoplasms (MPN) (Bose et al. Leukemia 2020; Mascarenhas and Rampal et al. Blood Advances 2020). This Phase 2 clinical trial of RUXO+AZA led by Dr. Naval Daver and Dr. Lucia Masarova (NCT01787487) is open for patients with chronic MF and splenomegaly or elevated blasts and MDS/MPN-U.

3. TL-895

TL-895 is a second-generation, oral Bruton's tyrosine kinase inhibitor (BTKi). The proposed mechanism of action for this approach in MF includes the downregulation of NF-kB, a key malignant pathway, and mobilization of CD34+ cells from the bone marrow niche. This open Phase 2 clinical trial (NCT04655118) investigates TL-895 in an "add-on/add-back" combination approach in patients with a suboptimal response to RUXO monotherapy.

4. Navtemadlin

Navtemadlin is an oral, small-molecule MDM2 antagonist and has demonstrated encouraging clinical activity in patients with R/R MF post JAK inhibitor failure (Vachhani, EHA 2023). MDM2 is aberrantly overexpressed in MPNs and is thus a potential target for novel therapy. This Phase 2 clinical trial (NCT04485260) investigates the combination of navtemadlin with RUXO in patients with suboptimal response (Mascarenhas, EHA 2023). Importantly, based on its unique mechanism of action, patients without TP53 mutations will be included. The ongoing Phase 3 BOREAS trial features navtemadlin vs best available therapy (excluding JAKi) in patients with R/R MF.

5. CK0804

CK0804 is a novel, allogeneic umbilical cord blood-derived regulatory T-cell ("T-reg") product, is one of the earliest immune/cellular-based therapy approaches in MF. In this open clinical trial, CK0804 is combined with RUXO in a Phase Ib study (NCT05423691) in patients with MF and splenomegaly, symptoms, or anemia. The novel product is given intravenously and can be administered in the outpatient setting.

6. INCB057643

Encouraging clinical results have been demonstrated in the MANIFEST studies that combine the pelabresib, a pan-bromodomain and extra-terminal (BET) inhibitor, with RUXO, including in the frontline setting. The pelabrasib frontline has completed accrual, and results are not yet published, but this has opened up a new era of BETi therapy for patients with MF. INCB057643 is a novel BET inhibitor. BET proteins are key epigenetic readers that control the transcription of several critical oncogenes, including C-MYC, BCL-2, NFkB. INCB057643 is being investigated both as a monotherapy in patients with MF and as an "add-on/add-back" approach in MF. In this open Phase I/II clinical trial (NCT04279847), patients with up to 19% blasts may be included.

7. Zilurgisertib

ALK2 (ACVR1) contributes to anemia in MF through hepcidin upregulation and represents a novel target. Zilurgisertib is a novel ALK2 inbititor, and this Phase 1/2 dose-escalation/expansion study (NCT04455841) is investigating it as monotherapy or in combination with RUXO in anemic patients with MF. The results of the ongoing multi-center clinical trial will be updated by Dr. Prithviraj Bose at ASCO and EHA 2023.

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

Leukemia Faculty Contacts (continued)

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Clinical Faculty

Abbas, Hussein	(713) 745-8433
Alvarado, Yesid	(713) 794-4364
Bose, Prithviraj	(713) 792-7747
Burger, Jan	(713) 563-1487
Chien, Kelly	(713) 745-7584
Kornblau, Steven	(713) 794-1568
Haddad, Fadi	(346) 234-4135
Hammond, Danielle	
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
Swaminathan, Mahesh	(832) 728-8778
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
Estrov, Zeev	(713) 794-1675
Fiskus, Warren	(713) 563-5901
Ganan_Gomez, Irene	(713)-792-7828
Han, Lina	(713) 792-7640
Ishizawa, Jo	(713) 792-7640
Keating, Michael	(713) 745-2376
Piya, Sujan	(713) 792-7305
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