Leukemia insights

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In this month's Leukemia Insights newsletter, written by Prithviraj Bose, MD, and Srdan Verstovsek, PhD, MD, and sponsored in part by the Charif Souki Cancer Research Fund, we summarize the investigational approaches available for patients with myeloproliferative neoplasms (MPN) at MD Anderson Cancer Center. Learn more about our Leukemia Program.

Entering a New Era in Myeloproliferative Neoplasms (MPN) Research with Multiple Phase 3 and Other Pivotal Clinical Trials

Myelofibrosis: frontline studies

1. **PACIFICA (NCT03165734):** Pacritinib is a relatively non-myelosuppressive JAK2/IRAK1/FLT3 inhibitor that may be particularly effective in myelofibrosis patients with a "myelodepletive" phenotype. This oral agent is being specifically studied in patients with <50,000/μL platelets at baseline, who have a dismal prognosis and for whom no guidance on dosing is available for either ruxolitinib or fedratinib. This phase 3 trial enrolls JAK inhibitor-naïve patients as well as those with a limited exposure to ruxolitinib and randomizes them 2:1 to receive pacritinib or physician's choice therapy, (low dose ruxolitinib, danazol, or corticosteroids). This trial is currently recruiting participants at MD Anderson.
2. **MANIFEST-2:** Bromodomain and extra-terminal (BET) inhibitors synergize with JAK inhibitors in myelofibrosis models. Following encouraging efficacy seen in the MANIFEST trial in JAK inhibitor-naïve patients (63% spleen response rate and 59% symptom response rate at 24 weeks), the combination of ruxolitinib and the oral BET inhibitor CPI-0610 will be compared to ruxolitinib plus placebo in this pivotal phase 3 trial.
3. **TRANSFORM-1 (NCT04472598):** Navitoclax, the predecessor of venetoclax, inhibits both the anti-apoptotic proteins Bcl-2 and Bcl-xL. Bcl-xL may be particularly important for malignant cell survival in the context of *JAK2* V617F, and synergism between ruxolitinib and navitoclax has been demonstrated in preclinical models of myelofibrosis. Based on promising results achieved with the addition of navitoclax in patients with a "sub-optimal" response to ruxolitinib (see below), this phase 3 trial will compare the combination of ruxolitinib and navitoclax to ruxolitinib plus placebo in JAK inhibitor-naïve patients with myelofibrosis. This study will open soon at MD Anderson.
4. **Ruxolitinib plus thalidomide (NCT03069326):** Thalidomide has long been known to be clinically active in myelofibrosis and low dose thalidomide (50 mg/d), in particular, is well-tolerated and can improve cytopenias. Apart from being a poor prognostic marker in myelofibrosis, severe thrombocytopenia poses a significant clinical challenge in everyday practice. In the first part of this phase 2 study,

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CONTACT OUR STAFF

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

encouraging platelet responses were seen in a number of patients (Rampal, ASH 2019). The second part of the study, soon to open at MD Anderson, will restrict eligibility to patients with baseline platelets <100,000/μL and both ruxolitinib and thalidomide will be provided free of cost to participants.

Myelofibrosis: add-on studies

1. **MANIFEST (NCT02158858):** As noted above, dual inhibition of BET proteins and JAK2 has been found to be synergistic in MPN models. In the add-on arm of the phase 2 MANIFEST study, CPI-0610, when added in patients with a sub-optimal response to ruxolitinib, produced encouraging spleen and symptom responses, particularly in patients who were transfusion-dependent, a number of whom also achieved transfusion independence (Verstovsek, EHA 2020). This cohort has, therefore, been expanded, and continues to accrue patients at MD Anderson.
2. **Navitoclax (NCT03222609):** *JAK2* V617F activates Bcl-xL and the combination of ruxolitinib and navitoclax is synergistic in preclinical models of *JAK2* V617F-driven MPN. Promising clinical efficacy in terms of spleen and symptom responses has been observed in this ongoing phase 2 trial in the add-on setting (Harrison, EHA 2020). This trial is open to accrual at MD Anderson.
3. **KRT-232 (NCT04485260):** *JAK2* V617F and transforming growth factor beta (TGF-β) lead to overexpression of MDM2, the physiologic antagonist of p53, in myelofibrosis. *TP53* mutations are rare in chronic phase myelofibrosis, making MDM2 inhibition an attractive therapeutic strategy. The oral MDM2 inhibitor KRT-232 is active in patients with JAK inhibitor-relapsed/refractory myelofibrosis (see below) and will now be studied in the add-on setting in patients with a sub-optimal response to ruxolitinib. This phase 1/2 trial is open to accrual at MD Anderson.
4. **PU-H71 (NCT03935555):** PU-H71 is an orally administered inhibitor of the chaperone protein, heat shock protein 90 (HSP90). HSP90 inhibition can degrade JAK2, thus circumventing resistance to JAK2 inhibitors. This agent is being studied in a phase 1 add-on trial in patients with a sub-optimal response to ruxolitinib. This trial is open to accrual at MD Anderson.
5. **Ruxolitinib plus thalidomide (NCT03069326):** Apart from JAK inhibitor-naïve patients as discussed above, this phase 2 trial also accrues patients with myelofibrosis who have been on ruxolitinib for at least 12 weeks and have not achieved a complete or partial response. As noted above, the second part of the study restricts eligibility to patients with baseline platelets <100,000/μL and provides free ruxolitinib and thalidomide to patients.

Myelofibrosis: ruxolitinib failure

1. **MANIFEST (NCT02158858):** BET inhibition down-regulates many oncoproteins of interest in the MPNs, e.g., NF-kappa B, c-Myc and Bcl-2 family members. This ongoing phase 2 study also has a monotherapy arm in which CPI-0610 is administered alone in patients who are no longer on ruxolitinib. The results thus far have been promising with benefit seen in terms of spleen, symptom as well as anemia responses (Talpaz, EHA 2020). Accrual to this arm of the study continues at MD Anderson.
2. **KRT-232 (NCT03662126):** As noted above, there exists a strong biologic rationale to test MDM2 inhibition as a therapeutic strategy in myelofibrosis. In the first results from this ongoing phase 2 study (Al-Ali, EHA 2020), a best spleen response rate of 16% was observed in patients with myelofibrosis with disease that had relapsed after or was refractory to ruxolitinib. This trial is continuing to recruit patients at MD Anderson, and is expected to be amended into a phase 3 trial.
3. **FREEDOM (NCT03755518):** Although the oral JAK2 inhibitor fedratinib is FDA-approved for the treatment of myelofibrosis, experience in the setting of ruxolitinib failure is limited (a spleen response rate of 30% and a symptom response rate of 27% have been reported). FREEDOM is a single-arm, open-label, phase 3b study of fedratinib, 400 mg daily, in patients who are resistant to or intolerant of ruxolitinib. Concomitant luspatercept is available for anemic patients. This trial is open to accrual at MD Anderson.
4. **MOMENTUM (NCT04173494):** The oral JAK1/2 inhibitor momelotinib may improve anemia via inhibition of ACVR1/ALK2, thereby suppressing hepatic hepcidin production. MOMENTUM is a randomized (2:1), phase 3 trial of momelotinib versus danazol in symptomatic, anemic patients with myelofibrosis who have previously failed an approved JAK inhibitor. This trial will open soon to accrual at MD Anderson.
5. **Pelcitoclax (NCT04354727):** Pelcitoclax is a Bcl-2/Bcl-xL inhibitor administered IV once weekly. This phase 1/2 trial enrolls patients who have previously received ruxolitinib or fedratinib, and were intolerant of, resistant/refractory to or lost response to the same. Patients with a sub-optimal response to ruxolitinib may also enroll. This trial will open soon at MD Anderson.
6. **PRT-543 (NCT03886831):** A novel epigenetic target of interest in the MPNs is the arginine methyltransferase, PRMT5. PRT-543 is an oral inhibitor of PRMT5 that is being studied in a phase 1 trial in patients with advanced solid tumors or hematologic malignancies, including myelofibrosis. This study is open to accrual at MD Anderson.

Myelofibrosis: anemia

1. **Activin receptor ligand traps:** This novel class of fusion proteins ameliorates anemia of diverse etiologies by sequestering ligands of the TGF-β superfamily that bind to the activin receptor to suppress terminal erythroid differentiation. Encouraging activity was reported in an ongoing MD Anderson phase 2 study of sotatercept (NCT01712308) for anemia of myelofibrosis, both when used alone and in conjunction with ruxolitinib (Bose, EHA 2019). Luspatercept, recently approved for the treatment of anemia in beta-thalassemia and myelodysplastic syndrome with ring sideroblasts, was studied for anemia of myelofibrosis in a phase 2 trial (NCT03194542) with promising results, particularly in transfusion-dependent patients receiving ruxolitinib (Gerds, ASH 2019). This cohort of the trial has since been expanded, and is recruiting patients at MD Anderson. A phase 3 study, INDEPENDENCE, of luspatercept in this population, is also forthcoming.
2. **INCB000928 (NCT04455841):** This is an oral ACVR1/ALK2 inhibitor that is being studied, both alone and in combination with ruxolitinib, in anemic patients with myelofibrosis in a phase 1/2 trial that will soon open to accrual at MD Anderson.

Elotuzumab for patients with myelofibrosis not candidates for JAK inhibitor therapy

Work from MD Anderson and Japanese investigators has shown that the fibrocytes that lead to bone marrow fibrosis in myelofibrosis are derived from monocytes which express SLAMF7. Elotuzumab is a SLAMF7-targeting monoclonal antibody approved for multiple myeloma. This phase 2 study (NCT04517851) enrolls patients with *JAK2*-mutated myelofibrosis who are not candidates for JAK inhibitor therapy (e.g., due to cytopenias/lack of splenomegaly or symptoms).

PTG-300 (hepcidin mimetic) for phlebotomy-requiring polycythemia vera (PV)

Polycythemia vera is characterized by iron deficiency, which is exacerbated by phlebotomy. PTG-300 is a hepcidin mimetic that is administered subcutaneously once a week. To be eligible for this ongoing phase 2 trial (NCT04057040), patients must be phlebotomy-requiring. Concomitant cytoreductive therapy is permitted, but not required. The goals are elimination of the need for phlebotomy and correction of iron deficiency. This trial is open to accrual at MD Anderson.

Ropeginterferon alfa-2b for hydroxyurea-resistant/intolerant essential thrombocythemia (ET)

Ropeginterferon alfa-2b is a novel, monopegylated interferon formulation approved in Europe for the treatment of patients with PV without symptomatic splenomegaly. It is administered subcutaneously, initially every 2 weeks and eventually every 4 weeks. This pivotal phase 3 trial (NCT04285086) is comparing ropeginterferon alfa-2b to anagrelide in patients with ET that is resistant to or intolerant of hydroxyurea. This trial will open soon at MD Anderson.

Avapritinib for patients with advanced systemic mastocytosis (PATHFINDER)

Avapritinib is a highly potent and selective inhibitor of mutant *KIT* recently approved for the treatment of *PDGFRA*-mutated gastrointestinal stromal tumor. The *KIT* D816V mutation drives the vast majority of cases of systemic mastocytosis (SM). In the phase 1 EXPLORER trial, an overall response rate of 77% was reported, and median overall survival was not reached for any of the 3 subtypes of advanced SM, i.e., aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (Gotlib, EHA 2020). Avapritinib at a dose of 200 mg orally daily is now being studied in the confirmatory phase 2 PATHFINDER trial (NCT03580655). This trial is open to accrual at MD Anderson.

Pemigatinib for FGFR1 (8p11)-rearranged myeloid/lymphoid neoplasms (FIGHT-203)

Myeloid/lymphoid neoplasms with *FGFR1* (8p11) rearrangement are an extremely rare and aggressive group of malignancies with a poor prognosis. Pemigatinib is an oral inhibitor of fibroblast growth factor receptors (FGFR) recently approved for the treatment of *FGFR2*-rearranged cholangiocarcinoma. FIGHT-203 (NCT03011372) is an ongoing, pivotal phase 2 trial of pemigatinib for *FGFR1* (8p11)-rearranged myeloid/lymphoid neoplasms. In preliminary findings from this study, an overall response rate of 85% was reported (Verstovsek, ASH 2018). This trial is recruiting patients at MD Anderson.

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.

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
Konopleva, Marina	*Deputy Chair, and Chief, Section of Leukemia Biology Research*	(713) 794-1628
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

Leukemia Faculty Contacts

(Continued)

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

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
Jain, Nitin	(713) 745-6080
Kornblau, Steven	(713) 794-1568
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
Freireich, Emil	(713) 792-2660
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
Ruvolo, Peter	(713) 745-9211
Wei, Yue	(713) 792-9854
Yang, Hui	(713) 792-2558
Zhang, Weiguo	(713) 794-4085