Leukemia insights

SEPTEMBER 2019

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

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.

Innovative Treatment Strategies for Classic and Atypical Myeloproliferative Neoplasms (MPN)

In August 2019, the FDA approved the JAK2 inhibitor fedratinib for the treatment of patients with myelofibrosis (MF), only the second drug approval in the classic myeloproliferative neoplasm (MPN) space after ruxolitinib was approved for MF in 2011 and polycythemia vera (PV) in 2014. Hopefully, this is the first of many regulatory approvals as a number of investigational agents appear promising in recent and ongoing trials. Below, we summarize the investigational approaches available for patients with MPN at MD Anderson.

1. Pemigatinib for myeloid/lymphoid neoplasms with *FGFR1* rearrangement (NCT03011372)

Myeloid/lymphoid neoplasms with a rearrangement of the *FGFR1* gene located at 8p11.2 represent an exceedingly rare but aggressive malignancy with no standard treatment options and a dismal prognosis. Eosinophilia is usually present and should trigger testing for rearrangements involving *FGFR1*, and also *PDGFRα* and *PDGFRβ*. Verstovsek et al. (ASH 2018) reported a response rate of 85% in this ongoing pivotal trial (FIGHT203) of pemigatinib, an oral inhibitor of FGFR1/2/3.

2. Avapritinib for patients with advanced systemic mastocytosis (NCT02561988)

Virtually all cases of systemic mastocytosis (SM) are driven by activating mutations at position D816 in the *KIT* gene. The median survival of patients with AdvSM is reported to range from 2 months (for mast cell leukemia) to 3.5 years (for aggressive SM, ASM). The multi-kinase inhibitor midostaurin is approved for patients with AdvSM, but response rates by modern criteria are low, and the drug causes myelosuppression and GI side effects. Avapritinib is a highly potent and selective inhibitor of mutant KIT. An overall response rate of 77% by modified IWG-MRT-ECNM criteria was reported in the Phase 1 EXPLORER trial (Radia, EHA 2019). Avapritinib is now being studied in the Phase 2 PATHFINDER study in patients with AdvSM. Limited reimbursement to offset travel costs is available.

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3. KRT-232 for patients with previously treated, high-risk PV (NCT03669965)

MDM2 inhibition (by idasanutlin) has been shown to be effective in patients with high-risk PV who are resistant to or intolerant of hydroxyurea (Mascarenhas, Blood 2019). KRT-232 is a highly potent, oral antagonist of the MDM2-p53 interaction. The first part of this study aims to select the best dose and schedule of KRT-232, which is then taken into a randomized comparison against ruxolitinib in the second part. To be eligible, patients must be resistant to or intolerant of hydroxyurea, or have previously received interferon. Prior ruxolitinib is not an exclusion.

4. PTG-300 for phlebotomy-requiring patients with PV (NCT04057040)

PTG-300 is a hepcidin mimetic that is administered by subcutaneous injection, initially weekly. This study enrolls patients with PV who require phlebotomies (three or more, at least four weeks apart, within 24 weeks prior to study entry; the most recent one should be within eight weeks of study entry). For those on cytoreductive therapy (hydroxyurea, interferon, ruxolitinib), the dose must be stable for ≥24 weeks with no planned change.

5. Sotatercept for patients with MF and anemia (NCT01712308)

Treatment options for anemia in patients with MF are limited, and the problem is often compounded by the use of JAK2 inhibitors, e.g., ruxolitinib or fedratinib. Sotatercept is a first-in-class activin receptor ligand trap that improves anemia by sequestering ligands of the TGFβ superfamily and preventing their interaction with the activin receptor. In an investigator-initiated trial at MD Anderson, sotatercept produced a 35% response rate (a mix of anemia response and transfusion independence) in patients not on JAK inhibitor therapy (Bose, EHA 2019). In patients on a stable dose of ruxolitinib for ≥8 weeks, the response rate was 23%. Results are pending from a similar, industry-sponsored trial of luspatercept, which is similar to sotatercept.

6. Luspatercept for patients with MF and anemia (NCT03194542)

A closely related congener of sotatercept, luspatercept demonstrated statistically significantly superior rates of transfusion independence in patients with MDS and ringed sideroblasts in a pivotal trial (MEDALIST, Fenaux, ASH 2018). As noted above, results from the trial of luspatercept in patients with MF and anemia are expected soon. One cohort from this trial (patients on a stable dose of ruxolitinib and red blood cell transfusion dependent) is being expanded to gain more experience in this difficult group.

7. Fedratinib for patients with MF who have failed ruxolitinib (NCT03755518)

The JAK2 inhibitor fedratinib was approved by the FDA in August 2019 for the treatment of patients with MF. In a recent re-analysis of the JAKARTA-2 trial employing stringent definitions of ruxolitinib refractoriness, resistance and intolerance, the rate of ≥35% spleen volume reduction on fedratinib at 24 weeks was 30%, and the rate of ≥50% reduction in total symptom score was 27% (Harrison, ASCO 2019). FREEDOM is a Phase 3b, single-arm, open-label trial of fedratinib 400 mg daily in patients who have "failed" ruxolitinib according to these new, stricter definitions.

8. Pacritinib for patients with MF and platelets below 50 x 10^9/L (NCT03165734)

There is currently no approved therapy for patients with MF and severe thrombocytopenia (platelets <50 x 10^9/L), and these patients have a poor prognosis. Pacritinib is a relatively non-myelosuppressive JAK2 inhibitor that has been studied with mixed results in two Phase 3 trials in patients with MF. A subsequent dose-finding study in ruxolitinib-pretreated patients with MF (PAC203) has completed accrual, and results are expected later this year. PACIFICA, a pivotal trial of pacritinib versus physician's choice (including low-dose ruxolitinib) in patients with MF and platelets <50 x 10^9/L, will open soon.

9. KRT-232 for patients with MF who have failed a JAK inhibitor (NCT03662126)

Up-regulation of MDM2 by $JAK2^{V617F}$ supports MDM2 inhibition as a therapeutic strategy in $JAK2^{V617F}$-driven neoplasms. Additionally, TGF-β is important in MF pathophysiology and increases MDM2 expression. As alluded to above, KRT-232 is a potent MDM2 inhibitor. Part 1 of this study aims to determine the optimal dose and schedule of KRT-232 in patients with MF who have failed treatment with a JAK inhibitor. This dose will then be explored in a larger number of ruxolitinib-exposed patients in the second part.

10. Tagraxofusp for patients with MF who have failed a JAK inhibitor (NCT02268253)

Tagraxofusp is a diphtheria toxin-containing, CD123-targeting fusion protein recently approved for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) that is also being studied in patients with CMML and MF. CD123-expressing plasmacytoid dendritic cells are present in the MF microenvironment and may be tumor-promoting. The drug is administered IV on days 1-3 every 21 days in this Phase 1/2 study. Patients must be refractory to, intolerant of or have relapsed on JAK inhibitor therapy.

Preliminary results (Pemmaraju, ASCO 2019) demonstrate activity in terms of spleen size reduction with a manageable safety profile.

11. CPI-0610 after, added to and with (in JAK inhibitor-naïve patients) ruxolitinib (NCT02158858)

CPI-0610 is an orally administered inhibitor of bromodomain and extra-terminal (BET) proteins. BET inhibitors synergize with ruxolitinib in preclinical models of MF by down-regulating numerous oncoproteins (NF-kappa B, c-Myc, Bcl-2 [Kleppe, Cancer Cell 2018]). The MANIFEST trial is studying CPI-0610 alone or added to ruxolitinib in patients who have had an insufficient response to the latter, and CPI-0610 in conjunction with ruxolitinib in patients not previously treated with a JAK inhibitor. Early results (Kremyanskaya, ASCO 2019, Hoffman, EHA 2019) are promising with activity observed in terms of spleen, symptom and anemia responses, as well as some encouraging signals with respect to bone marrow fibrosis improvement.

12. Parsaclisib added to ruxolitinib in patients with a sub-optimal response to ruxolitinib (NCT02718300)

Parsaclisib is an orally available, delta-isoform-specific inhibitor of PI3kinases. In this trial, parsaclisib is added to ruxolitinib in patients with MF who have been on the latter drug for six months or more but who still have a spleen palpable ≥10 cm below the left costal margin or 5-10 cm with active symptoms of MF. Based on early data from this trial (Daver, ASH 2018), parsaclisib appears to have a good safety profile with fewer immune-related toxicities than seen with other agents in this class.

13. PU-H71 added to ruxolitinib in patients with a sub-optimal response to ruxolitinib (NCT03935555)

JAK2 is a "client" of the chaperone protein heat shock protein 90 (HSP90); HSP90 inhibition, therefore, can lead to degradation of JAK2, possibly affording a way to circumvent resistance to JAK2 inhibitors through the "persistence" phenomenon (Bhagwat, Blood 2014). In the current trial, oral PH-H71 is being studied as an "add on" therapy in MF patients with a sub-optimal response to ruxolitinib.

14. Ruxolitinib plus thalidomide in patients with MF (NCT03069326)

Thrombocytopenia presents a particularly challenging management problem in patients with MF and, like anemia, is often worsened by ruxolitinib or fedratinib, especially early on. Previous studies suggest efficacy of low-dose thalidomide (50 mg daily) in ameliorating thrombocytopenia. This two-institution (MD Anderson/Memorial Sloan Kettering), investigator-initiated study enrolls patients with MF who are ruxolitinib-naïve or have been on ruxolitinib for ≥3 months without having achieved a CR or PR per IWG-MRT criteria. Thalidomide is added after 12 weeks of ruxolitinib monotherapy in the former patients. Early results are promising, particularly platelet responses (Rampal, ASH 2018, EHA 2019).

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.

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