ManagingMPN

New and Emerging Therapies in Myelofibrosis

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MediCom recently spoke with a leading expert to discuss several exciting agents in clinical trials that might help us further improve outcomes for myelofibrosis patients in the future.

What are some of the most promising investigational therapies for myelofibrosis (MF)?

Dr. Vachhani: We have come a long way in treating MF, but we still have a ways to go. There are certain high-risk mutations like ASXL1, EZH2, IDH1/2, SRSF2, AND U2AF1 that have poor response. We also still need to overcome the existing limitations of MF therapy; eliminating anemia and other side effects associated with JAK inhibitors would be an important advancement, as would targeting the downstream pathways of MF for a more tailored approach. Fortunately, we have several exciting agents in clinical trials that might help us further improve outcomes for these patients.

One of the most promising of these therapies is selinexor, which is currently under evaluation in combination with ruxolitinib in JAK inhibitor-naïve MF patients as part of the phase 3 XPORT-MF-034 trial (NCT04562389). This agent was granted a Fast Track designation for MF by the FDA in July 2023 based on the phase 1 portion of this study. As of the April 10, 2023 data cutoff, 91.7% of evaluable patients treated with selinexor plus ruxolitinib achieved a SVR ≥35% and 77.8% experienced a total symptom score (TSS) improvement ≥50% (TSS50%).[1] The corresponding rates in the intention-to-treat population were 78.6% and 58.3%, respectively. Importantly, researchers also reported improvements in major spleen and cytokine-related symptoms in all Myelofibrosis Symptom Assessment Form domains. This significant degree of SVR is very exciting, and we look forward to topline results from the phase 3 trial, which are anticipated in 2025.

Pelabresib is a bromodomain and extra-terminal domain (BET) inhibitor that has been shown in mouse models to synergize with JAK inhibitors to reduce the burden of myeloproliferative neoplasms (MPNs) and potentially extend survival. In the phase 2 MANIFEST trial, pelabresib was evaluated in several different settings: 1) pelabresib monotherapy after ruxolitinib failure,

2) add-on pelabresib to MF patients with inadequate response to ruxolitinib, and 3) JAK inhibitor-naïve MF patients receiving combination pelabresib and ruxolitinib.[2] By week 24, a substantial proportion of patients had achieved a spleen volume response (SVR) ≥35% (SVR35%, 68%, increasing to 60% at week 48), TSS50% (56%), improvements in hemoglobin (Hb, 36%), improvements in bone marrow (BM) fibrosis (28%), and reduced JAK2V617F variant allele fraction (VAF, 25%). Pelabresib has advanced to phase 3 (MANIFEST-2) in JAK inhibitor-naïve patients with or without ruxolitinib. Results from the MANIFEST-2 study are awaited in Q4 of 2023.

Navitoclax is a second emerging therapy that shows promise for MF. This agent inhibits B-cell lymphoma-2/extra-large (BCL-2/BCL-xL), which is linked to the JAK/STAT pathway. In the phase 2 REFINE open-label trial, navitoclax was utilized in different treatment settings.[3-5] In cohort 1, navitoclax was added to patients receiving ruxolitinib therapy.[3] This combination resulted in achievement of SVR35% in 31% of the cohort and achievement of TSS50% in 33%. Navitoclax/ruxolitinib combination therapy also improved BM fibrosis in 38% of patients and reduced JAK2V617F VAF by ≥20% in 23% of patients. Notably, improvement in BM fibrosis and VAF by ≥20% was associated with improved OS. However, this regimen did result in a high rate of reversible thrombocytopenia (88%), which may need to be addressed down the road. In cohort 3, this combination was evaluated in JAK inhibitor-naïve patients.[4] At endpoint, SVR35% was achieved in 52% of patients, BM fibrosis improvement in 35%, complete resolution of BM fibrosis in 22%, and reduction in IMbark, VAF by ≥20% or ≥50% in 50% and 36%, respectively. Cohort 2, included patients who are JAK inhibitor-experienced but not currently taking a JAK inhibitor.[5]

We are also keeping a close eye on imetelstat. This agent is a first-in-class telomerase inhibitor that demonstrated good efficacy compared with best available therapy (BAT) in the phase 2 IMbark study, which included patients with intermediate-2 or high-risk MF who relapsed or were refractory to JAK inhibitors.[6] At 24 weeks, the SVR rate was 10.2% and the symptom response rate was 32.2% (in the 9.4mg/kg dose). At a median follow-up of 27.4 months, the median overall survival (OS) was 29.9 months and the 12- and 24-month survival rates were 84.0% and 57.4%, respectively). Based on these findings, imetelstat is now being evaluated in the phase 3 ImpactMF trial which, like the IMbark study, is comparing imetelstat to BAT in JAK-relapsed or -refractory intermediate-2 or high-risk MF.[7]

Bomedemstat is an oral inhibitor of lysine-specific demethylase-1 (LSD1), a histone demethylase that is essential for self-renewal of malignant stem cells and progenitor maturation. Found to be clinically active against MPNs, this agent was evaluated in an open-label phase 2 study in JAK inhibitor-relapsed or -refractory MF patients with a platelet count ≥100 x 10^9/L.[8] In patients evaluable at 24 weeks with baseline TSS ≥20, 65% experienced a reduction in TSS, with 19% reporting TSS50%. SVR was also apparent in 66% of participants, with 28% achieving an SVR ≥20%. Additionally, 85% with BM fibrosis improved by ≥1 grade or remained stable, and 14% of participants requiring transfusions became transfusion independent.

Navtemadlin (KRT232) is also being developed to target murine double minute 2 (MDM2), a negative regulator of p53 which is overexpressed in circulating malignant CD34+ MF cells. Navtemadlin works against MF by restoring p53 activity to drive apoptosis of wild-type TP53 tumor cells via the expression of pro-apoptotic BCL-2 family proteins. Accordingly, that agent was recently combined with ruxolitinib in patients with primary or secondary TP53 wild-type MF who had suboptimal response to ruxolitinib monotherapy in a phase 1/2 study.[9] Eight patients (42%) treated with this regimen achieved SVR ≥25%, while 6 patients (32%) achieved SVR ≥35%. Additionally, a TSS50% was reported in 6 patients (32%). Navtemadlin is now being assessed in the phase 3 BOREAS study in relapsed/refractory MF and another planned phase 3 study of patients with suboptimal response to ruxolitinib alone, and we are hopeful the results will be positive.

Are there any investigational agents for MF-associated anemia?

Luspatercept was mentioned in the second newsletter of this series because it is included in the National Comprehensive Cancer Center (NCCN) guidelines, but theoretically, this agent is not yet approved for anemia in MF patients. Luspatercept is a recombinant fusion protein that improves anemia by trapping transforming growth factor beta (TGF-β) and inhibiting growth differentiation factor 11 (GDF11), which is a critical inhibitor of late-stage erythroid differentiation. This agent is approved for the treatment of anemia in myelodysplastic syndrome (MDS) and beta thalassemia and was recently assessed in a phase 2 study in MF. Transfusion-dependent (TD) patients with and without concomitant ruxolitinib therapy in 21% and 10%, respectively, achieved the primary endpoint of Hb increase of ≥1.5 g/L. Transfusion independence was also achieved in 32% and 10%, respectively. The ongoing phase 3 INDEPENDENCE trial (NCT04717414) is comparing luspatercept to placebo in TD patients receiving JAK inhibitor therapy.

What do you anticipate for the future of MF treatment?

I anticipate a treatment approach with a more refined stratification system based on an individual's splenomegaly, symptom, cytopenia, and mutational status. I am hopeful that we will be able to better address cytopenias and, in general, develop therapies with more appealing toxicity profiles. I would also like to witness the development of therapies that target specific high-risk mutations that we could use to tailor therapy based on mutational status. The therapies mentioned above represent an important step on this path, but there is potential for achievement of even greater outcomes as our understanding of MF grows.

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