Leukemia insights

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In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, M.D., Lucia Masarova, M.D., and Prithviraj Bose, M.D., we summarize available clinical trials for patients with myeloproliferative neoplasms (MPNs) that focus on targeting the driver mutations of either JAK2 or CALR. Learn more about our Leukemia program.

A new era of targeted therapy in myeloproliferative neoplasms (MPNs): Specific targeting of mutant JAK2 & CALR in novel Phase I clinical trials

The three classical myeloproliferative neoplasms (MPNs) are: 1) polycythemia vera (PV) 2) essential thrombocytosis (ET) and 3) primary myelofibrosis (MF). A new era of driver-mutation specific/selective targeting is underway. There are 3 known driver mutations that account for ~90% of our patients: JAK2, CALR and MPL. The JAK2V617F mutation is the most commonly occurring driver mutation across the MPNs (PV, ET, MF) and the calreticulin (CALR) mutation is the 2nd most common (occurring in ~20-30% of ET and MF). To date, the JAK inhibitors have been the only class of targeted agents approved for MPNs, however notably, their mechanism of action is, in part, inhibition the wild-type JAK-STAT pathway, i.e., they are not mutation-specific or selective. This leads to cytopenias as an on-target effect of JAK2 inhibition. We now have four novel clinical trials (2 targeting JAK2 and 2 targeting CALR mutation), most of which focus on inhibition of the mutant driver oncoproteins, while sparing the wild-type.

Clinical trials targeting the mutant JAK2 pathway:

The JAK2V167F mutation was first elucidated 20 years ago by four independent groups. It is remarkable that only two decades later, we now have the first mutant specific/selective inhibitor and the first type 2 inhibitor now available for patients in Phase I clinical trials.

1. AJI-11095. A Phase 1 study of AJ1-11095 in patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia

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myelofibrosis (PET-MF) who have failed a type I JAK2 inhibitor (JAK2i). AJI-11095 is a type II JAK2 inhibitor (NCT06343805). This clinical trial is for patients with MF who have failed therapy with one or more of the currently available JAK inhibitors, all of which are type I. Unlike the experience with BCR-ABL1 or BTK inhibitors, we do not see resistance-conferring point mutations in JAK2. Instead, most resistance is felt to be due to the "persistence" mechanism, where JAK-STAT signaling can persist despite a type 1 inhibitor being bound to JAK2. This occurs via heterodimerization between JAK2 and other members of the JAK family. Type 1 inhibitors (all 4 FDA-approved agents commercially available: ruxolitinib, fedratinib, pacritinib, momelotinib) bind to the active conformation of JAK2, while type II inhibitors bind to the inactive conformation. Preclinically, type 2 JAK2i have been shown to be able to reverse the persistence phenomenon. AJI-11095 is an extremely potent type 2 inhibitor of both wild-type and mutant JAK2. The clinical trial is enrolling. Patients must have had at least one prior JAK inhibitor. Dr. Bose is the PI.

2. **INCB160058. A study to evaluate the safety, tolerability of INCB160058 in participants with myeloproliferative neoplasms.** This a novel Phase I clinical trial of a JAK2V617F-mutant specific oral targeted agent (NCT06313593) for patients with relapsed/refractory myelofibrosis with a documented JAK2V617F mutation and exposure to one prior JAK inhibitor. The clinical trial is enrolling. Dr. Pemmaraju is the PI.

Clinical trials targeting mutant CALR:

The unique biology of mutant calreticulin lends itself to immunotherapeutic approaches. CALR deletions and insertions in exon 9, seen in 20-30% of patients with primary and post-ET MF, affect the C-terminal of the chaperone protein, leading to a loss of negative charge and calcium binding. Importantly, mutant calreticulin loses its endoplasmic reticulum retention motif and is secreted extracellularly, where it binds to the thrombopoietin receptor, MPL, to exert its oncogenic effect.

1. **JNJ-88549968.** This international Phase 1, first-in-human clinical trial (NCT06150157) features a T-cell redirecting bispecific (CD3 x mutant CALR) antibody, administered subcutaneously every 3 weeks in patients with MPNs with CALR mutations. The study is enrolling with focus on both patients with CALR-mutated myelofibrosis post one prior therapy, as well as patients with CALR -mutated ET. This study has dose escalation and expansion phases. Dr. Pemmaraju is PI.
2. **INCA033989.** This is a fully human IgG1 monoclonal antibody against mutant CALR being investigated in an ongoing international phase 1 trial with dose escalation and expansion phases (NCT05936359). Patients with CALR-mutant MF must have previously been treated with a JAK inhibitor and have relapsed/refractory disease or be intolerant. Splenomegaly, disease-related symptoms and platelets >50 x 109/L are required. The trial also features a CALR -mutant ET cohort. The antibody is given IV every 2 weeks. This trial is enrolling. Dr. Masarova is PI.