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The Mechanism of Action of JAK Inhibitors for Myelofibrosis

Announcer:
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Dr. Mascarenhas:
Hi, I'm John Mascarenhas from the Icahn School of Medicine of Mount Sinai and here in New York City and today I'll be reviewing the mechanism of action of three approved JAK inhibitors and one likely soon-to-be approved JAK inhibitor for myelofibrosis.

In this first slide, I'm showing the classic JAK/STAT signaling pathway which is hyperactive in myelofibrosis and is driven by mutations involving genes such as JAK2, CALR and MPL. Although 10% of patients lack these driver mutations and are considered triple-negative, yet all these patients have hyperactivity of the signaling pathway which signals through cytokine such as erythropoietin and thrombopoietin that then ultimately activates STATs through JAK mediators that regulate gene transcription and sends signals for proliferation and inflammatory cytokine production.

It is increasingly recognized that there are alternative pathways that are relevant to the biology of myelofibrosis and this is an example of one with the cartoon depicting the toll-like receptor Myddosome/IRAK1 pathway that ultimately results in activation of NF-κB and inflammatory cytokine production such as TNFα, IL-6, IL-8, and IL-10.

This signaling pathway is not muted with JAK1/JAK2 selective inhibitors and is triggered by inflammatory cytokines such as IL-33, alarmins, and IL-1 which have been shown to be upregulated in myelofibrosis. Here is the kinome profile of the four relevant JAK inhibitors, the three approved JAK inhibitors, ruxolitinib, fedratinib, and pacritinib, and the fourth JAK inhibitor that's under FDA review, momelotinib. You'll notice that these are all JAK2 inhibitors. Ruxolitinib and momelotinib are equal potent JAK1/2 inhibitors, whereas fedratinib and pacritinib spare JAK1.

They also have different adverse event profiles as shown on the right and we will talk about these in a minute. Not surprisingly, ruxolitinib which is a very effective JAK inhibitor approved for myelofibrosis in 2011, is a JAK1/2 inhibitor associated with treatment emergent cytopenias. Grade 3/4 thrombocytopenia, anemia and neutropenia we're seeing in 13%, 45% and 7% of patients treated in the comfort study respectively. Although these cytopenias are anticipated, they are easy to manage with dose holding and modification.

Here I'm showing the adverse event profile of fedratinib, which was evaluated in the Jakarta-1 study. This was a upfront study comparing fedratinib at two different doses, 400 milligrams daily, which is now the approved dose, 500 milligrams daily and placebo. This drug was very effective in reducing spleen and symptom burden but is also associated with on-target myelosuppression as shown here, as well as GI toxicity as it is a FLT3 inhibitor with diarrhea, vomiting, and nausea occurring in at least half the patients. Although Grade 3/4, nausea, vomiting and diarrhea only occurred in about three to 5% of the patient. This usually occurs within the first one to two months of treatment, is easy to manage with anti-emetic and anti-diarrhea and rarely is a reason for discontinuation.

One you be aware, there is a black box warning for Wernicke encephalopathy in which eight out of the 608 patients that were treated in

the program appeared to suffer from Wernicke encephalopathy. This is easy to manage with checking thymine or B1 levels upfront when prescribing fedratinib and every three months and repleting as necessary. Delving further into the kinome profile of the approved JAK inhibitors, pacritinib, ruxolitinib, fedratinib. As I mentioned before, pacritinib and fedratinib are also FLT3 inhibitors, and importantly down below pacritinib is the only IRAK1 inhibitor, which stands for IL-1 Receptor-Associated Kinase 1.

There may be some benefit in sparing JAK1 as I show you here as JAK1 has been implicated in megakaryopoieses and platelet production and inhibiting this could lead to and exacerbate thrombocytopenia. Therefore, pacritinib is an interesting drug as it inhibits both JAK2 which leads to hematopoietic growth factor production and proliferation as well as IRAK1, which again mediates NF-κB and STAT production which can also down-regulate pro-inflammatory cytokine and growth factor production.

So one may be able to deliver this drug and inhibit two relevant pathways to the biology of myelofibrosis which would likely explain why this drug was effective in Phase III testing in patients with low platelet counts. Here I'm showing the spleen volume response at 24 weeks of 35% or greater in patients with platelet counts less than 50,000 in the Persist-2 Randomized Phase III study which compared pacritinib to best available therapy in patients with platelet counts less than a hundred thousand irrespective of their past treatment with a JAK inhibitor.

In this analysis, 22% of pacritinib treated patients at 200 milligrams twice daily, which is the approved dose, achieved SVR 35% versus 3% in the best available therapy arm which half the patients received ruxolitinib.

If you look at patients specifically with platelets less than 50,000, 29% of patients achieved SVR 35% versus 3%. And importantly as a IRAK1 inhibitor which likely leads to less myelosuppression, clinical improvement of two grams per deciliter in hemoglobin or conversion from transfusion dependence to independence at week 24 was seen in 25% of the patients treated with pacritinib 200 milligrams twice daily between baseline and week 24 compared to 12% in the BAT arm.
And if you look to the right of the slide, even in those patients who were receiving transfusions and continue to receive transfusions, there was a drop in the units per month transfused from 1.06 at baseline to 0.67 at week 24 in the pacritinib arm.

It has been recently appreciated that other kinases may be important for effects on anemia. Here I'm showing you ACVR1 or ALK-2 in which ACVR1 activation leads to increased hepcidin gene expression, and hepcidin decreases plasma iron and hepcidin levels have been shown to be elevated in myelofibrosis. Therefore, momelotinib which also inhibits ACVR1 in addition to JAK1/2 signaling, leads to reduction in hepcidin levels and improvement in iron release for hematopoiesis.

This likely explains why in the Momentum study which was the Randomized Phase III study that was just resulted and reported at EHA and ASCO in 2022, comparing momelotinib to danazol in patients who have been previously treated with ruxolitinib and remain anemic.

I should say 31% of patients were transfusion independent at week 24 compared to 13% at baseline in the momelotinib treatment arm versus 20% at week 24 in the danazol treatment arm and this was statistically significant for a non-inferiority comparison. So, you can see on the right the anemia responses and in terms of mean hemoglobin improvement were significant and rapid with momelotinib and durable across the 24 and beyond weak period into the open-label period of the Momentum study.

Lastly, I want to point out recent data that was presented by Steven Oh, that pacritinib also apparently is an ACVR1 inhibitor. In fact, here in comparison to momelotinib may be a more potent ACVR1 inhibitor and this may also explain, in addition to the IRAK1 inhibitory properties of pacritinib, the ability to see anemia responses up to 25% in the 200 milligram twice daily arm in Persist-2.
So, broadening this discussion, we have three approved drugs, all JAK2 inhibitors, ruxolitinib and momelotinib are JAK1/2 inhibitors. Momelotinib is also an ACVR1 inhibitor. Pacritinib spares JAK1, is a IRAK1 and ACVR1 inhibitor and fedratinib is a selective JAK2 inhibitor. Each drug likely finds itself a niche with distinct toxicity profiles that are in large part dictated by their kinome profiles. I hope I've provided some insight and some information regarding this aspect of JAK inhibitor therapy in myelofibrosis and I appreciate your attention to this talk. Thank you.

Announcer:
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