Meeting Highlights in Myelofibrosis from the ASH Annual Meeting
Questions & Answers

Dr. Kuykendall: Where would you place the newer JAK inhibitors over first-generation JAK inhibitors in myelofibrosis?

When we think about newer JAK inhibitors, I think all of them are quite similar in some ways, in the sense that they're inhibiting JAK2, but I think that they have some varying additional inhibition profiles, also some different off-target effects that can lead to some different toxicities. When we think about it right now, we have ruxolitinib approved in 2011, fedratinib approved in 2019, and then more recently, pacritinib, which was approved last year on an accelerated basis. I think very clearly right now, ruxolitinib is the most often used.

There's a lot of comfort with dosing. I think the challenges there, are in low platelet counts, certainly in anemic patients, it doesn't help with that. It can limit the dosing of ruxolitinib, and we know that dose matters. It's dose-dependent in terms of spleen volume reduction. I think fedratinib has the potential benefit of being fully dosed in platelets between 50,000 and 100,000, still causes some anemia and thrombocytopenia, but it seems very potent from that standpoint, has some FLT3 inhibition.

That brings with it some GI toxicity that was quite concerning early on, but now seems to be somewhat mitigated with giving a high-fat meal and maybe antiemetics and antidiarrheals as needed. Then pacritinib has this niche for lower platelet counts, less than 50,000. That's what its accelerated approval is for, but also seems to be effective outside of that realm. We'll see where exactly that falls. Then I think the big question is where does momelotinib sit? For a long time, we thought if this gets approved in a few months, this is an agent that could help with anemia, which is something we struggle with, certainly with ruxolitinib and fedratinib.

Now pacritinib is also making a case for that as well, with its ACVR1 inhibition and potential to improve anemia. I think that overall, it's hard for me to say one JAK2 inhibitor is better than another. They've rarely been compared head-to-head. If there were any comparisons, it was momelotinib and ruxolitinib. We don't necessarily think that one is necessarily better than another, but certainly they're different and they have different toxicity profiles. I think that it allows us to individualize therapy for patients a little bit more than we've been able to do previously.

In the future, there could be a potential for a mutation-specific JAK inhibitor down the road, and that would be certainly very exciting over our current JAK inhibitors that more broadly inhibit the JAK/STAT pathway. Any other thoughts from Dr. Ali or Oh?

Dr. Oh: I think you covered it quite comprehensively and nicely, Dr. Kuykendall. I will just reiterate that there certainly is a great deal of overlap between these JAK inhibitors, the four that we're expecting to have officially approved pretty soon. Also, given that being on an individualized approach to find the best profile works for specific patients, and maybe

that what you start with may end up being something different than what a patient may ultimately later on find is the best fit for them, both in terms of the specific benefits, but also the toxicity profile.

Dr. Kuykendall: I'll give Dr. Ali the last word with the last question, which is with ASCO and EHA on the horizon, what do you think may be the hot topics related to all you have discussed today? What are you looking forward to at EHA and ASCO? Anything specific or more of a continuing the story on some of the things we already talked about today?

Dr. Ali: I think definitely updated results on some of the combinations that we talked about. Also, there's another combination that's looking at selinexor, which is a XP01 inhibitor. It's also looking quite effective in the upfront setting. I am mainly looking at the updated results for the study, and some of the other combinations as well.

Dr. Kuykendall: Wonderful. Thank you very much for your attention.