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The Long-Term Safety of Momelotinib for Myelofibrosis: A Poster from ASH

**Announcer:**
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by GSK. Here's your host, Dr. Charles Turck.

**Dr. Turck:**
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the long-term safety data from a pooled analysis of a trio of phase 3 randomized controlled trials on the treatment option momelotinib for patients with myelofibrosis is Dr. Douglas Tremblay. Dr. Tremblay is a hematologist affiliated with Mount Sinai Hospital and an Assistant Professor at the Icahn School of Medicine in New York. Dr. Tremblay, it's great to have you with us today.

**Dr. Tremblay:**
Thank you so much for having me. I really appreciate it.

**Dr. Turck:**
So, Dr. Tremblay, would you give us a sense of the rationale and the overall objective of the pooled analysis?

**Dr. Tremblay:**
So in myelofibrosis, there are now four different JAK inhibitors that are approved for treatment. And while we have really great long-term safety and efficacy data for one of those JAK inhibitors, which is ruxolitinib, there's less known about the other JAK inhibitors' long-term safety effects. And that's because for two of those JAK inhibitors, pacritinib and fedratinib, the clinical trials had to end early, so long-term data is really sparse on the safety of those agents. But momelotinib, which is the newest JAK inhibitor approved for myelofibrosis, has a benefit of having three randomized controlled trials with years of follow-up, so that we can really look at not only the efficacy and how this drug really improves clinical endpoints, including splenic symptoms and anemia, but also long-term safety. And this is needed because patients are staying on these drugs for longer periods of time, and so really getting a sense and understanding of the long-term safety data is important to identify any sort of late-term toxicities that may be relevant for patients.

**Dr. Turck:**
And what can you tell us about the design of this analysis, the trials included in it, and which clinical endpoints they examined?

**Dr. Tremblay:**
This study pooled three different clinical trials, as you mentioned: SIMPLIFY-1, which is a randomized controlled trial of ruxolitinib compared to momelotinib in patients who are JAK inhibitor naïve, SIMPLIFY-2, which is a randomized controlled trial of momelotinib versus best available therapy in patients who've previously been treated with ruxolitinib, and then the most recent trial is MOMENTUM, which is momelotinib versus danazol in anemic myelofibrosis patients who have previously been treated with a JAK inhibitor.

So this encompasses a total of 725 myelofibrosis patients, which is a very large number of patients treated with momelotinib, and they also looked at a long-term extended access program, which was able to gain even more data, especially about non-hematologic adverse events. So there are certain adverse events that are of clinical importance that are relevant, especially with longer-term use of JAK inhibitors, and those include development of malignancies in especially acute myeloid leukemia as well as other secondary malignancies. Opportunistic infections have been somewhat of a concern with ruxolitinib, and so understanding what some of the opportunistic infections that could arise is important, and then also peripheral neuropathy, which was an adverse event that came up earlier in the development of momelotinib.

And finally with JAK inhibitors as a whole, there's been a long-standing concern, especially in the rheumatologic space, about thromboembolic events and blood clotting. And so this analysis also really looked at this as well. Now from a technical method standpoint, there's a lot of variation in how long patients were exposed to momelotinib, so they used a method that is called an exposure-adjusted adverse event rate to really try to understand how long patients were exposed for and really adjust based on that.

**Dr. Turck:**
And, Dr. Tremblay, before we jump into the results and the safety analysis we'll be discussing, and for some context, would you tell us generally about what these trials found as far as the efficacy of momelotinib is concerned?

**Dr. Tremblay:**
Sure. So I'll basically try to summarize these trials and really focus on MOMENTUM, which is the most recent one. So in these trials, what they really show is that momelotinib is a very effective JAK inhibitor at improving spleen sizes and improving symptoms. And there's some nuances to the finding's symptoms in SIMPLIFY 1 and SIMPLIFY 2, but I'll mainly focus on MOMENTUM, which really lead to the approval of momelotinib in 2023.

So it compared patients who've been previously treated with a JAK inhibitor to momelotinib versus danazol, and these were symptomatic patients with a primary endpoint looking at who had a better symptom response. And not surprisingly, there was significant benefits in symptom responses with momelotinib compared to danazol, so better at symptoms and better at spleen reduction. Also not surprising—and the most important finding—is that danazol, which is an active comparator arm in this trial, was used to really assess what the sort of benefits were in terms of improvements in red blood cell transfusion needs. This is a very high unmet need in myelofibrosis, and in MOMENTUM, what they found is that there is a significant improvement in those patients in terms of improving hemoglobin levels and trending towards improvements in transfusion independence with momelotinib versus danazol. This led to the FDA approval of momelotinib based on this MOMENTUM trial that really showed benefits in the second-line setting with spleen symptom and also improving anemia.

**Dr. Turck:**
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Douglas Tremblay, and we're discussing the long-term safety of the treatment option momelotinib for myelofibrosis.

So now that we know some background about the clinical trials included in the analysis we'll be discussing, what can you tell us about momelotinib's long-term safety and tolerability?

**Dr. Tremblay:**
So what this study really demonstrated is—and they did not focus on the traditional endpoints in myelofibrosis but just spleen and symptoms; these have been previously reported. But I think a few findings are really important. The median duration of momelotinib exposure was 11.3 months. And as of the data cutoff, about 12 percent of patients were treated for more than 5 years, including 75 percent of patients on the extended access program.

And discontinuations were largely due to myelofibrosis progression or complications like infection. So that 11.3 months is a little bit challenging to interpret because this included front-line patients in the SIMPLIFY 1 trial as well as second-line patients in the SIMPLIFY 2 and MOMENTUM trials. But still, 11.3 months is a pretty good duration of treatment exposure for momelotinib.

So in terms of efficacy, there was a lot of data that I thought was interesting with regards to survival. So the median overall survival in this population is difficult to characterize because it's so heterogeneous. But in this trial, the median OS was not reached, and the estimated survival probabilities at 2 years was around 75 percent. At 4 years, it was around 60 percent. Around 6 years was around 50 percent, which considering that many of these patients were second-line treated myelofibrosis patients really did suggest that there is a good overall survival here as well.

The other efficacy endpoint that really focused on in this analysis was how hematologic values changed up until about 48 weeks of treatment, and that's really where data collection ended for this program. What they showed is that in patients who were treated with momelotinib, they really had significant improvements in hemoglobin, which has already been described. And importantly, those patients who were randomized to best available therapy or danazol and then switched over to momelotinib then gained improvements in hemoglobin as well.

So there's really nice figures here that show really significant jumps in hemoglobin levels in patients treated with momelotinib, which further goes to cement the efficacy of momelotinib as an anemia-improving drug.

**Dr. Turck:**
And with all this in mind, how do these results add to what we previously knew about momelotinib? And what kind of impact might this

analysis have on our patients?

**Dr. Tremblay:**
Well, some of the safety information I thought was important too as it relates to the diarrhea being a common AE as well as nausea and cough, but the things that were really reassuring, I think, is that there was no late-term toxicities. There was no jump-in toxicities over time. There were things like malignancies and opportunistic infections that occurred, but they were generally a low grade, not as serious, and were not associated with significant increases over what is expected with this age group. And because there's no time trend to it, it doesn't suggest cumulative toxicity with exposure or late-onset toxicities as well. And in fact, most toxicities decreased over time.

So I think that it's important that the safety analysis is performed so that we really have long-term safety data to inform our patients about what happens with longer-term treatment with these drugs. And I think something that is needed with more JAK inhibitors in general is with patients living longer with myelofibrosis and being on these drugs for a longer period of time, how can we really assess the risk/benefits as it relates to the risks of these long-term toxicities? And thankfully, in this analysis, there wasn't a huge safety signal that was at all concerning with longer-term use.

But there are some caveats here; I think it's important that we really think about some of the issues with this as well the limitations since long-term data is important. And it's not available with the other two JAK inhibitors, but it's also really important to look at real-world safety data as well. So it's not enough just to say these are very subclinical trial patients that have been followed on a very strict regimen, but how do these drugs work in the real world where patients don't necessary mirror the patients that are in clinical trial? And I think that's something that needs to be established for momelotinib and other agents in myelofibrosis.

**Dr. Turck:**
Well, we've certainly covered a lot today, but before we close, Dr. Tremblay, are there any final thoughts you'd like to leave with our audience about the safety analysis of momelotinib or myelofibrosis more broadly?

**Dr: Tremblay:**
I think this analysis, in particular, gives some reassurance for the safety of momelotinib, particularly with some of those safety concerns regarding thrombotic events, peripheral neuropathy, and secondary malignancies. There wasn't a major signal that these were issues that got worse over time, and there's cumulative toxicities. So I think there's reassuring data, and this will help me counsel my patients about some of the longer-term safety effects of momelotinib.

This study should really be applauded for looking at safety as an endpoint because as patients are doing better with this disease and quality of life is such an important metric in myelofibrosis, I think safety is something that needs to be factored into the decision-making regarding JAK inhibitor selection now that we have so many options.

And again, I think that this data is really compelling, but how do we move this into the next step where we look at how the drug and other drugs perform in daily practice and not clinical trials? I think that is something that is really needed to understand if this clinical trial experience that's reported here is recapitulated in the real world.

**Dr. Turck:**
Well, as those comments bring us to the end of today's program, I want to thank my guest, Dr. Douglas Tremblay, for joining me to discuss the long-term safety data on momelotinib and how they might impact the way we treat our patients with myelofibrosis. Dr. Tremblay, it was great having you on the program.

**Dr. Tremblay:**
Thank you so much. I really appreciate it, Dr. Turck.

**Announcer:**
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