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https://reachmd.com/programs/cme/notable-highlights-and-advances-in-myelofibrosis-from-ash-2022/14983/

Released: 12/22/2022
Valid until: 12/22/2023
Time needed to complete: 1h 18m

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Notable Highlights and Advances in Myelofibrosis From ASH 2022

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Dr. Mascarenhas:
Hi, I'm John Mascarenhas from the Icahn School of Medicine at Mount Sinai in New York City, and I'm thrilled to be joining my good friend Srdan Verstovsek from MD Anderson. Srdan, thanks for joining us.
Dr. Verstovsek:
Hello John.

Dr. Mascarenhas:
So I think right now we'll pivot towards some of the data that was presented at ASH as it relates to the JAK inhibitor space. And maybe you could start us off with what was new at ASH as it relates to momelotinib and maybe some longer term follow-up?

Dr. Verstovsek:
As we know, momelotinib is a new JAK inhibitor that we would expect to be approved by summer 2023. Not because primarily that would be increasing the spleen and symptom control, but because of anemia benefits. So the phase 3 randomized study called MOMENTUM study was a blind and randomized study comparing danazol to momelotinib for the benefit of symptom control and anemia benefit. And that was transfusion independence. It was better than control. And that's why we talk about possible approval for these two benefits, which is unlike any other.

What we learn at this ASH is that these benefits are long lasting. We have a 48-week follow-up presented. People don't want to lose benefit much at all. We also had a presentation on long-term safety, not only from that study but also from prior studies. There were two other phase 3 studies done in the past, and now we have hundreds of patients followed. It appears to be very safe. There is no one single major problem, like no amazing bad GI or neurological or anything like that. It seems to be very tolerable, and the dose intensity is very good. Hardly anybody changed the dose.

And also from practical point, some small but very important points of how to change from one JAK inhibitor to the other. Because MOMENTUM study was in secondary setting, so people were previously treated with ruxolitinib. And what we know from a past experience now reanalyzed, is that you don't need to worry much about changing ruxolitinib to momelotinib. They're similar in tackling the JAK1 and JAK2. So antiproliferative antiinflammatory potential, in particular are similar and you don't need to worry about the rebound of symptoms in people who suddenly stop ruxolitinib. Momelotinib will pick up the benefit and you can change it without much of a worry. So quite a few long-term safety and practical points on momelotinib at ASH this past week.

Dr. Mascarenhas:
Excellent. There were two presentations that involved momelotinib I thought were interesting. I'll add to it. One was the idea that patients, and this was shown with the simplified study originally and now with the MOMENTUM study, the fact that patients who attained

anemia responses, which is what in many ways differentiates momelotinib from the other JAK inhibitors, were more likely to also enjoy survival benefit. And I think that's an interesting component to this.

We know that anemia is a poor prognostic marker in this disease and incorporated into risk stratification models. But it is interesting to see that correction of anemia, resolution of anemia, improvement anemia would also potentially set that patient on a better clinical outcome course. Whether that's the inherent biology of the disease, or those patients are responding, or it's literally improving anemia. I think is not quite clear, but it's an interesting finding nevertheless.

Dr. Verstovsek:
And along these lines of a survival benefit or a clinical benefit and a correlation with any biological parameters that we usually measure, like a bone marrow or fibrosis. That was interesting presentation on the long-term follow-up average five to six years, if I'm correct, of several hundreds of patients treated with momelotinib or ruxolitinib from this past phase 3 studies, which revealed no correlation between the bone marrow change and the clinical outcomes.

For example people had a worse fibrosis over time, but they still improved the anemia. Or the other way around if there was improvement in the fibrosis, there was no improvement in the spleen. So basically there no connection between any of the benefits, anemia, spleen or symptoms, and the change for worst or for better of the bone marrow fibrosis. Telling us that more practical issues like anemia response and transfusion independent appear to be more valuable as a marker for survival benefit rather than the biological marker of a change in this case, of a fibrosis score.

Dr. Mascarenhas:
Yeah, excellent point. I think what I took away from that abstract was that if one were treating with a JAK inhibitor, particularly monotherapy, and it's probably true of any JAK inhibitor, we shouldn't really be looking at bone marrow fibrosis because it really doesn't help guide us in treatment in any respect. It doesn't associate with any of the meaningful clinical outcomes. And really in the commercial space when using in the community, one should not be looking to repeat bone marrow biopsies to assess bone marrow fibrosis response because it really is not a meaningful biomarker when treating with these drugs, and is an unnecessary procedure unless patients have an actual change in their disease features.I think to balance out this discussion, maybe you could highlight for us if there were any updates on fedratinib, which as you pointed out is often relegated to the second line setting.

Dr. Verstovsek:
Interestingly, some years ago fedratinib was also published as a changing the bone marrow fibrosis. But as you said, we do not need to do any bone marrow biopsies with any JAK inhibitor to look at changes in biological parameters. We only need to do biopsy if there is a progression, the bloods go up or you lose the response and you want to explain that and start something new.

So fedratinib is primarily used in clinical practice in a second setting. And at this ASH there was a final result of the phase 2 open-label study called FREEDOM study, which was throughout United States, in a second line setting, specifically very well defined group of people who are resistant and refractory intolerant to ruxolitinib. And we got a confirmation which we suspected from the past study that about a quarter of the patients have very good response. We call this about half of the spleen gone or a 35% volumetric reduction, and many people feel better about the same range. So 25, maybe 30% response rate, which is really good actually in a secondary setting because not too many medications can achieve that, not even investigational agents.

I take this as my benchmark, what to expect from therapy in a secondary setting. Quarter to a third response rate. The same with pacritinib. If we recall the studies overall response rate is about 25, 30% even in second line. What happened with the updates on the pacritinib at ASH?

Dr. Mascarenhas:
So the pacritinib updates were centered in large part around a recent understanding and discovery that pacritinib is also an ACVR1 inhibitor. And ACVR1 is a pathway that's related to hepcidin and anemia responses, and was first really appreciated in the setting of momelotinib. It was appreciated very early on in the early phase studies that momelotinib did have this anemia response that was quite durable as been published.

And then as the drug was in further clinical development, that response was tagged to the fact that momelotinib was an ACVR1 inhibitor. And then more recently Steve Oh and colleagues looked at the kinome profile of pacritinib and also recognized that it is also an ACVR1 inhibitor, which fedratinib and ruxolitinib are not. And that might also explain why at least give some mechanistic explanation probably, and I don't think it's that simple, in addition with other pathways that are relevant like IRAK1 per pacritinib, why you do see some patients developing transfusion independence who are transfusion dependent or have a two gram per deciliter increase in hemoglobin in about a quarter of patients that were treated in the PERSIST-2 study, which again were patients already with low platelets and significant cytopenia.

You have two drugs now that hit this relevant pathway and can provide in a proportion of patients spleen, symptom and potentially even anemia benefit, which really I think broadens our ability to help our patients. Another interesting pacritinib abstract was tying in the significance of thrombocytopenia with some of the features that we don't typically think of. So the fact that thrombocytopenia when looking at symptoms or even individual symptoms and spleen related symptoms, symptoms that you don't normally think of as a symptom that would associate with thrombocytopenia, were more closely associated with thrombocytopenia than even anemia in this analysis by Dr. Palmer and colleagues.

I think our conventional understanding or appreciation of the significance of cytopenia is evolving. And we recognize that it's not just a hallmark of the disease and a feature of disease progression, but can also be used as a biomarker to identify patients who are probably more in need and consider therapies that are now evolving beyond the traditional ruxolitinib and fedratinib approaches.

Dr. Verstovsek:
And there were not many updates on the ruxolitinib alone, but there were a bunch of, as its customary these days, reports on the combinations on top of ruxolitinib.
Now very briefly, very briefly, we are waiting for phase 3 results while we are learning more about the longer term follow up of patients on the combinations with the pelabresib for example, or with the navitoclax or parsaclisib, they are available. They improve the spleen of symptoms, maybe even anemia in some cases. The phase 3 studies are focused specifically on boosting that spleen and symptom response, and hopefully in a couple of years we'll have some of those mature enough.

But for now, I think in general, without going into much details, they appear promising to me. I would like to see also durability of that benefit as the next step. I think we wrote the editorial together on that particular point, right?

Dr. Mascarenhas:
Yep. Absolutely. I totally agree with you. It's an exciting time to be in clinical investigation in this field as the paradigm might shift from monotherapy JAK inhibitor, the combination. And I would even throw out there that it would be fascinating to see how some of these agents that clearly have even single agent activity, but better in combination with the JAK inhibitor, do with some of these now emerging inhibitors like pacritinib and momelotinib.

Can you effectively add ABT inhibitor or a BCL2 inhibitor and get similarly maybe even better results with these other JAK inhibitors. I think there's a lot to be done. I know that you and I will continue to be busy and continue to interact on many levels.

I thank you for joining us and sharing your knowledge and experience today as we discuss some of the highlights at ASH 2022. So thank you for listening and we'll sign off.

Dr. Verstovsek:
Thank you.

Announcer:
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