MPN Roundtable Year in Review: The Impact of New Data in Myelofibrosis on the Evolving Treatment Landscape

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Dr. Bose: Hello and thank you for joining us today. I am Dr. Prithviraj Bose, Associate Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston, Texas. I have the pleasure of having with me today, Dr. Ruben Mesa, Professor of Medicine and Director of the Mays Cancer Center at UT Health, San Antonio MD Anderson, and the Mays Family Foundation Distinguished University Presidential Chair in San Antonio, Texas, and welcome.

Dr. Mesa: Thank you very much. Thank you.

Dr. Bose: So, we're pleased to be talking today about some of the most relevant data and clinical applications of new advances in myelofibrosis presented at this year's major congresses in hematology, EHA and ASH. We will focus on the recent findings in the space of JAK inhibitor therapy, the evolving role of these agents in the current treatment paradigm and the best practices regarding the clinical use of these therapies.

Ruxolitinib was recently approved for the treatment of steroid refractory acute graft versus host disease. At ASH this year, there was some data from a pilot study of peritransplant administration of rux in patients with myelofibrosis. So, this was a small study, it was actually 12 patients as presented at ASH.

The objective was to identify the MTD and the recommended phase II dose of rux in this setting. They started at Day -3 pre-transplant and gave rux continuously through Day +30, and they looked at 2-dose levels 5 and 10 milligrams twice daily, and they tapered off the rux by Day +33.

And the primary endpoint here was safety. Again, this is really the first time rux is being dosed through the transplant and again, as I said 12 patients, six in each arm so the 5 and the 10 milligrams b.i.d. The median age was around 53; for the lower dose 68, for the higher dose group, the one year survival was 80%, PFS was 68%, non-relapse mortality was 21%. Importantly, all patients engrafted and median time to engraftment was about 19 days in the lower dose arm and 16 days, so pretty similar in the higher dose arm.

They did not observe any hematologic dose-limiting toxicities. They did have some grade three and higher adverse events, which to me do not appear related to the rux, but there were some cardiac pulmonary and GI toxicities that were grade 3 and higher in the 5-milligram group. There was one case in the 10-milligram group of grade 3 or higher lung toxicity. There were two deaths, one from respiratory failure in the lower dose group and one from acute GVHD in the higher dose group. Acute GVHD was uncommon and median time was 20 days, a median time to onset of acute GVHD was 20 days in the lower dose group and 51 days in the higher dose group. Grade 3 to 4 acute GVHD was uncommon, seen in only one out of the 12 patients.

Now, they looked at PK and this was dose proportional. There were really no surprises with the PK. Now, given that rux was recently approved for acute GVHD, steroid refractory, one wonders how this might change things in the way we practice. Now, my take on this is, in general, what we do now is that we taper off the rux over five to seven days and basically give the last dose the day before they start conditioning. And now here, we have an example of giving it right through the transplant. Ruben, your thoughts?

Dr. Mesa: Well, I think that's an important study really for a variety of reasons. First, the stoppage of rux pre-transplant always introduces another variable, because there can be disease rebound and increase in cytokines, patients feel worse, and there have been rare examples of patients having some amount of a withdrawal syndrome that can occur as well. So there's a variety of negatives with stopping ruxolitinib and indeed, we've learned in many ways although there's condition that starts on day one, the myelofibrosis is not gone. So there are variety of reasons to think that continuation of rux even from the myelofibrosis end probably makes sense to do throughout the transplant process. This I think helps further validate some of the safety around that and it may have some benefits as it relates to GVHD. We know the process of a patient getting cured of myelofibrosis is not an instant one. The JAK2 allele burden tends to go away, but it usually takes several months. It takes months for the fibrosis to resolve, for the spleen to shrink. I think the evolution of ruxolitinib continuing on through the peritransplant process, and eventually being tapered months after the transplant, probably is where we will likely end up, that may be more beneficial for the patients, it may be more biologically accurate than just acutely stopping the drug.

Dr. Bose: Data from the REALISE trial were also presented this year that was Dr. Cervantes at EHA 2019. This trial looked at an alternative ruxolitinib dosing regimen in anemic patients with MF. So a little bit different from dosing it according to platelet count as we normally do. Can you review with us the data from that trial?

Dr. Mesa: Sure. Happy to. So as background, the dosing in the product label for ruxolitinib was developed from the phase III study that was led at our institutions that Dr. Bose and I have been at, and was very focused around a rapid response within 24

weeks and around the platelet dosing. We know in clinical practice, we've learned a tremendous amount over the several years since approval, and that sometimes starting at a little lower dose, and then increasing the dose may be beneficial as it relates to less kind of drug emergent anemia and better tolerability.

So this study was a prospective approach, where they started at 10 twice a day for 12 weeks, and then titrated the dose up. It was a multicenter phase II for patients who would benefit from ruxolitinib, and then they would titrate up to either 15 or 20 milligrams twice a day, based on efficacy as well as being mindful of the platelet count.

They included 51 patients with a median duration of exposure of over 38 weeks and the pattern that they observed, matched what we've seen in practice. That there was an initial drop in the hemoglobin but then stabilization and the platelets levels then remain constant. Patients were then able to slowly increase the dose as planned, and the degree of kind of drug emergent anemia and cytopenias was less than had been a concern.

The most common adverse events they saw, not surprisingly, were anemia and thrombocytopenia with no significant non-hematologic AEs, with good improvement in symptoms as really one might expect. So as conclusion, this alternative dosing regimen starting at 10 twice a day, with a gradual uptick at week 12 was efficacious in patients with myelofibrosis in baseline anemia. Safety and efficacy was comparable to our prior studies. The splenic response rate was similar in both transfusion and non-transfusion dependent patients. So I think that it's a solid and impactful set of data, that the takeaway for the treating physician is that this is not an unreasonable approach to dosing, that can help to minimize drug-emergent anemia, but still really maintain efficacy and safety. How about yourself? How do you think this might impact your practice?

Dr. Bose: You know, I think it's very reassuring that doing it this way preserves the spleen response rate. Granted, this was by palpation, but it looks pretty solid. And we've always felt that we need to optimize the dose of rux to get the best spleen response, but this tells us that if we do it for 12 weeks at a moderate dose and then go up, we are still where we want to be. I think that's very useful and very, very, very reassuring for those who already do that.

Dr. Mesa: I think that dose intensity is important. I know that it's a particular area of passion of your colleague and my friend, Dr. Verstovsek, that you know, that dose intensity over time is important. It may not need to be present at day one. But trying to get patients to that 15 or 20 milligrams twice a day dose really does matter. You know, one thing I've observed in the patients referred to me is that there's not a insignificant number of patients that really are underdosed with ruxolitinib, you know.

Dr. Bose: I think so.

Dr. Mesa: Five twice a day or 10 once a day, and these doses are just not efficacious, and they're probably underutilizing the value of the therapy.

Dr. Bose: Now, in August of this year fedratinib, the JAK2 inhibitor was approved by the FDA for the treatment of myelofibrosis and actually had a pretty broad label given to it. Can you start us off with some background on fedratinib?

Dr. Mesa: Sure, of course. So highly relevant for folks and now that fedratinib is our second approved therapy for myelofibrosis, but still many have not yet had a firsthand experience in using it. So these new analysis that we're presenting at ASH, hopefully will be helpful. Fedratinib is an oral JAK2 inhibitor. It's selected for the JAK2, and it does have a broad label in either primary or secondary MF in patients with the platelet count over 50,000. There were two key studies that have been done in the past the JAKARTA study, which was the randomized phase III in JAK inhibitor naive patients and JAKARTA 2 which was the second line study.

One of the studies that I present at this year's meeting analysis from our colleagues is a reanalysis of the second line study with JAKARTA2. Now the JAKARTA2 study is relevant for a couple reasons as a second line study, but it was done several years ago and at that time, patients were ruxolitinib either resistant or intolerant, but it was relatively soon after the approval of ruxolitinib. So there were a variety of patients that not had not really had a, a robust exposure to ruxolitinib before being enrolled in that study. So we wanted to look back on that data with a modern eye that was more stringent in terms of analyzing efficacy.

What is the efficacy of a patient that we would say truly failed rux in this day and age? So we had two populations and intention to treat population, which were 97 patients that were enrolled in the study and we broke them down by either being resistant or intolerant. We then define a further stringent cohort where that one they had been on ruxolitinib for at least three months or more, versus the greater than 14 days, which had been for trial entry and then that the response to rux had to be defined as either greater than 50% reduction for baseline splenomegaly or for improvement in symptoms? We similarly had more rigorous criteria for being refractory or intolerant.

As we reanalyze the data then what we identified was it in this more stringent cohort, we could clearly define that about a third of patients had a clear response, even with this much more rigorous set of criteria, with about two-thirds of the patients being considered refractory and about a third of the patients being intolerant to the therapy.

We saw that efficacy both was regarding improvement in the spleen volume as one of the key endpoints and that whether a patient was relapsed or refractory or intolerant, the rates of efficacy were right about a third of the patients, pretty much no matter how we define them. And as we had looked at even the waterfall plots of response, we saw

that the patients, whether we label them as resistant and tolerant were somewhat interchangeable regarding the efficacy that was expected. Now, the other issue we've looked at is we looked at the longer term of these studies was regarding thrombocytopenia.

And that's the other update that we have at this year's meeting, where we looked specifically for the patients with a platelet count between 50 to 100,000, both in the JAKARTA1 and the JAKARTA2 study that were treated at the 400 milligram dose. What we identified in brief, was that the efficacy was relatively comparable for those that had a platelet count of 50 to 100,000 versus above 100,000. This is relevant because at the current time, patients who have a platelet count between 50 and 100,000, we could treat them with ruxolitinib on its label, but typically have done so with a dose modification. So, we can use the full dose of the 400 milligram. Additionally with this reanalysis, we did not find any significant increased risk of hemorrhage or other toxicities by doing that.

Finally, we present updates at this meeting regarding fedratinib as it relates to the health-related quality of life both from the JAKARTA1 and the JAKARTA2 study. We identify very strongly that even with a more rigorous criteria now, 1) the improvement in MPN symptoms is very clear in both the frontline and the second line; 2) the improvement in quality of life is clearly demonstrated both by the comparison with the EQ5D measure of quality of life in the JAKARTA upfront study, as well as the ELQC30, as well as the patient global impression of change for the JAKARTA2 study. So in aggregate, we see with even a fresh look at the data from fedratinib, we see one in the frontline setting, it's clearly efficacious. It clearly can be used at full dose at 400 in patient with a platelet count of 50 to 100,000, clearly has efficacy for splenomegaly and symptoms that clearly are superior to placebo. Second, we see that in the second line setting, again, either with thrombocytopenia or not there's efficacy, there's safety and an even in a more stringent cohort of patients, the efficacy is at least a third for patients who have been previously treated with ruxolitinib. So, there are several different clinical aspects related to this. But my key takeaways for colleagues as they ask me about this is one without question, we immediately have, you know data which shows that fedratinib is an important second line consideration. Without question, there are patients out there that are being treated now with ruxolitinib that due to the lack of another option, or unwillingness or being ineligible for clinical trials remain on ruxolitinib. So right away, it's an option for them and certainly the updated NCCN Guidelines and I believe you are one of the contributors to those guidelines clearly views it in that setting. Second in the frontline setting is certainly has that approval. Surely these data raise potentially some differentiation by being able to be used in full dose in individuals with a platelet count between 50 and 100,000. How about yourself? What are your takeaways of this new fedratinib data?

Dr. Bose: I think it, it provides an important new option, as you said in patients who failed ruxolitinib. I'm glad that we have at least a framework of defining ruxolitinib failure

provided by these more stringent criteria that were used in the reanalysis. And it is very, you know, reassuring to see that even with those rigorous criteria, you have this 30% rate of SVR and a 27% rate of TSS improvement, that makes it a pretty solid drug in the second line setting. Regarding, you know, possible frontline use. Again, you know, we have years of data with rux. We are comfortable with it. It has a survival benefit. So I think rux remains the cornerstone of frontline therapy, but the point you made about the platelet counts in the 50 to 100 range where the rux label would suggest using only 5 b.i.d., there, the fact that the efficacy here is the same and the dose is the same that's very intriguing. Now again, you and I probably are using 10 b.i.d. in those patients, but at the same time we are probably not using the most efficacious dose of rux. Whereas here, it seems like we can do that. I think that's that's very interesting.

Dr. Mesa: Now a couple of practical points to raise for the community oncologist regarding its use, it's all over overcomable. Fedratinib is straightforward to use, but there are a couple additional considerations. So first, there is a black box warning based on a very low rate, less than 1% of neurologic events like the Wernicke's that occurred in the earlier studies. And with that, there are specific recommendations of checking thiamine levels to be sure that they're not low in patients before therapy. It's unlikely to be low but it's important to check, second vitamin supplementation. Again, one can obtain thiamine fairly inexpensively from pretty much any drugstore. It is just a vitamin B1. Additionally, there can be GI side effects. So I typically treat patients with some ondansetron or some other sort of antiemetic. And if necessary, some loperamide. Usually I find that a little bit of antiemetics are a little constipating anyway, so you rarely have to do both, and usually can kind of wean that away. So both of those are considerations, particularly the thiamine piece. I think once people get used to that it's really not a big deal, but that is an additional consideration. Any other useful suggestions you'd have for folks?

Dr. Bose: No, I think those are the major points you know, it does inhibit FLT3. So you are going to see the nausea, vomiting, diarrhea, and as you said, some of those drugs would help. Are you routinely supplementing thiamine?

Dr. Mesa: I am for the time being, you know, it's a pretty benign thing. A lot of patients already are on a multivitamin that has enough thiamine with it. It doesn't take that much thiamine to be at the full kind of recommended daily allowance of thiamine. I suspect as our prospective data with a new studies, like the FREEDOM and the FREEDOM2 study evolve, these needs may end up going away. It's not it's not truly clear the fedratinib causes a thiamine deficiency.

Dr. Bose: Right.

Dr. Mesa: I think it's still just a little bit of a question that remains from the other studies. So I think all of that is done with an abundance of caution, but the likelihood of inducing Wernicke's is I think is very unlikely.

Dr. Bose: Now, Ruben, you've been very involved in the development of pacritinib. You led the PERSIST-1 study, and this year at ASH, we have some data about pacritinib as well. Do you want to discuss some of the pooled data from the PERSIST trials that were shown this year at ASH?

Dr. Mesa: Sure, of course. So pacritinib is another of the JAK inhibitors, advanced in its development but still not approved. Its potentially a unique differentiator and also a JAK2 and FLT3 inhibitor as well as inhibiting other kinases, such as IRAK1, and its differentiator had been that it has been able to be dosed even at full dose in patients with marked thrombocytopenia.

So first, there were abstracts really trying to further look at the issue of dose, based on the prior studies with pooled data, and help to confirm that the 200 milligrams twice a day dose that had been used in the PERSIST2 studies, likely is the more efficacious and safer dose than pacritinib at 400 milligrams once a day in terms of efficacy and safety. And that's very helpful as we try to pivot toward you know, further registration studies, as well as for approval.

Additionally, a key part of that was, was safety. And again, as we looked at those pooled analysis, you know, the rates of one grade 3 to 4 hemorrhages were relatively comparable between pacritinib or patients on best alternative therapy. Likewise, as we looked at rates of cardiac events, the rate of those events was 8% pacritinib patients and 12% on BAT. There were similar rates of death on study. So, pacritinib had been on a hold that resolved in the past, and part of that hold had been this issue of was there a higher rate of events? We had wondered whether by including patients with marked thrombocytopenia or were we just treating a more elite group of patients as a baseline. And this pooled analysis would tend to suggest exactly that, that again, if we're going to treat patients that have very advanced disease, you know, there's a certain rate of them that are going to have events occur, but nothing that gives us a signal that there is a increased risk related to the pacritinib itself.

Dr. Bose: Indeed and platelets less than 50 identifies a very poor prognosis.

Dr. Mesa: Very high risk group of patients. Absolutely.

Dr. Bose: So we also have data this year from the PAC203 study and as Ruben alluded to, after PERSIST1 and PERSIST2, there was a brief clinical hold on pacritinib with concerns about safety that was subsequently lifted and this then led the company to conduct a dose finding study, called PAC203 in which about 150 to 160 patients were

randomized 1:1:1 to three doses of pacritinib 100 a day, 100 twice a day, or 200 twice a day with the usual endpoints of SVR and TSS reduction.

Now 164 patients were included, 161 of which were treated. Again, there were those three dose levels, and essentially the response rates were low, talking about 35% as we are here. Now bear in mind that this is a population that is pre-treated with the ruxolitinib. It is not a frontline population and the rates were low, but they were the highest in the 200 twice a day group, around 9.4%.

The major treatment emergent adverse events were GI. Again, there's the FLT3 inhibition aspect to this. So you're going to see that and of course, hematologic AEs of thrombocytopenia and anemia. Again, this is a less myelosuppressive JAK inhibitor, but you do see some of that, and many of these patients were going into the trial with low, low count, but they were no increased rates of grade three or four hemorrhages or cardiac or other events. There were some deaths from a number of different causes, but again, none of them appeared related to the drug. And the conclusion essentially was that 200 twice a day was the way to go. This was the dose at which the highest response rate was seen and this is being taken forward in a trial called PACIFICA, which is going to target a low platelet population of less than 50,000.

Dr. Mesa: So one of my takeaways from this, as I looked at the actual response curves was that the majority of patients at the 200 twice a day had a reduction in splenomegaly and had benefit. They only, you know, the 10% reached the 35% volume reduction. Now, I would tend to consider one, the 35% volume reduction was a number that we as an academic community came up with arbitrarily, it was not a validated number. And over time, we had found that individuals that had over a 10% volume reduction on ruxolitinib had a survival advantage. But I wonder what we'll really find over time is that again, some much lower threshold particularly in the second line setting is relevant as an endpoint in treating patients with myelofibrosis. And that if we looked at those same 200 milligram twice a day, and patients with marked thrombocytopenia to have a poor outcome, maybe those that again have greater than a 10% volume reduction are really benefiting from the drug. And that the cut off a 35% really undersells the value of the drug.

Dr. Bose: Absolutely, almost any degree of spleen volume reduction is meaningful clinically to a patient certainly 10% and higher.

Dr. Mesa: Yeah, you know, for mine, I think, I don't think that there's a magic to the reduction of the spleen. I think that the reduction in the spleen is a biomarker of response to JAK inhibition. I think JAK inhibition has a variety of benefits to the patient. Yes, those things that are most superficial, splenomegaly symptoms etc., but I do believe that there likely is a benefit in terms of the cytokine environment, the inflammatory markers, the progressive kind of microenvironment niche that exists within the bone marrow, and that patients who truly have a benefit that you could say that's

why that 10% really helps to separate who's really responding really will end up having a benefit. I think we'll be able to quantify that better once we have better markers of progression free survival.

Dr. Bose: Now as we head into the PACIFICA trial now, which is again for platelets less than 50,000 and actually allows low-dose ruxolitinib as a comparator. Do you expect some data in 2020 from this trial?

Dr. Mesa: We do. We're hopeful that we'll get some data toward the end of 2020 and we really look forward to that study. You know, important for folks seeing these videos again, for patients with myelofibrosis that have the ability to participate in clinical trials, particularly if they failed frontline therapy. It's important to continue to consider those studies, even, although you can prescribe fedratinib in the second line setting, there is even now the FREEDOM-2 study in the second line that again patients can consider and there's advantages to us learning more from that prospective data.

Dr. Bose: Right. Now there's also momelotinib, which is also in late stage development. This drug was resurrected after initially appearing to have been abandoned. There was, they were the SIMPLIFY-1 and SIMPLIFY-2 trials. I believe you lead the SIMPLIFY-1 study. Do you want to tell us about the new analysis presented at this most recent ASH meeting.

Dr. Mesa: Happy to do so. So, momelotinib is a JAK1 and JAK2 inhibitor and helps to improve anemia as well as splenomegaly and symptoms. The SIMPLIFY-1 study the, the goal of this study had been to demonstrate non-inferiority for splenomegaly, non-inferiority for symptoms, and superiority for anemia. The study met the goal in splenomegaly. It slightly missed in terms of the non-inferiority for symptoms and then because of that was not able to be evaluable for anemia. But in aggregate, it was a large study head to head that showed a lot of benefit to using the momelotinib. It was a bit of a victim of its own design. But there's both a prospective setting this plan as well as retrospectively looking at the data. And they again, we're looking at the raw data to really be able to best quantify from that randomized study, what was the benefit in terms of anemia?

So what we've presented in this year's meeting is that in terms of transfusion independence, at week 24, there's clear superiority of momelotinib versus ruxolitinib as well as a clearly lower rate of transfusion dependence, both at week 24, but also looking at it at a rolling 24-week timeframe, realizing that that's a dynamic process, kind of throughout the study.

Additionally, we take a little different approach in terms of, let's say, transfusion free survival, if you would, with either zero transfusions of which momelotinib was clearly superior to ruxolitinib or the time to either receiving three or less transfusions or five or less transfusions. So again, trying to separate you know that one transfusion versus

somebody really becoming transfusion dependent, and it showed that there was clear superiority with momelotinib regardless of those metrics as to how it was looked. So I think really the takeaways is there clearly is activity as it relates to momelotinib for anemia, while still having improvements in splenomegaly and symptoms. And we're presenting additional data at this meeting as been discussed in the past, that part of this may be activity on other mechanisms, such as ACVR1 and have site in the have to do with anemia, and this may be part of the mechanism why we see momelotinib have an incremental benefit on anemia compared to, let's say fedratinib or ruxolitinib or potentially even pacritinib. You know, so, I think for the community oncologist, I think it's good to know that these other drugs are in development, they're not quite available to them yet. But if patients have anemia, they potentially have access to centers that have this as a clinical trial. I would certainly encourage them to consider enrolling patients

Dr. Bose: And you know, we are looking at now the MOMENTUM study. That's the prospective study you alluded to that's coming up that randomizes patients 2 to 1 to momelotinib or danazol and it has a primary endpoint of symptom control, given that in SIMPLIFY-2, which was the trial of momelotinib in rux pre-exposed patients, they had a good signal in terms of symptom benefit. So that is the primary endpoint there with anemia as a key secondary endpoint. So that will be something to look forward to in 2020, hopefully.

Dr. Mesa: I think so, I think it will be key, certainly anemia is a major gap in terms of our therapeutic options. And we'll be discussing in a moment, some of the combination studies that look to accomplish improvement in splenomegaly symptoms and anemia with a combination of drugs, but if one is able to do it with one drug, there may be both efficacy as well as certainly economic advantage to doing so with a single agent?

Dr. Bose: Absolutely, absolutely. So that's a perfect segue now I guess to get into some of these combination approaches that people are investigating to optimize rux to perhaps address some of the shortcomings of rux and see how we can come up with synergistic combinations that address those. Now, there are quite a few of these.

We're involved in one. It's us at MD Anderson and Memorial Sloan Kettering. It's an investigator initiated trial of ruxolitinib and thalidomide. In the past, our group had looked at ruxolitinib and lenalidomide, and the problem with that was that the two drugs were difficult to give simultaneously. They were too myelosuppressive. Now thalidomide of course the original IMiD is not, is not myelosuppressive, and what we saw in this study again you know, it's still early days. We have results on about 20 or so evaluable patients at this ASH meeting. But we saw a nice increase in platelets. That's been a particularly difficult aspect of this disease to improve and we're seeing some very nice platelet responses which we attribute to the thalidomide here. Importantly, we have used a low dose, in fact, Ruben, you are one of the pioneers of this many years ago, with the 50 milligrams a day dose of thalidomide combination with ruxolitinib, and

we've of course seen responses in other disease parameters as well. But then I think the main contribution of thalidomide appears to be in the platelets.

Dr. Mesa: Well, I think it's a very important observation coming from the study, having been involved with the early thalidomide studies. And again, that really became a very hopeful drug, particularly for cytopenias and relevant because in many countries around the world, it was easy to obtain. So, there were many patients who had been treated with low doses of thalidomide and prednisone as having efficacy. So it's nice to see these data. I think it's a natural combination as well as potentially being an accessible combination for, for many around the world, which, again, a bit like our prior study that we have published with ruxolitinib and danazol, you know, having that second drug be not overly expensive as well as being able to be accessed is key.

Dr. Bose: Absolutely, absolutely.

Now, ruxolitinib has also been combined with the other IMid, pomalidomide by the Germans and that was presented at EHA at 2019 and also at ASH. So this was a Phase I B2 trial. There were two cohorts. One that got the low dose of pom, 0.5 milligrams. Now again, pom, like thal and len have been, has been looked at by itself or with prednisone in studies in myelofibrosis. Now here you had two cohorts, the 0.5 and the other cohort, you started at 0.5 and could go to 1 and then 2. And again, the main thrust here was in improving anemia.

So they did see that, overall they saw a nice improvement in anemia with this combination. But, and as far as I should say, also safety, they didn't really see an excess of adverse events really attributable to the combination. It did not seem to be overtly myelosuppressive. That was nice, given that we saw that with lenalidomide, although there was some hem tox that led to some patients discontinuing. However, the overall response rate in the anemia, in the lower dose cohort at least was actually only 18%. So, so not that high. But then a number of patients stayed on for 42% of patients actually stayed on for more than 12 cycles. And this is something I believe that is still ongoing.

Dr. Mesa: So it is an interesting study. I think it's a nice contrast with the thalidomide study. I suspect if I was going to be considering, you know, use of ruxolitinib with an IMiD in 2020 off label, I think I'd be more attracted to the thalidomide. You know, both our centers participated with the single-agent pomalidomide studies in myelofibrosis. It was active, it was not active enough to become approved on its own. I suspect with the expense with pomalidomide, likely one of our other novel combination studies with a BET inhibitor something else likely will end up becoming more attractive than utilizing pomalidomide.

Dr. Bose: So speaking of combination trials with ruxolitinib, one of the interesting ones has been the MANIFEST trial of the Constellation Pharmaceuticals bromodomain inhibitor, CPI 0610.

So this trial had several cohorts. One was as monotherapy in patients who had failed ruxolitinib, which could be resistance or intolerance, and other was an add-on to ruxolitinib in patients having a suboptimal response and the most recent arm on which we don't have a lot of data is in patients who are JAK inhibitor naive who got the combination. So here what we saw was, again, talking here about that add-on cohort, which was the higher number of patients, the suboptimal responders to rux.

We saw that among those who are transfusion-dependent, they had a 25% rate of spleen response. And those who were transfusion or I should say non-transfusion-dependent in them, the screen response rate was actually zero. Now, these are small numbers, there were only 13 patients non-transfusion dependent and 12 that were transfusion-dependent, but sort of kind of strikes you as a difference in the spleen response rate and you wonder if the biology could be any different there. And then for symptoms also you saw a higher response rate of 54 in the transfusion-dependent and 38 in the transfusion-non-dependent.

And finally, as I mentioned, there is also a monotherapy arm and again, among those patients, some are transfusion-dependent, some are not transfusion dependent, and there you actually saw this nice hemoglobin increase. So this appears to be a drug that really modifies aspects of disease biology so that the hemoglobin really improved in those patients. And finally, they saw an improvement in bone marrow fibrosis. Again, most pronounced in the cohort where it was added to rux, and particularly in the transfusion-dependent patients. Again, I don't know the logic yet, but somehow this combination appears to be more effective, at least thus far in small numbers in transfusion-dependent patients where the drug is added to ruxolitinib.

Dr. Mesa: I think it's very intriguing set of data without question, I mean, the drug clearly appears to be active. I would be cautious just by the numbers in terms of putting too much weight on whether there is an efficacy difference between transfusion-dependent and non-transfusion-dependent patients. It really may just be that phenomenon. All of that said, there certainly could be a biological difference that we don't yet appreciate, you know there are patients that have a stable anemia with a hemoglobin of 8.5 and can have that for years and others that are transfusion dependent right away. Do they have a difference in biology? Is it splice mutations? Is it some other metric we don't yet know and that links somehow to response? I think only time will tell but some interesting data without question.

Dr. Bose: Sure, and speaking of other agents, another agent of interest is navitoclax.

Now, this is the BCL-2 BCL-XL antagonist or BH3 mimetics, sort of a forgotten cousin of venetoclax, but this has been, has re-entered development, perhaps is the best way to put it. It was studied earlier and somewhat shelved, at least temporarily because of the thrombocytopenia that BCL-XL inhibition causes. But here it was studied in an add-on trial presented by Claire Harrison at ASH 2019. These were patients on ruxolitinib for at least 12 weeks, and with a suboptimal response, who then had navitoclax added. It was started at 50 milligrams and then depending on the platelet count, the dose was increased to 300, and importantly, most patients did make it to the 300. They reported on 34 patients, most of whom were heavily pretreated with kind of two years of median prior ruxolitinib and in these patients of course the baseline platelets were on the high side because again, this is a drug that really can bring your platelets down. So that's understandable. The main baseline hemoglobin was 10.8. And like I said earlier, 68% of patients got to the 300 milligram dose of navitoclax. There was some ruxolitinib dose reductions later in the trial. Now of 24 of the 34 patients that were evaluable for efficacy, they reported a 29% rate of 35% or better SVR at 24 weeks. Again, that's sort of been the gold standard in all, in all trials that was kind of a major endpoint. They had a TSS reduction of about 20%, 20% improvement from baseline TSS and 42% reached the 35% or better SVR at any time point. And so that is, these are the first results from this study, and this remains an intriguing combination. What do you think?

Dr. Mesa: Well, I was excited to see this study and we've participated in this study. In part, I have a paper for those that can dig deep in the archives on apoptosis and myelofibrosis. Actually the subject of my Kay award almost 20 years ago, but nice seeing really trying to tap into that mechanism of action in that apoptosis is abnormally regulated in patients with myelofibrosis? Surely, I like seeing kind of the incremental benefit that they had in patients that were already on ruxolitinib and that really kicked up the level of response to a greater level. So encouraging to see and I think we will see more as this evolves.

Dr. Bose: So then I alluded to this a little bit earlier when we were talking about the active receptor and the momelotinib story, but there's very interesting data at ASH 2019 on luspatercept, a drug that was just recently approved for beta thalassemia. So this is an active receptor ligand trap. Do you want to take us through the data in myelofibrosis?

Dr. Mesa: Sure. Sure. An intriguing drug that has activity in anemia now approved in hemoglobinopathies.

There's a study that many of our centers have participated in looking at the benefit of the luspatercept given every 21 days in different cohorts of patients. First, either with or without ruxolitinib. Second, either kind of transfusion-independent but anemic versus a transfusion-dependent, and then patients would receive the drug and then if clinical benefit that could remain on the drug. What we saw in terms of efficacy was that individuals receiving ruxolitinib and the luspatercept seemed to have more benefit than

luspatercept alone, which is an intriguing observation in and of itself. What about the combination, because ruxolitinib is typically thought of as having drug-emergent anemia. So the fact that the combination was a bit more beneficial is intriguing in and of itself. Likewise, we saw individuals who were transfusion dependent, have perhaps a bit more benefit than those not. Again, is there a biological clue there. Is it just the impact of small numbers. It's difficult to know. But I think the takeaway is that there certainly is activity of luspatercept potentially in myelofibrosis with ruxolitinib, and certainly, there are planned prospective studies to try to further elucidate that and see whether the indication should be expanded for luspatercept to also be considered for patients with myelofibrosis.

Well, why don't we bring it home with this? Why don't we each make kind of a comment as to, you know, what we would have our colleagues really have as a takeaway? Maybe I'll throw out the first one and say, you know, what I share with colleagues is I've seen kind of during my career, particularly in evolution from the mid 2000s to now is we've really evolved from having to, you know, beg, borrow, and steal drugs from other indications, to test them in myelofibrosis. What we see now is a very mature, robust pipeline of drugs specifically being tested for myelofibrosis, better understanding the biology of the disease, intentionally focused on mechanism of action, both single agent and combinations. So really a very much a maturing field, a lot of positives. How about yourself, final thoughts?

Dr. Bose: You know, exactly. It is so, so rewarding to see that there's so many preclinical studies, specifically being done in this setting in murine models showing synergism and those being translated to the clinic. I think that's, that's very exciting. That's how it should be and you're exactly right. The field has really matured. And it's wonderful to see so much drug development effort in our field.

Dr. Mesa: Well, great. Well, it's been a great pleasure being on this program with you. Thank you.

Dr. Bose: Thank you.