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EDITED TRANSCRIPT

SRRA.OQ - Sierra Oncology Inc to Host KOL to Discuss Updated Phase 3 Myelofibrosis Data Presented at ASH - Conference Call

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PRESENTATION

Sara Parigian - *LifeSci Advisors, LLC - VP of KOL Strategy & Management*

Good morning, and thank you for joining us on the Sierra Oncology KOL call. (Operator Instructions) As a reminder, this webinar is being recorded and a replay will be made available on the Sierra Oncology website following the event.

I would now like to turn the call over to your host, Stephen Dilly, Chief Executive Officer of Sierra. Please go ahead, Stephen.

Stephen G. Dilly - *Sierra Oncology, Inc. - President, CEO & Director*

Thanks, Sara, and thanks particularly to everyone that's joining us today to hear about Sierra and momelotinib.

Next slide, please. I'm going to be making and others are going to be making some forward-looking statements today. So please do take note of our safe harbor statement.

If I could have the next slide, please. We've got a packed and exciting agenda today with 3 external speakers and our own Barbara Klencke, taking you through a lot of stuff that was presented recently at the American Society of Hematology meeting. So I don't want to get in the way of those exciting presentations. But I would like to say a few words about who we are at Sierra and what we do.

So next slide, please. So we're taking an evidence-based approach to work out who therapies are for. And importantly, also who may be they're not for, where there's a better alternative. And this is really important to bring up when we're working in a field like myelofibrosis, which is increasingly crowded, with an entrenched agent that people love in ruxolitinib. In other words, we need to provide people with the reason to get excited about momelotinib, and you're going to hear some of that today.

Next slide, please. The important thing to note is that momelotinib has 3 receptor targets, JAK1 and JAK2, like the other JAK inhibitors, but also ACVR1. And what we're doing is really asking the question specifically, are there patients where this is a really good thing and patients where it's a less good idea. In other words, what's our differentiated profile. And you're going to hear some really exciting first insights into that in the presentation by Dr. Kiladjian about patients with different baseline platelet profiles, but expect more of the same to come in because what we're trying to say is we have a very good drug potentially for myelofibrosis, but it's particularly good in this group of patients as a starting point.

We are right in the middle of our Phase III MOMENTUM study. We're expecting results in the first half of 2022. We have the luxury of a database of more than 800 myelofibrosis patients, which leads us to presentations like today. We believe we have an attractive commercial opportunity and increasingly, we've got the resources to take advantage of that with an experienced management team funding through pivotal data. And we've got some other stuff in our pipeline at the right time we might turn some attention to.

So next slide, please. Here's our news flow. We really are super excited about the recent presentations at ASH that you're going to hear more about today. And then moving into next year, next year is going to be a huge year for us at Sierra because, first of all, at some stage, we're going to be announcing completion of enrollment into the MOMENTUM trial and at that point, it's a 6-month study, you can add 6 months plus a few months for us to process the data and be looking at top line data in that first part of 2022. In the middle of the year, we'll have further interesting analyses at the EHA meeting around that time. Now I have to point out that those 2 lines meeting exactly in the middle of June 2021 is an accidental graphics, that is not a prediction, okay? Sometime in mid-2021, we will complete enrollment. As we move into 2022, we'll see top line data. And then a few months after that, we expect to file an NDA with the FDA for approval. And in Europe, possibly a few months after that. And that should lead to, all things being positive, approval and commercialization in 2023, which is really not that far away.

Next slide, please. So right now, we at Sierra are maniacally focused on successful completion of the MOMENTUM clinical trial. This is a very high-touch study. It makes a huge difference to look at patient quality, data quality, keeping patients in the study, making sure we're acquiring the endpoints that we need. This is a huge focus of the company right now. Increasingly, as we get confident, we've got that in good shape. Our attention moves to the regulatory and commercial execution and preparation. Again, these are areas we're doing an extremely good job and we'll make a big difference because the regulatory strategy is important, how do we get the appropriate label for momelotinib so it can be used in the best possible way. And how do we introduce it to the market in the most efficacious way. And then finally, once that is nailed down, we can start thinking about the future bigger potential. We believe we have an agent with particular utility in combination because of its likely ease of use. And then -- and only then we turn our mind to additional things coming into the pipeline. So that's who we are. It's a very focused story right now. We're super excited.

And at this point, next slide, please, I'm going to hand over to Dr. Barb Klencke, our Chief Development Officer, who's going to give you a more detailed look at myelofibrosis and momelotinib in particular. Thank you.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Well, thank you, Stephen. Good morning, everyone. So today, I'm going to share a bit of background information on myelofibrosis as well as our investigational agent, momelotinib, which is a JAK1, JAK2 and ACVR1 inhibitor, which is in -- currently in Phase III clinical trial development. We'll talk about that in a few minutes, though, after I cover the background. I'll do so rather quickly, though, because I do want to get on to allowing our 3 global myelofibrosis experts to delve deeply into some recently reported momelotinib data.

Next slide. So myelofibrosis is a rare bone marrow cancer. Common manifestations of disease include constitutional symptoms, an enlarged spleen and progressive anemia. The only curative therapy is an allo stem cell transplant, but this is an appropriate treatment option only for a small minority of patients. JAK inhibitors are the mainstay of treatment. But the approved JAK inhibitors address spleen and symptoms, but not the anemia because they themselves can lead to myelosuppression. Dose reductions are common and some patients never receive a JAK inhibitor due to low platelet counts or severe anemia.

Next slide, please. Despite the availability of current treatments, multiple unmet medical needs remain. In particular, improved survival, treatments that improve or address anemia and transfusion dependency, and treatments that really provide a substantial durability of effect are 3 of the most important needs amongst the number of others.

Next slide, please. Myelofibrosis is a rare condition with about 18,000 patients living with this diagnosis in the U.S. Hematologists and oncologists primarily manage the disease locally in communities. Medicare is the primary payer and currently approved JAK inhibitors are priced approximately $14,000 to $21,000 per month.

Next slide. There's a number of treatments -- there's a number of factors that need to be considered when making treatment decisions. For the last 10 years, there's been one choice for physicians. As more agents become available, there'll be an opportunity to make more subtle considerations for which treatments might be ideal for which patient. In the future, the presence of severe anemia and/or thrombocytopenia may well determine the choice of treatment. When momelotinib becomes available as a treatment options, these factors could really become core treatment considerations. As a community, we'll be able to customize treatment options rather than relying on a single product to treat everyone.

Next slide, please. Anemia is a common concern of presentation, and it generally progresses over time, either due to the disease and often as a result of treatment with other JAK inhibitors. Not everyone's anemic, but the majority of patients with myelofibrosis do suffer from anemia. Severe anemia has a significant impact on quality of life and on prognosis, and is generally managed with repeated blood transfusions, often required every few weeks. So clearly, better treatments for anemic patients are needed.

Next slide. Anemia of myelofibrosis is multifactorial. But myelofibrosis due to a constitutive activation of the JAK-STAT pathway is, by nature, a very inflammatory condition. There's thus a major component of what's turned anemia of inflammation that contributes to the anemia of myelofibrosis. This anemia of inflammation is driven by high hepcidin levels, hepcidin being a hormone that controls iron homeostasis. High levels of hepcidin restrict the availability of iron, which suppresses the body's ability to make new blood cells. Both anemia and elevated hepcidin levels are indicative of poor survival and you can see this illustrated on the 2 curves. On the left, severe anemia is often associated with the survival of just a couple of years, very similar to that prognostic indicated by high hepcidin levels.

Next slide. So now let's discuss momelotinib, a JAK1, JAK2 and ACVR1 inhibitor.

On the next slide, we again mention the 3 major disease manifestations, constitutional symptoms, an enlarged spleen and progressive anemia. Targeting the JAK-STAT pathway has been shown to improve symptoms in splenomegaly, but it alone cannot address the burden of anemia. Currently, approved JAK inhibitors, as I said, are myelosuppressive, thus worsening anemia over time. What makes momelotinib different is that it also inhibits or targets ACVR1 and this can improve hepcidin levels, which increase hemoglobin levels and can improve anemia and transfusion requirements.

On the next slide, we go through our current and previous development program. SIMPLIFY-1 and SIMPLIFY-2 are 2 fully completed Phase III trials. From these trials, we've had a wealth of information and data that have led to a better understanding of momelotinib and have helped us design the currently ongoing MOMENTUM trial. This is a Phase III registration-enabling trial, and we'll go through the design in a moment. We also have an Extended Access program, which is a rollover protocol for patients who have been on these -- the prior SIMPLIFY studies and prior Phase II studies. And remarkably, we now have patients who have been treated for 10 years who remain on daily momelotinib on an ongoing basis.

Let's go on the next slide, and this covers the ongoing Phase III MOMENTUM study design. Patients are randomized to either momelotinib or danazol, given for a randomized treatment period of 24 weeks, at which time they may cross over to momelotinib or if they've been randomized to momelotinib, to continue. The primary endpoint is total symptom score at week 24. Secondary endpoints are transfusion independence and splenic response rate, both measured at week 24. We anticipate completion of enrollment in the middle of 2021 with top line data to follow in the first half of 2022.

On the next study -- on the next slide, today, we'll spend a bit -- the rest of our time really delving into previously reported and recently reported data from the SIMPLIFY studies. As I said, these outputs, the outcomes from these studies have really helped us design a very robust MOMENTUM study. Here, you see the designs of both SIMPLIFY-1 and SIMPLIFY-2, very parallel studies conducted at the same time. SIMPLIFY-1 in the JAK-naive patient population, JAK-treated patients, previously treated patients in SIMPLIFY-2. Both studies examined momelotinib versus either ruxolitinib in SIMPLIFY-1 or best available therapy in SIMPLIFY-2, which ended up being ruxolitinib in 88% of patients. Both of these studies had a 24-week randomized treatment phase and a long-term extension of open-label momelotinib. The primary endpoint for both studies was splenic response. Secondary endpoints of total symptom score and transfusion independence. SIMPLIFY-1 in the front line JAK inhibitor naive population compared momelotinib to ruxolitinib in 432 patients. Patients must have had a baseline platelet count of at least 50,000, whereas SIMPLIFY-2 had no lower limit on the platelets.

All right. Next slide. Before I turn the presentation over to Dr. Mesa, I'll just take one moment to report -- to describe one aspect of the previously reported data, and that is the safety data. Notably, safety for momelotinib is generally similar to ruxolitinib during that 24-week double-blind period. Grade 3 and Grade 4 adverse events are very low for momelotinib, whereas anemia and thrombocytopenia were more common with ruxolitinib. Lower grade nausea is more common with momelotinib and a variety of low-grade events led to a higher early withdrawal rate from momelotinib in SIMPLIFY-1.

Next slide. I'd now like to introduce you to Dr. Ruben Mesa. He's the Director of the UT Health San Antonio, MD Anderson Cancer Center. He's been the principal investigator of more than 70 trials, including investigator -- the principal investigator of SIMPLIFY-1, and importantly, a co-PI of our MOMENTUM trial. Today, he's going to speak to you about data from the SIMPLIFY studies as presented at previous meetings, including the ASH 2019 meeting and this year's European Hematology Association Meeting.

Ruben, I'll turn it over to you.

Ruben Mesa

Well, thank you for the introductions, Barb. Good morning to everyone. Excited to be here and share these experiences. I've been pleased to be involved with the development of this [agent] really from its most early inceptions and the early trials out when I was at Mayo Clinic. Today, I'm pleased to provide an overview of the SIMPLIFY-1 and SIMPLIFY-2 trial designs as well as the previously reported safety, efficacy and importantly, the dose intensity data for momelotinib. These data were previously presented at the EHA meeting in June of 2020 virtually, as well as the ASH meeting last December.

So next slide, please. Now it has been recognized for some time that momelotinib has a unique ability to improve the anemia and transfusion dependency in patients suffering from myelofibrosis. The mechanism for this anemia benefit is also now understood and likely relates momelotinib's ability to acutely and chronically lower hepcidin levels via its inhibition of ACVR1. As shown in the left figure, SIMPLIFY-1 patients treated with momelotinib experienced a rapid increase in hemoglobin, which is maintained over time. In contrast, there is a significant decrease in hemoglobin for patients receiving ruxolitinib. Now patients who crossed over from ruxolitinib to momelotinib in the extended treatment phase of SIMPLIFY-1 showed a sustained mean hemoglobin increase at 2 or above baseline levels. So you see that nice increase in that figure.

What may not be as widely appreciated is that momelotinib also has a different effect on the platelet count as well as hemoglobin levels. As shown on the right figure, the platelet count is generally fairly stable in patients treated with momelotinib in contrast with a significant decline in platelet counts in patients treated with ruxolitinib, as was seen in the double-blind treatment period in SIMPLIFY-1. The mean platelet levels increased in patients who crossed over from ruxolitinib to momelotinib in the extended treatment phase, as you see on this figure.

Next slide, please. Now these were presented at EHA 2020 regarding the transfusion burden. And this increase in hemoglobin was associated with a clinically relevant reduction in red blood cell transfusions. I presented this data at last year's ASH conference and the figure on the right shows a relative transfusion burden for patients randomized to momelotinib in blue versus ruxolitinib in red in SIMPLIFY-1. This model incorporated the baseline characteristics as co-variants and demonstrates that the average patient received twice as many red blood cell transfusions on ruxolitinib at any time point compared to those receiving momelotinib. That is the reduction in the need for transfusion is evident through and after treatment initiation and continues to accumulate over time.

Next slide, please. Now another aspect of the safety profile of momelotinib that was reported earlier this year at EHA is the long-term safety from the SIMPLIFY studies. As Dr. Klencke mentioned earlier, there are several patients from the early Phase II experience with momelotinib who continue to receive treatment for more than 10 years now, and I've actually treated some of those very patients. Nearly 90 patients from the SIMPLIFY studies continue to receive momelotinib therapy, many of whom have now been on treatment for more than 5 years. In this table, we show the rate of common adverse events during the randomized treatment phase for patients in the momelotinib arm compared to the ruxolitinib arm that was shown by Barb earlier today.

What is also shown in this table in the green column are that the rates of common adverse events from a recent updated analysis where we wanted to look at the safety of long-term dosing. In total, 441 -- or 411, I should say, of the 432 patients who enrolled and SIMPLIFY-1 received momelotinib

either because they were randomized to that arm originally or because they had initiated momelotinib after a crossover after completing 24 weeks on the ruxolitinib treatment arm. Notably, the rate of these common adverse events was only slightly higher despite this much longer duration of treatment and followup. No new safety signals or cumulative toxicity were observed during this extended momelotinib dosing.

Next slide, please. Finally, we examined dose intensity of momelotinib in the 2 SIMPLIFY studies for the abstract from this year's EHA meeting. The average dose intensity was calculated on a weekly basis for all patients who remain on treatment at each week and is displayed as a vertical line representing the dose intensity for every week during the 24-week randomized treatment period as well as for the next 24 weeks of extended momelotinib treatment. The deeper the color, whether that be blue or gray, represents higher dose intensity. The top figure shows that all SIMPLIFY-1 patients randomized to momelotinib initiated therapy at the maximum recommended dose of 200 milligrams daily, as shown by the blue bars. High momelotinib dose intensity was then maintained throughout the 24-week randomized period and beyond the extended treatment with generally about 85% of active patients being able to remain on full doses of momelotinib. The mean daily dose was about 90% of the recommended dose throughout both the randomized and the extended treatment periods.

By contrast, the starting dose of ruxolitinib is dictated by the platelet count. Less than 60% of the ruxolitinib patients in SIMPLIFY-1 were able to receive 20 milligrams twice daily as their initial ruxolitinib dose. An ongoing ruxolitinib dose intensity was further compromised over the 24-week treatment period, generally because of emerging thrombocytopenia. Despite the preponderance of these ruxolitinib dose reductions, patients who switched from ruxolitinib to momelotinib were able to achieve sustained high-dose intensity on momelotinib through the extended treatment phase.

Next slide, please. So overall, these findings are consistent with momelotinib's differentiated pharmacological and clinical profile as an inhibitor of JAK1, JAK2 and ACVR1. Momelotinib appears to have a unique ability to increase hemoglobin levels, maintain platelet counts and decrease transfusion burden for myelofibrosis patients. The large majority of patients are able to receive full dose intensity of momelotinib during the extended treatment duration. Importantly, no new safety signals or cumulative toxicity were observed during extended momelotinib dosing. It seems quite possible that the ability to maintain platelet counts while also delivering full dose therapy that contribute to the ability to achieve such durability of dosing as well as the ability to achieve good outcomes with momelotinib irrespective of the patient's baseline platelet count, as my friend and colleague, Dr. Kiladjian will describe next. Thank you.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Thank you, Ruben. It's now my pleasure to introduce you to Dr. Jean-Jacques Kiladjian. Dr. Kiladjian is a professor of clinical pharmacology at Paris Diderot University. He's a consultant hematologist and headed the Clinical Investigation Center at St. Louis Hospital in Paris. Last week, Dr. Kiladjian presented the efficacy results of the SIMPLIFY-1 and SIMPLIFY-2 studies as they relate to the baseline platelet counts of patients enrolled to that study. So today, he'll go through that data with you. Dr. Kiladjian?

Jean-Jacques Kiladjian

Thank you, Barbara. Good morning, everyone. As Barbara said, I will show you now for SIMPLIFY trials and analysis, retrospective analysis we conducted for the week 24 outcomes including the clinic response, the symptom response, the rate of transfusion independence in patients with intermediate and high-risk myelofibrosis based on their baseline platelet counts.

Next slide, please. So this is the title of the poster.

Next, please. So the next 3 slides present efficacy outcomes for SIMPLIFY-1 and SIMPLIFY-2 for 3 groups defined by their baseline platelet count, at and below 150,000, between 150,000 and 300,000 and above 300,000. Here, Figure 1a shows transfusion independence rate for patients in SIMPLIFY-1. As you can see, momelotinib treatment elicited a higher and generally consistent transfusion independence response rate in each baseline platelet strata compared to ruxolitinib. As you can see on the top of this figure, the overall transfusion independence rate was 67% in the momelotinib arm and 49% in the ruxolitinib arm. In each of the 3 groups, defined by their baseline platelet count, momelotinib treatment elicited

a higher transfusion independence response rate compared to ruxolitinib with TI rates for momelotinib ranging from 62% to 72% across the pre platelet strata in SIMPLIFY-1.

On the right, you can see in Figure 1b, the transfusion independence response rate for patients in SIMPLIFY-2, which were, overall, 44% in the momelotinib arm and 21% in the best available therapy arm. In both studies, the transfusion independence rate in the momelotinib arm was preserved in patients with low platelet count.

Next slide, please. Here, we compare the splenic response rate by baseline platelet strata. In Figure 1c, we see splenic response rates were maintained in momelotinib patients in all baseline platelet strata in SIMPLIFY-1, whereas ruxolitinib patients saw a markedly reduced response rate in patients with lower baseline platelet counts at study entry. Figure 1d shows the lowest splenic response rate for all patients groups in SIMPLIFY-2, consistent, indeed, with the lack of mandatory washout from prior JAK inhibitor therapy in this study.

Next slide, please. Here, we can see the response for the symptoms using the Total Symptom Score, or TSS, response rate. In patients with lower baseline platelets in SIMPLIFY-1 on the left, the TSS response rate was again maintained with momelotinib. In comparison, TSS response rate decreased in ruxolitinib treated patients with low baseline platelets. In SIMPLIFY-2 in Figure 1f, momelotinib's TSS response rate were preserved across platelet strata and were higher compared to ruxolitinib in all strata, consistent with the TSS response rates in the overall population, as you can see on the top of this figure, overall, 26% for momelotinib compared to 6% for the BAT, best available therapy, arm.

Next slide, please. So in summary, the SIMPLIFY-1 at week 24 data show and teaches that for patients who have less than 150,000 platelets at study entry, momelotinib achieved substantially higher transfusion independence and splenic response rates and similar symptomatic response rates compared to ruxolitinib. For patients with baseline platelets between 150,000 and 300,000, generally, similar splenic and symptom response rates were achieved with both momelotinib and ruxolitinib, while there was a higher transfusion independence with momelotinib. For patients with more than 300,000 platelet at baseline, higher splenic and symptom response rates were achieved with ruxolitinib, although transfusion independence remained higher with momelotinib. In SIMPLIFY-2, momelotinib response rates for the 3 end points remain very consistent with the overall intention to treat response rates achieved with momelotinib in patients whose baseline platelets were below 150,000. And in addition, momelotinib's benefits were also preserved in patients whose baseline platelet accounts were under 100,000.

Next slide, please. In conclusion, this retrospective analysis of data from the SIMPLIFY studies demonstrate that momelotinib's activity profile does not appear to be affected by baseline platelet count, while in contrast, activity with ruxolitinib declined in patients with lower baseline platelet count. The benefit profile -- the benefit risk profile of momelotinib relative to ruxolitinib is comparable or favorable for momelotinib in JAK inhibitor-naive patients whose baseline platelets is below 300,000. So in my personal opinion, these data are probably especially relevant in the JAK inhibitor-naive setting. Should momelotinib become approved and available for patients who previously treated or not treated with JAK inhibitor, patients will have a variety of treatment option and the ability to individualize treatment decisions based on factors such as presence of anemia or pretreatment platelet count will likely improve treatment outcome for our patients. Thank you.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Thank you. Very good. So thank you, Dr. Kiladjian. I'd now like to welcome Dr. Srdan Verstovsek to the virtual floor. Dr. Verstovsek is a professor of medicine and hematologist-oncologist at the MD Anderson Cancer center. He has led more than 60 clinical trials of MPN drug candidates and is the co-PI of the MOMENTUM study. Last week, Dr. Verstovsek gave an oral presentation, highlighting the long-term outcomes including overall survival for momelotinib as reported -- as demonstrated from the SIMPLIFY-1 and SIMPLIFY-2 clinical studies. So he'll share that data with you today at this point. Serge, I'll hand it to you.

Srdan Verstovsek

Thank you, Barb, and good morning, everybody. Thank you for joining on today's call.

Let's go to the next slide, please. This is the title slide. So it is my pleasure now to present data from our American Society of Hematology oral presentation entitled, as you see, Robust Overall Survival and Sustained Efficacy Outcomes During Long-term Exposure to momelotinib in JAK Inhibitor-naive and Previously JAK Inhibitor Treated Intermediate and High-risk Myelofibrosis Patients. The SIMPLIFY-1 and SIMPLIFY-2 Phase III studies were both considered complete last year after patients who remained on extended momelotinib therapy were transferred into the rollover protocol, as described before, referred to as the Extended Access Program. We then conducted a prespecified analysis of the duration of transfusion independence, duration of splenic response and overall survival of the final data, which is very important and presented by me today to you.

So next slide, please. The previously reported noninferior landmark week 24 splenic response for momelotinib and ruxolitinib is shown in the bar graph at the lower left of this slide. With further follow-up beyond week 24, 40% of momelotinib treated patients achieved a splenic response at any time during SIMPLIFY-1. Moreover, this splenic response was durable with median time to loss of response not reached for subject regardless of whether they were initially randomized to momelotinib or initially randomized to ruxolitinib and then crossed over to momelotinib at week 24. This analysis includes more than 3 years of follow-up to remember that important information.

Next slide, please. Now the following 2 slides present final analysis of the duration of transfusion independence for the 2 SIMPLIFY studies. As previously reported, the rate of transfusion independence in SIMPLIFY-1 was nominally higher in momelotinib subjects compared to those randomized to ruxolitinib at 67% and 49%, respectively. Now for subjects who achieved transfusion independence for the 12-week or longer at any time during the study, the duration of transfusion independence calculates from the end of the 12-week period for the first RBC transfusion or hemoglobin less than 8, is shown here. The median time to loss of transfusion independence was not reached in SIMPLIFY-1 with more than 3 years follow-up. Transfusion independence was seen in subjects initially randomized to momelotinib and those randomized to ruxolitinib who then crossed over to momelotinib at week 24. This suggests that momelotinib therapy elicits and maintains durable transfusion independence.

Next slide, please. Transfusion independence was also durable when analyzed in SIMPLIFY-2. The same type of analysis was applied here. This is a population of patients previously exposed to ruxolitinib, remember that. At week 24, the transfusion independence response rate for the momelotinib arm was 43% compared to 21% in the best available therapy arm. Transfusion independence was also durable in this study as well, as I show for the previous study.

Next slide, please. Now the following 2 slides present final overall survival data for the SIMPLIFY studies by [low graph] analysis. Typically, when I see patients in my clinic for the first time, I give them a reality of what I am trying to achieve. I'm trying to achieve control of the signs and symptoms of the disease, control the spleen, symptoms and anemia, and I like them to live as long as possible with the control of the signs and symptoms of the disease. This is what I'm talking about here.

This slide displays the final overall survival data for JAK-naive patients in SIMPLIFY-1. Consistent with the known survival impact of the JAK inhibitors in JAK inhibitor-naive patients as described previously for ruxolitinib, robust overall survival was observed in both treatment arms in the SIMPLIFY-1 study. Median overall survival was 53 months in ruxolitinib to momelotinib crossover patients and not reached in originally momelotinib randomized patients. Recall that all subjects were allowed to receive open-label momelotinib for an extended duration after the end of the 24-week randomized treatment period. Therefore, this durable survival reflects momelotinib benefit on extended treatment with momelotinib or crossover to momelotinib regardless of the starting therapy.

Next slide, please. In patients who have previously received ruxolitinib, overall survival is generally quite short, this is very well known, indicating a substantial unmet medical need for safe and efficacious therapy in myelofibrosis patients previously treated with ruxolitinib. In SIMPLIFY-2, a robust median overall survival of 37.5 months was observed for the best available therapy, predominantly ruxolitinib to momelotinib crossover arm and 34.3 months for originally momelotinib randomized patients. The durable survival achieved here again reflects momelotinib benefit as patients in both treatment arms could receive extended treatment with momelotinib after completing 24-week randomized treatment period. These overall survival results are among the best survival reported in patients who have been previously treated with ruxolitinib.

Next slide, please. So in conclusion, this analysis demonstrated a robust overall survival on momelotinib in both JAK inhibitor naive and previously ruxolitinib treated patients. In particular, the median overall survival of 34.3 and 37.5 months observed in the 2 treatment arms or SIMPLIFY-2 compare very favorably with overall survival previously reported in patients who have previously received JAK inhibitor therapy.

So thank you very much for your attention.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Thank you. So thank you, Serge. That concludes the formal presentation portion of today's discussion. But now I'd like to ask our 3 myelofibrosis experts, Ruben, Jean-Jacques, Serge, to join me on the screen for a few minutes. I'll open with a few questions to the panel, and then we'll open it up for wider questions from the audience.

QUESTIONS AND ANSWERS

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Maybe I'll start with -- continue to think about this overall survival data that Serge just presented. And maybe Jean-Jacques, let me ask you, your thoughts about survival as an important endpoint in myelofibrosis. Classically, we've talked about spleen control and other symptoms. So what's the role of overall survival? And how do you -- what are your view of the data that we just discussed?

Jean-Jacques Kiladjian

Of course, that's the main question of our patients when we see them for the first time or when they come for referral. And as Dr. Verstovsek nicely highlighted, the patients who failed on ruxolitinib are usually very worried about the alternatives and what can be their survival since they know that this is really a poor prognostic factor. So the data we have from the SIMPLIFY studies are really very important, I think, in that view, because we can offer, not yet, at least in France, but as soon as momelotinib hopefully will be available in clinical practice, we may offer an option with well-defined and demonstrated benefit in overall survival. And I think this will be really a major improvement for our patients.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Thank you. Maybe I'll ask this question of all 3 of you because your -- you have all had the opportunity to treat patients with momelotinib throughout the development story of this agent. So maybe I can ask each of you to think -- to say a few words about the unmet medical needs in myelofibrosis, how momelotinib might address those particular needs, and what your patients have experienced. Maybe Ruben, I'll start with you.

Ruben Mesa

Sure. So I haven't been involved really with all the drugs that have been in development. I just have my colleagues. I'm deeply excited about momelotinib in that the issue of anemia is a significant unmet medical need, but it's not only about anemia. What's nice about the responses that we're seeing is that it's really hitting 3 of the most impactful areas that impact the patient. Anemia, their symptoms and their spleen. That the trio really is important in terms of a comprehensive therapy.

I do think that translates into patients not only living better, but living longer. So I do think the survival benefit is genuine. And I've seen it personally, that I think that -- as I do think that it is real in subsets of patients for ruxolitinib, I think it's very real with momelotinib as well in terms of first-hand experience. And I think that the parameters that we measure are both evidence of clinical benefit, but also reflect that the activity of an agent like this really has a favorable impact on the patient overall.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Thank you. How about Serge? Do you have some -- anything from your personal experience in your patients that you've seen? And how do you feel momelotinib may fit into the future armamentarium of treatment options for patients?

Srdan Verstovsek

I have, like Ruben, been involved with momelotinib from the very beginning, running the Phase I study with it and I have a long-term, very good experience with it in terms of all types of the clinical benefits that Ruben has described very well. We struggle with the ability or inability to control the spleen and the symptoms and anemia, which are 3 major problems that we face in daily management of patients with myelofibrosis, and we hardly ever talk about the survival benefit of any medications. We have evidence of the survival benefit on ruxolitinib. I'm very happy to see the survival benefit significantly suggested by the data today on the momelotinib. I'm not surprised. But the trio of the benefits that one drug can provide is quite different than any other attempts that we have so far, and I have been around about 20 years.

So in 1 pill, we have medications that can possibly counteract the spleen and the symptoms and the anemia in a large proportion of the patients and with a control prolonged life of the patient. So when it comes to -- and hopefully, the momelotinib will be used in a normal community setting once it gets approved, I think that will be the, obviously, the treatment of choice in a second-line setting where the medication is being developed in MOMENTUM studies. But there is certainly, and I agree with Jean-Jacques, a group of patients in the frontline setting, particularly those that are anemic with the spleen and symptoms that may be a good candidate for momelotinib, even in upfront attempts to control overall signs and symptoms with 1 daily, single medication without much of the difficulties. It's very simple. It is safe. And as we now know, works for a very long period of time.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Excellent thoughts. Jean-Jacques?

Jean-Jacques Kiladjian

Yes, I fully agree. And I have the same experience than Serge and Ruben. Maybe just what impressed me the most when I used this drug in comparison with the previous experience with ruxolitinib was the anemia response, because it's not when the patient responds to momelotinib on anemia, it's not just 1 or 2 grams of more hemoglobin, et cetera. It's really very fast and very important increase of hemoglobin that almost becomes normal again, although those patients who are suffering of anemia were transfused, sometimes failed on EPO or erythropoietin-stimulating agents, et cetera. So this was, I think, for me, the most striking difference with the other JAK inhibitors I have used. And of course, in addition, all the benefits that Serge and Ruben highlighted before. But this was really particular to this drug for me.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

So we're just coming out of a really exciting ASH this year. The number of drugs in development for myelofibrosis, really an exciting opportunity to see new therapies starting to become either tested in Phase III studies, combined in different ways, et cetera. So where do we think the future of myelofibrosis treatment is going? And how might momelotinib play a role? And I'm, in particular, wondering what you think about the opportunity for combination treatments. Maybe Ruben, do you have any thoughts? Do you want to comment on that?

Ruben Mesa

So I do think we're likely evolving to a situation where we'll be talking about JAK inhibition as a base and the addition of other agents, I would speculate that have alternative mechanisms of action added on, either at the time of diagnosis, perhaps in a subset or after some period of time. I do think momelotinib would be well positioned for those combinations because of the ability to maintain dose intensity, the favorable profile as it relates to platelets that many of the other agents that are interesting. The Constellation drug, the BET inhibitor, Navitoclax, IMG-7289, they all can cause thrombocytopenia. So I think the base of what the JAK inhibitor is in those patients who do get a combination, I think, will be important.

Likewise, the issue of anemia is an important one that, again, these other drugs may not necessarily kind of bring to the table. So I suspect, as opposed to the drug development world where it's either one or the other, I suspect it will be more about combos. When does a combination

start? I don't think that it will be in all patients, I suspect it will be more likely in a subset, either because of a molecular feature or after a period of time in suboptimal response. But I do think your agent is well positioned to be that base for a significant number of those individuals.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Very good. I'm wondering if we should open it up for questions from the audience.

Sara Parigian - *LifeSci Advisors, LLC - VP of KOL Strategy & Management*

Great. Thank you, Barb. So at this time, we'll be conducting a live question-and-answer session. (Operator Instructions). The first question comes from Maury Raycroft of Jefferies.

Maurice Thomas Raycroft - *Jefferies LLC, Research Division - Equity Analyst*

Can you hear me?

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

Yes we can.

Maurice Thomas Raycroft - *Jefferies LLC, Research Division - Equity Analyst*

Great. Thanks for the presentations. They are really good and helpful. Maybe for Dr. Verstovsek. Wondering if you think the data showing that SIMPLIFY-1 patients who do not reach median overall survival in the arm that started momelotinib and who were naive to a JAK inhibitor and stayed on momelotinib, do you think the data are representative? And did they strengthen the case of using momelotinib from the start in the 1-line setting?

Srdan Verstovsek

Yes. I think that the data is very compelling. It does follow the experience with ruxolitinib, the qualitative difference in the overall response and easier management. And I think this is additional factor that we have not talked about, it's the simplicity of management of the patients. Without those modifications, transfusions or frequent monitoring of the blood count is a testament to quality of the medication that then translates, as you can see, to prolonged durability of the benefit, which is a key factor of not just achieving the benefit, but having it for a long time. And eventually, strong suggestion that then patients might be living longer with a good control of the signs and symptoms. So I hope this answers your question. Very good question. Thank you.

Maurice Thomas Raycroft - *Jefferies LLC, Research Division - Equity Analyst*

Yes. Very helpful. And then the other question I had for the panel is, from SIMPLIFY-1 and SIMPLIFY-2, we've seen a lot of great perspective and retrospective data showing the anemia benefit of momelotinib benefit on transfusion burden, benefit in patients low platelet counts and then the survival benefit. I guess, do you expect all of these analyses to make it into a label for the drug? Or which data sets do you think are the most important to get into label?

Ruben Mesa

I can say that certainly, I think, all are very important in terms of how clinicians will view the drug. And those considerations, having been formally the NCCN panel chair for MPNs in terms of what those recommendations look like, I would certainly defer to my colleagues at Sierra in terms of what they think will be appropriate in the label itself. But I do think it will certainly impact practice.

Sara Parigian - *LifeSci Advisors, LLC - VP of KOL Strategy & Management*

Thank you, Maury. The next question comes from Jay Olson at Oppenheimer.

Jay Olson - *Oppenheimer & Co. Inc., Research Division - Executive Director & Senior Analyst*

Thank you very much for these extremely informative presentations. I'm trying to understand the relative importance of anemia versus thrombocytopenia. In the randomized portion of SIMPLIFY-1, momelotinib rapidly increased red blood cells and platelets, while ruxolitinib decreased both. I'm wondering, if you had to prioritize these differences, what is more important to watch for when you treat your myelofibrosis patients with ruxolitinib? Is it anemia or is it thrombocytopenia?

And recognizing that you do have supportive care treatments available to treat anemia and thrombocytopenia, considering everything available in your armamentarium, what are the largest unmet needs and potentially greatest advantages for momelotinib versus ruxolitinib in myelofibrosis patients?

Srdan Verstovsek

I can start here, and others may join me. I think this is a really good practical question. Anemia is present in majority of the patients, as we know, and it gets worse over time. And it is one of the major problems in management of patients with currently approved JAK inhibitors. It leads to underdosing from the very beginning, it leads to dose reductions without proper guidance on how to and when to dose adjust. While for the platelets, the platelets are low in a proportion of the patients at the beginning, perhaps 10% and it may worsen. But proportionally, there are many more patients that are anemic or experience anemia through therapy with currently available JAK inhibitors.

So anemia drugs that would improve that particular aspects are being developed specifically, as you know. In momelotinib, we have medications that can address the spleen symptoms and anemia all at the same time in a simple way. Therefore, I think that the qualitative advantages of momelotinib here are those that make it very attractive. Jean-Jacques, what do you think?

Jean-Jacques Kiladjian

I fully agree. And we also, in clinical practice, have to deal with the drug that are available. And for us, for the moment, it's only ruxolitinib and we know that when we stop this drug, we will see a drop in hemoglobin level for all patients. And some of them who were not transfusion-dependent will become transfusion-dependent, after starting ruxolitinib. So if we can avoid that with a drug that doesn't worsen anemia or even improves anemia, it would be great for those patients with borderline hemoglobin, let's say, at the beginning.

And for the platelets, it's the same the occurrence of thrombocytopenia is really a problem for patients treated with ruxolitinib because, as you saw in the trials, we have to decrease the dose and then we lose the dose intensity, we lose the benefits and the response. So also this is a very practical question. And if we can avoid to change the dose or reduce the dose because of a drop in platelets, also it's clear improvement for the patients and more chance to achieve their responses with only 1 drug. And this is also very important, as Serge mentioned, to have just 1 drug that address anemia symptoms and thrombocytopenia. It's a great advantage for patients rather than adding layers of different drugs that all will have adverse events and et cetera.

Ruben Mesa

A great discussion. Just one comment I would add and I agree with both what Serge and Jean-Jacques have mentioned, is that fundamentally, we've learned that both sets of cytopenias are really quite distinct. But I can say that anemia is a major driver of physician's choice in terms of drug utilization and concerns for their patients. So anemia is definitely something to improve. It improves quality of life. It's an important goal. Thrombocytopenia is really around safety and is something -- I mean less of concern for physicians, but up to a point. If below a certain number, it impacts practice, it decreases dose intensity and it probably decreases the overall effectiveness of the therapy. So each quite distinct, but I do think the improvement in anemia is key.

I would also say that the majority of supportive options we have for either of these cytopenias at the current time are really not very effective. So although we have ESAs and (inaudible), most of these things really are not very effective, and very little that's effective for thrombocytopenia. So the ability -- the profile of this drug really is distinct.

Jay Olson - *Oppenheimer & Co. Inc., Research Division - Executive Director & Senior Analyst*

That's super helpful. If I could maybe, I had 1 follow-up question. How would you compare the efficacy of momelotinib versus a combination of JAK plus that inhibition for increasing hemoglobin levels? And maybe if you could look into the future, do you expect momelotinib to have disease-modifying features such as bone marrow fibrosis improvement?

Srdan Verstovsek

There are 2 excellent questions. Let me answer the first one then. The combinations are the way to go, probably. In the future, we're going to be talking about enhancing what we do in terms of controlling the spleen symptoms and anemia. Perhaps there will be also the drug that will be improving the platelets, who knows in the future. But certainly, we hope that with the combinations that can be combined in a safe way and provide durability, we will improve our management of our patients and make them live longer.

We have evidence of these activities, as we just discussed in momelotinib as a single agent already. But being so safe and simple to give the momelotinib is excellent combination partners for the future. We are seeing combinations with ruxolitinib and BET inhibitor that you mentioned or Navitoclax. They do require quite an engagement of the part of the doctor and patients to juggle between the 2 drugs that may have overlapping toxicities. With momelotinib, you have much less of that, if any. So I think that there is a good potential for momelotinib-based combinations to be developed in the near future.

In terms of the disease modification, the real disease modification is when you make people live longer. I mean this is such obvious to me. If you make people live longer with a good control of the signs and symptoms, which is obviously related to some biological parameter, being the bone fibrosis, being the cytokine decrease, being something else that we do not know of yet. The ultimate disease-modifying outcome is survival prolongation.

So I am a little bit worried that we put too much strength or evidence on the bone marrow fibrosis modification as the evidence of disease modification without having any evidence that fibrosis modification decrease makes people live longer. Or connects to any clinical benefit, being anemia or spleen or symptoms. So I would separate the 2 and talk about life prolongation as the clear-cut evidence of the disease modification.

Ruben Mesa

And I would echo Serge's comment just because there's so much discussion of bone marrow fibrosis out there, but it is really an unproven endpoint. I think it's interesting, but myelofibrosis patients care about living longer or living better. For me, it's not clear at this point, that necessarily modest changes in the allele burden or modest changes in the fibrosis are necessarily correlated with either of those. I think we should study them over time. There may be methodology issues in terms of how granular that data is to even detect the difference, but living longer, living better. I think those are the most relevant endpoints.

Jean-Jacques Kiladjian

I will echo my colleagues just to say that as researchers, we are excited to find better biomarkers, et cetera, to see a nice decrease in the allele burden or the fibrosis. But when you go back to the clinic, I fully agree with Serge and Ruben, patients really don't care about that. They want to live better and longer. And I think that's the main issue. So these are really 2 different paths. One is to find possible curative treatment that is not yet available, of course. And I don't think we can achieve that with the current combinations. But the other is the clinical management of patients and how they can be happy with the help we provide them and with the better survival.

Sara Parigian - *LifeSci Advisors, LLC - VP of KOL Strategy & Management*

I'll now turn the call back to Mark for any questions that may have come in over the web.

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

Yes, just there were a number of questions that have come in. And a couple of them addressed or asked about resolving bone marrow fibrosis and whether more marrow antifibrotics are needed in myelofibrosis. It was touched on previously, but let me just open that up again to Ruben, Jean-Jacques and Serge if they have any additional comments on the need for further antifibrotics and myelofibrosis.

Ruben Mesa

Let me just add a bit to what I had alluded to. So I think there's a couple of issues. One, we only measure fibrosis on basically 3 levels. So the granularity of the data of change is difficult to reproduce, and there's very little kind of granularity to that data. Two, we know that the fibrosis itself is a secondary phenomenon in the disease that may have a variety of implications, both related to the chrome but also aspects of bone marrow environment. So I view it as investigational.

I think we do, as a field, seek a what is a good biomarker of progression-free survival. But I think fibrosis, although people call it disease-modifying, I don't think that, that has been proven. It may well end up being something that we're not measuring yet. What we have seen is proof that improvement in splenomegaly symptoms and possibly anemia probably do correlate with prolonged survival. So those, I think, get further validated every day in terms of how meaningful they actually are.

Jean-Jacques Kiladjian

Yes. If I may continue on the excellent answer. There is no doubt that there is an interest, and it should be done to test or evaluate antifibrotics in myelofibrosis. It is part of the disease process. It's maybe secondary and multiple factors can lead to worsening or existence of fibers in bone marrow. What will make a difference is that these antifibrotics, when evaluated in clinical studies, do provide clinically relevant endpoints, decrease in fibrosis, improvement in bone marrow function, anemia, thrombocytopenia. These are the correlations that we lack as of yet. So as a target, it's very viable, very interesting. But as the proof-of-concept that this means anything, that we don't have yet. But I am very excited about starting antifibrotics as the therapies for myelofibrosis. No question about that.

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

Thank you. There are 2 questions I'm asking about momelotinib and should it be combined with a BET inhibitor like Constellation's compound. And we've touched on that before, but any additional comments about those questions?

Perhaps not. That's fine. And another question asked about twice-a-day dosing and saying that the lower response in high platelet patients may be dose-intensity related. Has momelotinib been tested in a twice-a-day's dosing and would this be tolerated?

Again, I could open it up to Barb or Ruben, Serge or Jean-Jacques, or perhaps I can comment myself.

Ruben Mesa

So I guess -- just a second, Mark. What was the question?

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

The question is, has momelotinib been tested in a twice-a-day dosing? And was that tolerated?

Srdan Verstovsek

Yes. We had actually studied a Phase I/II study done, and I was the senior author on that paper. Vikas Gupta actually was the first author where we looked at the different ways of delivering momelotinib. And after all analysis of single or 2 daily doses, the suggestion from the efficacy and safety was that a daily dose is good to pursue. Now Mark would perhaps -- or Barb, have a comment from the perspective of the company, whether there are subgroups of patients that would be subject to different dosing in the future. But at the moment, I think we all are unison in what to do and how to proceed.

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

No, I would agree as well with what you're saying in that it did not show a significant advantage and the 200 once-a-day and the ease of use that, that presents with its level of efficacy and tolerability is the way to go.

Srdan Verstovsek

Yes.

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

Do we have time for a couple of more? Are there additional questions? What role might there be for the nearly approved agent, fedratinib and then also pacritinib now in pivotals? Again, Serge, Jean-Jacques, Ruben. Maybe Jean-Jacques, if you want to comment first?

Jean-Jacques Kiladjian

The question is about the relative pace of each of these drugs?

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

Yes. What might there be for fedratinib in pacritinib?

Jean-Jacques Kiladjian

Yes. Yes, yes. Clearly, pacritinib targets patients with very, very low platelets, below 20,000, for example, et cetera. So it's a very particular population of patients. Fedratinib, on the other hand, as -- for me at least, a profile that is quite close to ruxolitinib. So it can be used either frontline or after roxulitinib, but will not provide, let's say, additional benefits in terms of anemia or thrombocytopenia. It may restore some splenic response. And

for me, momelotinib is quite unique in that, as we mentioned earlier, and I would be happy to use momelotinib for those patients with low hemoglobin, low platelets to start with because I hope that we can help them with the spleen and symptom response without worsening and even with improving anemia.

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

Great. Thank you. Well, I think Barb, maybe you want to ask if there are any additional calls from -- questions from the audience. If not, we could wrap up, but perhaps you can ask one last time.

Barbara Klencke - *Sierra Oncology, Inc. - Chief Development Officer*

All right. I think we're very close to the end of the hour. Let me just really thank all of our panelists today, Dr. Verstovsek, Dr. Mesa, Dr. Kiladjian. Love to hear from you, your data and the discussions that you had about your experiences with momelotinib. We really appreciate it. And thank you to all of the audience listening today. And appreciate all of the questions. We're happy to address additional questions if they come in directly to the company. So for -- on behalf of myself, Dr. Stephen Dilly, and the rest of us from Sierra, thank you all very much.

Srdan Verstovsek

Thank you, everybody.

Jean-Jacques Kiladjian

Thank you.

Ruben Mesa

Thank you.

Mark M. Kowalski - *Sierra Oncology, Inc. - Chief Medical Officer*

Thank you.

Srdan Verstovsek

Have a good day.