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INCY.OQ - Incyte Corp Data Highlights from ASH 2020

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Robert Zeiser

PRESENTATION

Operator

Ladies and gentlemen, good morning, and welcome to the Incyte data highlights from ASH conference call and webcast. (Operator Instructions) As a reminder, this conference is being recorded.

It's now my pleasure to turn the call over Mike Booth, Head of Investor Relations. Please go ahead, sir.

Michael Booth - *Incyte Corporation - Divisional VP of IR & Corporate Social Responsibility*

Thank you, Kevin. Good morning, and welcome to Incyte's highlights from ASH conference call and webcast. The slides used today are available for download on the Investors section of incyte.com. I'm joined on the call today by Steven Stein, our Chief Medical Officer; and by Peter Langmuir, Incyte's Group Vice President, Targeted Oncology Therapeutics. Hervé and Christiana are also on the call and will participate as needed in the Q&A sessions. We are also very pleased to be joined by Professor Robert Zeiser from the University of Freiburg in Germany, who will provide the important medical context for and a summary of the REACH3 results of ruxolitinib in chronic GVHD. There will be 2 Q&A sessions. (Operator Instructions)

Before we begin, I'd like to remind you that some of the statements made during the call today are forward-looking statements, including statements regarding the commercialization of our products, our development plans and expectations for the compounds in our pipeline as well as the development plans of our collaboration partners. These forward-looking statements are subject to a number of risks and uncertainties that may cause our actual results to differ materially, including those described in our 10-Q for the quarter ended September 30, 2020, and from time to time in our other SEC documents.

I'll now pass the call to Steven for a few opening remarks.

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Thank you, Mike, and good morning, everyone. Incyte can be thought of as having numerous opportunities across 4 quadrants: 3 in therapeutics and one more financial in nature, as described in Slide 4. We have made excellent development progress so far in 2020, with successful Phase III results in chronic graft-versus-host disease and in atopic dermatitis as well as securing 3 new FDA approvals for Monjuvi, Pemazyre and Tabrecta. In today's discussion, we are going to be focusing on the key data sets from the American Society of Hematology, with over 40 abstracts accepted, including 7 oral presentations. And we have chosen data from ruxolitinib, parsaclisib and tafasitamab to highlight for you today.

Slide 6 shows the agenda for this 90-minute event. We are delighted that Professor Zeiser is joining us today, and he will begin our presentations with a summary of the disease and unmet need in chronic graft-versus-host disease, before sharing the REACH3 data that were presented for the first time over the weekend. After a Q&A session, I will share some important data from several ruxolitinib presentations including the EXPAND and RESPONSE-2 trials, before Peter presents updated data from the ongoing CITADEL program for parsaclisib in non-Hodgkin's lymphomas as well as the key highlights from several tafasitamab presentations, after which we'll open for a second Q&A session.

As I said, we are delighted that Professor Robert Zeiser is able to join us today. Professor Zeiser is the Head of the Tumor Immunology and Immune Modulation Section at the Medical Center of the University of Freiburg in Germany, and is a true pioneer in the treatment of patients with chronic and acute graft-versus-host disease. It was his initiative that first showed the potential utility of JAK inhibition in the severe complication of allogeneic transplantation in his paper published in leukemia in 2015. And, of course, he's the first author of the REACH3 presentation at ASH this year.

Professor Zeiser, thank you again for joining us, and I'll now pass the call over to you.

Robert Zeiser

Thank you very much for the kind introduction, Dr. Stein. It's a pleasure and honor for me to talk today about ruxolitinib for chronic graft-versus-host disease.

So a little bit on the background and the clinical features of this disease. What you can see here are typical disease features of chronic graft-versus-host disease. In panel A, you see a patient who has severe sclerodermatous chronic graft-versus-host disease. You see the (inaudible) patient. And his skin is extremely hardened, so he can't stand up normally. And he's lean forward because of his fibrotic changes.

In panel B, you see a local sclerodermatous change of the skin, indicating to you that this disease is very heterogeneous and sometimes affecting just certain areas of the body. The mucus membranes are also affected, as you can see in panel C. And (inaudible) as indicated in panel D, can also be hardened by the fibrotic changes which is -- induces difficulties in swallowing. The fingernails can be affected as seen as panel E; the eyes can be affected, panel F; and the lungs can be affected. If you investigate that by histology, you see increased collagen deposition as indicated in panel H, while lymphocyte infiltration as indicated in panel I and J.

That brings me to the next slide. So the background here is a chronic graft-versus-host disease with these features that I've just shown you, occurs in between 30% and 70% of patients that undergo allogeneic hematopoietic stem cell transplantation. And it is a leading cause of nonrelapse mortality and mainly also morbidity in those patients. Candidates of standard first-line therapy are glucocorticosteroids. However, only 50% of the patients respond and the other patients become refractory or corticosteroid-dependent. These corticosteroids have fewer side effects. So also the

patients that are dependent on steroids suffer not only from the disease, but also from the steroid-induced side effects. Currently no standard second-line therapy has been defined, and there have not been no successful large-scale randomized studies in this setting.

So coming to the pathomechanism of this disease. And the first step in the pathogenesis of chronic graft-versus-host disease is that tissue damages induced. As shown here in this simplified image, you see that there are damaged or dying cells that release certain metabolites like adenosine triphosphate, uric acid IL-33 or HMGB-1. And those then activate different types of immune cells, mainly at this point, innate immune cells that can then be activated and present antigen to the incoming donor T cells like monocytes, dendritic cells, macrophages, as indicated here, and those then produce inflammatory mediators. There's also been observed that in the early phase of chronic graft-versus-host disease, endothelial injury takes place, and that leads then to reduced microvessel density.

The second phase, T cells and B cells are activated, and they start to produce cytokines, including IL-21, IL-17 and interferon-gamma. Besides these activated T and B cells, and thymic damage that occurs during chronic graft-versus-host disease damages the epithelial cells and leads to a reduced education of the T cells, meaning that positive and negative selection of T cells in the sinus is disturbed. Besides that, also regulatory T cells and natural killer cells as well as invariant natural killer cells are reduced in the frequency and activity.

In Phase III, the end organ damage occurs, meaning that there is various fibrotic changes and inflammatory changes that I've shown you. And here, the mechanism is such that macrophages that are activated and produce TGF-beta or PDGF alpha and activate the corresponding receptors of fibroblast, which then produce extracellular matrix, which is deposited in the tissue and leads to the sclerodermic changes as well as the connection of collagen by those extracellular matrix molecules. B cells differentiate into plasma cells, and those plasma cells produced immunoglobulins, which are also deposited and which also cause local tissue injury.

So what are new targets? Highly experimental targets are those at (inaudible) events, for example, P2X7 receptor inhibitors, which interfere with the activation of these purinergic receptors, adenosine triphosphate. Now since (inaudible) inhibitors could be -- have activity and ST2 inhibitors. Then, toll-like receptor inhibitors or IL-1 beta inhibition quote have activity. These are very early and preclinical data, which are far away at this time point from a clinical application.

In the second phase, kinase inhibition comes into play, which is important for the activation of antigen presenting cells, but also B cells and T cells. They're depending on tyrosine kinase or ITK and ROCK activity. And this can be blocked with respective kinase inhibitors that can also be improved by giving keratinocyte growth factor, at least that has been shown in the mouse model that you can improve thymic function when providing KGF, which would expand regulatory T cells and also the thymic epithelial cells.

In the third phase, other targets come into play like pirfenidone has been shown in the mouse model of chronic graft-versus-host disease to have activity. JAK inhibition, as we have seen in mice and patients; tocilizumab, which interfere with the IL-6 receptor activation, imatinib to block kinase activation of cells in those fibroblasts. And, of course, targeting plasma cells with the immunoproteasome inhibitor bortezomib for that neutralization of IL-17.

So before I come to the main study, I'll show you some of our earliest results. We have treated here patients with chronic graft-versus-host disease at a time point where they had not responded to multiple previous therapies. You see in this bar diagram, the majority of them had 3 prior therapies, but some of them had up to 10 prior therapies, and they are not responding here. You see the skin of such a patient who then responded and achieved a complete remission even. You can see here the bar diagram on the right, showing that the majority of the patients achieved a partial remission, meaning a symptom improvement and 3 patients achieved complete remissions. There are also some patients who did not respond at all.

Those data where the motivation and the background, why a Phase III trial was conducted comparing ruxolitinib versus best available therapy in patients with steroid-refractory or steroid-dependent chronic graft-versus-host disease. And this is a clinical trial design, where patients had to be 12 years or older. They had to have steroid-refractory or dependent chronic graft-versus-host disease.

Due to a lack of response after prednisolone at this given dosage, disease progression or an increase of prednisolone dose above this rate here and 2 unsuccessful attempts to taper. Also they had to have a myeloid and platelet engraftment. These patients are then randomized in a one-to-one

fashion to receive either ruxolitinib 10 milligrams BID or BAT. And at week 24, the primary endpoint was assessed, which was overall response at this point, and there was an extension period and a safety follow-up in these patients.

Here, you see already the results of the primary endpoint. The primary endpoint was met. Overall response rate at week 24 was significantly higher in the ruxolitinib group as compared to the BAT group. You see here 49.7% versus 25.6%, a significant improvement in those patients. Also important failure-free survival was longer with ruxolitinib compared to BAT.

Another parameter was the modified Lee symptoms score response in these patients, symptoms scores essential to assess disease activity. And here, the response rate was significantly higher in ruxolitinib compared to BAT with 24% versus 11%.

We also measured best overall response in those patients, which was the best overall response that those patients achieved in a given time period. And that was also significantly higher in the RUX group compared to the BAT group with 76% versus 60%. And you see here the median duration of best overall response was 6.2 months in the BAT arm, but was not reached in the RUX arm, while BAT was also favorable in the RUX arm.

Of course, safety is an important concern in patients that are receiving severe immunosuppression. And here is a comparison of the safe -- the adverse events in the RUX arm compared to the BAT arm. Any grade adverse event was very similar in both group. Grade 3 adverse events, also very similar in both 57% adverse events leading to dose modification were also slightly higher in the adverse event in the RUX group that has, however, also because this group received much longer exposure to ruxolitinib, namely 41 versus 24 weeks. The deaths until data cutoff were not significantly different here.

The main side effects here were anemia and thrombocytopenia that were -- and anemia was significantly higher in the RUX group compared to the BAT group. Thrombocytopenia was numerically higher but didn't reach significance. Other complications were not significantly different.

So in conclusion, this is the first successful randomized Phase III trial in adolescent and adult patients with chronic graft-versus-host disease and inadequate response to corticosteroids. Ruxolitinib demonstrated significantly higher overall response rate at week 24 compared to BAT, significant improvement in failure free survival, and significantly greater symptom improvement as well as higher best overall response rate. Importantly, the safety profile of RUX was consistent with what was observed previously and what was expected in those patients.

Based on those data, RUX is the first agent to demonstrate superior efficacy to BAT in a Phase III trial of patients with chronic graft-versus-host disease that didn't show an adequate response to corticosteroids. And that will -- is likely to change the treatment landscape and finding support the use of RUX as second therapy after an initial steroid treatment.

Of course, we also need to discuss future unmet medical needs. Now that we have achieved that, what is the next question? So an important question is, can we combine ruxolitinib and also achieve a response in those patients that have failed ruxolitinib? So we have done that already in Freiburg, and we have 90 ruxolitinib with extra (inaudible) for ECP. And here, we observed in patients that were refractory to either ECP or ruxolitinib that they responded. This is a patient with skin -- chronic skin GVHD that was very resistant. And after the combination Ruxo and ECP, this patient had a complete remission. Also another patient with interferon GVHD showed a complete remission. Here, we have the response rate in those patients that were highly refractory. We, at least, had 10% complete remissions and 65% partial remissions.

So with that, I'm at the end of my talk, and I'd be happy to take your questions.

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Thank you, Professor Zeiser. Operator, now is the time for the first Q&A session. So please give your instructions and open the call for Q&A.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question today is coming from Cory Kasimov from JPMorgan.

Cory William Kasimov - *JPMorgan Chase & Co, Research Division - Senior Biotechnology Analyst*

I wanted to ask Dr. Zeiser. How are you thinking about RUX in chronic GVHD in comparison to some of the other novel agents that are being investigated? You mentioned some of the targets. You have products like CAP, MET, ROCK2 inhibitor and things like that. How do you think about RUX in that grand landscape? And do you expect physicians to relatively rapidly adopt this for chronic GVHD upon approval?

Robert Zeiser

Thank you for this important question. So the RUX inhibitor was also tested. It was tested also in a randomized trial. They are randomized into 2 arms, 2 different dosing schedules. But they did not randomize against BAT. So there's -- currently, there's no information if the RUX inhibitor is truly better than what is currently available as a second-line therapy.

And the RUX inhibitor trial showed also a high response rate, and -- but they measure just over -- best overall response rate, not at a defined time point. The best overall response rate that they reported was 73% in one dosage arm and 77% in the other dosage arm. So it is very close to what we observed as best overall response here with ruxolitinib. However, it's a different trial design. And it's -- so far, it doesn't allow for a direct comparison. I think the RUX inhibitor is still a very interesting pharmacological approach to interfere with chronic graft-versus-host disease. And it needs further confirmation, I think, in a head-to-head comparison to BAT in order to be implemented in our treatment algorithm.

The question is, can we combine it with ruxolitinib at some point? I think both are kinase inhibitors. Both inhibit signaling molecules and immune cells. And so the concern is that there could be also additive toxicity when you combine 2 kinase inhibitors, but that has to be investigated also in future clinical trials.

Operator

Our next question is coming from Evan Seigerman from Crédit Suisse.

Evan David Seigerman - *Crédit Suisse AG, Research Division - VP & Senior Equity Research Analyst*

So when you look at the potential for ruxolitinib in chronic GVHD, how many of your patients would you potentially prescribe? I'm just trying to get a sense as to what the actual opportunity is.

And do you see any potential for using this ahead of steroids? I know that's not the trial that we're looking at there. But from a theoretical and kind of biologic point of view, would that make sense at some point?

Robert Zeiser

Yes. Both are very important questions, so I will start with the first question. The first question is how many of my patients would receive ruxolitinib. And I can say that based on the REACH2 data -- REACH3 data, the majority of my patients would receive ruxolitinib as a second line therapy. There are a few exceptions. If patients are severely thrombocytopenic or if there is a known intolerance to the drug because these are, for example, MPN patients that had previous exposure, and then of course, this does not allow. And to treat with ruxolitinib, but this is clearly a very minor group of maybe 5% to 10% of patients.

The other patients with chronic graft-versus-host disease currently should receive ruxolitinib. It is not yet approved in Europe, but I think approval will come based on those data. And so we had a recent survey in Germany and already, the majority of the transplant physicians are treating their patients with ruxolitinib after steroid failure.

Your second question is related to whether we could already implement ruxolitinib in earlier treatment line. And even before steroid or together with corticosteroids, and I think so far, we don't know if that is an advantage for the patients because multiple drugs that were combined with corticosteroids have failed to show an improvement compared to steroids alone. But on the other hand, it would be very desirable to reduce the corticosteroids as fast as possible. And this could be potentially achieved when you combine corticosteroids with ruxolitinib. And I've heard from some colleagues that they already start doing that just to have a steroid-sparing agent. But currently, there is no good clinical data supporting such an approach.

Operator

The next question is coming from with Alethia Young from Cantor Fitzgerald.

Alethia Rene Young - *Cantor Fitzgerald & Co., Research Division - Director of Equity Research & Head of Healthcare Research*

Another couple for the professor. I was just curious, when you're looking at RUX and ECP as a combination, you saw some activity in skin, but did you see other activity in organs?

And then I actually was just curious as it relates to kind of lines of therapy, like what percentage of people kind of have maybe like might not be eligible for RUX just overall as you think about your whole population?

Robert Zeiser

Okay. So the first question related to the organ response, if I understood that correctly. When we combine ruxolitinib plus ECP, we saw that all different organs responded very similar. There was not a particular organ that would respond much better than the other organs or much worse than the other organs. So it was very -- the response rate in the different organs are very similar.

And then you were asking how many patients would be ineligible for ruxolitinib treatment, if I believe -- if I understood that correctly. And this is a small group of patients that is ineligible. For example, patients with severe pancytopenia or thrombocytopenia, those patients, it's difficult. Still, some of those patients, you can transfuse or you can taper other medications that causes pancytopenia. And so I would say the range is maybe 5%, at most, 10% who are primarily ineligible to ruxolitinib.

Operator

So next question is coming from Brian Abrahams from RBC Capital Markets.

Brian Corey Abrahams - *RBC Capital Markets, Research Division - Senior Biotechnology Analyst*

For Dr. Zeiser, it looks like in this study, the deaths were not significantly different between the 2 arms, despite the clear effect that you saw on response from some of the other parameters with ruxolitinib. So I'm just curious if this is just maybe a byproduct of the longer duration that patients are on RUX because of the crossover. Or anything to think about with respect to potential influence of AEs there? And would you expect that over time, you'd start to see some pull-through to overall survival benefits in this population?

Robert Zeiser

That is also an important question. There was no difference in overall survival or death rate. But this study was not powered at this time point of analysis to detect a difference in survival. And also in chronic graft-versus-host disease, death is not the major outcome parameter. It's more of the symptom score, basically that tells you something about the quality of life of these patients. The majority of these patients survive. You have survival rates of between 85% and 90% at 1 or 2 years even. So it is not expected that there will be a big difference in survival, even if you improve the disease significantly.

Another point that you already mentioned is a crossover from the BAT to the RUX arm, and that also leads as a confounder basically for the overall survival rate. And therefore, overall survival at this time point was not even measured. It will be reported in a later analysis. And it can be that on the long term, maybe with a follow-up of 2 or 3 years that there will be a difference, but not at this early time point.

Operator

Our next question today is coming from Tazeen Ahmad from Bank of America.

Tazeen Ahmad - *BofA Merrill Lynch, Research Division - VP*

Just a couple for me. Doctor, I wanted to get your thoughts on how you thought the Ibrutinib patients did in the BAT arm. And then secondly, I wanted to get your thoughts in a real-world setting, what kind of duration on therapy would you expect these GVHD patients to have on drug?

Robert Zeiser

Okay. So I start with the second question, the duration of therapy in those patients. So the duration of therapy in these patients is quite long. As you've seen, we measured our response at week 24. So this shows you that the biology of this disease is slow, time-wise. That's why it's called chronic GVHD. So after such a long period of time, 24 weeks, you assess if they have responded or not. And then all those patients that have achieved a partial response will probably continue with ruxolitinib, maybe not at the full dose, but at some kind of dose.

And I have patients who have received a therapy now for 3 years, for example, 3 and 4 years, and they have no problems with hematopoiesis. But they have a clear benefit. And always, when we try to taper, the chronic GVHD symptoms seem to come back. So it's a long-term therapy. At this point, we are not able to say exactly how long the patients need to be treated. But it is clear that they need to be treated much longer as compared to acute graft-versus-host disease where you can taper, if the patient has responded after 1 or 2 months.

Could you repeat the first question for me?

Michael Booth - *Incyte Corporation - Divisional VP of IR & Corporate Social Responsibility*

So it was how did patients who are post -- who are the BTK in the BAT group.

Robert Zeiser

Okay. And how many patients received the BTK inhibitor. So 17% received the BTK inhibitor, Ibrutinib in the BAT group. This is relatively low because the majority of the patients were recruited in countries outside of the U.S. and that's -- in these countries, Ibrutinib is not approved. And also the transplant community in Europe, at least, is not very convinced of Ibrutinib. Also there are some anecdotical reports where it has showed activity. Overall, this is -- in most people in the community have to view that this is not the best solution for chronic graft-versus-host disease.

Tazeen Ahmad - *BofA Merrill Lynch, Research Division - VP*

Okay. So in your view, I guess, how did those patients do?

Robert Zeiser

How did they do? So we didn't do a subgroup analysis in -- with these patients. But they were not -- there was -- we have looked at the response rate, and those patients with Ibrutinib were not responding particularly well. They were rather in the -- somewhere in the middle. ECP was the best alternative therapy.

Operator

(Operator Instructions) And that comes from the line of Tyler Van Buren from Piper Sandler.

Tyler Martin Van Buren - *Piper Sandler & Co., Research Division - Principal & and Senior Biotech Analyst*

Of course, the increases in response rates and further increased survival are great to see. I guess maybe wanted to go beyond the data that was presented, the numbers, and hear your comments on quality of life improvements. And in particular, in the symptom improvement, clearly a nice magnitude. But is there any specifics unique symptom alleviation that you're seeing with RUX as opposed to best available therapy or any components of the mLSS that -- or symptoms, in general, that you could call out?

Robert Zeiser

Yes. So we have not analyzed the -- or compared the different symptoms alleviation set, are measured in the modified Lee symptoms or at least I have not those data available at this point. But our improvement in the modified Lee symptom score, that is double the improvement seen in the BAT arm is clinically highly meaningful with 25% versus 11%. That is for the clinicians at large difference, which allows tapering of corticosteroids and which increases the quality of life of the patients. So far, we have not analyzed the individual or compared individual organs or measures.

PRESENTATION

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

So thank you for your questions, and thank you again, Professor Zeiser for your participation and insights. We really appreciate it.

Let's move on with the second segment of our event, and I'll begin with a summary of key ruxolitinib data from ASH. Ruxolitinib was first FDA-approved in 2011 based on the COMFORT Phase III trials. And in subsequent updated analyses, we have shown significant and long-term benefits in myelofibrosis patients.

The data on Slide 32 are from our real-world evidence team comparing 3 distinct groups of myelofibrosis patients. Those diagnosed before ruxolitinib was approved, the green line in the Kaplan-Meier curve; those diagnosed after ruxolitinib was approved but not exposed to ruxolitinib, the red line; and the blue line of those patients exposed to ruxolitinib after it was approved. There is a clear separation between all 3 curves, and the key comparison is between the red and blue lines, adding further evidence that treatment of myelofibrosis patients with ruxolitinib dramatically alters the outcomes for these patients. The hazard ratio for this comparison is 0.61 with a strong p-value.

The results of EXPAND study on Slide 33. The EXPAND study initially aimed to establish the maximum safe starting dose in patients with low baseline platelet counts and evaluated the safety and tolerability of ruxolitinib in this population in 2 strata based on baseline platelet counts. 10 milligrams twice daily was chosen as a maximum safe starting dose, and no new safety findings were found. Importantly, and as is shown in the panels on the

right side of the slide, 10 milligrams twice daily also provided clinically meaningful reductions in spleen length and improvement in clinical symptoms in this previously unstudied myelofibrosis patient population.

I'll now switch to polycythemia vera and the final results of the RESPONSE-2 trial. You will recall that ruxolitinib was FDA-approved in polycythemia vera based on the results of response, wherein ruxolitinib showed a superior and durable response in controlling hematocrit and improving splenomegaly versus best available therapy. This was in polycythemia vera patients with splenomegaly, who were resistant to or intolerant of hydroxyurea.

RESPONSE-2, on the other hand, was in polycythemia vera patients with no palpable splenomegaly. RESPONSE-2 establishes a long-term safety and efficacy of ruxolitinib in patients with hydroxyurea-resistant or hydroxyurea-intolerant polycythemia vera without splenomegaly. These 5-year efficacy results show durable hematocrit control as well as reduced allele burden over time. And both panels on Slide 35 show this effect in both cohorts of patients, those initially randomized to ruxolitinib as well as those initially randomized to best available therapy and then crossed over.

The 5-year results of RESPONSE-2 also show a 2x lower rate of phlebotomy in the ruxolitinib-treated group versus the crossover group, further illustrating the need for early intervention in these patients as well as a significant improvement in symptoms in patients treated with ruxolitinib versus those treated with best available therapy. It is also notable that on an exposure-adjusted basis, patients on ruxolitinib had lower rates of thromboembolic events versus best available therapy. This also held true in the ruxolitinib-treated group versus the crossover group or, in other words, early RUX versus delayed RUX, again, illustrating the need for early intervention in these patients.

The last slide in my segment also comes from our real-world evidence team. We sought to compare the risk of mortality and overall survival in patients newly diagnosed with high-risk polycythemia vera who experienced a thrombotic event versus those patients who did not experience one. We did this by an analysis of over 50,000 patients in the Medicare database. In this real-world study, approximately 1/3 of patients with newly diagnosed high-risk PV experienced a thrombotic event during follow-up. And these patients had a significantly increased risk of mortality versus those who did not experience a thrombotic event.

At both 1-year and 2-year landmarks, the Kaplan-Meier survival curves showed the dramatic effect that having a thrombotic event has on outcomes. Overall survival was significantly reduced in patients who experienced a thrombotic event compared to those who did not. These results further reinforce the need for therapeutic intervention in certain patients with polycythemia vera, where thrombotic risk mitigation is an important management goal in patients with p vera, for example, by treatment with RUX and, in particular, those with a prior thrombotic event.

I will now pass to Peter to describe the parsaclisib and tafasitamab highlights before we open for the second Q&A session. Peter, over to you.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

Thank you very much. So I will take you through some of the data for our lymphoma agents, parsaclisib and tafasitamab that are being presented at ASH. If we go to the next slide, please.

So starting with parsaclisib. This is our PI3-kinase delta inhibitor. It's a highly potent and selective inhibitor of the delta isoform of PI3 kinase and more potent and more selective compared to all of the other PI3-kinase inhibitors that are currently either approved or in development.

So on the next slide summarizes the 3 monotherapy development programs that are being presented at ASH this year. The CITADEL-203 study is in patients with relapsed/refractory follicular lymphoma, the CITADEL-204 in patients with relapsed/refractory marginal zone lymphoma, and then the CITADEL-205 study in relapsed/refractory mantle cell lymphoma. And we presented 2 sets of data here. One from patients who are BTK-naive and then a cohort of patients who had previously received BTK inhibitors. We know that this group is particularly hard to treat and so we included a cohort of these patients and those data were presented as well.

One note on the dosing regimen that we used. We know that a class effect of PI3-kinase delta inhibitors is the occurrence of immune-related adverse events that occur about 6 to 9 months after being on treatment. And early on in the development program, we identified that this is obviously a problem if you -- particularly if you have a patient who's able to walk but cannot continue on the drug because of this toxicity. And so

we took some time in the Phase I to explore some different dosing regimens and continue that in Phase II, looking at initiating with a fairly potent dose of 20 milligrams daily for 8 weeks and then switching either to 20 milligrams weekly or switching to a lower 2.5 milligram dose daily.

And so during these studies, we decided to move forward with the continuous daily dosing, so starting high and dropping to a lower dose, as the preferred regimen. And so it's worth just keeping that in mind as we look in the data because patients -- we have more patients on the daily dosing. They were not recruited synchronously in all cases. And furthermore, patients who are on the weekly dosing relapsed switched to continuous daily dosing.

So next slide. When we look at the adverse events overall, and I urge you to look at the data for this specific study because, again, each of these studies, patients were on treatment for longer and had different -- came with different backgrounds. But in general, the safety profile was acceptable. It was generally very well tolerated. When we look at patients with any serious treatment-emergent adverse events, the numbers are fairly similar across the 3 studies, including both the BTK naive and the post-BTK cohorts of the mantle cell lymphoma study.

In terms of the adverse event of special interest, we do see diarrhea and colitis. Diarrhea is around 10% rate for serious adverse events and colitis less than 10%. Again, this is expected for agents of this class. But otherwise, we don't see as much of some of the other immune-related adverse events that have been seen with other agents. Generally, these diarrhea, colitis events occur about 6 months after patients have been on treatment. And it will get better, in most cases, fairly quickly within 1 to 4 weeks after holding the drug.

In terms of dose modifications, a number of patients did require dose interruptions, but most of those were able to resume treatment. About 5% to 15% had dose reductions. And between 5% and 30% across the different studies ended up having to discontinue because of an adverse event.

For the next few slides, I'll take you through the waterfall plot for the RESPONSE data for each study. So first of all, the follicular lymphoma study. So the chart shows all of the patients, so both the weekly -- the patients who switched to weekly dosing in the green and the patients who switched to a low dose daily dosing in the blue. The overall response rate in the patients who switched to the daily dosing, again, this is the preferred regimen, was 75% and the median duration of response in that group was 14.7 months with a median progression-free survival of 15.8 months. So that response rate is extremely encouraging in this relapsed/refractory patient population.

If we go to the next slide, these are the patients with marginal zone lymphoma. The overall response rate in the daily dosing group was 57%. Again, a very encouraging number here. The median duration of response was 12 months and median progression-free survival was 19 months in all of the patients. But in the daily dosing group, we have not yet reached that median duration of response, nor have we reached the median progression-free survival. So again, encouraging data. And I should just add here that all of these responses were done by an independent review committee and not based on the investigator read.

The next slide is for the mantle cell lymphoma, and this one is the patients who had previously received Ibrutinib. Again, this is a very hard to treat group. These patients tend to progress very rapidly after progressing on Ibrutinib. The overall response rate was encouraging. We saw 29% of patients with a response in the daily dosing group. The median duration of response was 3.7 months. Median progression-free survival, also 3.7 in both -- in the overall population as well as the daily dosing group. So it's encouraging that we see tumor -- reductions in tumor size in most of the patients. But again, as expected, these patients tend not to do very well, in general, after progressing on Ibrutinib.

However, on the next slide, we see the BTK naive patients. And here, we see a 71% overall response rate in the daily dosing group. And in that group, the median duration of response was 9 months and median progression-free survival was 11 months. So again, a very encouraging result in this patient -- relapsed/refractory patient population.

And so the next slide summarizes the compelling efficacy data that we see across these 3 studies. Again, and if we focus on the daily dosing group, which is the regimen we're moving forward with, overall response rates of 75% in follicular, 57% in marginal zone and 71% in mantle cell lymphoma with good durable duration of response and median progression-free survival. That looks probably in a single-arm trial, very encouraging compared to currently available treatments.

And so the next slide, these data were shared here. The follow-up is ongoing. One thing we want to be very sure of, and we know FDA is going to want to look at this, is to have adequate follow-up to be able to demonstrate that these responses are durable. And at this point, we were very encouraged by the data, and we expect to have an NDA in the second half of next year. And this is obviously a significant opportunity. There are a lot of patients with relapsed/refractory non-Hodgkin's lymphoma. And we think these data are very encouraging and hopefully provide a meaningful treatment option for these patients.

On the next slide summarizes our development strategy. I talked about the monotherapy data. The other interesting trial that we have ongoing with monotherapy parsaclisib is a study in autoimmune hemolytic anemia. That's a proof-of-concept trial that's currently ongoing. But for non-Hodgkin's lymphoma, we know that the mainstay of treatment for these patients is generally combination therapy. And so we're looking at combinations, particularly with tafasitamab, and I'll talk about that in a moment, in relapsed/refractory B cell malignancy.

But also we have an interesting program ongoing with -- in myelofibrosis, where we're combining parsaclisib with ruxolitinib. And we have 2 studies underway right now within our LIMBER program, and this is our myelofibrosis program. One of these is in the frontline treatment of patients with myelofibrosis, and the other is in patients who are inadequate responders to ruxolitinib. So these are patients who are on ruxolitinib. They're having some benefit from it. You don't want to stop the drug, but they still have some residual spleen or symptoms. And what we're trying to do here is add parsaclisib onto ruxolitinib in those patients to see if we can improve the outcomes there. So as I said, we have 2 Phase III programs that are currently open to enrollment in that setting.

Next slide, I'm going to move on and talk about tafasitamab. So this is the monoclonal antibody against CD19 that we have a partnership with MorphoSys for joint clinical development and commercialization. And really, I'm going to focus initially on the opportunity for combining this drug with rpS3 kinase delta inhibitor parsaclisib. As you can see from the chart, the figure on the left, the CD19 is a self-surface protein found on B cells, particularly malignant B cells. And the PI3-kinase delta isoform is an important part of the downstream signaling pathway from there. And so there's a clear scientific rationale for combining these 2 mechanisms of action and potentially improving the anti-lymphoma activity.

Now you may have seen some data from the COSMOS trial. I believe this was presented last year at ASH, looking at combination of tafasitamab with idelalisib, the original PI3 kinase delta inhibitor. That was in patients with relapsed/refractory CLL and showed very encouraging efficacy and safety. And so based on the efficacy and safety profile we see with parsaclisib in non-Hodgkin's lymphoma, we're very eager to start a combination of parsaclisib with tafasitamab, and that trial is going to start in 2021. And looking at patients with relapsed/refractory B-cell malignancies, including both non-Hodgkin's lymphoma as well as CLL in patients who've received at least one prior anti-CD20 therapy. And so we think this is going to be a very interesting trial to watch over the next couple of years.

Next, I'd just like to talk briefly about some of the tafasitamab data that are being presented at ASH this year. First of all is an updated subgroup analysis from the L-MIND study with at least 2 years of follow-up. As you know, the L-MIND study was the study of tafasitamab with lenalidomide in the treatment of patients with relapsed/refractory DLBCL. This is a study that led to the approval of tafasitamab in the U.S. And what we're seeing in this presentation at ASH this year with this prolonged follow-up, is basically continued encouraging data for tafasitamab in combination with lenalidomide in this setting, and particularly of interest are the patients who have complete responses and the continued long duration of response and high overall survival in these patients. And that's highlighted on the slide here.

If you look at the bottom, the proportion of patients who are still in response at 24 months of the CR patients is 86.4%, and 90.6% of patients who are in CR are still alive at the 2-year time point. So this is -- continues to be extremely encouraging data that in this combination of tafasitamab and lenalidomide in relapsed/refractory DLBCL, that the very encouraging CR rate is translating into very encouraging long-term outcomes.

So next, I'll talk about the frontline DLBCL study. And this is the first-line study, which was a Phase I combination study looking at the combination of tafasitamab with or without lenalidomide on top of R-CHOP in the frontline treatment of patients with DLBCL. So 2 cohorts here. Arm A was just tafasitamab plus R-CHOP, and arm B was tafasitamab and lenalidomide with R-CHOP. Initial safety run-in phase and then the expansion phase following from that. And so we're presenting some data from this study, primarily safety data at ASH this year, and these are shown up on the next slide.

So on the left is the tafasitamab combination and on the right, is the tafasitamab, lenalidomide combination. As expected when you add lenalidomide in there, you do see more adverse events in the blood and lymphatic system disorders. So these are generally cytopenias. But overall, the safety profile was very encouraging. There were no new safety signals that were observed with either combination in this setting. And so as expected, it's -- there are more cytopenias when you add lenalidomide in there, but overall, it seemed to be well tolerated even despite that increase in some of the cytopenias.

So if we go to the next slide, summarizes the key global clinical development studies that are ongoing or planned for tafasitamab. So in the relapsed/refractory DLBCL setting, we know about the L-MIND study. We're just continuing to follow up those patients, as I mentioned, the study that led to the approval by the FDA. We also have ongoing the B-MIND study. This is a combination of tafasitamab with bendamustine compared to the combination of rituximab with bendamustine. This study is ongoing. We expect an update in 2022. The primary endpoint will be progression-free survival. We did have a futility analysis back a year ago, and that passed successfully.

In the frontline DLBCL setting, I talked about the first-line study that was presented at ASH this year. Those data will lead to the Front-MIND study, a large study comparing tafasitamab and lenalidomide on top of R-CHOP compared to R-CHOP alone, and this trial is expected to start in 2021. Primary endpoint for that study will be progression-free survival.

Obviously, we're very interested in looking at tafasitamab in other relapsed/refractory non-Hodgkin's lymphoma setting. We have the inMIND study. This is a Phase III study in follicular lymphoma, looking at the combination of tafasitamab plus lenalidomide plus rituximab. So tafasitamab plus R-squared compared to R-squared alone. This study will have a primary endpoint of progression-free survival and is expected to start in 2021.

I already mentioned the combination of tafasitamab with parsaclisib that will be in relapsed/refractory non-Hodgkin's lymphoma as well as CLL. That study is also expected to start in 2021. And then recently, we and MorphoSys announced a collaboration with Xencor to look at the combination of tafasitamab and lenalidomide with Xencor by specific antibody plamotamab, and that trial is also expected to start in 2021.

So I'll hand it back to Steven for the final conclusions.

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Thank you, Peter. Slide 55 summarizes the key takeaways from ASH from an Incyte perspective. We've shared data from the first-ever successful randomized Phase III trial in chronic graft-versus-host disease and are preparing the sNDA for submission in the next several weeks. We've shown additional evidence that ruxolitinib has transformed outcomes for thousands of myeloproliferative neoplasm patients. And new data at ASH give us additional important information to share with physicians on the importance of timely intervention in both myelofibrosis and p vera.

We have presented compelling data from parsaclisib in several non-Hodgkin's lymphomas, and we're looking forward to both submitting the monotherapy NDA and to exploring combination strategies for parsaclisib. We also believe that data at ASH further reinforce tafasitamab's attractive profile as a backbone therapy. And with our colleagues at MorphoSys, we look forward to launching the Phase III trial in first-line diffuse large B-cell lymphoma next year.

Operator, now is the time for the second Q&A session. So please give your instructions and open the call for Q&A.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question is coming from Marc Frahm from Cowen and Company.

Marc Alan Frahm - *Cowen and Company, LLC, Research Division - Director*

Maybe just on the plans for frontline -- the first-line DLBCL pivotal trial. I guess are you going to enroll a broad population, just kind of all comers, whoever enrolls? Or is there an enrichment strategy for the high-risk patients? And if so, is the primary endpoint going to be for all comers? Or will you start the hierarchical analysis in that high-risk population?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Peter, do you want to address the population we'll be addressing? Thanks.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

Yes. So the population will be a higher risk population overall, and the primary endpoint of progression-free survival would be in the overall population that we're enrolling there. We haven't completely finalized a design at this point.

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Marc, just to give you a little bit of further color. It's Steven. So we'll use the traditional International Prognostic Index to risk stratify. The intent, as Peter said, is to look potentially at IPI 3 through 5 initially. But the ultimate details will come once we close out all the regulatory feedback.

Marc Alan Frahm - *Cowen and Company, LLC, Research Division - Director*

Okay. Great. And if you bear with me for -- going back to part one. Steven, with the survival data, I recognize it's very immature today, but it is slightly higher death in the ruxolitinib. Can you file with the existing data set? Or does the FDA need to see maybe a little bit more follow-up to see that even itself out?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

No. It's Steven again. So thanks for the question. I think as Professor Zeiser said, the intent is -- it was not to demonstrate overall survival. It wasn't powered that way. He also alluded to the fact that the exposure was almost double on ruxolitinib versus best available therapy, and we haven't done an exposure-adjusted analysis. The other thing I'll say is the majority of the deaths are due to graft -- underlying graft-versus-host disease. So the quick answer to your question is there should be absolutely no concern in terms of filing this data from an FDA perspective. It's well on track.

Operator

Next question today is coming from Salveen Richter from Goldman Sachs.

Salveen Jaswal Richter - *Goldman Sachs Group, Inc., Research Division - VP*

On parsaclisib, could you just talk about the safety profile today and how you're thinking about the approach here in combinatorial, including the Jakafi the LIMBER portfolio?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Peter, do you want to go ahead? So parsaclisib safety profile in non-Hodgkin's lymphoma in general. And then the second part is that how does it speak to the combination with the RUX and the LIMBER program as well.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

Yes. I think in the non-Hodgkin's lymphoma setting, the safety profile was encouraging and generally in line. The types of adverse events were generally in line with what's been seen with other agents, so generally somewhat more favorable. We still see the diarrhea and the colitis, which is expected, but we don't see very many of the other immune types of adverse events that are commonly seen with other agents in the setting. And in terms of other toxicity, we see some neutropenia, but it's generally low grade. And overall, it seems quite tolerable. And I think that's sort of shown by the fact that in the patients as we've gone to this adjusted dosing regimen, the patients who respond are able to maintain a response over a prolonged period of dosing.

Interestingly, and we've shown some of the data for the myelofibrosis combination, I believe EHA was the last time we presented these data, we see less of those long-term toxicities there and we don't fully understand why that is. It may just be that lymphoma patients come in with a different sort of immune background to a patient of myelofibrosis that may be related to the prior treatments that patients have received. But in the myelofibrosis combination with ruxolitinib, it tends to be pretty well tolerated. We don't see any particular exacerbation of the cytopenias that you can see with ruxolitinib. And so again, it seems -- the combination seems amenable to long-term dosing.

I think the question that's still out there a bit will be how can we combine this drug with other agents in lymphoma because, again, that's the paradigm that we see here. And we have some initial combination studies that are ongoing that so far, the data look encouraging there. I think that we know that idelalisib had some toxicity issues with their combination studies, and we can learn from those. So for example, patients receive prophylaxis for Pneumocystis pneumonia on all of parsaclisib lymphoma studies. And we -- investigators know now to keep a close attention for febrile neutropenia and other infections. And so we're very alert to those concerns. But at this stage, we don't see any particular concerns about moving ahead with combination therapies in either the lymphoma or the myelofibrosis settings.

Operator

Our next question today is coming from George Farmer from BMO Capital Markets.

George Farmer - *BMO Capital Markets Equity Research - Analyst*

I'd like to go back to part 1, if that's okay. Steve, I noticed in the REACH2 trial, the acute GVHD study that you did, there was a proportion of patients that transform to chronic GVHD. I was wondering if you have any insight into that [matter] as what might be going on?

Robert Zeiser

So I'll take this question.

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Thanks, Professor Zeiser, go ahead.

Robert Zeiser

Yes. So transformation from acute to chronic graft-versus-host disease occurs in around 10% to 15% of the patients, and it's called overlap syndrome. This overlap syndrome, having features from acute and chronic graft-versus-host disease is rare and it's very hard to treat because it's very refractory to many treatment options. So in the REACH3 trial, we did not have such patients that had been exposed to ruxolitinib before and then, at some point, developed this overlap syndrome.

And in the REACH2 trial, there was a very small proportion of patients that was in the RUX group and that developed then a chronic graft-versus-host disease. But we had some of those patients, and none of them had severe chronic graft-versus-host disease. All had moderate or mild chronic graft-versus-host disease. Having mild chronic graft-versus-host disease is even an advantage in terms of protection from relapse because that is an indicator for alloreactivity, and alloreactivity protect those patients from relapse of the underlying hematological malignancy.

Operator

Our next question today is coming from Ren Benjamin from JMP Securities.

Reni John Benjamin - *JMP Securities LLC, Research Division - MD & Equity Research Analyst*

Can you talk a little bit more about the registrational path for CITADEL? I think Peter mentioned an NDA in the second half of '21. Is it just longer follow-up of the existing patients that are on the study? Or are the trials going to continue enrolling? Just to give us a more complete picture of what indications are also going to be filed as well.

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Reni, it's Steven. I'll answer your question. So the studies have completed. You've seen the complete data sets here with the efficacy and safety profile Peter presented to you. It's pretty standard from an FDA regulatory point of view to require roughly 12 months of follow-up on your last patient enrolled, particularly for responders. They're interested in, as Peter alluded to, duration of response. So we're in that phase now, and we'll get that complete follow-up in the early part of '21 and then put together a submission.

In terms of the actual regulatory strategy, will follicular, for example, be combined with marginal low-grade lymphoma type indication? That's something is still to be determined. Mantle cell will be distinct on its own. But it's -- we're just in a standard phase. It's not ongoing enrollment or anything like that. It's just gathering the required long-term follow-up to complete the registration packages.

Reni John Benjamin - *JMP Securities LLC, Research Division - MD & Equity Research Analyst*

Right. And then, Steven, just as a follow-up with the LIMBER program. Can you talk a little bit in the frontline setting, have you noticed any disease-modifying attributes to the combination with the PI3K-delta inhibitor? Or is it still primarily completely symptomatic?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Yes. I'll turn it over to Peter to answer you. And I assume you're alluding to both potentially fibrotic changes as well as allele burden changes. Peter, can you just go through what's been presented to date?

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

Yes. I mean we -- primarily, what we presented is changes in the spleen and symptoms. There was some preliminary data looking at improvement in fibrosis. But I think it's probably too early to say for that and similarly for allele burden. So the decision to move ahead with the Phase III studies was really based on the improvement in spleen and symptoms and the durability of those when you add the parsaclisib. And I think we'll really have to take the randomized studies to see what the real impact of the -- some of these other improvements in overall disease, burden like fibrosis and allele burden, what those look like.

Operator

Our next question today is coming from Mara Goldstein from Mizuho.

Mara Goldstein - *Mizuho Securities USA LLC, Research Division - MD of Equity Research Department*

ASH this year is clearly a little bit different being in a virtual format. I'm just wondering, given that we're now into the tafasitamab launch, just some feedback that you're getting on the real-world use experience with the drug and as you're approaching more data sets as well.

Hervé Hoppenot - *Incyte Corporation - Chairman, President & CEO*

On the launch of Monjuvi. No, we spoke about it recently. It's doing well. It's progressing. It's a population that is very unique in the sense that we have the only approved second-line treatment in DLBCL. And so the experience we get and all the feedback we get is really the importance of the safety profile that is very good in combination with lenalidomide compared to what the alternative would be, which would be chemotherapy plus with ruxolitinib. In many cases, it's what physicians were using in the past or are still using in some cases.

So there is a very good safety profile. And more importantly, there is a high level of complete response with a very long duration of complete response. So this mix of complete response rate, duration of response and safety profile is resonating very well. So we are making good progress, and we are happy with what we are seeing there.

Mara Goldstein - *Mizuho Securities USA LLC, Research Division - MD of Equity Research Department*

Okay. And if I could just -- I apologize, ask for a clarification on the CITADEL program, just around the adverse event profile. I just wanted to confirm that the elevation that you're seeing in immuno transferase values were laboratory. Or were there other interventions required for those grade 4s?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Peter, do you want to talk to that?

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

That's right. That means we see some elevations in transaminases. It tends to be much less than what's been seen with some of the other agents here. And we haven't seen any significant complications from most of those. But I don't know if that answers your question.

Operator

Next question is coming from Matt Phipps from William Blair.

Matthew Christopher Phipps - *William Blair & Company L.L.C., Research Division - Senior Biotechnology Research Analyst*

I know this is an interim look from the firstMIND, and it's a small number of patients and only 3 cycles, but a 91% response rate is pretty much exactly in line with both arms and the robust trial showed. And so do you have any sense on CRs at this point? And again, is the hypothesis to really drive deeper responses and more CRs with this new combination? And I know ritux didn't work as maintenance here, but have you ever considered trying tafasitamab as maintenance?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Yes, it's Steven. So just a reminder, to step back, the intent of firstMIND was obviously safety to look at both tafa on its own with R-CHOP and then tafa with R-CHOP, and to work out if there was going to be a sort of safety deal breaker in terms of going forward. And as you can see from the data, aside from, as Peter said, a little more cytopenia with the addition of lenalidomide that was expected, there was nothing concerning there. So obviously, it then goes to talking about beating R-CHOP to use the most active regimen. The efficacy part of this was, quite frankly, a pleasant surprise, and I'm glad we have that efficacy data to the degree seen with the 91% overall. We don't have further granular data for you to present yet.

In terms of maintenance, just from the indication itself, obviously, the use of tafa goes on for a while. But down the pocket would be something we'd be more interested in looking at different maintenance regimens in different lymphoma settings, but we can't give you granular details on plans yet.

Operator

Our next question is coming from Michael Schmidt from Guggenheim.

Michael Werner Schmidt - *Guggenheim Securities, LLC, Research Division - Senior Analyst & Senior MD*

I had another one on parsaclisib. I guess the commercial market for the PI3-kinase delta inhibitor class has been disappointing, obviously, for various reasons, including safety. And I guess with the clinical profile for parsaclisib as it has emerged in non-Hodgkin's lymphoma, I guess, where do you think the best opportunity is to compete maybe with other classes of drugs? Is it maybe in follicular lymphoma in marginal cell? And how do you think parsaclisib may be positioned relative to other treatment modalities in those indications?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

So Michael, it's Steven. I'll try go first, and Peter may want to add. I think what you're alluding to indirectly is if there's a crowded field in terms of different mechanism of actions being studied here, whether it's targeting CD19, CD20, BTK inhibitors, PI3-kinase delta, et cetera. We spent a lot of time working out the best therapeutic ratio here. We knew parsaclisib on its own was extremely active, and we see almost all the responses occur by the first imaging event. And then you see the independently confirmed response rates reported here in follicular marginal and the mantle cell that's BTK naive that are robust and durable with long PFS.

If you look at sort of third line follicular, second line marginal, second line mantle, and you look at U.S., Europe and Japan, they all remain #1 still incurable entities. There's about 10,000 third line follicular patients in those markets and about 5,000 each of marginal and mantle. So you're talking with upwards, if you take all 3 indications, of about a 20,000-patient opportunity in a setting where there's no cure.

So what I suspect will happen is physicians will rightly, should this be approved, look at the therapeutic ratio for their particular patient and then decide what treatments they want to use in that particular setting. Again to be repetitive, there's really high activity for this agent that we see early. And then the switch to daily dosing at a lower level at week 8 onwards, we think we've got the best in terms of maintaining the response as well as giving you a terrible profile. And that's how I sort of see it play out.

Peter, I don't know if you want to add anything.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

Yes. I mean maybe just to add. I mean, I think the delta class sort of has suffered from some negative data in the past. And I think that maybe has hurt parsaclisib a little bit. But I think if you look at the -- if you ignore the fact that it's a delta inhibitor, let's just look at the efficacy and the safety

that we see in the 3 monotherapy studies that are presented here, I think the data are extremely encouraging, and I think this is going to be hopefully a good treatment option for patients.

I think where we go next, obviously, we want to get into the combinations, either with standard of care. And clearly, I think that, that's an opportunity for parsaclisib, if we can do that safely. And I think the tafasitamab combination is one that may be extremely interesting because that's a drug that we know has great activity in the relapsed/refractory non-Hodgkin's lymphoma. So I think it seems to be very well tolerated. And the combination of 2 -- those 2 mechanisms may be a great path forward.

So I think that, again, as Steven said, there's a lot here. There are a lot of treatment options. There are a lot of different mechanisms being explored. But I think if we look at the efficacy data that we're presenting here at ASH, I think this is a very encouraging drug for patients that we hope to have available.

Operator

Our next question is coming from Jay Olson from Oppenheimer.

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

Congrats on the data. Maybe just a follow-up on parsaclisib. I noticed in your CITADEL program, there was a significant difference between response rates that were essentially reviewed compared to the locally assessed response rates as measured by MRI. Could you comment on what some of the factors are that would account for those differences?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Peter, do you just want to talk about independent review versus investigator and what drives differences?

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

Yes. I mean there are a number of things, and particularly in non-Hodgkin's lymphoma can be complicated because, obviously, these are tumors and lymph nodes and sometimes the radial just has a hard time to terminate that lymph node, abnormal or not. So I think there are a number of factors that were involved, whether it was -- which reasons that identified a baseline that they were going to follow, whether they consider that lesions -- certain lesions changed over time as many of the same things that we see in terms of -- in solid tumors as well in terms of independent versus investigator reading. I don't believe any of the investigators had any bias, but certainly doing an independent review takes out that physician judgment part of it and looks purely at the scans.

So I think that there were obviously differences between the investigator and the independent review. But directionally, the conclusions were the same. So we're still seeing very high response rate. We're still seeing prolonged duration of response. We're still seeing encouraging progression-free survival. So while individual patients may have some differences in how the site radiologist versus the independent radiologists interpreted the span, that again, directionally, everything seems to be consistent.

Operator

Our next question is coming from Stephen Willey from Stifel.

Stephen Douglas Willey - *Stifel, Nicolaus & Company, Incorporated, Research Division - Director*

Just a quick one on parsaclisib. So do you have any pharmacodynamic markers that essentially serve as a surrogate of on-target activity? Is something like Tregs here appropriate? And I guess, just curious if you looked at this at all in CITADEL, and then if you looked at this at all in MF, to kind of get a better understanding of what that lower MF dose is buying you in terms of delta contribution.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

It's a great question. And we've looked but we haven't identified anything -- any clear pharmacodynamic marker, either in lymphoma setting or in the MF setting that would identify which patients should or should not get parsaclisib, how to predict who's going to have a durable response or not. We've -- as I said, we've looked at this in both the CITADEL and somewhat in the MS studies as well. I think those data would be extremely important, given the number of agents that are available in non-Hodgkin's lymphoma and also the number of things that are being studied in MF now in the combination of ruxolitinib. But at this point, we don't have any clear data to be able to select patients either way for that.

Stephen Douglas Willey - *Stifel, Nicolaus & Company, Incorporated, Research Division - Director*

And then just as a reminder, is the parsaclisib dose in MF being used, is that 2.5 mg daily?

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

5 mg in MF.

Stephen Douglas Willey - *Stifel, Nicolaus & Company, Incorporated, Research Division - Director*

It's 5. Okay.

Operator

Our next question is coming from Tazeen Ahmad from Bank of America.

Tazeen Ahmad - *BofA Merrill Lynch, Research Division - VP*

Appreciate all the color so far. I have one question on parsaclisib in marginal zone lymphoma. As I understand it, you were only able to include these BTK-naive patients. Can you talk about, if we should expect to see data from Ibrutinib-failed patients? And then could you give us your opinion on durability of response? I know it's early data, but just wanted to get a sense of that.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

So at the question about durability, is that sort of BTK -- for the post-BTK patients or in general?

Tazeen Ahmad - *BofA Merrill Lynch, Research Division - VP*

In general.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

In general. So for marginal zone, so we actually had a cohort of post-BTK patients, but it basically, were not very many patients and it didn't enroll very well. At some point, we'll present the data there, but they were -- there were not very many patients. So it wasn't a very large data set.

In general, across the CITADEL studies, we see an encouraging duration of response in each of the groups and certainly in marginal zone. In particular, I think the duration is encouraging in the patients who have response. So...

Tazeen Ahmad - *BofA Merrill Lynch, Research Division - VP*

How big of a population is this? And do you have any color on why you weren't able to get enough Ibrutinib failures for this portion?

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

No. So it's just -- I mean, the marginal zone is about -- excuse me, 5,000 new patients per year so it's not terribly common. And I don't know whether there was an issue that just Ibrutinib was not being widely used, either in general or percentage we were going to. It may also be that, again, we know that these patients progress very quickly after -- when they've received Ibrutinib. Once they progress on Ibrutinib, they do tend to progress very quickly. And so it's possible -- we know in some cases, that there were patients who were not able to enroll in the trial just because their disease was advancing so rapidly. So I don't know if that was part of it as well.

Tazeen Ahmad - *BofA Merrill Lynch, Research Division - VP*

Okay. And then maybe one question in MCL. As far as durability of response in the prepared statements, I think you mentioned that durability was about 9 months. How does that compare to Ibrutinib patients?

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

Oh, gosh. I would need to take that up. I don't have the Ibrutinib data right in front of me. Are you talking about patients who receive Ibrutinib or the patients who got parsaclisib after Ibrutinib?

Tazeen Ahmad - *BofA Merrill Lynch, Research Division - VP*

Actually, both would be great, but we can follow up off-line. That's fine.

Peter Langmuir - *Incyte Corporation - VP of Oncology Drug Development*

The patients who got parsaclisib after Ibrutinib, the duration of response was about 3.5 months compared to about 9 months in the patients who are BTK naive. I don't have the Ibrutinib duration like for patients in the same setting who would be treated with Ibrutinib, I don't have the duration of response right on hand.

Operator

(Operator Instructions) First is coming from Tyler Van Buren from Piper Sandler.

Tyler Martin Van Buren - *Piper Sandler & Co., Research Division - Principal & and Senior Biotech Analyst*

As we think about the current and future uptake of tafasitamab in relapsed/refractory DLBCL, can you just discuss the current split for physician use and/or preference of lenalidomide and bendamustine. And even though it is early, if you see that changing in real-time with the Monjuvi launch? It'd be helpful to understand as we think about the importance of the B-MIND data for future utilization.

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Tyler, it's Steven. I'm not going to be able to answer you with details. I think it's too early in the launch trajectory to have that sort of split. But just to remind you, though, as a segue that as part of the development program, there is a bendamustine-rituximab versus bendamustine-tafasitamab study ongoing called B-MIND that is going to be a very important part of the development program because of the realization that there is renewable use as you're alluding to of bendamustine, Rituxan in this entity.

Operator

Our final question today is coming from Cory Kasimov from JPMorgan.

Cory William Kasimov - *JPMorgan Chase & Co, Research Division - Senior Biotechnology Analyst*

So I had a follow-up question to all this parsaclisib discussion, but from a longer-term perspective. Really just curious how you're thinking about the opportunities for this candidate. In the lymphomas that you presented at ASH, but also more broadly, is another way to say it is, what's the potential for parsaclisib to be a stand-alone driver for Incyte in the future in lymphoma that you see most of the promise with this asset in combination with RUX as part of the LIMBER program?

Steven H. Stein - *Incyte Corporation - Executive VP & Chief Medical Officer*

Thank you for the question. And it's interesting how much income in we've got on parsaclisib because we believed, for a long time, that we have an extremely active agent that we've worked out in quite an elegant way, the therapeutic ratio in these different settings. So in non-Hodgkin's lymphoma, we obviously presented mature data sets now in 3 different entities: follicular, marginal and mantle cell in single-arm studies and go on to submit those for potential approvals, which will then require, as Peter was alluding to, confirmatory studies looking at combinations.

Additionally, the tafasitamab deal itself was one of the important factors, was the ability to combine with a new generation PI3 delta inhibitor. They had already done work with idelalisib. It showed high activity, albeit in a small number of patients and wanted to use a new generation inhibitor. So that combination will be starting next year and will be very important, we think, in treating non-Hodgkin's lymphomas.

In terms of myelofibrosis, both the first-line study, 313, and the suboptimal responder study, 304, are open and will be enrolling next -- over the course of next year and are extremely important to the LIMBER program and we think also biologically to myelofibrosis patients because of PI3-kinase delta up-regulation in myelofibrosis.

And then also just to mention, we have a very important program going on in autoimmune hemolytic anemia with parsaclisib, the proof-of-concept studies underway. There's an unmet need there in patients post-CD20 antibodies that get into trouble or no longer respond. And we have some really interesting data there, and that study is really important to us. So it's quite a comprehensive effort across lymphomas as monotherapy in various combinations, it will be confirmatory studies in those settings with tafasitamab, in myelofibrosis, both sub-optimally and first-line with ruxolitinib and then in autoimmune hemolytic anemia as well.

Operator

We've reached the end of our question-and-answer session. I'd like to turn the floor back over to Mike Booth for any further or closing comments.

Michael Booth - *Incyte Corporation - Divisional VP of IR & Corporate Social Responsibility*

So thank you all for participating in the call today and for all of your questions. Of course, Christine and I will be available for the rest of the day for any follow-up request you may have. But for now, we thank you again, and we'll close the call. Thank you, and goodbye.

Operator

Thank you. That does conclude today's teleconference and webinar. You may disconnect your line at this time, and have a wonderful day. We thank you for your participation today.