Novartis AG

Novartis AG presents at 2023 American Society of Clinical Oncology (ASCO) Annual Meeting

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Event Participants

Executives 6

Unknown Executive, Sloan Simpson, Shreeram Aradhye, Jeff Legos, Reshema Kemps-Polanco, Rod Wooten

Analysts 8

Richard Vosser, Seamus Fernandez, Emily Field, Andrew Baum, Simon Baker, Steve Scala, Peter Welford, Harry Gillis

Unknown Executive Executive

Please welcome from investor relations , Sloan Simpson.

Sloan Simpson Executive

Hi, everyone. Thank you so much for joining us at the Novartis Investor event at ASCO 2023. Welcome to everyone in the room and also to those who are with us online. We realize it's quite late for those in Europe so really appreciate your being with us.

We are excited to share the Kisqali data from the Phase III NATALEE study in early breast cancer, talk a bit about the opportunity that we see there. But first, a couple of housekeeping notes.

So we'll have a presentation, obviously, followed by Q&A. We'll take questions from the room but the people online can also submit questions. We'll read them out for you here in the room. Please just make sure to wait for the mic and to say your name before asking your question. We will try to wrap up here the presentation and Q&A by about 8:15 so we can have our reception afterwards.

With us today, we have Shreeram Aradhye, who is the President of Global Drug Development at Novartis and our Chief Medical Officer. We have Jeff Legos, who is the Global Head of Oncology & Hematology drug development; and we have Reshema Kemps-Polanco, who is the U.S. Head of our Oncology business.

Now I just have to read our safe harbor statement. The information presented today contains forward-looking statements that involve known and unknown risks, uncertainties and other factors. These may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. For description of some of these factors, please refer to the company's Form 20-F and its most recent quarterly results on Form 6-K that respectively were filed with and furnished to the U.S. Securities and Exchange Commission.

And with that I would like to handover to Shreeram to kick us off.

Shreeram Aradhye Executive

Good evening, and welcome to this Novartis IR event at ASCO 2023. Very excited to be with you all. We're going to listen to the details of the NATALEE data from my colleague, Jeff Legos; and then the potential commercial opportunity from Reshema Kemps-Polanco.

But before that, I wanted to reiterate the fact that Novartis is well on its way now into becoming a pure play innovative medicines company. And many of you have heard about our strategy for our 5 therapeutic areas of focus amongst which solid tumors and hematology are 2 important pillars as we think about our pipeline -- cancer, prostate cancer and lung cancer and in hematology non-Hodgkin's lymphoma and myeloid cancers.

Our strategy revolves around for our marketed brands, generating the evidence that is necessary to expand their potential benefit to added populations. So for a brand like Kisqali, the use of NATALEE and to define its potential role in early breast cancer.

For Pluvicto, the opportunity for its use in earlier lines of therapy for patients prior to receiving chemotherapy in castrate-resistant prostate cancer as well as further expansion into hormone-sensitive prostate -- metastatic prostate cancer and for Scemblix with having established great data in third line use, the opportunity for having use in first line therapies based on our ongoing trial which is actually finished ahead scheduling for which we expect results early in 2024. But today, it's about NATALEE, which was a highlight at ASCO, as you have heard. We've also presented additional data that is available to you in the slides that we provided to you on JDQ, our KRAS targeting therapy as well as PHE, our T-Charge-based therapy in multiple myeloma. And if you have any questions, we'll be happy to answer those during the Q&A.

The most important thing that we want to talk about, of course, today is the fact that NATALEE has delivered the extraordinary results that we have spoken to you about. The hypothesis that went into testing NATALEE on creating NATALEE lays in the specific mechanism of action for Kisqali and its unique ability to selectively inhibit CDK4 8x greater than it does CDK6. The fact that a higher unbound average concentration that allows more drug to be available to act on tumor cells. And with the therapy that with this on-target action that allows a greater duration of G1SRS that can allow the micrometastases to go into a state of senescence and therefore, gives us a chance for Kisqali to be more effective at preventing the risk of recurrence in patients with breast cancer.

This mechanism has, of course, delivered extraordinary results for us with Kisqali in the metastatic setting, where we are the only CDK4/6 inhibitor that has a first-line category 1

recommendation in the NCCN guidelines based upon the fact that in all 3 Phase III studies, Kisqali has demonstrated a statistically significant overall survival benefit and set a new benchmark for survival with a median OS of greater than 5 years.

Having met this and made this difference in the metastatic setting, we have decided to use NATALEE as a means of generating the evidence to address a significant unmet need for women with early -- for those with early breast cancer.

Patients who are now diagnosed with Stage 2 or 3 given the increased surveillance breast -- at that early stage with breast cancer, a 1/3 of the patients with Stage 2 disease and half of patients with Stage 3 disease will experience a recurrence of their breast cancer over the coming years with a half of those recurrences occurring within 5 years.

If you think about a person who's been treated and diagnosed with early breast cancer and has undergone a surgical resection, and I have experienced this myself with several families and friends, the real risk of this systemic disease recurring in them over the coming years is something that they need to address. And even with hormone therapy, there is the need for an additional alternative for them to be utilized on top of the hormone therapy provided it offers a reliable quality of life and a tolerability profile that patients can continue to take this drug in a reliable manner.

And it was this goal in mind that NATALEE was defined and I look forward to now handing over to Jeff for him to share with you the design of the study and the extraordinary results that we have just laid out. Jeff?

Jeff Legos Executive

Thank you, Shreeram. I truly have the honor and privilege of actually sharing the primary analysis results from our Phase III clinical trial on behalf of our overall NATALEE steering committee, our investigators and co-investigators around the world and also an incredibly talent and amazing drug development and clinical development team.

Just by way of background, just a reminder of the overall study design. So 5,101 patients with HR-positive HER2-negative early breast cancer were randomized between January 2019 and April of 2021. Approximately 40% of those patients were randomized prior to the pandemic and about 60% were randomized during the pandemic, which is, again, an incredible testament of the great work commitment and passion on behalf of the study team and the investigators around the world.

These patients were patients with Stage 2 or Stage 3 disease. They were randomized 1:1 to receive Kisqali at a 400-milligram dose given once daily for 3 years in combination with endocrine therapy and comparing it to endocrine therapy, which is administered for up to 5 years as per standard of care guidelines.

One important note, I'd like to highlight, is the fact that when we talk about endocrine therapy, we specifically mean the nonsteroidal aromatase inhibitors. These include anastrozole or letrozole.

The reason why this is important is if you think back to the early studies that were done in

head-to-head comparisons looking at different endocrine therapies, it was clear that the nonsteroidal aromatase inhibitors were superior to tamoxifen with respect to the reduction in risk for disease recurrence. The hazard ratios ranged from about 0.85 down to 0.80 across a range of subgroups, showing clear superiority of the nonsteroidals over tamoxifen.

In addition, if you actually happen to stop by the poster session today at ASCO, there was some real-world evidence that corroborated that those comparisons continue to show clear benefit of the nonsteroidals over tamoxifen.

Therefore, it's important as you think about using or conducting the cross-trial comparisons looking at NATALEE versus other trials in breast cancer, such as monarchE that you take into account these important details and differences in overall trial design. The primary endpoint was invasive disease-free survival.

There were 3 key attributes of this study that we felt were very important in the overall design and conduct of the trial. First, we had chosen to include at-risk patients include in it rather than just focusing on only those patients at the highest risk for recurrence, and thereby, we had a broad patient population of Stage 2 and Stage 3 disease, including those without nodal involvement.

The second key design feature was that we understand the importance of maintaining patient compliance and adherence in early breast cancer trials and in fact, in any adjuvant setting. And for patients that are otherwise well and working, the importance of having a dose that allows them to resume their normal daily life and daily activities was very important. Therefore, we have selected to go with a 400-milligram dose relative to the 600-milligram dose, which is proven and established in metastatic setting because we felt that this would enable us greater tolerability at the same time while maintaining efficacy.

And the last, getting back to the importance of the pharmacology that Shreeram highlighted, we know that from extensive preclinical characterization as well as studies in the metastatic setting, the importance of the selectivity against CDK4, the importance of having more time on target and the importance of continuing to treat for longer periods of time to really induce this irreversible cells, in essence and because of this pharmacology and mechanistic rationale, we have chosen to treat these patients for 3 years of study duration.

So now if we go into a little bit more detail around patient population. The easiest way to interpret this chart is to focus more on the patients that were excluded from the trial rather than those that were included in the trial.

Specifically, patients with Stage 1a or Stage 1b were excluded. If you look at patients with Stage 3, 100% of patients were included in the trial. And then if you look specifically at patients with Stage 2 disease, other than one particular subgroup where the primary tumor range from 2 to 5 centimeters, and there was no nodal involvement. There was one additional criteria that was required for eligibility and that was either Grade III tumors or Grade II tumors with one additional risk factor.

If we look overall, the baseline characteristics were well balanced between the treatment arms, specifically with respect to the key stratification factors, which included menopausal status, anatomic stage as well as prior use of chemotherapy in the neoadjuvant or adjuvant

setting. I want to spend a few minutes on this slide because again, this is another slide that's important as we think about the amount of follow-up that had occurred at the time of this primary analysis.

So at the time of this analysis, which was our second interim for efficacy, the overall follow-up for the primary endpoint of invasive disease-free survival was 27.7 months.

At this point in time, about 57% or almost 60% of patients have completed at least 2 years of therapy and 20% of patients have completed 3 years of therapy.

Again, the importance of understanding this is critical in terms of making the appropriate comparisons when you're looking across trials.

I'm incredibly pleased to present here that at the time of this prespecified second interim analysis for efficacy, Kisqali met the primary endpoint with a clinically meaningful and statistically significant reduction in invasive disease-free survival reducing that risk of recurrence by 25%.

If you look at the Kaplan-Meier curves, you see the separation begins as early as 6 and 12 months and continues throughout the duration of follow-up. If you look at the 3-year landmark period, we are reporting an absolute benefit of 3.3%. And if you look at the overall benefit provided, the hazard ratio is 0.75 and the p-value is highly statistically significant at P equals 0.0014. As a reminder, if you didn't attend the ASCO presentation, the prespecified stopping criteria at this interim analysis for efficacy was a p-value of less than 0.0128.

In addition to meeting the primary endpoint, the data was also highly consistent across all prespecified subgroups regardless of nodal status, disease stage as well as menopausal status.

When we look at the reported hazard ratios on this particular table, you see a high degree of consistency across all of the prespecified subgroups. If you look on the right-hand side, we've also included the 95% confidence intervals. We could sit here and probably debate and discuss whether or not those that cross unity are meaningful or not. But I think what's most important as we look at this particular subgroup is coming back to the design principles.

First principle was we designed a study to include all at-risk patients. Second one was this was a primary intent-to-treat analysis across the entire patient population. And third, if you look at this table, no single subgroup was driving the overall efficacy nor was there any difference in the relative hazard ratio benefit observed across all of these prespecified subgroups.

In addition to the consistency that we see across all of these subgroups, the data was also highly consistent across all key secondary end points. Here, we had data showing a consistent benefit in distant disease-free survival with a 26% risk reduction. The reason why DDFS is important is this is one of the most important risk factors in terms of predicting overall survival. So very reassuring to see that Kisqali had reduced the risk of ultimately the recurrence of metastatic disease with a hazard ratio of 0.74 and a nominal p-value of 0.0017.

Since this was a nominal statistical test, the p-value to highlight statistical significance is

0.025 from a one-sided perspective and didn't have to be prespecified in terms of the stopping criteria.

In addition to the distant disease-free survival, I wanted to also include a Kaplan-Meier curve for recurrence free survival. This was not shown by Dr. Slamon during the ASCO presentation. But as you could see here, a very consistent reduction in the risk of recurrence with approximately 28% and a p-value of 0.0008.

In addition to that, another key secondary endpoint was an evaluation of overall survival. This was prespecified to be tested at this particular analysis. If you look at the table on the right-hand side of the slide, you see that Kisqali plus a nonsteroidal aromatase inhibitor had reduced the number of overall deaths as well as actually delayed the time of those deaths occurring. This resulted in a hazard ratio of 0.76 and a nominal one-sided p-value of 0.0563.

While this overall survival data remains immature, we are encouraged by the fact that we have this reduction in risk of death by 24% also consistent with other key secondary endpoints and also consistent with the benefit observed in the overall subgroups. There is additional follow-up for overall survival plan at the timing of the next iDFS analysis as well as all patients will be followed for at least 5 years following the last patient randomized in 2021.

Now shifting to safety. Overall, Kisqali at the 400-milligram dose was safe and well tolerated, with low rates of symptomatic adverse events. I want to start by the known adverse events of importance for Kisqali. And reportedly, neutropenia had occurred at any grade at 62% and grade 3 or higher at 44%.

There was actually only 0.3% of grade 3 febrile neutropenia. This is a known adverse event for Kisqali. Physicians are comfortable and used to managing it. We have those adverse event management guidelines that are clearly laid out in our product label in all clinical trials. And it's specifically relative to the 600-milligram dose, the 400-milligram dose had reduced the Grade 3 reported adverse events of neutropenia by about 1/3.

The other major and well-known and established adverse event for Kisqali is around QTC prolongation. And here, we report a very low rate of grade 3 QTC prolongation around 0.2%.

In addition to the known and most common adverse events for Kisqali, it's also important to highlight some of the other clinically relevant adverse events.

As you see here, arthralgia is reported as the highest adverse events with respect to the clinically relevant ones, that's reported at 36.5% in the Kisqali arm and then 42.5% and the NSAI alone arm. So clearly, this is an adverse event that's driven by endocrine therapy alone.

As we think about what I mentioned earlier and the importance of patients who are otherwise well and working to maintain normal daily activities, diarrhea is an important adverse event that could significantly compromise daily quality of life. This is a known adverse event for many anticancer medicines, including other CDK6 inhibitors within class. Here, the reported rate for Kisqali in early breast cancer for any grade is 14%.

And importantly, for grade 3 or higher adverse events of diarrhea, it was a very low 0.6%.

This overall safety profile did contribute to very limited treatment modifications when

administered for up to 3 years. I may spend a few minutes on this slide, just to clarify some of the misconceptions and inaccurate reportings that have occurred over the last few days. And I recognized the challenge when you're looking across trials with different follow-up periods and different combination partners, the challenge that this faces.

So firstly, the overall types and severities of adverse events as well as discontinuation rates due to these adverse events were predictable, manageable and consistent with those observed in the metastatic setting. There was no new safety signals identified with longer follow-up.

We had reported on Friday, the overall discontinuation rate for patients on Kisqali was 19%. This includes patients who discontinued Kisqali only or who also discontinued Kisqali plus endocrine therapy.

The main reason for these discontinuations were due to protocol mandated asymptomatic liver-related adverse events. This accounted for more than half of the protocol-mandated discontinuations. And specifically, what I mean by that is if the liver function test, the transaminases were not resolved within 4 weeks following dose interruptions, patients were required to mandatorily discontinue therapy. This is actually very different than how patients are handled currently in the clinic and in the real-world setting. But nonetheless, this accounted for more than half of our discontinuations that are reported here.

Secondly, in terms of other adverse events that had accounted for these discontinuations, the only other adverse event that led to a discontinuation greater than 1% was arthralgia and that was predominantly driven by endocrine therapy because that resulted in 1.3% of patients having to discontinue Kisqali plus endocrine therapy. During the discussion, during ASCO, it was highlighted that there was a difference -- a major difference in the discontinuations for Kisqali versus Verzenio. And it was highlighted that those differences were 19% for Kisqali and 6% for Verzenio. I just want to clarify, that reported adverse event discontinuation rate for Verzenio of 6% was based on patients who discontinued both treatments simultaneously. If you want a very similar number in terms of those patients that discontinued Kisqali plus the nonsteroidals, that number is actually 5%.

-- so very close in terms of the reported rate.

The other important factor to take into account was the amount of follow-up between the 2 trials at the particular reported rates. And those rates were actually pulled from the JCO article from 2020, where the length of follow-up was only about 16 months, and the proportion of patients that completed 2 years of treatment was only about 12.5%. Here, we are reporting data for patients that have been followed up for 27.7 months in terms of the primary endpoint and an overall trial follow-up of 30.4 months, and as previously mentioned, nearly 60% of patients have completed at least 2 years of therapy.

With respect to the pattern of discontinuations due to adverse events, most of these occurred very early in treatment and they occurred with a median time to onset within the first 4 months.

So if you look at the overall impact of symptomatic adverse events, they were low. They were not key drivers of dose reductions or discontinuations and the reported dose reduction rate

for Kisqali was 22%.

So in summary, I would just like to highlight that these results do support Kisqali plus endocrine therapy as a treatment of choice in a broad-patient population of early breast cancer or at-risk for recurrence. The efficacy was robust as highlighted by the statistically significant and clinically meaningful improvement in iDFS, where the primary endpoint was met at the second interim analysis for efficacy. There was consistent benefit across all prespecified subgroups and there was consistency across all key secondary endpoints, including a trend for improvement in overall survival.

At the same time, it would also actually continue to display a very favorable safety profile with no new safety signals, a well-tolerated 400-milligram dose with a limited need for dose modifications or dose reductions and the symptomatic adverse events were low and not key drivers of discontinuation. Our global regulatory filings, including the U.S. and Europe, are expected in the second half of 2023.

And with that, I would like to turn it over to my colleague, Reshema.

Reshema Kemps-Polanco Executive

Good evening, everyone, and thank you for allowing us to share our data here. And what I'd like to do over the next few slides is to talk about what -- how we will take what we believe is compelling clinical trial data and really translate that into a meaningful commercial opportunity for the organization.

So you saw earlier, Shreeram shared a slide that showed the total breast cancer population is really represented by -- with 75% of the patients being HR positive, HER2 negative.

One of the things that I -- we believe is really important is if you look at the bar chart here is that only Kisqali has shown a clinically meaningful benefit across a broad continuum of the disease, 50% of these patients.

And so you see here beginning in stage from Stage 2, Stage 4, I'll start with Stage 4 in the metastatic setting, where we currently have the approval, only Kisqali has demonstrated a consistent overall survival benefit across 3 Phase III trials regardless of combination partner, regardless of line of therapy or menopausal status. And that sets the foundation. As we move into the adjuvant setting, hopefully, with an approval in the near term. When you look at the clinically meaningful benefit there, when you look across Stage 2 and Stage 3, again, regardless of nodal status. And so what we believe this will confer in terms of competitive benefit is that we have the potential with Kisqali to simplify patient selection.

And when I think about the competitive landscape in which we will be entering, if I would characterize the commercial opportunity, I think there's one phrase to be remembered, and that is more than double the opportunity, more than double the patient population.

So when we compare where Kisqali is currently approved today in the metastatic setting, as we move into the adjuvant setting, it's more than double the patient opportunity. And we believe that this will be a significant growth catalyst for the company.

Secondly, if we compare the currently approved CDK4/6 in the adjuvant setting, and we're in

the patient population that was studied when you compare it to the NATALEE population that was studied, again, a broader population, it is more than double the opportunity.

And so we believe this will also confer a real competitive advantage. And so what is our belief for a level of confidence that we will be able to realize the commercial opportunity? I think it really starts with our foundation in the metastatic setting. And we've seen continued momentum over the last year in performance, and I'll start here with the sales evolution upwards of 80% growth year-over-year. So very strong sales performance.

really driven by our new patient share uptake today, 1 out of every 3 new patients stats therapy in the metastatic setting in first line with Kisqali, and that is continuing to grow month over month. And we've seen this accelerated share uptake at the expense mostly of Ibrance. And third, a broadening base of total prescribers -- and this is really -- and these are the physicians who are really representing this share uptake represented by both breadth of prescribing as well as death.

One of the notable achievements I'd like to point out here is really our success in market access. And we believe that this has contributed to the performance I've just shared with you on the slide. So what we've seen in the last year is that more than -- we've seen growth of more than 50% of covered lives to label. And we've seen an accelerated removal of step edits. And so this has allowed Kisqali to be on par with other CDK4/6s.

However, in many cases, we're seeing that Kisqali is being favored on formularies and actually Ibrance now being stepped behind Kisqali. And even now, as I stand here before you, we have recent wins that are beginning in June that are not yet in the trend that I just shared with you, which we believe will continue to deliver the momentum and growth that we're seeing.

And why are payers doing this? It's because payers do follow where we have approval, where we have compelling data and they follow guidelines. And as I'm sure you're aware, there was an update earlier this year in the NCCN guidelines, where only Kisqali was listed as a Category 1 preferred agent in the first-line setting in the metastatic breast cancer patients. And so this has helped us to really accelerate access to medicine.

Importantly, we're seeing also broad coverage not only in the Medicare segment but also in the commercial segment. And so if you think about why that's important, if you think about the continuum from Stage 2 to Stage 4 that I talked about earlier. Those patients who are diagnosed in adjuvant setting tend to be a lot younger and really are in the Commercial Insurance segment. And if I think about those who are diagnosed in the metastatic setting, a minority of them are found in the Medicare segment. And so we feel confident that we will be able to have broad coverage once Kisqali is approved in the adjuvant setting.

And so if you think about -- you need a compelling data in a differentiated CDK4/6, which we believe that we've shown. Patients need to be able to access the medicine, which we've shown broad coverage, and then we need to make sure that physicians are in a position to prescribe the drug. And so we believe that we're coming from an area of strength here because most of the physicians that are prescribing in the metastatic setting are also the same prescribers who will be prescribing an adjuvant setting.

And so that acceleration that I shared with you with the new writers is important because

these 5,000 high-prescribing physicians have about -- represent 70% of the potential in the adjuvant setting.

And so while we believe it will take some time to really change this is a paradigm shift as we think about the CDK4/6 in the adjuvant setting.

Today, in the adjuvant setting, most of the patients are on endocrine therapy. And so we expect a rise of the class. And we believe that Kisqali will be extremely competitive in this space, given the breadth of data that we've shared.

So in closing, we believe that we're going to be highly competitive once this product is approved in the adjuvant setting. And we believe this because if you think about the data, spanning the disease continuum from Stage 2 to Stage 4 in the metastatic setting, there is no other CDK4/6 that has demonstrated the breadth of data with 3 overall survival studies in the metastatic setting as well as the recent data here in the adjuvant setting, regardless of nodal involvement and regardless of Stage 2 and 3.

And so if you think about this, most of the patients are actually in the community setting. That's one point I forgot to make when I was talking about the prescriber base, nearly 80% of the patients are actually in the community setting and so we believe that this will serve to simplify not only patient selection, but also patient management. And that's really because of the data that Jeff shared around the low rate of symptomatic adverse events. And because of all of this, we do believe that over time that Kisqali will become the CDK4/6 of choice for HR-positive, HER2-negative breast cancer across a broad disease continuum.

At this time, we will -- I'll turn it over to Shreeram for us to take questions.

Shreeram Aradhye Executive

Thanks, Reshema. Come on, Jeff. So I think before we get to Q&A, once again, I think we are here at a time when we know that we have the opportunity to meet a real unmet need in patients with Stage 2 and 3 early breast cancer who are at risk of recurrence. We have demonstrated data that shows consistent results across the entire population study, not driven by a unique subset that needs to be identified as being specifically at risk, a safety and tolerability profile that allows ease of use with limited need for dose modifications and the enthusiasm, perhaps best reflected in the quote from Dennis Slamon, who has been involved in this field for many decades now and his enthusiasm about these results as having the potential to fundamentally change how we treat patients with Stage 2 and 3 HR-positive HER2-negative breast cancer. Something that I also heard in multiple interactions that I had at the meeting.

With that, we are now hard at work to make sure that we're planning our discussions with the health authorities to get those submissions in before the end of this year.

With that, I'll open it up for Q&A.

Shreeram Aradhye Executive

My ask is going to be that when you ask a question, please identify yourself. And we'll just go in the order of how you get the mics going to people. So please -- go ahead.

Richard Vosser Analyst

Okay. It's Richard Vosser from JPMorgan. First question, could you give us some of the absolute iDFS rates, maybe at 3 years for the Stage 2 and the N0 subgroups. I think it's very important when putting that data into context, given the limited number of events, if we can see the absolute benefits there?

Second question, the presenter and the discussion talked a lot about the neutropenia rates and the presenter was PI was reasonably concerned about those relative to Verzenio in the patient population. So how do you think that term relates when balancing treatment decision between the 2 products in particularly in the Stage II patients where the majority of the Verzenio data is.

And also, could you just give us the idea -- sorry -- the safety profile in the subgroup for the N0s and the Stage 2 patients, was it the same, consistent across the trial?

Shreeram Aradhye Executive

Jeff, do you want to take that?

Jeff Legos Executive

Yes. So thanks for your question, Richard. I'll try to make sure I address all 3 questions separately and clearly for you. So if I captured it correctly. So first was the absolute iDFS rates at specifically the landmark estimates for 3 years, by stage and by nodal status.

So firstly, we absolutely are very much looking forward to share an even more detailed presentation of those individual results. And I promise you they will be shared at an upcoming future Medical Congress. The investigators specifically are excited to share that detail with you.

What I can say and reiterate is the hazard ratio is a very important measure of overall efficacy because it takes into account the entire patient population by stage and/or nodal status. So we feel confident in the reported hazard ratios that reflect the true reduction in recurrence of risk, but they will be coming.

The second piece was, I think, around neutropenia rates. And the neutropenia is an adverse event that does occur across all CDK4/6 inhibitors, albeit at different rates and possibly different grades. I think what's important to probably highlight is beyond the individual rates themselves, what is the impact of this adverse event on patients. So neutropenia first is a laboratory measurements that often is asymptomatic, transient and reversible. The overall rate of grade 3 neutropenia, albeit high at 44% had very little impact on patients with respect to discontinuation.

Patients who had to discontinue therapy due to neutropenia was only 1%. And with respect to any additional sequela caused by neutropenia, whether it's febrile neutropenia, and/or infections of any etiology and/or opportunistic, those rates were also very, very low.

In terms of the safety profile in individual subgroups, what I can say is it was highly consistent and not dependent on any particular subgroup. So the reported rates were consistent in

independent of stage and/or nodal status.

Seamus Fernandez Analyst

Seamus Fernandez from Guggenheim Securities. So a couple of quick questions. So first, can you just give us a sense in the NATALEE data. What specifically the comparisons, if you were to kind of compare just discontinuations for Kisqali alone, versus the combination. I think there's a little bit of -- there may be a little bit of confusion around that.

So maybe you can help us along those lines. And then if I know you're not comfortable comparing across trials, but the data are published for Verzenio. So maybe you can just help us understand the relative comparisons there.

Second question is how important do you think the monarchE 3 study is from Eli Lilly relative to the competitiveness of that data set versus the data that you've seen or that you have so far from an overall survival perspective in the metastatic setting.

And the last question, is we did see some separation between the individual populations, the older patient population, very high discontinuation rate for Verzenio presented in the recent data set. Just hoping to get a better sense of what your data looks like in the NATALEE study.

Jeff Legos Executive

Thanks, Seamus. And really appreciate the question, and I completely acknowledge the challenge of multiple different data sources, multiple different data cuts, multiple follow-up periods to make sure that we really have the accurate and correct information. So in terms of the overall discontinuation rate due to adverse events for Kisqali, it was 19%. And this includes patients who discontinued Kisqali alone or Kisqali plus the nonsteroidal aromatase inhibitor.

The reported rate for us, for patients who discontinued both therapies is 5%. So then the delta then would be 14% discontinued Kisqali alone, which is also very important because these patients were allowed to continue on their standard of care endocrine therapy treatment as per protocol and as per guideline.

Now the reported rate by the discussion Dr. Harbeck, during the ASCO summary was a 6% discontinuation rate for Verzenio. That was the discontinuation reported for a combined Verzenio plus endocrine therapy. So that 6% compares similarly to the 5% that I just highlighted here. The other thing that I also tried to cover during the presentation was the data that was reported at that particular time.

The rates that she had highlighted was from the JCO publication in 2020, where the follow-up for that particular trial at that data cut was 16 months and the percent of patients that actually had received a full 2-year course of Verzenio was 12.5%.

So similarly, as we talk about the data cut that was shared today or specifically on Friday, here, we have a median follow-up of 27.7 months for the primary endpoint, and 57% of patients have already completed at least 2 years of dosing.

Now for your second question on monarchE 3 and the competitiveness, maybe I'll talk about

it first just from a clinical perspective, and then I'll pass it over to Reshema in terms of the competition. And I think here's another area where rather than debating individual trial versus trial. I think what is incredibly reassuring for me is the consistency of survival benefit across all 3 MONALEESA trials regardless of the menopausal status, regardless of endocrine therapy, regardless of patient population. And specifically, the overall benefit was in that 25% to 30% range, which was highly statistically significant. And maybe I'll answer your last question, and then I'll turn it over to Reshema for the competitiveness on monarchE 3.

With respect to the separations by populations, I don't think we've gone down to that granularity of breaking down efficacy by just a decade of age. The overall median age for patients included in our trial was 52. So a fairly young group of men and women overall, but we would be happy to sort of provide a full analysis at a future congress.

Reshema Kemps-Polanco Executive

Sure. And I can just comment on what we're seeing in terms of the competitiveness in the shares in the metastatic setting. So as I shared with you, you see the dramatic uptake of Kisqali in that setting, again, 1 out of every 3 women who are new patients in that setting are going on Kisqali. What we're seeing is, again, that's coming mostly from Ibrance, where Verzenio mostly being flat in that area.

And that's likely because of where their focus is today. I don't want to be presumptuous about that. But based on -- I won't repeat what Jeff said, but for all of those reasons, what we're hearing and even when I talk to medical experts here at the Congress, it's pretty well established that Kisqali is becoming the CDK4/6 of choice in the metastatic space. And so I believe this creates a great foundation once we have the approval in the adjuvant setting for us to be successful there as well.

Emily Field Analyst

Emily Field from Barclays. I was just wondering if you could provide some context around the adjuvant wider study, just the motivation and rationale for running that study and what you would hope to learn from that, that we won't eventually be learning from NATALEE. And then in the discussion of the protocol-mandated discontinuation due to elevated liver enzymes, you mentioned that that's not how it's going to play out in the real world. I was just wondering if you could put some extra context on that? Is that you expect maybe perhaps a longer drug interruption in patients would go back on drug in the real world setting?

Or just if you could clarify that, that would be helpful.

Shreeram Aradhye Executive

Yes. I think on the wider study, all I'll say is that, that's a planned study that aims to generate additional evidence that is going to be of relevance on the continued use of Kisqali in this setting so that in a more real world practice setting to answer questions that are going to be of relevance to treating physicians. The size design and its overall plans are under evolution. But I don't -- but it really is meant to be a study that is our commitment to continuing to ensure that we are answering questions that people may have beyond what are answered by NATALEE and will be specifically designed to answer those questions.

Jeff let me get you to answer the other question on.

Jeff Legos Executive

Yes. No. First Shreeram thanks for addressing the wider comment. And I think now that we have the data in the public domain and we have engaged with a lot of our medical experts, specifically in this Congress, it's important now that we think about how this trial could be refined to answer any residual or remaining questions that they may have after now seeing the data.

With respect to how this will play out in the real world, Emily, you're exactly right. Patients would have the opportunity to sort of interrupt the therapy for a longer period of time and physicians are already accustomed to doing that based on their experience in the metastatic setting.

I can't quantify exactly how much longer those interruptions will be or how many patients will resolve or wouldn't resolve, but it definitely is consistent with the clinical practice today.

Andrew Baum Analyst

Andrew Baum, Citi. Just going back to the first question you received about the absolute benefit in the T2s and N0s. I mean what is the number needed to treat for prevention of: one, recurrence, given that is such a significant component of the unique Kisqali treatment set that you have? And is that enough to persuade physicians to prescribe?

Second question is related to the first. I don't think you shared the quality of life. Maybe you did, maybe I missed it. But in that sense, I would just be keen to know what that looked like.

And then finally, for such a landmark study, there's no paper yet. So the question is, has it been filed and the peer review has sent it back? Or is it yet to be filed and when could we expect it?

Jeff Legos Executive

Go ahead. Thanks, Andrew. Again, yes, three questions here, so I'll start with the last one and maybe work backwards. So with respect to the paper, it hasn't been filed yet, but we have engaged with the journal, and we are working hard with our co-authors to submit the paper, and looking forward to that being submitted and in press over the coming months.

With respect to your question around quality of life, no, we did not present that today. Yes, we are very excited to present the full details around the quality of life analysis at an upcoming Congress.

But what I can share generally is that quality of life was maintained, preserved when you added Kisqali on top of the nonsteroidal aromatase inhibitors.

With respect to your absolute benefit and the number needed to treat, at least for me, it feels a bit premature to be trying to calculate or compute that based on the current data set. I think it's important, right, to continue to follow these patients over time to realize and recognize the full benefit that Kisqali will achieve with these patients over time. These landmark rates are consistent with and potentially, numerically in line with the overall iDFS benefits.

Shreeram Aradhye Executive

Yes. I mean and I think, Andrew, it's -- this is the first readout of a trial. I think if I reflect on the reactions I've had from the people that I have met at this meeting, whether this is enough to persuade people, I've heard exciting -- excitement from a number of people.

Now the work needs to be done to make sure that we can refile this and get the right label. And I'm pretty confident that if you have a drug that has a consistent benefit, the fact that people will find a way to access it is pretty real. So a little bit too early to start talking about numbers needed to treat data will mature, but we'll stay tuned.

Reshema Kemps-Polanco Executive

Can I just add a couple of points on that in terms of do we believe physicians will be persuaded? Based on what I heard here in talking, I must have talked to 15 medical experts since the data has been released. And what we know from an unmet need is 1 out of 3 patients in Stage 2 have a recurrence, and this can come back 5 years, 10 years, 25 years. And we do believe that women will advocate for this once they are educated. And so one of the things that we've already started is disease education in anticipation of an approval.

I also had an opportunity to interact with a number of the patient advocacy groups who are very excited about this data. So if you pair the advocacy from patients, the expectation of access and physicians' willingness, and we do believe they will be willing to give this drug to them if patients ask for it, especially because the rates of symptomatic AEs are quite low, so they feel that patients will be able to stay on it. And remember, these patients, they haven't really taken up the CDK4/6 class just yet because nothing has been approved and they worry about a drug that they can well tolerate.

And so we do believe that Kisqali will meet all of these needs. And so I expect that we will have -- it will take some time. I want to temper that, but I do expect that we will have a nice uptake in that space.

Simon Baker Analyst

It's Simon Baker from Redburn. I've got a couple of questions, if I may. Firstly, do you have any data on whether there were any imbalances or differences in choice of aromatase inhibitors across the 2 groups? Or was that fairly well balanced? And then a second question, and don't shoot the messenger, I am playing devil's advocate here.

But one of the comments that was alluded to by the discussion and also more explicitly from the presenter of the update on the POWER study on Saturday was the performance of the controller at 87.1% was pretty good. The performance of the Kisqali arm was 90.4% and the point that she was making was that is a reasonably significant incremental toxicity for a relatively modest benefit. So should we be thinking about who are the nonresponders, who are the 13% that are not responding on standard of care rather than laying it overnight. I'm just interested in how you answer that question.

Then finally, you gave you some excellent insights into the U.S. market opportunity. I wonder if you could share the same for the rest of the world.

Shreeram Aradhye Executive

Jeff, do you want to take the first part?

Jeff Legos Executive

Yes. So Simon, thank you. I think the first question is fairly straightforward, right? There was no major imbalance across arms and they really even removed the major -- there was no imbalance across treatment arms with respect to the NSAI of choice in the particular trial.

I guess with respect to the question on the nonresponders on the standard of care and/or even on the experiment alarm. Obviously, as the first data emerges, we have not completed or conducted the full biomarker analysis to try to understand if there was any other additional factors that could help predict or help us understand which patients are likely to respond best versus those patients that are likely to respond least, either on the existing sort of standard of care, endocrine therapy and/or on the combination of Kisqali plus the nonsteroidals. We have done an amazing job collecting a high number, high percentage of baseline tissue samples. We also have plasma ctDNA levels immediately after surgery and then serially throughout the entire course of the trial. And we look forward to working closely with our translational research committee on the NATALEE study to design and understand those results.

Shreeram Aradhye Executive

Okay. Rod, do you want to take the answer on -- Rod Wooten, Head of Global Product Strategy.

Rod Wooten Executive

We see this as a significant global opportunity. I think it's important to remember, not only the data that Reshema shared in terms of our share growth in the metastatic space that's replicated in our -- across the globe. Kisqali is the fastest-growing CDK4/6 across the world, and that's not in any one single geography. We see that in all of our geographies. In fact, 55% of our sales actually come from outside of the U.S.

and 65% of our volume. And then if you look at the patient population opportunity, Reshema shared a slide and you can see in the EU5 alone, you've got a comparable Stage 3 and Stage 2 population.

So we see a significant opportunity here filing again in the second half of the year. And of course, we'll be working with health care authorities and regulators for reimbursement. But the fact that, again, you've got a substantial patient population and benefit across. We're anticipating to continue to have good access and reimbursement in that space. So this is a very large global opportunity.

Steve Scala Analyst

Thank you. Steve Scala from Cowen and Company. Congratulations on the data. Thanks for your comments today. And I appreciate that you just spent an hour answering the question I'm about to ask.

But oncologists prescribe based on data on hand, and in the high-risk population, the competitor seems to beat Kisqali based on the most important aspects of the data at hand. It offers a better hazard ratio in high-risk patients 2 years versus 3 years, which is a big deal and longer durability data, and they'll always have longer durability data than Kisqali has. So for oncologists that cite these points, what is your reply?

Secondly, a follow-up on wider, but one could interpret the wider trial as Novartis not being fully confident in NATALEE's ability to get the desired label. So I guess the question really comes down to when does wider end relative to the patent expiration of the drug?

Shreeram Aradhye Executive

Well, I'll give you a pretty short answer on the wider part. And Jeff, I'll let you answer the other part of the question. The intent of wider is not based on any lack of confidence in the data we have from NATALEE in meeting regulatory needs for securing the label that we need. Wider is intended to be able to answer questions that may continue to come from those that will use the drug in a community setting, and that is its purpose, its design will be refined in order to ensure that those questions can be answered over the long term of use as the drug continues to be made available to patients, but it has absolutely no relevance to any lack of confidence on our part.

In fact, we are very confident in the fact that we have shown consistent benefits on efficacy. We have seen a tolerability profile and a benefit risk and are looking forward to those discussions with regulators to make plans for our filing before the end of this year.

So Steve, so do you want to follow up?

Steve Scala Analyst

When does...

Shreeram Aradhye Executive

That will depend upon all the questions that we plan to answer and how long it takes to generate [the need] to answer them. So some of it will come along the way. Others may take some longer. But I think to be refined as we roll out the design of that trial. Jeff, do you want to answer the other question?

Jeff Legos Executive

Yes. No, thanks for the question, Steve, and appreciate the disclaimer that I've tried to address that over the past hour.

So maybe first and foremost, I mean, this is an incredibly sophisticated audience, and we're looking at every individual data point across substage of disease and prespecified subgroup. And we're trying to look for those trends or differences using data cuts with different points of follow-up, and we're comparing an absolute hazard ratio or confidence intervals across 2 trials that are very different in their design.

And even with the best and most logical comparisons across trials, trying to relate a subpopulation to a subpopulation that also remains incredibly difficult.

I'll come back to one of the points I made earlier, just to reiterate the choice of comparator and/or combination partner. The reason why I made that point and the reason why it is important is we know that as of today, anywhere between 65% of premenopausal women are treated with nonsteroidal aromatase inhibitors, up to as high as 80% across all patients regardless of menopausal status. So in terms of a comparison, a hazard ratio or delta, we felt that it was important that we have the best available standard of care based on head-to-head efficacy and the Kisqali hazard ratios are compared relative to that.

The competitor trial uses a different mix of comparators within their control arm. So already, it's almost difficult, if not impossible, to dissect out the difference between a hazard ratio in a specific high-risk subgroup of patients with different amounts of follow-up.

I think how will doctors make the decision and what have been the conversations we had around ASCO. They're looking for simplicity. They're looking for a streamlined clinical decision-making. They're looking for reliability, reproducibility.

And they're also looking at the totality of the data, which balances the overall safety profile, in particular, those symptomatic AEs, which can be quite debilitating and disruptive to daily quality of life.

In addition to the overall hazard ratios, they also are reflecting on their experience in the metastatic setting and the consistency of data, especially efficacy, safety and tolerability based on the experiences that they've gained over for the past several years.

Unknown Executive Executive

I'm just going to ask a question on behalf of Graham Parry, who's on the web. And a couple of his questions have been addressed already, but there's a third -- 2 more questions still to come.

With the overall survive hazard ratio being 0.76, which is borderline statistically significance. How important do you think that will be when we try and compete with Verzenio. That's one of his questions.

And the second question which he asked was what's needed to drive adoption in the intermediate-risk population, either Stage 2. And what's your realistic target penetration? Is it 25%? 50%? What is it?

Jeff Legos Executive

Thanks for the question, Graham. And sorry unable join us here in person in Chicago, but with respect to the overall survival data. As previously mentioned when we were talking about expectations for health authorities and previous guidance that we had received, the message was around no detriment in overall survival. And I think here, although the data is still maturing. We are very encouraged that the early data suggests that we have this improved trend in overall survival.

Additional analyses will also be done as per protocol at the time of the 500 iDFS events and including patients all the way out to 5 years of follow-up following the last patient randomized. And maybe, Reshema, I'll turn it over to you in terms of the competitiveness and the adoption

in Stage 2.

Reshema Kemps-Polanco Executive

Sure. Thank you for the question, Graham. I think in terms of what is it going to take, it's going to take education. And education to redefine what we mean by risk. And so when you look at the compelling outcomes that we have in these patients who were previously thought to be lower risk or low risk.

We're seeing that it is a high unmet need, evidenced by the consistent results that you see across the subgroups. And so we believe that education on the physician side, but also, as I mentioned earlier, education on the patient side is going to be a critical -- critical lever.

And we believe that, again, these patients will advocate for this once they understand what their risk is. And so what we also are going to have to work through is what is the conversation of the dialogue like between the patient and the physician now that they're -- once the drug is approved, and there is a treatment option for this segment of patients.

In terms of competitiveness, even across Stage 2 and Stage 3, I do want to go back to even the question around Stage 3. Physicians are prescribing Verzenio mostly for those Stage 3 patients because besides endocrine therapy, that's what they have. They don't have another choice.

We do believe when another choice is introduced once the drug is approved, they will balance things like quality of life. And we do know, and we hear that, we heard it here. The patient management is important. And remember, again, nearly 80% of these patients are treated in the community by physicians who may specialize in breast, but they're also seeing other tumor types.

And so simplification around who can benefit from the drug is going to be important. And what we see in CDK4/6 prescribing, we're seeing it in the metastatic setting, where they typically pick one. And we see that they're picking Kisqali in a metastatic setting.

And so while we see -- we expect to see the class grow in the adjuvant setting, we believe that Kisqali will be the one that will cover the disease continuum between Stage 2, Stage 3 and even into metastatic disease.

Peter Welford Analyst

It's Peter Welford from Jefferies. I think I've got 3 left. Just one, is this the data set the maturity of data set that's going to go into the regulatory filings? Or will there be any sort of follow-up or longer follow-up that will go into the filings by the end of the year. Yes.

I was just interested in the hazard ratios and the events, et cetera, you've got.

Secondly, then we you talk about the baseline sort of demographic mix of the patients. Maybe I've missed it, sorry if I did, but I didn't see anything -- in terms of the sort of geographic where the patients are from, race, et cetera. Just thinking about from the regulator point of view, given that obviously acutely sensitive issue at the moment or perhaps forever.

And then just thirdly, just understanding the adjuvant wide, coming back to it, I want to clarify because [indiscernible] says that's actually a single-arm study. Is that actually right, is it evolving, and it won't be a single-arm study you're saying when it actually starts enrolling.

Shreeram Aradhye Executive

So I think wider is a single-arm study, the modifications of the design may involve the use of synthetic controls that all is currently under discussion and review based on the questions that we expect to need to answer. But I think at this point in time, that design is under review.

And Jeff, in terms of the demographics?

Jeff Legos Executive

Yes, good question, Peter and obviously geography was one of our key stratification factors to make sure that it was well balanced across treatment arm and I presume you may be interested in specific geographies like the U.S., where we have enrolled about 900 patients in the NATALEE trial.

So we believe that, that would clearly substantiate the number and/or the percent of patients required with respect to traditional sort of health authority guidance.

And I guess your last set was around the maturity of the data set in the file and/or the label. And I would just reiterate the comment that Shreeram had shared earlier. We have provided our top line data to health authorities around the world, and we are looking forward to discuss that data with them in the upcoming pre-submission meetings.

Unknown Executive Executive

Yes. There's another question from [Andy Washkowitz]. There seems to be interest in CDK4 specific inhibitors and CDK2 specific inhibitors. Do we have programs there? And do you believe this is an opportunity?

Shreeram Aradhye Executive

Jeff? We do.

Jeff Legos Executive

So Andy, thanks for the question. And it's actually really pleasing and reassuring kind of the move towards these next generation selective inhibitors because a lot of that is driven by the research of the ribociclib and the Kisqali team, where for many, many years, we have been focusing on the importance of that selective CDK4/6 inhibition relative to CDK or selective CDK4 inhibition relative to CDK6. So very proud that we've been part of characterizing that biologic rationale and continuing to demonstrate the benefit.

And with respect to internal programs at Novartis. Yes, we are looking at specific inhibitors of these cyclin kinases.

Unknown Executive Executive

Thank you. I think we have time for one last question.

Harry Gillis Analyst

Harry Gillis from Berenberg. So just returning to a few of the questions that we had on the majority of the data. So I think the absolute rates of OS were 2.4% versus 2.9%. I was just wondering as you sort of move into discussions with regulators and eventually file, do you think the FDA might require more mature data than this?

Shreeram Aradhye Executive

I didn't hear the last part of your question. Could you repeat that? Sorry.

Harry Gillis Analyst

Do you think regulators may require more mature data, specifically looking at OS?

Shreeram Aradhye Executive

Specifically looking at OS. I think, Jeff, do you want to take that, yes.

Jeff Legos Executive

I think, Harry, your eyes are probably much better than mine that you were able to decipher the landmarks from the Kaplan-Meier curves. And I would come back to the principle at the timing of this interim analysis for efficacy. And the overall survival hazard ratio at 0.76, right? I do think is representative of the benefit across all of the patients, albeit that data is still maturing.

So with about 30 months of follow-up, right, and more to come, I'd rather focus on the overall kind of hazard ratio and the trend for improved survival rather than looking at the specific landmarks with respect to that curve.

Shreeram Aradhye Executive

Okay. I think with that, we come to an end of this session. Thank you for attending. We are all very excited about the data that we have and hard at work now to do the necessary steps to make this a potentially available treatment to patients with early breast cancer worldwide.

So thank you very much for coming, and I look forward to the reception. Please join us.