Novartis AG

Shareholder/Analyst Call - Novartis AG

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Event Participants

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Samir Shah, Shreeram Aradhye, Jeff Legos

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Graham Parry, Gary Steventon, Andrew Baum, Peter Welford, Mark Purcell, Simon Baker, Michael Nedelcovych, Richard Vosser

Operator Operator

Good morning and good afternoon and welcome to the Novartis conference call and live webcast. [Operator Instructions] And the conference is being recorded. [Operator Instructions] A recording of the conference call, including the Q&A session, will be available on our website shortly after the call ends.

With that, I would like to hand over to Mr. Samir Shah, Global Head of Investor Relations. Please go ahead, sir.

Samir Shah Executive

Thank you very much and good morning and good afternoon, everybody. And thank you for taking the time to join us on the first of our 2 conference calls today. And this obviously relates to the ESMO presentation relating to Pluvicto. Before we start, just the safe harbor statement. The information presented today contains forward-looking statements that involve known and unknown risks, uncertainties and other factors.

These may cause the actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. For a 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.

The participants, which you'll see in the slide deck, which is available on Novartis website, so the participants today will be Shreeram Aradhye, he's actually the Global Head of Development and Chief Medical Officer for Novartis, together with Jeff Legos, who's actually our Global Head of Oncology Development. And with that, I'd like to hand across to Shreeram.

Shreeram Aradhye Executive

Thank you, Samir. Good morning and good afternoon, everyone and thank you for joining our call. As Novartis has become a focused pure-play medicines company, oncology is a key area -- therapeutic area for us. And within it, prostate cancer is a really important indication. If we go to the next slide, we -- with 1.4 million prostate cancer cases worldwide, this being the second most common cancer in men and a 30% 5-year survival, we believe that there is still a significant need for developing therapies that have better efficacy and tolerability for these patients.

On the next slide, you all know the results that we had from our Phase III VISION study where we convincingly showed a benefit on both the risk of progression as well as the risk of death with Pluvicto in a metastatic castrate-resistant prostate cancer post-taxane setting as published in the New England Journal.

Next slide. Emboldened by those results and the subsequent performance of Pluvicto, where it is now approved in 37 countries and more than 7,400 patients have been treated with Pluvicto in that setting, we designed an ambitious program, on the next slide, to explore the role for Pluvicto in additional indications in this important disease. Today, we will discuss the results of PSMAfore, and you're all aware that in addition, we are looking at PSMAddition, as well as PSMA delayed castration, as 2 additional important trials that Novartis is now evaluating.

Next slide. We were excited to present our data yesterday where PSMAfore demonstrated both a robust efficacy and a favorable safety profile. I'm sure that you all have a lot of interest in these results and I'm delighted to hand over to Jeff Legos, my colleague for a detailed review of the data of PSMAfore.

Jeff, let me hand it over to you.

Jeff Legos Executive

Thank you, Shreeram and good morning, good afternoon, everyone. It's truly my honor and pleasure to be here following yesterday's presentation of the PSMAfore results that we're highlighting during the ESMO presidential session by Dr. Sartor. Hopefully, I'll be able to provide some additional detail and context around yesterday's presentation.

Let me start on Slide 11 with a brief overview of the PSMAfore study design. The study population was patients with progressive metastatic castrate-resistant prostate cancer who had previously progressed on a prior second-generation androgen pathway inhibitor, which I'll subsequently refer to as an ARPI and also were candidates for a switch in their ARPI. I'd like to underscore the importance regarding the inclusion criteria that patients were required to be eligible for a switch in ARPI. Specifically, if the treating physicians believe that the patient need it or should receive chemotherapy as its next line of treatment, it's likely that this patient would not have enrolled or participated in the PSMAfore clinical trial.

Over the period of July 2021 to May of 2022, 468 patients were randomized 1:1 to receive lutetium PSMA-617, which I'll subsequently refer to as Pluvicto or a change in their ARPI. If we move to Slide 12. The PSMAfore trial was thoughtfully designed based on a very well-

established set of data for Pluvicto and leveraged several key insights around the regional differences in clinical practice and the remaining global unmet medical needs in search of new, safer and highly effective therapies for patients in this particular disease setting.

Specifically, the dosing regimen that was chosen was based on Pluvicto's low kidney absorption in an already proven safety profile in the stricter post-taxane setting and the currently approved dose regimen of 7.4 gigabecquerels Administered every 6 weeks for 6 cycle was maintained in the PSMAfore trial in earlier line of treatment. With respect to the choice of comparator, here are some key data and insights found in a meta-analysis of more than 2,500 patients with metastatic castrate-resistant prostate cancer where approximately 25% of patients had died without receiving any subsequent therapy beyond their first-line ARPI.

Although the standards of care may differ by geography or the type of institution and clinical prognosis, a large majority of patients are often unwilling or ineligible to receive taxane-based chemotherapy and therefore, a switch in ARPI was chosen as the comparator arm of choice in hope to potentially provide a new, safe and effective therapeutic option that would also allow patients the ability to delay, reduce or eliminate the debilitating need for chemotherapy.

Based on the strong overall survival benefit observed in the VISION study that has led to approval in 37 markets, there was a high potential for loss of equipoise and an increased risk of patient dropout in the control arm to go seek PSMA-617 through alternative mechanisms. Therefore, we employed a physician-recommended patient-centric design to allow patients on the control arm, the option to cross over to receive Pluvicto but only and only after blinded independent central confirmation of radiographic progression. I'd like to reiterate that crossover to Pluvicto was entirely an option for patients in treatment. The protocol did not mandate which subsequent therapy that the patient should receive but rather the treating physician would decide whether other available standards of care, including a taxane or Pluvicto crossover was the most appropriate therapy for his or her clinical judgment to be administered to the patient.

These key design features were essential to ensure not only the integrity of the overall trial by eliminating any bias to the primary endpoint of radiographic progression-free survival but also important to reduce the likelihood of any patient dropout. And in fact, only 1 patient had withdrawn consent from the entire study or was lost to follow-up in the PSMAfore study. And just as a reminder, this trial was largely conducted in the midst of COVID.

If we move to Slide 13. So as a reminder, the primary endpoint for the PSMAfore study was radiographic progression-free survival via a blinded, independent central review. The study was powered at 95% for a hazard ratio of 0.56 after 156 radiographic progression-free survival events using an overall one-sided alpha of 2.5%. OS was a key secondary endpoint and we employed a [indiscernible] design that was planned for OS using a [hierarchical] testing procedure that would only be performed if radiographic progression-free survival was significant. The first look at survival was at the time of the rPFS primary analysis but that was limited by a very low information fraction and short study follow-up of just over 7 months.

The updated analysis that I will share with you today presented by Dr. Sartor at yesterday's

ESMO presidential session and is based on a 45% information fraction for OS corresponding to 135 deaths. Other secondary endpoints are also included on this slide. Due to the anticipated crossover rate, the protocol had also prespecified that the primary methodology for overall survival was to use a rank preserve structural failure time crossover adjusted analysis.

If we go to Slide 14, overall, here are the patient demographics and baseline clinical characteristics, which are broadly similar between treatment arms and representative of the intended treatment patient population. Minor differences across treatment arms were observed and included a slightly worse prognosis population for Pluvicto based on a higher percentage of patients with higher Gleason scores and baseline PSA values.

If we move to Slide 15. As you could see on the left-hand portion of the slide, Pluvicto demonstrated a clinically meaningful and highly statistically significant improvement in radiographic progression-free survival at both the primary endpoints as well as the updated analysis. If you look at the Kaplan-Meier curve, the curves separate early, remains separated throughout the entire duration of follow-up with Pluvicto reducing the risk of disease progression or death by nearly 60%, corresponding to a median radiographic progression-free survival twice as long as the ARPI arm, respectively, at 12 months versus 5.6 months.

If we move to Slide 16, this benefit in radiographic progression-free survival was consistent across the prespecified subgroups, regardless of baseline clinical characteristics, well-known prognostic factors, which androgen receptor pathway inhibitor was previously received and in what setting it was given in. As you could see on the far right-hand portion of the slide, the majority of the 95% confidence intervals exclude [indiscernible] with the exception of a very few small subgroups where there is less than 10 patients and the confidence intervals remain wide.

If we move to Slide 17, please. PSA response rates are commonly used as additional outcome measures in the metastatic castrate-resistant prostate cancer setting. Here on the waterfall plots, you could see that the confirmed PSA50 response was 2.5x more frequent on the Pluvicto arm compared to patients who had received a second treatment with the androgen receptor pathway inhibitor at a 57.6% confirmed decrease in PSA greater than 50%.

If we move to Slide 18, other clinically relevance, especially those for patients, include symptomatic skeletal events as these are often morbidities related to bone metastases and unfortunately, our very burdensome and common problem for patients with metastatic castrate-resistant prostate cancer. A symptomatic skeletal event is defined as a bone fracture, spinal cord compression, tumor-related surgical intervention, thus requiring radiation therapy to relieve bone pain or death, if that was a preceding event.

As you could see on the slide, Pluvicto more than halved the number of symptomatic skeletal events as well as prolonged the time without asymptomatic skeletal event thus demonstrating an overall 65% reduction in the risk for patients having a symptomatic skeletal event when treated with Pluvicto.

If we move to Slide 19. In order to evaluate the direct effect of Pluvicto on tumor size beyond just bone metastases, objective response rate was assessed in patients with soft tissue

disease using standard RECIST 1.1 criteria. Pluvicto demonstrated a confirmed response rate in 51% of these patients compared to 15% of patients treating with an ARPI switch and these responses were quite durable at 13.6 months.

It's also quite noteworthy that more than 20% of patients treated with Pluvicto achieved a complete response. And this data highlights the potential for a even greater eradication of cancer cells when Pluvicto is used in earlier disease settings, especially relative to the data that was observed in VISION.

If we move to Slide 20. So following the reduction in risk of symptomatic skeletal events, coupled with a very impressive objective response rate of 51%, including 20% complete response, it's not surprising that Pluvicto also delayed the time to worsening on 2 separate health-related quality of life measures that overall assess the physical, social, emotional and functional health of the patients as well as deterioration in pain scores for patients.

Taken together, all of the efficacy data shared over the past 6 slides demonstrate that Pluvicto provides a direct antitumor benefit across a range of clinically meaningful endpoints and is also accompanied by patients reporting an improved quality of life compared to daily oral ARPI. The interpretation of this data is neither confounded nor complicated due to additional subsequent therapies that patients received after confirmed disease progression.

If we move to Slide 21. For the remaining secondary endpoint, overall survival is a very important parameter for any cancer trial and it defined as the time from randomization to death due to any cause and includes the results -- or includes the effects that are attributed to both the primary treatment assignment that patients are randomized to as well as any subsequent treatment administered during this overall time period. Therefore, it's important to note that the interpretation of overall survival cannot be done in isolation and it can also be impacted or confounded by crossover. Specifically in PSMAfore, if you look at the consort diagram on the left-hand side of the slide, it is noteworthy that of the 146 patients who discontinued an ARPI following blinded independent central confirmation of radiographic progression, 123 of these patients or 84% had crossed over to receive Pluvicto.

So to try to put this in better perspective, with such a high rate of crossover, you can think of this OS analysis as almost comparing Pluvicto to Pluvicto, just at different times of starting Pluvicto therapy. If you look on the right-hand side of this slide, at the time of the second interim analysis, a total of 134 deaths were observed, which corresponded to a 45% information fraction.

Although we could have never have predicted that nearly all patients who progressed onto an ARPI would crossover to Pluvicto because this was completely optional and physician choice, the statistical analysis plan had prespecified that the RPSFT methodology as the primary overall survival measure that does adjust or account for crossover. Using the most appropriate statistical methodology for crossover, the observed hazard ratio for overall survival was 0.8.

But based on the low information fraction, the 95% confidence interval remains wide, ranging from 0.48 to 1.33. In analyzing overall survival using a traditional unadjusted intent-to-treat analysis, which also includes patients who die for any reason and specifically 3 patients who

were randomized to receive Pluvicto had died before ever receiving their first single dose of Pluvicto. And this analysis also includes 1 patient who died from COVID-19, which was unrelated to disease. The observed hazard ratio was 1.16, also with corresponding wide 95% confidence intervals that range from 0.83 to 1.64.

So if we move to Slide 22, I'd like to use this slide to hopefully better visualize the impact that Pluvicto has on patients who were initially randomized to receive an ARPI switch. If we take a look at the swimmers plot that compare the radiographic progression-free survival times shown in gray, plus the overall survival time up to the point of data cutoff from the time of radiographic progression-free survival highlighted in orange, you actually see there is a difference in patients who did or did not receive Pluvicto as a crossover treatment at the time of blinded independent central confirmation.

What is consistent and common that you see across both plots is that very large proportion of patients did have rapid disease progression. However, if you look at both the shape of the plots as well as the total area under the curve in orange, it is quite clear that Pluvicto increases both the number of patients that were alive as well as the length of time that they are surviving and the estimated 12-month survival rate is actually 92% for patients that had crossed over to receive Pluvicto. In contrast, if I draw your attention specifically to the lower plot, this provides additional evidence that, unfortunately, a reasonable number of patients die without ever receiving subsequent therapy as highlighted earlier in terms of the unmet medical need that we are trying to advance. The estimated 12-month survival rate for patients that had not received Pluvicto as part of crossover is approximately 1/3 lower for this group.

One of the key takeaways from this swimmers plot for me is that it's quite evident that the difference in patient outcomes apparently appears to be attributed to Pluvicto in terms of crossover in this trial and thus provides further or additional evidence that Pluvicto is a highly effective treatment for patients even when administered after a second ARPI.

If we move to Slide 23, I think another important component that needs to be assessed when you're trying to interpret the overall survival hazard ratio or an estimated landmark survival based on the swimmers plot, it's important to also look at how patients were treated after radiographic progression-free survival and to see if there was any observed difference between treatment arms. As you could see from the table, the Pluvicto crossover rate occurred in 84.2% of patients who were initially randomized to an ARPI switch.

As a reminder, to what I talked about in the methodology, crossover was optional and required that 2 conditions must be met. Condition #1 is that blinded independent confirmation of radiographic progression occurs to minimize any investigator or patient bias to which treatment they were received. And then secondly, the crossover has to be recommended by the treating physician as the most appropriate next treatment amongst all available standards of care, including taxane-based chemotherapy.

If you look on the right-hand side, these are patients who were initially randomized to a subsequent ARPI. And in addition to the 84% crossover, another 6 patients had also received PSMA RLT directed therapy outside of the study. Please note that the chart only highlights 5. There is a sixth patient that was excluded from the chart. There are also 2 kind of key

important takeaways from this trial.

I think importantly, it shows that other than Pluvicto as well as these patients who received PSMA-directed therapy outside of the trial, it's noteworthy that additional 30 patients were required to receive concurrent radiation primarily due to extensive bone metastases on the ARPI arm.

And then subsequently, it actually highlights that other than these 2 therapies, all other available standards of care were routinely used in a similar proportion of patients across treatment arms. What this table also highlights is that it makes it very difficult to isolate the true effect of Pluvicto because so many patients on the control arm had received either Pluvicto, other types of PSMA-directed radioligand therapy or concurrent radiation because symptomatic bone metastases or pain.

If we move to Slide 24. At the time of the updated data cutoff, the median follow-up time was 15.9 months, which represents a sufficient follow-up time so that all randomized patients had adequate time to complete their intended course of therapy. As of the data cutoff, 63% of patients had received the full 6 cycles of Pluvicto and 75% received at least 5 doses. So this represents a very mature follow-up to assess the overall safety of Pluvicto relative to an ARPI change. As you could see from the overall safety table, Pluvicto had a lower rate of Grade 3 or higher adverse events, very low rate of dose adjustment at 3.5% and a similar 5% rate of discontinuation due to an ARPI.

If we go to Slide 25, the majority of adverse events were low grade and consistent with the known safety profile of Pluvicto based on the previous established VISION trial in a post-taxane setting. Xerostomia or dry mouth is the most common adverse event observed. However, only 1% of patients had reported a Grade 3 or higher adverse event. And this actually only led to discontinuation in 1 patient, suggesting that xerostomia or dry mouth is quite manageable and allows patients to live and resume a normal daily quality of life. Anemia was the only Grade 3 adverse event that was reported in more than 5% of patients but did occur at a similar 6% rate across treatment arms.

If we move to Slide 26, please. Overall, we have accumulated more than 2,000 patient years of safety data across the VISION, PSMAfore and post-marketing setting, which overall support the favorable safety and well-tolerated profile of Pluvicto. If you look at the exposure-adjusted safety via indirect cross-trial comparison between both PSMAfore and VISION, it's noteworthy that there is a much lower incident rate per unit time for Grade 3 or higher adverse events as well as for severe adverse events. An important takeaway from this slide is that the overall safety profile relative to the VISION patient population supports the broad clinical development plan where we are continuing to evaluate Pluvicto in even earlier lines of therapy in earlier stages of disease.

If we move to Slide 27. So in conclusion, Pluvicto demonstrated a clinically meaningful and highly statistically significant improvement in the primary endpoint of radiographic progression-free survival. Pluvicto also demonstrated robust efficacy against the important secondary endpoints such as PSMA -- PSA50 response, time to symptomatic skeletal events, objective response rate and overall health-related quality of life.

I'd like to reiterate that the clinical benefit observed for the primary endpoint and all of these secondary endpoints are based on mature or final analysis, which provide further support for the robust efficacy of Pluvicto. Since all of these are direct measures of Pluvicto randomized against a switch or a second treatment with an ARPI, the interpretation of this data is not impacted by any subsequent therapy nor is it confounded by the results of crossover.

The overall safety of Pluvicto is favorable compared to an ARPI switch with lower reported rates of Grade 3 or higher adverse events, lower rate of severe adverse events, less frequent dose adjustments and the overall low rate of discontinuations. The data in PSMAfore in a much healthier population also compares favorably to the sicker post-taxane population with lower incident rates of high-grade adverse events based on a cumulative data set of more than 2,000 patient years.

If we just move to the last slide, Slide 28. So overall, PSMAfore was a very well-designed and well-controlled study. The physician recommended patient-centric crossover design that allowed patients on the control arm, the option to crossover to receive Pluvicto but only after central confirmation of radiographic progression-free survival enabled a very robust and independent assessment of the primary endpoint and likely reduced any risk of patient dropout due to physician decision.

The high rate of crossover further reiterates the unmet medical need that both patients, physicians and investigators are seeking for safer and more tolerable and highly effective therapies. These key design features were essential to ensure the integrity of the trial by eliminating any bias to the primary endpoint as well as reduce the likelihood of patient dropout with only 1 patient withdrawing consent during the PSMAfore study.

However, I would fully acknowledge that the challenges that this crossover design and the fact that almost all patients had received Pluvicto following radiographic central confirmation of progression does impact our ability to reliably assess endpoints such as overall survival, since the randomized treatment assignment is no longer isolated. And especially at the time of this data cutoff, the follow-up does remain short at 15.9 months and only 135 -- or 134 deaths have occurred. So specifically, if we look at the conclusions, at the time of the interim analysis, there remains only 45% information fraction. There was a very high crossover rate of 84% plus patients who receive PSMAfore directive therapy in another setting does confound our ability to interpret the overall survival analysis at this point in time.

The PSMAfore trial is ongoing and it will continue to the next interim analysis where we would expect approximately another 90 to 100 additional deaths, which would correspond to a 75% information fraction and our submission -- our regulatory submissions to health authorities will follow in 2024 after we reach our next interim analysis of 75%.

Thank you very much and I will now turn it back over for Q&A.

Operator Operator

[Operator Instructions] Our first question comes from the line of Graham Parry from Bank of America.

Graham Parry Analyst

So the main question, I think, is just what is it that the FDA actually needs to see on overall survival to accept the file just given this is so confounded. So do they need to see now some statistically significant and clinically meaningful benefit on the crossover adjusted analysis? So the 0.8 as a ratio that you're seeing there, sort of moving into statistical significance. Do they need to see that the ITT analysis as a ratio falls below 1 as a evidence of no harm, which is, I think, what was referred to previously by yourself and [indiscernible] and of course as being sort of what the hurdle was here? Or is it some sort of -- most analysis that looks like what you have today but just with more events.

So just precisely, what is it they're looking for? And importantly, when do you expect that data to be available for filing?

Jeff Legos Executive

Thank you for the question, Graham. And I think with respect to the first question around what is the FDA looking for, there is no absolute definition and/or number which they are seeking. And if I sort of just draw your attention back to the FDA industry investigator workshop this summer, the FDA highlighted the principles of which they are seeking in order to assess overall survival or in order to establish no detriment. And what they clearly highlight is a few key important principles that I think are quite important here. So I think, firstly, beyond the trial itself is, has the investigational agent demonstrated overall survival in any setting.

And for Pluvicto, the answer is yes. We have the overall survival benefit in the VISION trial, which was not impacted by crossover. Subsequently, the FDA also looks at, are there any other confounding factors that need to be taken into account when interpreting the overall survival data. And I think in this particular situation, the incredibly high rate of crossover is something that's very important and impactful in trying to understand overall survival.

But unfortunately, at this point in time, what I think remains true is that our data does remain immature. So I think having more mature data will help with a much more reliable assessment of the overall survival results. With respect to the analyses that the FDA will look at is, they obviously will take into account the totality of the data as well as looking at both the unadjusted and adjusted analyses for overall survival.

Now for your second question with respect to timing, I have highlighted that the next interim analysis will occur at 75% information fraction. We are continuing to track these events closely. But for any time-to-event end point, we obviously need a little more time to get a precise estimate as to when exactly those events are going to occur. And what we plan to do is update everyone in the new year, at the time of the annual results, once we'll have greater confidence around the exact timing of that data.

Operator Operator

Our next question comes from the line of Gary Steventon from BNP Paribas Exane.

Gary Steventon Analyst

Just on biomarkers and PSMA uptake. Are you able to share the proportion of patients in the

trial that had SUV mean levels of 10 or greater on PSMA [indiscernible] and when we can expect to see that data cut? And then just linked to that quickly, how practical do you think that biomarker is?

Jeff Legos Executive

No. And maybe I'll start with the inclusion criteria, which is standard across all Pluvicto trials where we do require at least 1 PSMA positive lesion using our gallium 68-11 diagnostic. And in this particular trial, what was notable is of the patients who were screened for PSMA expression, 92% -- 92.1% of patients met that eligibility criteria. So a very high proportion of patients even greater than what you would see in the literature, which reports about 80%. With respect to your second question, we have done subsequent analyses from the VISION trial and do show that SUV max or SUV mean does play an important role in the predictive outcome for patients.

And without getting into specific r-squared correlation values, usually, the higher the expression, the better the outcome. We are obviously -- we have collected that data from the PSMAfore trial as well. We are currently analyzing and we expect that to be presented at a future data congress.

Operator Operator

Our next question comes from the line of Andrew Baum from Citi.

Andrew Baum Analyst

Assuming that PSMAfore gets added to label, could you clarify the impact on the market potential? I get that some patients, maybe 15% may progress very rapidly and we'll be able to capture those. But I'm more interested in the ability to use it across multiple lines of therapy. Could you talk to that? And although it's not on label, how many of your existing patients are seeing more than the label 6 cycles of therapy.

Jeff Legos Executive

Thanks for the question, Andrew. And maybe just thinking about how and where the drug has already been studied or used. So from the VISION trial, we have established a very clear benefit risk with respect to usage in a post-taxane setting. And it is our belief by moving this into the pre-taxane setting that this represents about 2 to 3x an increase in the number of patients that can become eligible for treatment. One of the reasons why we believe this to be true is, as mentioned earlier, about 25% of patients who receive first-line androgen pathway inhibitor never receive a subsequent treatment for their disease and often go and die without any further therapies.

If you look at patients who receive a second line of therapy in the metastatic castrate-resistance prostate cancer setting, approximately another 25% of patients have a second line of treatment that then ultimately never see a third line of treatment.

So moving this into earlier lines of therapy become quite important to increase the patient eligibility. With respect to the number of doses, the approved dosing regimen allows up to 6 cycles of Pluvicto. Based on the strong efficacy as well as the safety of Pluvicto, there is merit

in actually studying potential rechallenge, retreatment or subsequent lines of therapy in these settings but that data is not yet available.

Operator Operator

Our next question comes from the line of Peter Welford from Jefferies.

Peter Welford Analyst

I just wanted to return to the survival analysis here. And I guess there's sort of 2 parts to this, which is, one, given that presumably a lot of patients who did crossover are also likely to still have not yet completed their course of Pluvicto. I guess how do you assess necessarily that the overall survival for the all-comers population is in fact going to worsen. And I guess related to that, do you have any data in terms of the number of cycles crossover patients received Pluvicto [indiscernible] versus on the other hand, as you said, I think 75% managed to receive at least 5, if they were originally assigned to Pluvicto.

Jeff Legos Executive

And I think your question reiterates or highlights the need to accumulate additional events and to have further follow-up so that we could adequately assess how patients did after crossover as well as what the impact of crossover is on a larger proportion of patients, especially with respect to the overall survival analysis. So we continue to look forward to the interim analysis to better address the questions that you've just raised.

Operator Operator

[Operator Instructions] Our next question comes from the line of Mark Purcell from Morgan Stanley.

Mark Purcell Analyst

I was just going to ask in terms of the patients that are most appropriate for Pluvicto therapy, the discussion yesterday sort of highlighted different patient subgroups. One was already mentioned PSMA [indiscernible] which the discussion felt was the most appropriate patient group for the use of Pluvicto. But then you've got some germline somatic mutations, lots of p 10 and p 53 and things like that. So how would you help us to think about which patients are likely to be the most appropriate? And then [indiscernible] Pluvicto, that is and then given your comments around the sort of challenges of sequential therapy, the sort of 25% not receiving therapy in a subsequent line.

How are you thinking about the potential for combination therapy, which would maybe circumvent some of these patient subgroup considerations?

Jeff Legos Executive

Yes. And I think some important questions around sort of clinical practice and optimal patient benefits. And if I think about how we are looking to help answer those questions, we have a very large body of clinical data already established as well as a substantial amount of post-marketing evidence that all collectively will help inform which baseline disease characteristics, prognostic factors, genetic or molecular alterations and our SUV uptake,

mean or max are most clinically relevant predictors of long-term benefit.

In addition to that, we'll also use all of these baseline biopsies and/or samples to be able to better inform potential mechanisms of resistance to identify those patients who are most sensitive or responsive to Pluvicto versus those that may be more resistant and that will ultimately inform or guide optimal based combination therapy. So collectively, all of this data will be quite helpful in assessing that.

And as you've seen from Shreeram's presentation, we have a large body of evidence that continues to accumulate and 2 additional trials that are ongoing or soon to start in an earlier line of therapy in combination with an ARPI and then also in an earlier stage of disease, local regional disease in patients that have oligometastatic disease. And with respect to kind of all of the questions around sequencing, I would just reiterate maybe my comment that I made to Andrew's question as well, is we have already demonstrated the benefit in a post-taxane setting. I believe this data corroborates that benefit at least in terms of the end points that are mature, final and/or not confounded by crossover.

And we also have data from the Phase II study that has actually shown the benefit over a taxane where we actually had higher improvements in PSA response of 66% versus 37%, a RECIST objective response rate of 49% versus 24%, progression-free survival of 0.63 and then a much lower rate of Grade 3, Grade 4 toxicities versus taxane-based chemotherapy at 1/3 versus 53%. So I think there's already a larger body of data than maybe some folks would appreciate with respect to when and where and which patients this drug could be used in.

Operator Operator

[Operator Instructions] Our next question comes from the line of Simon Baker from Redburn Atlantic.

Simon Baker Analyst

Just looking at the subgroup analysis, the result looks very robust across the subgroups that you presented. One you didn't present was on ECOG status, doesn't have any data on that. And while saying that the result is consistent, it does appear that patients who are older and patients who are European seem to do even better. I just wonder if you had any thoughts why that might be.

Jeff Legos Executive

Yes, I think -- and I think with respect to your first one around overall subgroups. I know all of our -- Dr. Sartor had presented a larger amount of subgroups at yesterday's ESMO presentation. And if you look at ECOG status and/or baseline LDH levels, right, the benefit was also clear for both. In addition to that, we have looked across geographies and other than kind of the Asian countries where we had a very small percentage of patients, I think, in general, all data would suggest very clear clinical benefit.

I would always caution when trying to interpret kind of smaller numbers across subgroups and saying that, 1 region had done better than the other. And I think with respect to region here, I think both 0.52 and 0.40 are quite clinically meaningful in terms of European patients

versus North American patients.

Operator Operator

Our next question comes from the line of Mike Nedelcovych from TD Cowen.

Michael Nedelcovych Analyst

My understanding had been that it was pre-agreed on some level with the FDA that the overall survival endpoint needed to show only no detriments. Am I misunderstanding that? Or has there been some change?

Jeff Legos Executive

And I think clearly, you are referring to the guidance that we had previously shared externally. And I think the definition of no detriment continues to evolve using kind of these real-world examples. And I think in particular, what is clear is, you cannot look at a single data point, point estimate and ignore the other facts of the ongoing clinical trial, especially something like this, where the crossover rate is as high as 84%.

So I think during the FDA workshop this summer, they were actually wrestling through exactly what that definition would look like. And you also see, if you take a look at that data, there are some definitions around hazard ratios, confidence intervals. I think for here, the most important part is the totality of the data and the fact that we need additional maturity in order to be able to reliably assess the overall survival.

Operator Operator

Our next question comes from the line of Richard Vosser from JPMorgan.

Richard Vosser Analyst

Just a question on the other ongoing trials in particularly the PSMAddition trial but others as well. How are patients crossing -- how is crossover treated in those trials? I think the control arm is allowed to crossover as well. So how would that be interpreted in terms of those trials? And how will we think about in terms of the submission timing given the OS issues we've seen here with -- in the PSMAfore trial.

Jeff Legos Executive

And maybe before I address the question, maybe I'll comment about a very interesting scientific hypothesis that actually is driving the rationale for the PSMAddition trial. We know very well from our translational data as well as the literature that hormonal blockade does influence PSMA expression. So in this particular trial, it's reasonable to believe that hormonal blockade using an androgen receptor pathway inhibitor, hormone-sensitive prostate cancer setting could influence the expression of the PSMA receptor and then make these patients even more eligible for benefit from Pluvicto. So interesting scientific hypothesis that we are testing there.

With respect to your question specifically, crossover is also an option in the PSMAddition trial. However, the kinetics are much different. So if you think about what had occurred in

PSMAfore, the time to radiographic progression in the control arm happen very, very quickly, right? 5.6 months on average, which means patients -- some patients or 50% of the patients were progressing even before that 5.6 months and then crossing over to Pluvicto almost immediately. Now in contrast, in PSMAddition, because this is a much healthier population, the majority of patients will have completed their course of Pluvicto or have been on hormonal therapy for potentially a few years before their disease would progress on average.

So the median progression-free survival are much longer in that particular setting. So there will be longer windows between the time a patient could progress and then ultimately receive subsequent therapy. So I think that was one more important notable difference. And I think on your last question with respect to the overall survival events, we have also built in a multi look analysis at survival into that trial and we have done the appropriate power calculations and the number of events that would be expected at the time of the primary readout as well as at subsequent follow-up points in time.

Operator Operator

Due to time constraints, this concludes our question-and-answer session. So I'll hand the call back to Samir for closing remarks.

Samir Shah Executive

Thank you very much. I just want to say thank you for participating in this call and we look forward to the next call within a few minutes. Thank you.

Operator Operator

This concludes today's conference call. Thank you for participating. You may now disconnect. Speakers, please stand by.