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PFE - Pfizer Conference Call to review Palbociclib Phase 2 PALOMA-1 Results at AACR Annual Meeting 2014

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OVERVIEW:

PFE discussed the results of palbociclib Phase 2 PALOMA-1 study presented at AACR on 04/06/14.



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PRESENTATION

Operator

Good day, everyone, and welcome to the Pfizer review of palbociclib Phase 2 PALOMA-1 results, which were presented today at the AACR Annual Meeting 2014. Today's call is being recorded.

At this time, I would like to turn the call over to Mr. Chuck Triano, Senior Vice President of Investor Relations. Please go ahead.

Chuck Triano - Pfizer Inc. - SVP, IR

Thank you, operator. Good afternoon and thanks for joining us today to review the palbociclib Phase 2 PALOMA-1 study results, which were presented earlier today at the American Association for Cancer Research Annual Meeting here in San Diego, California. I am joined today by Garry Nicholson, President of Pfizer Oncology, and Dr. Mace Rothenberg, Senior Vice President, Clinical Development and Medical Affairs and Chief Medical Officer for Pfizer Oncology.

The slides that will be presented on this call can be viewed on our homepage, Pfizer.com, by clicking on the link for Review of Palbociclib Phase 2 PALOMA-1 Results at AACR Annual Meeting 2014, which is in the lower right-hand corner of this page.

Before we start I would like to remind you that our discussions during this meeting will include forward-looking statements. Actual results could differ materially from those projected in the forward-looking statements. The factors that could cause actual results to differ are discussed in Pfizer's 2013 annual report on Form 10-K and our reports on Form 10-Q and Form 8-K and in the press release concerning the PALOMA-1 trial that was issued today. Our SEC reports and press releases are available on our website, Pfizer.com.

With that, I will now turn the call over to Garry Nicholson.



Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

Thank you very much, Chuck, and everyone, we appreciate your interest in palbociclib and the fact you are joining us today. We are very pleased that the PALOMA-1 study was presented today at the plenary session at AACR. It obviously highlights the potential for palbociclib to be a new standard of care for ER-positive breast cancer patients.

As you have seen from a prior release, we are delighted with the results, particularly the magnitude of the PFS primary endpoint benefit and also the consistency of the secondary efficacy endpoints and the adverse event profiles entirely consistent with what we've seen previously. Before I turn it over to Mace, I would like to say a few words about our pipeline. I believe that slide is up now.

You will see 4-1BB, which is our immunotherapy antibody. It has continued to advance in clinical studies. The target is CD137 and there's a strong rationale there for success based on its T-cell activity. I also want to point out the ALK/ROS inhibitor, which is now in a clinical study and we have reason to be optimistic based on what we see in the preclinical profile.

One other word about palbociclib before Mace speaks, and this is with regard to our interactions with the FDA. We have a very productive and ongoing interaction with the FDA starting, of course, with the breakthrough designation. Everything is on track with that interactive process, but we are not able today to confirm the exact regulatory strategy.

We do envision a path to filing based on PALOMA-1 data that was presented today, but at a future point the FDA will have seen what they need to see in the way of information and they will clarify the next steps. We will communicate about that at the appropriate time.

So now Mace is going to take you through the exciting data that was presented today here in San Diego. Mace?

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

Thanks very much, Garry and Chuck, and thanks to all of you for joining us today. What I would like to do is to really summarize the presentation that was given today at the plenary session of AACR by Rich Finn of UCLA. His presentation was entitled The Final Results of Randomized Phase 2 Study of Palbociclib, a Cyclin-Dependent Kinase 4/6 Inhibitor, in Combination with Letrozole Versus Letrozole Alone for the First-Line Treatment of ER-Positive, HER2-Negative Advanced Breast Cancer, a trial that was known by various names, Study 1003, also PALOMA-1, also TRIO-18.

So in this slide, this is the primary endpoint, progression-free survival in this trial. What we see is that the combination of palbociclib and letrozole significantly prolonged progression-free survival in this group of patients. The median progression-free survival, as you can see, is 20.2 months in the combination group versus 10.2 months in the letrozole alone group. That hazard ratio for progression is 0.488, representing more than a 50% reduction in risk of progression for the combination arm.

This difference was statistically significant at a level of P 0.0004. This is statistically significant and an important median progression-free survival result in the context of current therapies. What I mean by that is that this is the longest median progression-free survival ever reported in a randomized trial in first-line ER-positive breast cancer.

As some of you may know, this trial was done in two parts. Part one had all ER-positive breast cancer patients accrue, that was 66 patients, and part two had two selection criteria in addition to ER-positivity that included cyclin D1 amplification or loss of p16. These results were consistent in part one and two, one confirmed the other, and the results were statistically significant in both of those parts.

We also had important secondary endpoints and this slide shows best objective overall response rates. As you can see from this slide, the objective response rate was also increased in the palbociclib arm 43% for the combination versus 33% for letrozole alone. And also, if you include those individuals who had stable disease for more than six months in this, your clinical benefit response rate goes up to 81% for the palbociclib plus letrozole alone arm versus 58% for letrozole alone.



Another important secondary endpoint was overall survival. But again this is a secondary endpoint; the primary endpoint being progression-free survival. This overall survival analysis was triggered not by the number of events, but by the timing of the final analysis for the primary endpoint of progression-free survival.

As you can see, there was in this initial assessment the median overall survival in the combination arm was 37.5 months versus 33.3 months for letrozole alone arm. That hazard ratio was 0.813 and we are encouraged by this trend at this early point in time. The follow-up overall survival analysis will be conducted as more events accrue.

To remind you, progression-free survival, as Garry has said, has been the basis for regulatory actions in this disease, not overall survival. As we all know, the overall survival in this group of women is upwards of three years and we will have to wait quite a long time to have that period of time pass before we know more about this.

We also recognize that regulators have looked for consistency in measures of efficacy and when you line all these up between the primary endpoint of progression-free survival, the objective response rate, the clinical benefit response rate, and overall survival, they are all consistent and heading in the right direction for the combination showing advantages.

With any cancer therapy, we have to look at the adverse event profile as well. What we can see from this study -- and this is all causality adverse events; not just those that were suspected to be due to the drug, but all causality events. This is a drug that was generally well tolerated with a safety profile combination that was consistent with our previously reported data.

What we found that the most common side effects are cytopenias, most notably neutropenia. However, the neutropenia observed with this combination was not cumulative and was clinically manageable. The neutropenia I want to remind everyone is an on-target anti-proliferative side effect of palbociclib and signifies the inhibition of CDK4 and its effects on bone marrow. So this is important.

What I also like to point out from this chart, when you take the neutropenia, anemia, and thrombocytopenia out of the picture, there's no grade 3 or 4 adverse event that occurs with a greater than 4% incidence. So these side effects are very well understood, very specific to primarily the bone marrow. And aside from that we see very few grade 3 or 4 other side effects.

So in terms of the conclusions from the PALOMA-1 study, I think that could be summarized in these five bullets. I think we need to focus on the magnitude of benefit. Greater than a 50% reduction in risk of progression, which is the longest PFS in any first-line randomized trial in ER-positive breast cancer.

We can understand the impact by looking at the number of women who fall into this category worldwide, which numbers about 145,000 women each year in the G7 nations. We have to recognize and acknowledge the novel mechanism of action of this drug and the insights into the underlying biology of the CDK pathway as it relates to ER-positive breast cancer and the bridging of those biological insights to the development of this rational and effective therapy in this group of women.

We have to acknowledge that we are the first to this point in the development of this class of compounds, and then also recognizing the future potential in breast cancer and beyond. And in my final slide this is an overview of the development plan in ER-positive, HER2-negative breast cancer. Today -- as of today we have initiated four Phase 3 trials, three in advanced breast cancer that involve more than 1,200 patients.

We have PALOMA-2, an ongoing study in a similar patient population to those that we have just described in PALOMA-1: first line ER-positive HER2-negative breast cancer with palbociclib, with letrozole, with either palbociclib or placebo. That is a placebo-controlled double-blind study.

PALOMA-3, in women who have already received and progressed on prior endocrine therapy, is randomizing women to fulvestrant plus palbociclib or placebo. And again, another Phase III randomized double-blind trial.



And recently activated PEARL study, which is comparing palbociclib plus exemestane to capecitabine. The goal in this trial and in all of these trials in advanced breast cancer is to improve progression-free survival over standard of care and to delay the need for initiation of chemotherapy in this group of women.

In the early stage high-risk breast cancer group, we have initiated the PENELOPE trial in conjunction with the German Breast Group. This is in women who have received prior neoadjuvant or preoperative chemotherapy without radiation therapy and are considered to be at high risk for relapse. This trial will involve more than 800 patients and has also been initiated.

So with that I would like to now turn it back over to Chuck Triano. Thank you.

Chuck Triano - Pfizer Inc. - SVP, IR

Thank you, Mace, and thank you, Garry. At this point, operator, if we could please poll for questions and then we will move to the Q&A session.

QUESTIONS AND ANSWERS

Operator

Chris Schott, JP Morgan.

Chris Schott - JPMorgan - Analyst

Chris Schott, JP Morgan. I just had two questions here. First, one of the points raised today by the discussion in the plenary presentation involved your Phase 2 being an open-label study.

I guess my question is in the absence of mature OS data at this point, how relevant do you think the open-label nature of your study is going to be from a regulatory standpoint? Have you had any feedback from the FDA on that, or just any perspective you could provide?

The second one is just a really quick one just to confirm those earlier comments that I think Garry had made. I just want to confirm; you feel confident that there's a path for filing this product off of PALOMA-1 and you don't anticipate needing the full results for PALOMA-2 before filing? I just wanted to confirm that that's what you're looking at this point. Thanks very much.

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

I will handle the first question and I will turn it over to Garry for the second question. Regarding the issue of open-label study, obviously when physicians and patients know what treatment they are on there's always a concern of whether physicians have particular bias or patients, for that matter, have a particular bias either in favor or against the investigational arm.

What this means potentially is that patients can be taken off prematurely if there's a sense that they are on the wrong arm, let's say, or continued on therapy beyond when they would be considered to be evidence of progressive disease. So this is a bias that is potential for any open-label study.

However, when you look at the magnitude of the difference in progression-free survival of 10 months between the investigational arm and the standard arm, any bias that may have led to one arm being prematurely terminated in a particular patient or the other arm being continued is really trivial compared to that 10 months. So we think that if there were any bias this would not be impacting the difference that we see.



There are also ways of potentially correcting for this even in open-label trial through statistical methods. I will turn over the second question to Garry.

Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

Chris, we are definitely not at the point with our interactions with the FDA to say that we will move ahead with the Phase 2 PALOMA study. That would be at some future point where they continue to tell us what they are looking for, they look at the information we provide, and then we would make that decision at a later point in time.

Operator

Tim Anderson, Sanford Bernstein.

Tim Anderson - Sanford Bernstein - Analyst

Thank you. Tim Anderson, Sanford Bernstein. Can you just talk about filing in US versus Europe? It seems like the odds of filing in Phase 2 may be much higher in the US, because I don't think Europe very often accepts Phase 2 data for filing. So I'm wondering if you can just differentiate between the discussions with US and European regulators.

And then a second question goes back to the neutropenia and the leukopenia and whether you think there can be any differentiation among the different CDK 4/6 inhibitors. Because Eli Lilly keeps kind of saying that they think they have a more tolerable drug and I guess at least our early data from last year showed that they didn't have very high neutropenia rates. And they have mentioned maybe there's a differential affinity for CDK 4 versus CDK 6.

So you mentioned it's class-based, but do you think within that realm that there might be differentiation?

Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

Tim, there are differences between the US and Europe in terms of what they look for and it's different by drug, by tumor, by stage, but we are not interested in forecasting or speculating now about whether the FDA will or will not accept. We have just got some more work to do with them and they will see what they need to see, so we are going to wait on that type of question until a later point.

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

With regard to the neutropenia and leukopenia, it's very difficult for us to comment about another company's product. What we do know is it has a different profile. Our compound is a very specific CDK 4/6 inhibitor. What we know and is in the public domain of Lilly's is that also it's other CDKs and also non-CDK kinases as well, and that actually might be the reason behind some of the differences in adverse event profiles.

But let me get back to the neutropenia, because certainly whenever we are talking about cancer therapy and neutropenia comes up it comes up as a risk and the risk is increased risk of infections and fever and potential sepsis and death from that. But we also are recognizing with this class of compounds that the nature, the clinical feel for this neutropenia is different than that that is induced by cytotoxic therapy. It is primarily grade 3 and not grade 4 and it also has not been associated in PALOMA-1 with any episodes of neutropenic fever or infection. So despite an overall incidence of over 50% of grade 3/4 neutropenia, that disconnect with its clinical manifestations we think is important and reflective of its unique mechanism of action.



Operator

Vamil Divan, Credit Suisse.

Vamil Divan - Credit Suisse - Analyst

Credit Suisse. I just had a question from the session of the morning also between the part one and the part two groups. To us it seemed like there's a pretty big difference in both the palbo arms and the control arm. I was wondering if you could just talk to that.

It seemed like palbo did much worse, but the control did much better when you look at the part two relative to the part one. Is there anything you are seeing from as you look at the data that can explain some of that, maybe in the demographics or otherwise? And is there anything you can talk about regarding PALOMA-2 or your other work that would suggest whether the patients are going to be more like what was in part one versus what was in part two of the study? Thanks.

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

Okay, very good. Let me start by saying this is a positive study overall in terms of meeting its primary endpoint of progression-free survival. When we broke it down into part one and part two, each of those parts was statistically significant showing an improvement in progression-free survival for the combination. Let me also point out that these are point estimates and what we are really looking for is the overall effect of this.

When you look at -- when you take a look at the part two progression-free survival hazard ratio, it is about 0.51. When you actually look at the entire experience, that is 0.49. Those two things are very close to one another and we think reflects the fact that however you parse this, whether you take this as the entire trial or you take it part by part, we are seeing a drug that substantially reduces the risk for progression in this group of women.

In terms of PALOMA-2 and PALOMA-3, we are -- as we had mentioned, we are not selecting patients' biomarker because we did not find that any of the biomarkers used in part two improved our ability to detect women who will benefit from palbociclib any better than women with ER-positive breast cancer. So that's what we are using as our selection criteria for PALOMA-2 and PALOMA-3.

Operator

Alex Arfaei, BMO Capital.

Alex Arfaei - BMO Capital Markets - Analyst

Good afternoon and thank you for taking my questions. It seems the PFS benefit was not surprisingly better in patients without previous chemo and hormone therapy, more of the subgroup analysis that was done. In other words, in truly first-line patients, the combo seems better -- to be more efficacious.

I am wondering to what extent are you controlling for this in PALOMA-2 to make sure you have more first-line patients. Then a follow-up on the prior question. Given that this is an open-label study, are there any plans to have the results also evaluated by independent and blinded reviewers? Thank you.

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

Let me start by -- in terms of how we are going to control for patients with or without prior chemotherapy or hormonal therapy. This is a stratification criteria, so we will be able to at least balance it for both arms, control and investigational, in order to make sure that we have any impact from that equally weighted between the two.



In terms of being able to validate these results, we have been engaging in these discussions with the Agency.

Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

Then in terms of the blinded independent review, yes, there is a blinded review of this trial and that information will be made available to the FDA.

Operator

David Risinger, Morgan Stanley.

David Risinger - Morgan Stanley - Analyst

Thanks very much. I dialed in a little bit late, so I apologize. I have two questions.

First, could you re-articulate your plans to file the drug with the FDA? Wasn't quite clear what you were saying. I know that when you issued a press release a few months ago, you said that you planned to have discussions and I'm assuming that you have had discussion with the FDA given your breakthrough therapy designation on the data that you presented today. So if you could help us understand what the FDA wants beyond this data and when you might be able to file that would be helpful.

Then second, if you could just step back to a bigger picture and talk to us about the top few cancers beyond breast cancer that you are most excited about palbo potentially succeeding in down the line. Thank you.

Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

Sure, I will start and this is with regard to the FDA. As I mentioned, we do have really productive interactions with them. They've been highly collaborative. We have got meetings scheduled into the future, but AACR fell ahead of the meetings where we are going to make some discussions or decisions about how to proceed.

We won't get into the details about what we are showing to the FDA and when we are showing it because it's still very interactive and we are making really good progress. So until we get to the point where it is apparent based on their point of view what they are going to need for filing, we will not make a decision and, therefore, don't have anything to talk about today.

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

To take on the second part, your question about what other tumors we are looking at beyond ER-positive breast cancer, the two that we have already initiated efforts in evaluating because we feel that they show significant promise is melanoma. We have a collaboration with the French National Cancer Institute to evaluate in patients with BRAF mutant melanoma in combination with vemurafenib. And also in a previously announced collaboration with Glaxo Smith Kline, we are evaluating this in NRAS mutant melanoma patients with their MEK inhibitor, trametinib.

The second area is non-small cell lung cancer. We have a collaboration ongoing with Dana-Farber Cancer Institute looking at it in KRAS mutant non-small cell lung cancer and squamous cell lung cancers, and an agreement with the Friends of the NIH and Friends of Cancer Research and SWOG to evaluate palbociclib in patients with certain genotypes with squamous cell lung carcinoma. So those are the two areas that we have had our most activity in.



Operator

Mark Schoenebaum, ISI Group.

Mark Schoenebaum - *ISI Group - Analyst*

Thanks a lot for taking the question and getting away from Wall Street. Congratulations on the data.

I was wondering -- some of this has been touched on, but number one, can you give us any color whatsoever about when you might be able to update the Street with a proposed filing timeline in the US? Maybe this is a question for Chuck. Would this be something we should be expecting the first half of the year or midyear, the back half?

Number two you mentioned that PFS has been an endpoint used to support regulatory approval. Is there a drug or drugs that you would point the investment community to that we could go study as precedent? For example, a drug that you think is particularly important as a precedent?

Then the final question is can you talk about if there are interim analyses baked into the Phase 3 program, particularly Paloma-2, the study that is attempting to reproduce the data in today's Phase 2 study? And when those interim looks may occur. Thank you.

Garry Nicholson - *Pfizer Inc. - President, Pfizer Oncology*

I can start. Maybe Chuck can add something to the first point, Mark. Thanks for your recognition of this result. We are really pleased about it.

As we have said a couple times, we do envision a path to filing with this data as a real possibility but we are just not far enough along with the FDA yet. There are so many different parts to a submission, as you know well, and it's in the process of being assembled, reviewed, and discussed. They have been very open with meetings with us and making themselves available, so we are just moving ahead on track, on plan.

What we said before is that when we have a clear understanding about what the requirements are and what we have in our hands, we will make that known. We will communicate that. Chuck, do you want to add to that?

Chuck Triano - *Pfizer Inc. - SVP, IR*

I think that's right, Mark. Once Pfizer Oncology has made a decision one way or another that would be communicated, but we don't want to right now get into a specific timeframe. To Garry's point, we just don't have enough information, but I would reiterate we are moving along. Progress is being made and you will hear from us one way or another once we have made a determination here what the next step is.

Mace Rothenberg - *Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology*

Let's turn to your second and third questions. In ER-positive breast cancer, because of the relatively long survival and also because of the potential benefit of delaying progression, progression-free survival has been the approval endpoint for all the aromatase inhibitors. So this is really the standard for ER-positive breast cancer.

When you look across all cancers, PFS has been the regulatory standard for the vast majority of those. In terms of interim analysis, every one of our Phase 3 trials has interim analyses built in and these are done in conjunction with Independent Data Monitoring Committee, non-Pfizer experts in the field who have access to the data at key points in time to be able to view the safety, efficacy, and potential futility of the study. We do have that in place for PALOMA-2 and PALOMA-3.

Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

And, Mark, just to add a comment or two about the primary endpoint of progression-free survival, as Mace mentioned, all of the drugs approved for metastatic ER-positive HER2-negative breast cancer have been approved on the basis of PFS as a primary endpoint. And that includes Afinitor, the Novartis product.

What the FDA and EMA and others will do, they will take a look at PFS and obviously it needs to be positive, and they will look at the totality of all the other efficacy endpoints. Of course, the benefit risk and take that into account. And they will look at overall survival, as they always do.

Generally speaking, what they are looking for is no bad news about a surprise when the treatment arm might be worse than the control arm in terms of overall survival. But they realize that we are dealing with a patient population here, as Mace mentioned, where typically the survival is measured in three-plus years. And PFS in and of itself, the definition of PFS being the time from randomization until a patient progresses or dies is an adequate clinical endpoint that regulatory agencies have said, in addition to being perhaps a surrogate, in and of itself it is valid for approval.

So we are very confident as we have interacted with the Agency, they have not -- have completely agreed with us that PFS is and should be the reason why the drug gets approved. And then look at the rest of the evidence along with that. Mace, do you want to add anything?

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

No, (inaudible) excellent. Thanks for the context and color there.

Operator

Seamus Fernandez, Leerink.

Seamus Fernandez - Leerink Partners - Analyst

Thanks very much, thanks for the question. Just wondering if you could give us a little bit of color on the differential that we saw between the second interim analysis and then sort of subsequently to the final analysis. If we actually look at the differential of about 7.5 months to I think it was around 26 months, to then the subsequent final analysis showing 10 months and 20 months, it would seem like those incremental events that occur and had a significant narrowing in the effect size.

Again, we've seen this in other studies, so I'm just wondering if there is a material difference in the patient population or the baseline characteristics as you continue to evaluate those patients as you move forward, whether it be from PFS events in part one or in part two. Then my second question is really as we think about pricing and the ability to kind of price a product that could be dosed as long as this product, how important is demonstrating an overall survival benefit in the context of the long-term benefits of this product? Thanks a lot.

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

Thanks, Seamus. I will take the first and give Garry the second. So in terms of the differential, again this virtual doubling in progression-free survival is remarkable. This is the longest progression-free survival that has been attained in this setting so I take this as very positive news, very impressive news.

The other point that I think gives us comfort is the fact that the control arm of letrozole did as it has done in the literature in terms of its performance of 10 months. That is very consistent. So I think that as we saw the data mature there were changes, but those changes give us even more confidence in the quality of the data. Garry?



Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

Just one quick point on that before moving to the pricing question. Dr. Baselga, the discussant, used the word striking to describe the difference between PFS in the treatment arm and the control arm. We have heard that from other people as well. It is a -- a 10-month improvement is impressive. A 20-month overall value is impressive and then the hazard ratio in terms of the reduction and the risk of progression is very impressive. So that's the basis for why we are delighted about that.

You raise a very important point about the pricing environment. It's difficult to look ahead. We don't do any discussions about our pricing analyses and certainly that would be premature given the stage we are at right now. But without question there are a couple of agencies -- for example, IQWiG in Germany, NICE in the UK, ANVISA in Brazil -- that have talked about seeing overall survival routinely as at the point in time when they assess whether they make the drug available -- access or not, or when there's a decision about pricing.

I would want to separate that distinctly from our work with EMA to get the drug approved in Europe, which is based on a primary endpoint of progression-free survival. And as we demonstrated with Xalkori, we had a positive PFS and no overall survival difference because we allowed crossover. And the drug was approved, of course. Then we worked through the situation with Germany and then later the Cancer Drugs Fund in the UK.

Fortunately, there's access to patients across Europe and so each one is a distinct and individual project. Without doubt, the overall survival discussion comes up on the reimbursement side and the way we handle that is back to the totality of the evidence and talking about patient selection and the benefit. And of course, we will be looking ahead to an environment in healthcare where we have to be very much on top of all the different factors involved in the cost of taking care of women with ER-positive breast cancer. And we will take that into account when we make those decisions.

Operator

Jami Rubin, Goldman Sachs.

Jami Rubin - Goldman Sachs - Analyst

Just a follow-up again on the regulatory pathway. I guess my take away is that what I'm hearing you say is that you think the data -- I heard you say that you envision a path forward with this specific study, Phase 2, and we are not waiting for the completion of the overall survival data because that's too far out. And it really just boils down to the FDA's comfort level with the Phase 2 study versus the Phase 3.

Is that the correct way to think about it? And would there be an interim analysis from PALOMA-2 or PALOMA-3 reporting out in the near term, say this summer that would still allow you -- you could collect that data and allow you to file on this Phase 2 study? So that's the first question, if you could clarify that.

Then, secondly, just a question that we get from investors is the precedent set by the PARP inhibitors. As you know, we've had a PARP inhibitor show very good Phase 2 in breast cancer but failed in Phase 3. Why is this different?

Then just lastly, if you could comment on the competitive landscape. Novartis is already in Phase 3 in breast cancer. Lilly will be moving into Phase 3. How do you, so far -- based on what little data we've seen from the other agents, how do you assess the differences and where do you think palbo will stand out? Thanks.



Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

I will begin. Mace can maybe move to the PARP question and then we can come back and perhaps both talk about the competition. So with the FDA what we are trying to communicate, Jami, is that the PALOMA-1 study is a reasonable place to have a discussion relative to an approval and we can envision that being a possibility. But we want to be very clear that we're just not far enough along that yet to know whether it is or not.

We are moving as rapidly as we can and we are making good progress, but it's a reasonable discussion to make and we want to provide them with all the different parts of information that they need to see. Then we will together -- they will see what they need to have and they will communicate that to us and we will make a decision at that point about whether we are able to move ahead or not. Chuck, you want to add anything to that?

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

Actually if I could add something, you know, we are characterizing this as a Phase 2 study. Let's really break that down because I think the more you understand the design of the study, the more you can appreciate the potential power of the results.

This is a randomized study and not all Phase 2 studies are. It had two parts, part one and part two, so we actually have one result confirming the other result, each one showing significant improvement in progression-free survival.

And in terms of the size of the study, when you have this size of difference between the two arms, you don't have to do 1,000-patient study. And in fact in the era of personalized and precision medicine, this is actually what we are all working towards. So I think that the trial is actually a strong one by all those characteristics.

To get to the PARP comparison, I'm glad you raised that because that has come up in some discussions and I really want to put that to rest because, as Dr. Baselga mentioned, this is the elephant in the room. Well, let me try and get out my elephant gun and put that to rest.

This was -- again comparing this to the iniparib experience. Our trial had two parts, one confirming the other. Iniparib did not. We understand the target, the drug, and the mechanism of action in ways that the PARP inhibitors did not.

We are in breast cancer but a different breast cancer entirely, ER-positive breast cancer. They are in triple-negative breast cancer. We built our therapy on the standard of care aromatase inhibitors. They built theirs on chemotherapy. So I think that these are very significant differences between the experience and, therefore, to say that one could inform the other I think is just wrong.

Then lastly, with regard to competitors, I mentioned earlier something about some of the differences in side effects. They are different molecules.

We know what we have with palbociclib. We know its effects, both good and bad. We think the overall benefit-to-risk relationship looks very favorable for a drug that has this level of impact with metastatic breast cancer, so we feel very confident about this regardless of where the competition is.

Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

We feel the randomized evidence that was presented today in combination with letrozole is the basis for our optimism. We see the other drugs out there. I'm sure they will be developed as rapidly as they can.

The program that we presented or Mace talked about with multiple Phase 3s and moving it to early disease is a demonstration of our commitment to the full development of palbociclib on the fastest possible time frame. I do want to come back to your point about interim analyses, though, because I think we skipped that earlier.



All of the Phase 3s will build endpoints for an interim analysis; however, they are designed, those Phase 3 programs, to finish. It's possible that a trial could be stopped for one of three reasons and one of those reasons could be for superior efficacy beyond expectation. Then that obviously would lead to the un-blinding of the study. It would be made available to regulatory authorities as part of a submission.

But we designed the trial to go all the way to completion because it gives us the most information about patients and we think that will be beneficial over the years. So while the interim analyses will occur, and it's hard to tell when because it's based on when the PFS events occur, we don't necessarily expect, unless the trial is stopped for efficacy reasons, that that will become part of our regulatory strategy. Mace, is that a fair way to put it?

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

Yes.

Operator

Steve Scala, Cowen.

Steve Scala - Cowen and Company - Analyst

Couple questions. The cut off for the hundred PFS events was November of 2013, but I thought the final data capture was February 15, 2014. If I am correct, then why didn't we see data today until February 15, 2014?

Secondly, you mentioned the Lilly CDK from a safety standpoint but Dr. Baselga did say today that he thought the responses showed striking -- they were strikingly impressive or their responses were profound or something. I assume you disagree with his take on the Lilly data. Can you tell us why?

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

Thanks. Well, let me start with the second question. I don't disagree with Dr. Baselga about too many things because he is really an acknowledged expert here. What he was pointing out was that there was clear evidence of antitumor activity in the patient scan he demonstrated and I think no one would disagree with that.

We are not saying anything about the lack of efficacy of the Lilly compound because it clearly does have efficacy. What we do know is where we stand with regard to the development in ER-positive breast cancer for Phase 3 trials that are initiated -- scheduled to enroll more than 2,000 patients.

So we feel that we understand the drug very well. We understand the way to give it in ER-positive breast cancer is with an aromatase inhibitor. The experience that Dr. Baselga referred to was with single-agent Lilly compound, so we are at very different points in time from Lilly and other competitors.

With regard to the progression-free events and when they occurred, you are correct that this snapshot was taken as final analysis. The primary completion data, as it's called, was late November of 2013. All the events, the progression events and the response events were as of the database that was snapped at that time. There has been further follow-up but that has not been incorporated into any additional analyses, so everything you saw today was based on the November 13 data.



Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

What we do see -- when we do that kind of snapshot, we go in and we do the quality control on the database. We get back in touch with investigators. We do all the necessary work to get to a top-line report and that takes some weeks to get there. Then, as we always do, once we have a top-line report and we have had a chance to understand it and communicate it with investigators, we go public with it in a timely manner.

Steve Scala - Cowen and Company - Analyst

Can I ask, if you can still hear me, do you have the data as of February 15 and can you tell us whether it's reassuring relative to what you have as of November 13? Or how would you characterize the data as of February 15?

Mace Rothenberg - Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology

There is no additional data that we are aware of that we have subjected to the same kind of analysis that we have for the primary completion day of November, so I'm not exactly sure where you got the February date from.

Operator

Jeff Holford, Jefferies.

Jeff Holford - Jefferies & Company - Analyst

Thanks for taking my questions. Could you perhaps help us on what you think the timeline will be to getting mature overall survival data for PALOMA-1? Then second, you mentioned you didn't get your next FDA meeting in before AACR. Can you tell us which month maybe you will be meeting with them next?

Then the last point is I noticed that you do keep mentioning the magnitude of PFS effect and I do remember the time when the Avastin label in breast cancer was reviewed some of the panelists and FDA members talked about a kind of four- to six-month PFS as being clinically meaningful and above that would still support accelerated approval. Would that be at all consistent with the sort of discussions you have been having with them up to this point? Thank you.

Garry Nicholson - Pfizer Inc. - President, Pfizer Oncology

In terms of the overall survival analysis, we continue to follow overall survival and there will be further analyses in the future, so that's what we can say from this. Recognizing that the overall survival analysis that was shown today was done at the time of the final analysis for the PFS and there had been 37% of patients on the study who had passed away.

We have an active and ongoing engagement with the FDA and so we are in near-constant communication with them to make sure they know what we are thinking, we know what they are thinking. And that will continue.

Then in terms of the magnitude of PFS effect, again reminding you that not all breast cancer is the same and, while it's encouraging what you said about citing the FDA's guidance here, we consider every situation to be unique based on the characteristics of the patients, the drug, and the available therapies. Again that is something that we are in discussion with the FDA about, what constitutes a significant benefit in this group of patients in this line of therapy.



Operator

Alex Arfaei, BMO Capital.

Alex Arfaei - *BMO Capital Markets - Analyst*

Just wondering if you noticed any imbalances in post-progression treatment that could have narrowed the survival gap. I appreciate it's early data, but just really curious if you had -- obviously there are a number of different agents that are available in the second-line setting that could have a meaningful impact. I'm just wondering if there were any differences between the two arms, thank you.

Mace Rothenberg - *Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology*

I wish I had information to share with you on that, but I'm afraid we don't, and so really can't address that question.

Garry Nicholson - *Pfizer Inc. - President, Pfizer Oncology*

Normally what happens, with only 37% of the women having progressed, 30 in each arm basically, there's not a lot that you can conclude from overall survival information that is so immature. Particularly when you have some patients that live a long time. We need to get to the point where we have a median.

So we are collecting as much information as we possibly can, but we have not done that kind of analysis at this stage.

Operator

Seamus Fernandez, Leerink.

Seamus Fernandez - *Leerink Partners - Analyst*

Thanks, so I just had a quick follow-up on the part two portion of the study. I just wanted to get a better understanding of -- can you walk us through the mechanism and how we should think about part two?

It just seems that this mechanistically sort of driven patient population with positive RB biomarkers would seem to have at least a similar effect size. And I'm just wondering if there's any view as to why the effect size was so different from the part one portion of the study. If there's any insights into that, that would be really helpful to know.

Mace Rothenberg - *Pfizer Inc. - SVP, Clinical Development and Medical Affairs & Chief Medical Officer, Pfizer Oncology*

Just to give you a sense, the biomarker selection that was used for part two was based on preclinical data that was emerging from the laboratory. That it seemed that, in addition to the ER positive characteristics of the tumor, that those tumors in the laboratory that were most sensitive had cyclin D1 amplification and p16 loss. So, again, trying to always incorporate that kind of latest insight and thinking into our drug development approaches, we then decided to move on and to change and amend the study into a study that accrued only those patients.

While that study was accruing, we were doing the analysis on the patient samples from part one to see in patients whether these characteristics made a difference. And in fact the answer was no; that patients benefited equally whether they had the presence of one or both those biomarkers versus the absence of both of those biomarkers.



So that really pointed out the limits of our knowledge. And it actually pointed to the fact that in this particular disease ER positivity -- and we now know mechanistically why there's such an important relationship between the CDK 4/6 pathway and ER signaling and the idea that we have very high level of activity in women who have ER-positive breast cancer and wild type RB.

It turns out that in ER-positive breast cancer the vast majority also have wild type RB, so that became the biomarker, if you will. So there was really nothing more that we could learn from that part two and so that was stopped when it was.

So that was our thinking and the evolution of part one to part two and that's why we felt comfortable combining the two, because those biomarker selection criteria did not seem to make a difference when we looked at it in part one. In terms of the difference in effect size, it -- I again want to point out that given the statistical significance in both of these, and not only that but the clinical significance of the difference, I don't think that there really is a difference.

Both of these are positive. Both of these show a very robust improvement and benefit from palbociclib and are actually very consistent when you look at the entire trial together of what you might expect from standard letrozole alone in this group of patients and a significant improvement that we see by adding palbociclib to letrozole in this setting.

Chuck Triano - Pfizer Inc. - SVP, IR

Thank you. I would like to thank you, Mace and Garry, for your time this afternoon and for the audience. Thanks for your attention this afternoon.

Operator

This concludes today's conference. You may now disconnect.

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