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PFE - Pfizer Inc Analyst and Investor Call to Review Oncology Business and ASCO Data Presentations

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OVERVIEW:

Co. provided an update on its Oncology business and ASCO data presentations.

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CORPORATE PARTICIPANTS

Chuck Triano *Pfizer Inc - SVP of IR*

Liz Barrett *Pfizer Inc - President & General Manager of Oncology*

Mace Rothenberg *Pfizer Inc - Chief Development Officer of Oncology*

Chris Boshoff *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

Bob Abraham *Pfizer Inc - SVP & Group Head of Oncology R&D*

CONFERENCE CALL PARTICIPANTS

Chris Schott *JPMorgan - Analyst*

Marc Goodman *UBS - Analyst*

Vamil Divan *Credit Suisse - Analyst*

Vlad Nikolenko *Evercore ISI - Analyst*

Gregg Gilbert *Deutsche Bank - Analyst*

Geoff Meacham *Barclays Capital - Analyst*

Steve Scala *Cowen and Company - Analyst*

Damien Conover *Morningstar - Analyst*

PRESENTATION

Operator

Good day, everyone, and welcome to Pfizer's analyst and investor call to review oncology business and ASCO data presentations.

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, sir.

Chuck Triano - *Pfizer Inc - SVP of IR*

Thank you, operator.

Good morning from New York, and thanks for joining us today to review Pfizer's oncology portfolio and clinical trial data that was presented at the ASCO Annual Conference during the past few days. Today we're pleased to have with us Liz Barrett, President and General Manager of Pfizer Oncology; Mace Rothenberg, Chief Development Officer of Pfizer Oncology; Bob Abraham, Senior Vice President and Group Head, Oncology R&D; and Chris Boshoff, Senior Vice President, Immuno-Oncology, Early Development and Translational Oncology. We will have some prepared remarks from Liz and Mace with accompanying slides, and then we will move to a Q&A session with the group.

Of course, our discussions during this conference call will include forward-looking statements about, among other things, our oncology strategy, our in-line products and our oncology pipeline that are subject to substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. The forward-looking statements in this presentation speak only as of the original date of this presentation, and we undertake no obligation to update or revise any of these statements. Additional information regarding these factors can be found in Pfizer's 2015 annual report on Form 10-K and in our subsequent reports on Forms 10-Q and 8-K.

With that, I will turn the call over to Liz Barrett. Liz?

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Good morning, and thank you, Chuck.

Good morning, everyone, and thanks for joining our post-ASCO briefing. We've all just returned from a very busy meeting.

Our vision for Pfizer Oncology is to be a leader in oncology by speeding cures and breakthrough medicines to patients, redefining life with cancer. I am sure you can appreciate we spent quite bit of time wording this to ensure it's a collective vision for our Pfizer Oncology team.

While the cure for cancer continues to elude us, recent advancements are providing hope for more and more patients. And we believe we can partner with the cancer community and support patients to thrive with their diagnosis, therefore redefining life with cancer. We have a strong foundation to build from, having launched four new medicines in the past four years, and celebrating 10 years since Sutent transformed the way renal cell patients are treated.

To achieve this vision, we're focusing on three key areas. The first, establish Ibrance as standard of care in ER-positive HER2 negative breast cancer, with a comprehensive clinical and commercial plan, with no stone unturned. Win in the broader immuno-oncology space, with avelumab as a foundational backbone. Develop rational combinations of immunotherapy that utilize the unique characteristics of each tumor type, to elicit the greatest benefit for patients. And lastly, speed breakthrough medicines to patients by identifying transformational assets at an early sign of efficacy, and streamline development.

Key to successfully executing the strategy will be partnerships and collaborations. Given a significant number of immunotherapy targets and potential combinations, no one company will be able to interrogate all of the possibilities. We have increased our collaborations in the past year, and will continue to focus externally and make this a priority.

Despite the significant progress made with PD-1/PD-L1, the majority of patients will not respond to these as monotherapies. And we need to find more effective ways to utilize a patient's immune system to fight cancer. As you are aware, data from utomilumab, in combination with a checkpoint inhibitor, was presented at ASCO, and the feedback from the presentation and data has been very positive. We expect to have up to 10 immuno-oncology agents in the clinic by the end of the year, uniquely positioning Pfizer to be amongst the leaders in the broader immuno-oncology area.

As I mentioned, ASCO was extremely busy for us, with our biggest showing yet. Pfizer medicines were represented in 50 abstracts across 15 tumor types. Particularly exciting for us was the presentation of PALOMA-2, the Phase 3 study showing significant benefit of Ibrance in combination with letrozole, or just letrozole alone, in metastatic breast cancer. And Mace will talk more about that in a moment.

Other highlights is the Phase 3 study of avelumab in Merkel cell carcinoma, that demonstrated statistically significant benefits for patients who have previously been treated for MCC, Xalkori in patients with cMET Exon 14-altered non-small cell lung cancer, and lorlatinib, our next-generation ALK inhibitor, that was specifically designed to overcome the resistance mechanisms of current ALK inhibitions.

I am now going to turn it over to Mace to walk through some of the specific data we reported at ASCO.

Mace Rothenberg - *Pfizer Inc - Chief Development Officer of Oncology*

Thanks very much, Liz. And really, all the years that Pfizer Oncology has been in existence, which I think is eight, this, by far and away, was our best ASCO in terms of not only the quantity, but the quality of our presentations. And really, I would like to lead off with this, which was one of the most impactful presentations.

This was PALOMA-2, which was a Phase 3 trial of palbociclib plus letrozole versus placebo plus letrozole, as first-line treatment for women with ER-positive HER2-negative advanced breast cancer. What you can see here is the difference in progression free-survival, between those who receive the combination median progression-free survival, is 24.8 months, versus those who receive the placebo plus letrozole, whose median progression-free survival was 14.5 months. Again, a difference of approximately 10 months, which is very similar to the original randomized study with PALOMA-1, in a very similar patient population.

So this trial was designed to be confirmatory to PALOMA-1, and in fact, accomplished that mission. So we were very happy. And in fact, in speaking with a number of oncologists afterwards, who are breast cancer experts, they pointed out that this is the first Phase 3 trial in this setting to exceed a two-year progression-free survival. So, a very significant achievement for this. No other safety signal to observe, and these data will be submitted to FDA and other regulatory agencies to support a filing for palbociclib in this setting.

The next slide is actually the first of two slides of our combination of pembrolizumab, a PD-1 inhibitor, and utomilumab, our 4-1BB inhibitor. I think if there was a theme of immuno-oncology at this year's ASCO, it was of emerging combinations. And I think that this was very gratifying on two levels. The first that you see here, is the impact of this combination on immune subsets that was taken from peripheral circular and key lymphocytes.

As you may know, utomilumab, as a 4-1BB target agent, is designed to really enhance the number and survival of CD8 lymphocytes. And what you see here in these four charts is, in fact, that in patients who had a response or stable disease, compared to the one patient that progressed disease, you actually see that in these data from patients.

So it's actually confirmed pre-clinical hypotheses that if this drug is going to work, it's going to do so by stimulating the lymphocytes. In fact, when you look at total lymphocytes, the CD8 cause of lymphocytes, CPR of 45, memory T cells as well, there is a consistent trend for patients who have had clinical benefit from this combination, have a greater stimulation of their immune system.

This now actually is associated with the data shown here on the waterfall plot, which demonstrates that we had significant activity. We saw six objective responses in the 23 patients who were enrolled. And these included some patients with tumors that we know are sensitive to checkpoint inhibitors, like renal cell, non-small cell lung cancer, and neck cancer. But also some others, including a small-cell lung cancer and in anaplastic thyroid carcinoma patients, who also had a response.

This is really just an initial signal, if you will. None of this is definitive. None of this can prove that the combination is better than single agent. But I think the important element here is that we saw activity, and what is not shown on these slides is the tolerability of this regimen. And that is a concern in many, because you are now combining a checkpoint inhibitor, which are now stimulating the immune system, and there are concerns that you might actually see very significant normal tissue adverse events. In fact, we saw a very low rate of Grade 3 or Grade 4 adverse events in this Phase 1 trial.

Since this trial, we've actually done a similar dose exploration study with avelumab, which is a PD-L1 inhibitor that we are co-developing with Merck KGaA. And we have now moved that into a cohort expansion phase in that trial. Obviously, that's early on; we have no data from that trial to share right now.

Another important presentation view is the first presentation to pull a data set of 65 patients who had previously treated Merkel cell carcinoma. Merkel cell, so as you may know, is a very rare skin tumor, even rarer than melanoma. But very aggressive, especially after patients that we see prior chemotherapy, as they have in this trial. Other interventions are widely considered to be ineffective. What we saw here, in contrast, was more than half the patients having some tumor shrinkage. And used with this specific criteria, we had more than a 30% objective response rate with single agent avelumab. And these responses were not only deep, but they were long-lasting.

So we feel very encouraged by this. In fact, this is going to be the basis for our initial filing with Merck KGaA for regulatory approval of avelumab in this disease. So with that, I'd like to turn it back over to Liz for some final comments before we open it to questions and answers.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Thanks, Mace.

This slide highlights some of our pipeline assets with the potential to advance in the short- and mid-term. We will continue to launch Ibrance around the world, with an approval expected in Europe by year-end. With our alliance partner Merck KGaA, we hope to file our first indication for avelumab in a small but high-unmet-need area of Merkel cell carcinoma, as Mace shared with you the data.

Actually, this Sunday we will be presenting data at the European Hematology Association meeting on inotuzumab as a treatment for relapsed ALL patients -- and has previously received a breakthrough designation. We're working with regulatory authorities around the world on a path forward to bring this important advance to patients. We have many other assets we are advancing, including those that were highlighted earlier in the presentation.

So with that, we'll open it up for questions. So, Chuck?

Chuck Triano - *Pfizer Inc - SVP of IR*

Yes. Operator, can you please poll for questions?

QUESTIONS AND ANSWERS

Operator

(Operator Instructions)

Chris Schott, JPMorgan.

Chris Schott - *JPMorgan - Analyst*

Great. Thanks for the questions. I just had two for you, the first one on Ibrance. I would just be interested in your perspective on Lilly's CDK data that we saw at ASCO. It seems like the drug might have a bit more single agent activity relative to Ibrance. And I would just be interested in how you think about that product from a competitive standpoint?

My second question was just to elaborate a little bit more on the 4-1BB asset. I guess my question is, do you believe you are seeing robust efficacy beyond what you would have anticipated from a PD-1 alone? And maybe just elaborate a little bit more on the next steps here in terms of, are there specific tumor types that you will be focusing on going forward, as we think about development? Thanks very much.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Sure. And I guess on the competition, Lilly, we don't like to talk a lot about our competition. I think it's early data, I think, is what I will really say about their CDK. I think we have to wait and see the data. I think we also had treatment in combination in later lines of therapy in some of our trials where we had good responses. We do believe that going forward, though, the standard of care will really be in combination with ER therapy.

So I think for us, with the competition, both Lilly and Novartis, I think it is early, and we just need to wait and see what the data is. I think what I would say is that we feel very confident about Ibrance, about how well it is doing so far, and how we expect it to continue to do now and in the clinical trials that we have upcoming. So with that, I'm going to actually turn it over to Chris Boshoff to talk to you about 4-1BB and where we see 4-1BB -- the data -- so far. And then a highlight of what we see maybe going forward.

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

Thank you, Liz. So firstly, as Mace pointed out, the data with Keytruda were early data. So at this stage, we cannot conclude that is definitely better than Keytruda by itself. Although as Mace, again, pointed out, there was some encouraging signals, including the complete remission of small-cell lung cancer and a deep partial response in anaplastic thyroid cancer. Which perhaps you would not expect with Keytruda by itself.

We just remind you, we presented last year at ASCO 2015, data with 4-1BB with rituximab induction. And it was very encouraging data on non-Hodgkin's lymphoma, particularly in follicular lymphoma. And we are currently accelerating that program, which is a rituximab induction, followed by single agent 4-1BB. We are continuing our program with 4-1BB and our OX40. So that combination is in the clinic now, and we hope to report later this year, early next year, data on that combination.

4-1BB plus avelumab -- we've completed the dose escalation and we started expansion cohorts. We are accelerating that program in a number of tumor types, including a cohort of patients previously treated and that have failed or refract between avelumab and Keytruda. Mace, would you like to add anything to 4-1BB?

Mace Rothenberg - *Pfizer Inc - Chief Development Officer of Oncology*

I think that you said it all, Chris. Thank you.

Chuck Triano - *Pfizer Inc - SVP of IR*

Thanks, Chris. Next question please, operator.

Operator

Marc Goodman, UBS.

Marc Goodman - *UBS - Analyst*

Yes, I was hoping you could talk more about the OX40, and what you learned at ASCO about that product, and how you're thinking about it differently?

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Chris?

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

I will start, and then perhaps hand it over to Bob. So the data that was presented with OX40 was with atezolizumab from Roche. These were early data with various doses used. And I'd point out that most of -- or that many of those patients were previously treated with a checkpoint inhibitor and failed the checkpoint inhibitor. So it's difficult to assess efficacy at this stage, because it's early data.

What was very nice about the data was the encouraging and manageable safety profile, as well as the very nice [fonicurd] and dynamic data they showed, where the biology made sense, and that was very encouraging. And our OX40 program is currently in a number of studies as we're completing the dose escalation. We got early encouraging signals without single-agent OX40. And we started the combination programs, as I pointed out, with our 4-1BB utomilumab, and as well as with avelumab. Bob, would you like to add anything on OX40 as a target?

Bob Abraham - *Pfizer Inc - SVP & Group Head of Oncology R&D*

I think you summarized it very well, Chris. I think the only thing I would add is that we are very much attracted to the biological rationale of strategies that stimulate CDA-positive T cells, perform their killing activity, along with CD4-positive T cells, which is the major target for the OX40 strategy. So biologically, we think this combination is compelling.

Chuck Triano - *Pfizer Inc - SVP of IR*

All right, thanks, Bob. Next question please, operator.

Operator

Vamil Divan, Credit Suisse.

Vamil Divan - *Credit Suisse - Analyst*

Great. Thanks so much for the call and for taking my questions. If I could, on Ibrance, I was just curious if you can give us a little bit of an update there in terms of when we will see data outside of breast cancer? I know you've obviously outlined a very strong breast cancer plan, but just curious outside of that?

And also in terms of thoughts, maybe if you could, in terms of combination approaches there with PD-1/PD-L1? Or with the -- I think PARP is another one of the ones people have been getting excited about. And curious about any thoughts on combining that maybe in the breast cancer side?

And then second one would be just following up on the OX40. I think you guys have talked earlier about triple combinations approach with avelumab, OX40 and the 4-1BB. Maybe you can just update us, if you have any refreshed thoughts coming out of ASCO, and the latest [round] timing for that?

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Great, thanks. Mace, do you want to take the Ibrance? And then maybe Chris can take the OX40 and 4-1BB.

Mace Rothenberg - *Pfizer Inc - Chief Development Officer of Oncology*

We believe that Ibrance is one drug that actually has certain characteristics of being two drugs. And what I mean by that is, that it is very far-advanced and, in fact, now approved, with three randomized trials in ER-positive breast cancer. We have a very large clinical program looking at this in earlier stages, in later stages, in combinations with various other agents. So it is well-established in breast cancer.

In contrast, we know relatively little about the clinical activity of CDK4/6 inhibitors outside of that. And it seems a bit curious, because here is a process that should be common to all cancers. But yet, we think that it really requires, for optimal activity, a combination just like we've seen in breast cancer. So rather than just leap into a lot of single-agent signal-finding studies, we are working closely with Bob Abraham and his group, as well as a number of external experts. We've really explored this in pre-clinical models to try and understand what the best partner is for Ibrance in other tumors.

And so actually, that has revealed some things that we didn't expect initially. So for instance, we have identified that cetuximab is a good partner for palbociclib. And now have clinical data from investigator-initiated trials in Washington University in St. Louis, advanced activity in squamous cell carcinoma of the head and neck. In fact, we're following that up with a multi-center trial of that combination in those patients.

Similarly, in pancreatic cancer, we saw activity in combination, and the partner drug was Abraxane. And interestingly, in these pre-clinical models, there was no further improvement with the addition of gemcitabine, which has been a cornerstone of treatment for pancreatic cancer for 20 years, to that doublet. So we're actually now evaluating the doublet of Abraxane plus palbociclib in pancreatic cancer. It is still into its escalation, but focused on pancreatic cancer, and we're watching those results very carefully.

We've seen some very promising activity in mantle cell lymphoma in combination with ibrutinib, that we are encouraged by. We also have ongoing trials in a variety of other tumors, including non-small cell lung cancer and melanoma. So we think that we're going about this in a fairly careful way. We have some single-agent trials that are underway. For instance, in lung cancer, we are anticipating in the NCI Southwest Oncology Group's lung map study, looking at palbociclib in single-agent and squamous cell lung cancer. And also with the CRUK's lung matrix study -- just to be able to understand it more in that disease. So I think that we are evaluating this drug thoroughly, thoughtfully, and waiting to see if we can find a strong signal like we've seen in ER-positive breast cancer.

So now, the next question was on combination with PD-1/PD-L1 or other agents. Chris or Bob, do you want to take the combination checkpoint (multiple speakers)?

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

Yes, I'll just talk to that, because we often ask that question, to combine avelumab with palbociclib. So really, we want to focus on combinations that make biological sense, that are rational. We know that palbociclib does block T cell proliferation. And of course, all checkpoint inhibitors need T cells to be active and functional. So we have been exploring pre-clinically, in Bob's group, ways to perhaps sequence in certain tumor types -- palbociclib plus avelumab -- rather than simply combining them. Bob, would you like to comment anything else on that specific combination?

Bob Abraham - *Pfizer Inc - SVP & Group Head of Oncology R&D*

No, Chris, I think you covered it pretty well, thanks.

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

The next question was regarding the combinations of avelumab with OX40 and 4-1BB. And as we've pointed out, we've generated in-house, in Bob's group, pre-clinical data, as well as with our collaborators at MD Anderson, to really show that these combinations of avelumab plus OX40/avelumab plus 4-1BB, are synergistic or additive in a number of different pre-clinical tumor models. And in fact, the triplet of OX40 and 4-1BB plus avelumab also appears to be synergistic in certain tumor models.

So we're currently doing the various combinations in the clinic. And we hope to potentially start early next year the triplet of avelumab and OX40 plus 4-1BB. 4-1BB mainly targeting CD8-positive T lymphocytes, and OX40, CD4-positive T lymphocytes -- that there is a biological rationale to combine those three molecules.

Chuck Triano - *Pfizer Inc - SVP of IR*

Great, thank you. Next question please, operator.

Operator

Mark Schoenebaum, Evercore ISI.

Vlad Nikolenko - *Evercore ISI - Analyst*

Hi, guys, thank you. It's Vlad Nikolenko on behalf of Mark Schoenebaum. I have two questions, if I may, one of them about 4-1BB. So based on the presentation, it looks like the drug looks very safe, and you haven't reached those limited toxicities. So do you think that you maybe under-dosed 4-1BB in combo with Keytruda? And do you plan to take now 4-1BB dose higher in future trials?

And the second question is about palbo. So Ibrance has been on the market almost a year and a half, so what do you see currently, in real-life settings -- in terms of actual duration therapy, is it consistent with what has been observed in clinical trials? And whether it will be potentially as long as what we've seen in PALOMA-2 -- 25 months in [ITT] population? Or like more than 30 months in a centrally reviewed data set for PALOMA-2? Thank you.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Chris, do you want to answer the 4-1BB? And then I will take the Ibrance.

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

Okay, so I'll start with the 4-1BB dosage. In the single-arm study, the Phase 1, we actually dosed from [north-by-north] 6 mgs per kilogram up to 10 mgs per kilogram. And in a combination with Keytruda, up to 5 mgs per kilogram. In a decision for the recommended Phase 2 data, we decided that on the totality of the data -- both the biological data, because we did read biopsies to actually see where they hit the target.

As well as Mace pointed out, the peripheral blood signals where we see that there's activation of certain substrates of T lymphocytes. As well as the doses where we actually saw with the single-agent efficacy data, as well as what we saw efficacy data with the combination with rituximab. And on that basis, we made a decision on the recommended Phase 2 dose -- which is in fact, much lower than the 5 mgs per kilogram that we went up to in the Keytruda. And we do not believe we are under-dosing 4-1BB.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Thanks, Chris. On the duration of therapy on Ibrance, I mean, it's still early, actually, to tell you, even though we launched -- it was a year ago February. If you think about the patients -- which typically happens in oncology, right? Regardless of the fact that the initial indication was first-line, a lot of our initial use was in the later lines of therapy. And therefore, you would expect a shorter duration of therapy.

We are seeing about what we expected in those lines of therapy, and it is still too early to tell on our first line -- the first-line patients. Our expectation so far, is that we will see physicians treat to progression, and so I think obviously you have to take into consideration the compliance factor that goes along with that. But we would expect the progression-free survival, less some portion of compliance and dose reduction, to occur for a duration of therapy. So it's still, again, too early for us to tell you exactly what we are seeing in real-world data. But we do have plans in place to understand that better as patients start to come off of therapy.

Chuck Triano - *Pfizer Inc - SVP of IR*

Thanks, guys. Next question, please.

Operator

Gregg Gilbert, Deutsche Bank.

Gregg Gilbert - *Deutsche Bank - Analyst*

Thank you, I have a few. It seems that the companies that have a PD-1 or PD-L1 inhibitor are in general agreement that there is little differentiation between the agents in a monotherapy sense. I'm not sure I've seen this before in any therapeutic category. But is that how you see it as well?

And secondly, I am sorry if I missed this -- what determines when you use avelumab with 4-1BB, versus pembro with 4-1BB? Is that just a legacy issue, or is there something more to what goes into that choice?

And then lastly, perhaps a bit premature and more about the strategy and development and near-term thing. But are you considering combination studies with agents that you or your partners own, along with bio-similars that you are developing in-house? Thanks.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

So Chris, do you want to take the question around the PD-1, PD L1 alike?

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

Yes. Currently the data we have seen with the various anti-PD-1s and anti-PD-L1s are, as you correctly point out, they are very similar or comparable in terms of efficacy and safety signals. So how we believe we will differentiate is the combination strategies we will use.

Mace Rothenberg - *Pfizer Inc - Chief Development Officer of Oncology*

And the other element to keep in mind is that avelumab is the only checkpoint inhibitor that induces antibody-dependent cellular cytotoxicity. Initially, it wasn't sure whether this was going to be a benefit or a liability, because some felt that this activity could actually lead to lysis of the infiltrating T lymphocytes. Pre-clinically, that was not the case, and it looks like there's clinical data to support that as well.

It's very difficult to determine what element of ADCC may be in play clinically, but that's something that we are looking at as well, both as a single agent, as well as in combinations. And it may be more relevant in certain tumors than others. So I think we should also keep in mind that it distinguishes itself in that way.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

So I think to answer the question on the Keytruda question, yes, that was a legacy that was in place before we had our partnership with Merck KGaA. So going forward, all of our combinations that we will be doing will be in combination with avelumab. So that sort of answers that question.

And then lastly, on the combination with biosimilars, we are looking and talking to our partners and our established products unit about how we might -- if there is an opportunity for us to go forward and do clinical development. Together, we would want to take advantage of that.

Chuck Triano - *Pfizer Inc - SVP of IR*

Great, thanks, folks. Next question, please.

Operator

Geoff Meacham, Barclays.

Geoff Meacham - *Barclays Capital - Analyst*

Good morning, guys, and thanks for taking the question. Got a few on Ibrance. So from looking at the PALOMA-2 deck, the Grades 3/4 neutropenia leukopenia look like an outlier. So my question is, how do you think that will play out outside the clinical trial setting, and then looking to the adjuvant breast opportunity for Ibrance?

And then as a follow up, from your experience so far with Ibrance, and I guess when you look at the mechanism, is there any common theme of patients that do relapse, that -- just curious here what the CDK4/6, what the compensatory mechanisms could be for disease progression of people that were sustainably suppressed on Ibrance?

Mace Rothenberg - *Pfizer Inc - Chief Development Officer of Oncology*

Okay, I will take that. The incidence of Grade 3/4 neutropenia was pretty consistent in this trial, as it had been before. We do see a majority of patients who have significant neutropenia. But keep in mind that it is a different mechanism of neutropenia than the mechanism that oncologists are typically familiar with, and that is with cytotoxic chemotherapy. And as a result, we see a much lower rate of febrile neutropenia than would have been expected. In fact, I think in PALOMA-2, it's an incidence of about 2.5%.

Again, how this might impact in the real world, what we've seen is that this does not appear to be an impediment, that the uptake of Ibrance in the marketplace has been very good as we've seen over the past year. And in terms of the adjuvant setting, we're doing two large adjuvant studies, PENELOPE-B as well as PALLAS studies. And those are both studies that we've designed in collaboration with some of the leading breast cancer experts, clinical researchers in the world. And this was something that they couldn't wait to get their hands on. Accrual to those studies is ramping up and very robust. We met with them while we were in Chicago. There's a great deal of excitement, because they feel that this has a tolerability profile that is very well-suited for women with early-stage breast cancer. So we really haven't seen that side-effect get in the way with our expansion of evaluation of Ibrance into early-stage breast cancer.

In terms of the mechanism of reaction -- of resistance rather -- I will start, and then turn it over to Bob Abraham. This is something that we are very interested in. When patients progress, are they progressing due to resistance of the anti-hormonal agent, or resistance to the CDK4/6 agent? Frankly, that's something that we need to know. And there are two ways of approaching this. One is to empirically just change the aromatase inhibitor and see what the response rate is. And the other is to actually biopsy these patients and see what the mechanism is, and to see if that can inform our subsequent treatment decisions.

In fact, we're supporting investigator-initiator research on both fronts, because we think this is very important. We certainly don't want to deny patients who may benefit from the continuation of the CDK4/6 inhibitor, that benefit, just because they progressed due to resistance to the anti-hormonal therapy. But we really have to learn more. And working with researchers from around the world, we are really working hand-in-hand to find that out.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

I think the other thing, before you turn it over to Bob, is around the data in mutation that we presented at ASCO as well, that shows that regardless of the status of mutation, that the benefit was still significant with Ibrance. So, Bob?

Bob Abraham - *Pfizer Inc - SVP & Group Head of Oncology R&D*

Yes, thanks, Mace. You summarized really well. I think the pre-clinical data -- and we're really intensively exploring mechanisms of resistance to CDK4/6 inhibitors, one mechanism that isn't entirely anticipated by the biology is loss of [retinal glysoma coti], that will definitively cause resistance to CDK4/6 inhibitors. Fortunately, our experience to date, both pre-clinically and clinically, is that doesn't appear to be a frequent event, but we will see how the clinical data unfolds as it matures.

We are exploring other, and have uncovered other, mechanisms that I can't go into in detail, but alternative mechanisms to mediate the phosphorylation and the inactivation of RB, alternative kinases that play a role in this process. And also some very interesting epigenetic alterations that can also lead to resistance. And we're following these up intensively.

Chuck Triano - *Pfizer Inc - SVP of IR*

Great, thanks, Bob. Next question, operator.

Operator

Steve Scala, Cowen and Company.

Steve Scala - *Cowen and Company - Analyst*

Thank you. I have a couple questions. What is the outlook for crizotinib, given the data from Roche's alectinib? Do still see growth in the molecule, or should we anticipate a decline over time? And how does the Pfizer follow-on ALK inhibitor compare to alectinib on extent of blood brain barrier penetrability? And any other metric you wish to cite?

And then the second question is, a meta-analysis at ASCO of lung cancer study suggests PD-1 may be safer than PD-L1. I'm just wondering what your take on this meta-analysis is? Thank you.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Okay, so I will just take the first question on the crizotinib. I think for Xalkori, around the world, when you look at it from a global perspective, we still see it to be a very important asset for lung cancer patients. I think a couple of important points on Xalkori is, one, as you know, we just got approval for ROS1 in the US.

We also just received approval a few months ago in Europe for first-line patients. And so I think when you think about Xalkori in the future, Xalkori around the world, we still believe that there will continue to be utility in many markets. And in some markets, even last year, receiving approval for the first time ever in Xalkori, in markets like Brazil -- in large markets like Brazil. So I think -- and we also are talking about the cMET, which was also presented at ASCO.

And so I think that there will be a role for Xalkori going forward in non-small cell lung cancer. Obviously, we have to wait to see the data of the broader ALEC study outside of Japan for alectinib before we could comment on what we expect from a long-term perspective. But we also -- there was some data at ASCO around retreating with crizotinib -- after having failed on other ALK inhibitors, coming back to crizotinib, depending on the mutations.

So I think that there a lot of things that we still have to explore. But we feel like there is still an important role for Xalkori around the world in the treatment of ALK inhibitors, as well as ROS, and potentially seeing that in the future. So with that, I will turn it over to Chris to answer your second question.

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

Thank you. I think without the head-to-head study to compare PD-L1 with PD-1, it will be very difficult to conclude that one class is safer than the other. To perhaps point out that the majority of the data currently that's in the public domain for PD-L1 will be with [inaudible] avelumab, or with from atezolizumab from Roche. We presented separately -- we had a separate presentation at ASCO on 1,300 patients, on the safety profile of the

first 1,300 patients treated with avelumab. We've now actually in fact treated over 2,200 patients. And our safety profile, again, is very comparable to what's in the literature for nivolumab or for Keytruda.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

And then the question on lorlatinib in blood brain barrier?

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

So Bob can expand on that, but lorlatinib certainly crosses the blood brain barrier. In fact, it was designed to cross the blood brain barrier. We got very nice signals in patients with brain metastases, and lorlatinib also overcomes an 1202R, one of the most difficult resistant mutations that develop on alectinib. So we have a number of patients now with brain metastases who have progressed on alectinib at a rate skewed, or continue to respond to lorlatinib. And Bob, what you like to add (multiple speakers)?

Bob Abraham - *Pfizer Inc - SVP & Group Head of Oncology R&D*

I can do nothing but confirm what you've just said, Chris. It does appear that alectinib crosses the blood brain barrier. And so lorlatinib was certainly designed with the intent of being penetrant through the blood brain barrier, unlike Xalkori.

Chuck Triano - *Pfizer Inc - SVP of IR*

Terrific. And operator, if we can take our last question, please.

Operator

Damien Conover, Morningstar.

Damien Conover - *Morningstar - Analyst*

Great, thanks. Good morning, everyone. Just one question left. I just wanted to ask a question about the potential rights left to the CTLA for tremelimumab that you partnered -- or that you largely gave to AstraZeneca. But I believe you still have rights in vaccine development with the drug. Can you talk about -- if that is true, can you talk through any sort of strategy that you might be able to lean into, seeing all the very strong data we have seen with CTLA-4 over the past weekend? Thank you.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Chris?

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

So I will just start by saying that is correct. So we obtained the rights to use tremelimumab in the context of a vaccine. And I would like to pass this to Bob to expand on some of the recent business opportunities we have done to look at pre-clinical CTLA-4s. Bob?

Bob Abraham - *Pfizer Inc - SVP & Group Head of Oncology R&D*

Yes, Chris, thanks. What we've talked about to this point to in the discussion has been agents that are capable of reactivating an immune response in what we call an inflamed tumor -- a tumor that's got a T cell infiltrate. The T cells are there, but they are rendered non-responsive by various mechanisms associated with a tumor micro-environment, including of course, the expression of PD-L1, PD-1. But other mechanisms are involved as well.

We think it's very important, and a very complementary part of our strategy to address so-called cold tumors, tumors that are incapable of being recognized by the immune system because they have not -- they are not immunogenic enough to generate any sort of immune response. And are characterized by the complete absence of effector T cells in the tumor. This situation strategy such as vaccines or oncolytic viruses potentially are capable of stimulating T cells to recognize tumor-associated antigens.

In that context, it's clear now that -- and perhaps obvious from past history with regard to vaccines -- that once T cells are stimulated to recognize tumor-associated antigens, they enter this tumor-associated micro-environment, they themselves become exhausted. So it's become clear that to initiate an immune response, even in the presence of vaccines, is likely going to require a co-administered immuno-stimulatory -- either a checkpoint inhibitor or some other mechanism -- to stimulate the T cells and overcome this exhaustion phenotype.

One of those mechanisms is CTLA-4. And I think the strategy that Pfizer is pursuing now is more in local administration, rather than systemic administration, or CTLA-4. This will provide the stimulatory effect of the molecule without, hopefully, the systemic side-effects of CTLA-4 administration, in the context of a vaccine only.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Thanks. And anything else with it?

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

We can just perhaps ask Bob regarding BioAtla and the exclusivity to develop their CTLA-4?

Bob Abraham - *Pfizer Inc - SVP & Group Head of Oncology R&D*

So the strategy there -- did you say BioAtla, Chris? I'm sorry I didn't quite hear.

Chris Boshoff - *Pfizer Inc - SVP of Immuno-Oncology, Early Development & Translational Oncology*

Yes. BioAtla, yes.

Bob Abraham - *Pfizer Inc - SVP & Group Head of Oncology R&D*

So BioAtla has got a very interesting approach, basically, we call conditionally activated antibodies, or CABs. And the idea here is that these antibodies are incapable of recognizing antigens until they are placed in a certain type of micro-environment. In this case, an acidic micro-environment that is frequently present in human tumors due to excessive lactate -- glucose lactate secretions. It causes a drop in tumor-associated pH's. As opposed to normal body pH of around 7.4, it could be as low as 6.5.

And these antibodies actually shift their confirmation in a way that causes them to become capable of recognizing, through binding and exerting, affect their function on CTLA-4. And again, the strategy here is that we hopefully will be able to administer a molecule that will induce or activate

T cells in the local micro-environment without the systemic consequences of more global T cell activation obtained with the current generation of anti-CTLA-4 antibodies.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Thanks Bob.

Chuck Triano - *Pfizer Inc - SVP of IR*

Thanks, Bob. And with that, I would like to turn it back to Liz for just a couple of closing remarks.

Liz Barrett - *Pfizer Inc - President & General Manager of Oncology*

Sure. Thanks, Chuck. As we talked about earlier, we had a great ASCO. It was nice to be considered one of the winners of ASCO, when they published their winners and losers of ASCO. And hopefully, we've been able to provide you a nice overview of where we see our vision for Pfizer Oncology in the future. We have a growing business. We have a strong base portfolio. But we also have a nice pipeline, and we have the right organization to investigate that. So we're looking forward to our continued growth, and continuing to help patients, again, redefine life with cancer. So thank you very much.

Chuck Triano - *Pfizer Inc - SVP of IR*

All right. Thanks Liz, and thanks to the Pfizer team, and thanks to all the analysts and investors for joining us today for the call.

Operator

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