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MRK - Merck & Co Inc Conference Call to Discuss ESMO 2016 Highlights

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OVERVIEW:

MRK discussed its oncology strategy and provided key data on KEYNOTE studies.

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PRESENTATION

Operator

Good afternoon. My name is Anthony and I will be your conference operator today. At this time I would like to welcome everyone to the Merck & Co., Inc. ESMO 2016 highlights call.

(Operator Instructions)

I would now like to turn the call over to Teri Loxam. Please go ahead.

Teri Loxam - *Merck & Co., Inc. - IR*

Thanks, Anthony, and thank you to everyone who is joining us today, especially given there is a lot going on. I'm joined by Dr. Roger Perlmutter, our EVP and head of Merck Research Labs; Adam Schechter, EVP and head of Global Human Health; and Dr. Roy Baynes, SVP and head of Clinical Development and Chief Medical Officer.

Before I turn the call over to Roger I would like to remind you that some of the statements that we make during today's call may be considered forward-looking statements within the meaning of the Safe Harbor provision of the US Private Securities Litigation Reform Act of 1995. Such statements are made based on the current beliefs of Merck's management and are subject to significant risks and uncertainties.

If our underlying assumptions prove inaccurate or uncertainties materialize actual results may differ materially from those set forth in the forward-looking statements. Our SEC filings including item 1A in the 2015 10-K identify certain risk factors and cautionary statements that could cause the Company's actual results to differ materially. Merck undertakes no obligation to publicly update any forward-looking statements and you can see our SEC filings on Merck.com.

With that I'd like to turn the call over to Roger Perlmutter.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

Thanks, Teri, and thank you everyone for joining with us this afternoon. We are here today at the European Society for Medical Oncology meetings in Copenhagen where there's been a lot of interesting data that has been presented.

And what we will do is place these data in context in terms of our overall program in oncology. We will mention the key data that were presented at ESMO. We will talk briefly about the execution and the global launch and then take your questions.

So to understand our overall strategy in oncology, our goal really for the last several years has been to establish Keytruda as a foundational treatment and monotherapy and in combination across multiple tumor types. We believe based on the salient advantages of Keytruda in a variety of different settings that people will begin to think of it first in the treatment of cancer and will add other treatments to Keytruda. And our goal is to make that possible by studying Keytruda in a wide variety of different tumor types.

First as monotherapy and that exploring combinations, and also taking advantage of biomarker strategies to identify patients most likely to benefit from Keytruda treatment. We've made a lot of progress in the last five years since Keytruda entered the clinic. And we've made a lot of progress, in particular, since we gained registration for the first time for Keytruda in September of 2014.

It was at that time the first anti-PD-1 therapy to enter the market in the United States. And since that time we've gained approval in melanoma, in first-line in advanced melanoma, in non-small cell lung cancer and more recently in head and neck cancer. And we've advanced the program in a variety of ways; most importantly, today we've talked about our progress in non-small cell lung cancer but in addition here at the ESMO meeting we have the opportunity to present some data, important data for example in urothelial cancers.

I should point out that we have demonstrated clinical activity for Keytruda in more than 20 different tumor types. We had the opportunity to present quite a lot of that data at ASCO in June of this year. We have more than 30 registration-enabling studies ongoing and we have breakthrough designations from melanoma, second-line non-small cell, in the setting of microsatellite instability and Hodgkin's lymphoma and also in first-line non-small cell lung cancer based on our most recent data.

It is by any measure the broadest program of any checkpoint inhibitor and may be the broadest program ever undertaken for a single agent in oncology. I view Keytruda as the first truly broad-spectrum anti-neoplastic agent that's ever been introduced into clinical practice. If you look at clinicaltrials.gov today, which I did just as I walked into this room, 362 studies currently listed on clinicaltrials.gov and more than 100 combination trials are represented there.

This slide shows you just some of the registration studies that we have ongoing, which span a broad range of different tumor types, tumor types of great importance to human populations around the world. And beyond Keytruda we have a variety of other molecules in development including two different GITR antibodies, a LAG-3 antibody, an IL-10 molecule, CEACAM small molecules directed at CDK and BET-bromodomain inhibitor as well as PI3 kinase delta, plus an awful lot of other programs in the background which we won't speak about today.

But it is a very broad oncology program and getting broader all the time. And it's founded on the platform of using Keytruda as the foundational approach.

Now we had an opportunity during ESMO to present a variety of studies as I mentioned in lung cancer. But today we're going to focus on the data from the Keynote-024 study which compared in first-line non-small cell lung cancer a Keytruda use with standard platinum chemotherapy. And also we'll talk about the Keynote-021 study, the G cohort, a second Phase 2 study that looked at the combination of Keytruda with carboplatin and Pematrexed and gave us some really surprising and, I think, important insights.

We will also have a chance to tell you a little bit about our first-line bladder study that I mentioned earlier, Keynote-052. Those are three important studies but represent just some of the studies that we had the opportunity to discuss here at ESMO including long follow-up from Keynote-010, for example, our second line non-small cell lung cancer study.

So without further ado I will turn the slides over to my colleague Roy Baynes and let them talk about those data. I will just mention to you that we expect over the next 12 months that we will have the opportunity to pursue many new filings.

We expect approvals for non-small cell lung cancer in multiple jurisdictions. And that includes the first-line non-small cell lung cancer data that Roy will mention. They have other novel combination data, and we're moving additional targets into the clinic as I mentioned.

So with that, Roy, tell us about the key data.

Roy Baynes - *Merck & Co., Inc. - SVP, Global Clinical Development & Chief Medical Officer*

Well, thank you very much Roger. I'm going to start off and review Keynote-024.

This was the study where we compared monotherapy with chemotherapy in the front-line treatment of non-small cell lung cancer in patients who expressed more than 50% tumor proportion score positivity for PD-L1. These data were simultaneously published today in The New England Journal along with a very provocative and interesting editorial by Bruce Johnson.

The trial design was fairly straightforward. We basically took patients who were front-line, metastatic non-small cell lung cancer, this was irrespective of histology. We did PD-L1 screening -- sorry, I should just mention we are on slide 12 at the moment for those were following on the slides.

We screened for PD-L1 staining and, in fact, patients had to be more than 50% tumor proportion score positive. We looked for ECOG performance 0 and 1. We excluded activating EGFR mutations at ALK translocations.

We excluded untreated brain metastases and we required that there be no active autoimmune disease requiring systemic corticosteroid therapy. 305 patients were identified. They were randomized 1 to 1 to receive pembrolizumab at a fixed dose of 200 milligrams intravenously every three weeks for up to two years or to receive a platinum doublet chemotherapy for four to six cycles and they were then allowed to go on to maintenance, particularly if they were non-squamous patients.

At progression patients were allowed to cross over on the chemotherapy arm to receive pembrolizumab at the same dose for up to two years. In the intention-to-treat population 50% of patients actually crossed over and if we excluded patients who had ongoing responses or ongoing chemotherapy without progression 54% actually crossed over. The primary endpoint was progression-free survival by RECIST criteria by independent central blinded review.

Secondary endpoints were overall survival, overall response and safety and there was an exploratory analysis of duration of response. The baseline characteristics were well-balanced across this trial. There was a minor imbalance in never smokers and a minor imbalance in brain metastases.

This is the slide showing the progression-free survival data, this is slide number 14. And I think we can see here that we have divergence of the PFS curves that occurs at around about three months and essentially leads to an unambiguously significant hazard ratio of 0.5. That is to say there was a 50% reduction in the risk of disease progression or death.

There are two landmark analyses indicated. At six months the progression-free survival was 62% versus 50% and at 12 months was 49% or 48% versus 15%.

The second half of this graphic shows the forest plot showing the remarkable consistency across the subgroups. And, importantly, I want to point out that in patients that were divided by PD-L1 status into those between 50% and 74% TPS positive and from 75% to 100% positive these were remarkably consistent, so there was no difference in PFS between those two categories. And, again, remarkable consistency of findings with everything essentially on the right side of unity.

Turning now to the overall survival and objective response data, as we look at the overall survival again there was clear divergence of these curves. They diverged early and they proceeded to progressively diverge. The hazard ratio again was an unambiguous 0.6.

This reflects a 40% risk reduction of death. Landmarks at six and 12 months showed OS curves of 80% versus 72% and 70% versus 54% respectively.

When we look at the objective response criteria there was a striking difference in ORR. 45% versus 28%, and I draw your attention to the six patients on monotherapy achieving a complete response. When we look at the patients who indeed did respond the time to achieve this response was broadly similar between monotherapy and chemo.

The duration of response has not been reached for pembrolizumab patients whereas for chemo patients the median was 6.3 months. And, again, to remind you 50% crossed over in the ITT population and 54% had crossed over when we basically look at the patients who had not yet or who had progressed and excluded those who had not yet progressed or were still on chemotherapy without progression.

When we look at the adverse event summary, it's important to note there was a significant difference in the total exposure on the pembrolizumab on versus chemotherapy arm. When we look at treatment-related AEs and particularly grade 3-4 AEs they were significantly less on the pembrolizumab monotherapy arm, 26% versus 51%.

And, importantly, the majority of these did not lead to discontinuation. Discontinuation rates were 7% on the pembrolizumab monotherapy arm and 11% on the chemo arm. And there was a single treatment-related that on the pembrolizumab arm and three deaths on the chemotherapy arm.

Turning now to Keynote-021G, this is the G cohort of Keynote-021 and this was a randomized comparison of carboplatin plus Pematrexed versus the same chemo plus pembrolizumab in frontline. This, too, was published today simultaneously in The Lancet. And as I look now at slide 19 I'm showing you the design of Keynote-021.

Again, key eligibility criteria, these were front-line patients, they were non-squamous patients. So the reason for them being non-squamous was the chemo is specific to the non-squamous population.

Again, we excluded activating EGFR mutations or ALK translocations and patients had to provide a sample for a PD-L1 assessment. Again, ECOG status [that was allowed in] was performance status 0-1 and, again, we excluded untreated brain metastases. Again, we excluded patients who had pneumonitis that was active and requiring systemic steroids.

123 patients were randomized 1 to 1 to receive either pembrolizumab at 200 milligrams Q three-week for two years together with carboplatin to an AUC of 5 mg/ml/min along with Pematrexed at 500 mg/m2. And this was administered three weekly for four cycles, maintenance Pematrexed was permitted.

The other arm received simply the chemotherapy at the same dose and schedule along with Pematrexed maintenance at the physician's choice. Patients were followed until disease progression. At disease progression patients were allowed to cross over to the pembrolizumab arm from the pure chemotherapy arm and there in that crossover they would receive pembrolizumab at 200 mg Q three-week for up to two years along with whatever stage of chemotherapy they were on.

They were 51% crossed over it in the intention-to-treat population and, in fact, 73% crossed over when we exclude patients who were ongoing with response or ongoing with chemotherapy without progression. The primary endpoint of the study was overall response per RECIST, again by blinded independent central review.

Key secondary endpoint was progression-free survival. Other secondary endpoints included overall survival and safety. There was an exploratory relationship analyzed between anti-tumor activity and PD-L1 by tumor proportional score.

On slide 20 we are looking at the patient characteristics in this study. You will see that the population was an older population, median age 63 to 66. One finding in this trial was there was a slight excess of females on this trial that was, again, balanced across the two arms.

Typically this would be 60% males in a front-line lung cancer patient. Here we have roughly 60% females. ECOG performance status 1 was balanced and the histologies were essentially adenocarcinoma.

We had smoking status that was broadly balanced slightly in favor of pembro plus chemo in terms of the never smokers. And brain metastases were slightly imbalanced, again on the pembrolizumab arm. When we look at PD-L1 status by tumor proportion score this was well balanced between arms divided into roughly a third less than 1%, a third between 1% and 49% and about a third greater than 50%.

On slide 21 we have the key primary endpoint or the primary endpoint which is the objective response rate. And this was 55% on the combination arm and 29% on the chemo arm. This was highly significantly different, p-value 0.0016 and this reflects almost a doubling in response rate.

Interestingly the time to response was more rapid in the combo arm. The duration of response has not been reached or the median has not been reached for either arm and an ongoing response is present in 29 patients on the combo arm and 14 on the chemo arm.

When we look at this by subcategories it's important to note that patients who were PD-L1 negative, that is to say less than 1%, or PD-L1 positive, greater than 1%, had virtually the same response rate: 57% and 54%. So there's really no difference in terms of overall response benefit between PD-L1 negative and positive.

And, again, the small numbers in these various subsets when you break it down further, so I'm not going to make too much of it, but clearly there's a fairly substantial response rate in the greater than 50%s. And if we look at the chemotherapy arm, again, broadly similar by categories.

On slide 22 we got to test progression-free survival. This was step-down testing. Once overall response rate was shown to be statistically significant we were able to in a hierarchical fashion test progression-free survival.

And what you see on this progression-free survival curve is that, again, the curves diverge almost immediately and the shape of the curve in the combo arm looks a little different from what we've seen on monotherapy arms. Don't want to make too much of it, but clearly a different pattern with no early death following progression-free survival on the control arm.

Hazard ratio for progression-free survival was robust at 0.53. This represents a 47% reduction in the risk of disease progression or death. And indeed the median progression-free survival on the combo arm was 13 months versus 8.9 months on the chemo arm.

I must point out, however, that as you look across that curve at the 50% mark between six months and 8.9 months, that number is actually 51%. So it came perilously close to reaching the median at, in fact, six months which is what you would expect typically for such chemotherapy.

Again, 51% crossover in the ITT population and 73% crossover when we exclude patients who had an ongoing response. So not surprisingly because of this high rate of crossover we don't see a meaningful difference in the overall survival curves. But the overall survival curves at this early time are actually very, very encouraging.

At six months we've got 92% of both arms alive and at 12 months it is projected that 72% to 75% will be alive directionally favoring the pembrolizumab arm. This is immature and this is going to have to be followed over time and see how it matures.

In terms of the safety data on slide 23, median exposure was, again, significantly longer on the pembro plus chemo arm. So that means the opportunity to develop adverse events was significantly greater because of the longer exposure.

If we look at the grade 3-4 toxicities these were seen in 39% of the combo arm and 26% of the chemo alone arm. But, in fact, they led to discontinuation roughly the same percentage of patients on each arm. In fact, there were few deaths on this arm, one on the combo arm and two on the chemo arm related to treatment.

Moving now to slide 24, I am just going to highlight the presentation on Keynote-052. This is our front-line study in bladder cancer in patients who are, in fact, unable to receive platinum.

So this was a single large study. It actually enrolled 350 patients and as pre-specified this is an analysis on the first 100 patients in this interim.

At this interim we evaluated overall response and we also used this to try and determine the PD-L1 high expression cutpoint for use in the rest of the bladder program. These patients had advanced urothelial malignancies. They had received no prior chemotherapy for metastatic disease and they tended to be poorer performance status patients, and we will explain why in just a moment.

We allowed ECOG performance 2 into this trial. They had to be ineligible for cisplatin based on greater than or equal to one of the following criteria. They either had to have some renal impairment or poor performance status reflected as an ECOG performance status 2 or they could have had grade 2 or greater neuropathy or hearing loss or they could have had cardiovascular impairment.

The secondary endpoint for these studies were, in fact, duration of response, progression-free survival, overall survival and overall response in all patients. We also looked at PD-L1-positive and high expressing patients. We looked at safety, tolerability, and as I said we used this to try to develop an assay cutpoint.

The baseline characteristics of these first 100 patients reflect exactly what we were trying to study. These were older patients; in fact, 34% of these patients were older than 80 years of age.

45% had ECOG performance status 2, 20% of the cancers were in the upper part of the urinary tract, 80% were in the lower part of the urinary tract. And an inordinately high percentage, 87%, had visceral metastases and 27% of those involved the liver.

In terms of prior treatment, patients might have had prior perioperative therapy. They might have had prior BCG therapy and the reasons for their being cisplatin ineligible were 43% were based on performance status, 45% on renal dysfunction, 2% on neuropathy, 10% on hearing loss and 11% a combination of ECOG performance status 2 and renal dysfunction.

When we look at the primary endpoint analysis at this interim on slide 27 we see that the objective response rate was a very respectable 24%. 6% were complete responders, 18% partial responders and 15% had stable disease. 48% had progressive disease as their best overall response.

Here on slide 28 we are looking at the waterfall plot. On this plot anything below the x-axis reflects tumor shrinkage. Anything above the x-axis reflects tumor growth.

This was by central review. And what we can see here is that 52% of patients experience some tumor shrinkage. A rather strikingly impressive waterfall plot.

In terms of adverse events, the drug was very well tolerated. You can see that in terms of grade 3-4 adverse events they were really relatively low rate of these, 4% fatigue and pretty much that was the major one. When we look at immune-mediated events again we see some hypothyroidism, some pneumonitis and some nephritis, but the vast majority of these were, in fact, grade 2 or grade 2 and 3.

There was a low discontinuation rate, only 5% discontinued due to a treatment-related AE and there were no deaths related to treatment-related AEs. So the key takeaways from these keynote studies presented here at ESMO are that Keytruda is the only PD-1 antibody to demonstrate superior efficacy in front-line non-small cell lung cancer treatment in a randomized control clinical trial.

Keytruda should become foundational for treatment or a substantial portion of front-line metastatic non-small cell lung cancer patients either as monotherapy or as combination with chemotherapy. PD-L1 testing will allow for selection of patients for whom monotherapy will be optimal in terms of benefit risk profile. Keytruda also demonstrates very significant anti-tumor activity across multiple tumor types including, as I've just highlighted, in front-line bladder cancer in patients who, in fact, are cisplatin ineligible.

So I thank you for the attention. And I'm now going to pass this on to Adam Schechter to talk about the launch.

Adam Schechter - *Merck & Co., Inc. - EVP & President, Global Human Health*

Thank you, Roy, and good afternoon or good evening, everyone. It's really a pleasure to be here in Copenhagen this evening.

And today really was about the science and it's about the potential benefit for certain cancer patients around the world. I'm very glad to be here with my [emeril] colleagues Roger and Roy who have done an outstanding job in the development program for Keytruda.

What I will do now is provide just a brief commercial update. Obviously, I will also provide additional context at our upcoming quarterly analyst call.

If you look at where we are with the launch we are currently launching Keytruda globally across multiple different tumor types, and there's more to come as Roger and Roy outlined. We are executing on our strategy to become a leader in oncology. We are investing significantly behind launches around the world.

We already have melanoma launched in more than 50 markets and in most of the markets where we have melanoma launched we are the market leader. We are launching second-line lung indications in more than 30 markets around the world including the United States. And in the United States we also are launching the indication for head and neck cancer.

I've talked to you in the past about the importance of discussing the value of biomarkers with payers and clinicians which will help guide them with meaningful clinical decision-making and help to optimize patient treatment. Hopefully with the data that you've seen today presented by Roy you can see that PD-L1 measurement should become much more standard in the future than it has been in the past.

As I've told you before, this has been an obstacle for us in second-line lung therapy. We believe that that obstacle will be significantly reduced as we move forward with the first-line data that was just presented.

Obviously, we continue to prepare for additional launches around the world and including first-line non-small cell lung cancer. And it's important to note that although we don't have the first-line indications at this time we are in physicians' offices, obviously, for second-line where we haven't second-line approved but also with EMEND we are in all markets around the world talking to physicians with lung cancer.

So I look forward to our continued launches. And at this point I will turn it back to Teri.

Teri Loxam - *Merck & Co., Inc. - IR*

Thanks, Adam. And before we get to questions, I should have pointed out at the beginning that the slides are posted on the IR section of the Merck.com website. So you can pull those down at any time.

We're going to move on to the questions, Anthony.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Tim Anderson, Bernstein.

Tim Anderson - *Bernstein - Analyst*

Thank you. A few questions.

The Keynote-021 results, you showed ORRs by PD-L1 expression cohort but what about PFS by that same measurement in terms of different PD-L1 expression cohorts? Commercially with 021 it seems to me that even though this is a midsize Phase 2 trial I'm wondering if it could actually trigger a change in commercial usage of the combo, especially in PD-L1 negative patients where you showed a benefit. I'm guessing you will ask for compendia organizations to consider this data for example.

My second question is I'd love to hear what you think the possibilities are for why in high expressers you guys saw a benefit in 024 in PFS, but for the Bristol data set from 026 there was not even a trend in high expressers? I know you are probably reluctant to talk about competitors, but from a scientific standpoint what are the possible explanations for why that discrepancy would exist? I struggle to find one. Thank you.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

Tim, this is Roger. Let me take the second one first and then I will let Roy talk about the 021 data.

With respect to the Bristol-Myers CheckMate-026 data, we just saw those data in the last hour. So we're responding to it in real-time just as you are.

The categories of explanation, though, you know well. What people had believed was that some aspect of trial design was responsible for the different results. Obviously, our Keynote-024 result is very powerful and the CheckMate-026 data are flat-out neutral or worse in some cases.

So it is a surprising result. It had been expected that the difference in biomarker would explain the result, but their presentation suggests that that's probably not true and there could be some other aspect of trial design of the kinds of patients who are enrolled that might explain it. So that's one category.

The other category of explanation, of course, is that the two drugs really are different in some fundamental way and that we see that evidence in first line. Against that, of course, is that there is first-line data that they previously presented from earlier phase studies in which they had more positive, seemingly more positive results. So it's difficult for us looking at it at this level of resolution to interpret it, that it's not obvious why that should be true, but we're going to study their data and just as they are studying ours and trying to understand how those two very different results could be achieved when in the past the drugs have behaved in a more similar way.

With respect to that Keynote-021 data and PFS by PD-L1 expression, my feeling is that we probably should look to with a magnifying glass at the tertiles or quartiles of PD-L1 expression because there just aren't enough patients there. But, Roy, maybe you would want to comment.

Roy Baynes - *Merck & Co., Inc. - SVP, Global Clinical Development & Chief Medical Officer*

I agree, Roger. I think we get into fairly small patient numbers when we start slicing and dicing this. And so we did do the cut by ORR less than or greater than 1%. We have not done the analysis for PFS.

In terms of compendium I will let Adam speak to that. But this is a randomized controlled clinical trial with robust data. And I will hand over to Adam to talk about what might happen with that.

Adam Schechter - *Merck & Co., Inc. - EVP & President, Global Human Health*

Thanks, Roy. And as you mentioned, Tim, if you look at Keytruda plus chemo in the trial there are impressive results for the PD-L1 positive but also the PD-L1 negative patients. The good news is the data is readily available already for them now that it's published in The Lancet.

You knew that compendia process, it is independent, it's outside of our control, obviously. But we're hopeful that based upon the results that patients will have the opportunity to benefit from the chemo Keytruda combination and we will see what the compendia of folks decide. But we are hopeful that this would be available.

Operator

Geoff Meacham, Barclays.

Geoff Meacham - *Barclays Capital - Analyst*

Good afternoon, guys. Thanks for taking the question. For 024 you saw similarities on PFS between the greater than 50% and up to 100% expression level.

I know the median hasn't been reached yet for OS, but can you speak to the OS performance relative to the force plot? And then based on what you've seen so far from competitors commercially, is there a logic to using Keytruda in lung patients with expression of say 25% or 35% that haven't quite hit the 50% cutpoint in first-line? Thanks.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

I'm not sure I understood exactly what you wanted. What we did was try and look to see whether the 024 results in any way could have been skewed by the presence of a number of individuals had very, very high PD-L1 expression levels and the answer is no. So the data look very similar when you look at those individuals who are in the greater than 75% as opposed to those in the 50% to 75% if that gets at your question, Geoff.

The other question you ask is one that in a way has a little bit to do with the whole biomarker and how it is analyzed. Keep in mind that these are pathologists who are reading slides and counting cells and they score a cell as being positive or negative. And we have a sense of what the variability is, the precision of that assay from one rater to another and it's not perfect, not surprisingly. So there are going to be individuals who would be scored as a 40% who might have been scored at 50% or that sort of thing.

Now that will tend to make people move in the direction of thinking about whether or not Keytruda would be an appropriate treatment for those individuals. Of course, we also have an ongoing Phase 3 study, the 042 study, which looks at the down to 1% level which will provide the kind of information that we need to have in order to understand how useful, in that subpopulation how useful Keytruda monotherapy would be.

Operator

Chris Schott, JPMorgan.

Chris Schott - *JPMorgan - Analyst*

Great, thanks very much for the question. First one for me is can you just elaborate a little bit in terms of your view of the role of monotherapy versus combination therapy in frontline lung?

You guys obviously had great data today from 024. But even in that greater than 50% population it seems like your chemo combo and some competitive data suggest that we could go even higher with response rates. So just your latest thoughts on, just again, is this market ultimately a hybrid monotherapy combo market or do you see the market moving more combo over time?

My second question was just to elaborate a little bit more on the role that you think 024 has for Keytruda in second-line lung? Do you think that it's likely to see a halo effect given the broader use in frontline or is this simply you just need more testing is good for your ability to market your product in second-line? Thank you.

Roy Baynes - *Merck & Co., Inc. - SVP, Global Clinical Development & Chief Medical Officer*

Thanks, Chris, very much for the question. This is Roy Baynes.

As we look at how we think this is going to play out it's hard, obviously, with the data just having come out to predict exactly what that's going to look like. But what we have shown is that across frontline lung cancer irrespective of histology, so this includes squamous and non-squamous with a cutpoint greater than 50%, we have an unambiguous, large effect size in terms of PFS and OS, that despite there being very significant crossover. So based upon randomized controlled data it would be a very, very reasonable position for a physician in the frontline to look at monotherapy in that setting.

The chemo combo question is a little different. So here we have actually looked at non-squamous patients and we've shown here irrespective of PD-L1 status that we have improved response rate as well as an improved progression-free survival rate. So it's, again, a very reasonable option for a physician to think about that.

Now in terms of the regulatory status of these they are going to be a little different. So 024 we have disclosed is, in fact, under review. It's been accepted for review with a PDUFA date of December 24.

The 0 to 1 data we have not disclosed how we're going to approach that. But as Roger and Adam have indicated, it could potentially support compendia at this point.

When we look at the halo effect of testing, I think Adam has indicated that testing has been a barrier for us in second-line. But I can tell you, talking to a number of key thought leaders today everyone is instructing their hospitals to start testing, those that aren't testing. Those that are will continue testing.

And so in very short order all front-line patients or a majority of front-line patients will know their PD-L1 status. And that will be very helpful in informing treatment options in second line.

We have shown previously that, in fact, the outcomes are broadly similar whether we use archival specimens or fresh specimens. So PD-L1 status will increasingly be known by a patient and I believe, and certainly talking with KOLs extensively, there seems to be a perception that if they know the PD-L1 status the hurdles to using it in second-line go away.

Adam Schechter - *Merck & Co., Inc. - EVP & President, Global Human Health*

I agree with that. This is Adam.

I completely agree that my discussions with key opinion leaders at this meeting have been very similar. And I believe we will see a very significant increase in the measure of PD-L1 which in first-line also helps us for second-line.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

And Chris, one thing to say, and Roy I think would agree with this, the decision on how to treat the patient, for example a patient comes in and they have a non-squamous tumor and they have a proportion score that's high and they could receive monotherapy and you're asking yourself as the physician then in discussion with your patient, should that person receive chemotherapy as well, that will be influenced a lot by the state of health of that individual. You are going to look very differently at a patient who has a lot of comorbidities and whom adverse effects would be problematic. You wouldn't want to give chemotherapy then to that person if you thought, gee, I can get a pretty good result with monotherapy which is better tolerated.

On the other hand, in a person who has no such comorbidities, maybe a younger individual who's found incidentally to have advanced non-small cell lung cancer, that you might treat that patient with a combination I suspect. And it will be up -- of course, that would not be on label as we understand it. None of this is on label at the moment, but I can imagine that thought process taking place.

Operator

Vamil Divan, Credit Suisse.

Vamil Divan - *Credis Suisse - Analyst*

Great, thanks so much for taking my questions. So I just had two.

One follows up on what you are just discussing which is this in discussion, by the discussion after the presentation today just in terms of the total addressable market from the 024 study, just given you guys, obviously, only looked at high expresses and also patients that were not on EGFR or ALK positive. So can you just talk a little bit about from a practical perspective what percentage of the front-line in market do you think you can actually address in a non-labeled manner with the 024 data, assuming it gets approved later this year?

And, secondly, you talked a lot about earlier regarding everything you are doing in monotherapy and combination therapy, could you just touch a little bit specifically around the CTLA-4? From an investor perspective a lot of folks on that combination with PD-1 or PD-L1. And where do you stand in terms of what's your interest in that combination, and where do you stand in terms of developing specifically in lung cancer for that indication?

Adam Schechter - *Merck & Co., Inc. - EVP & President, Global Human Health*

This is Adam. Let me answer your first question.

So as you know, lung cancer is divided into two major types: you have non-small cell lung cancer and then you have small cell lung cancer. The non-small cell lung cancer is the most common type. It's about 85% to 90% of all the lung cancers.

If you look at the United States, the big five European countries and Japan there's about 500,000 patients that are drug treated for non-small cell lung cancer in those countries on an annual basis. If you look at all the data we presented at ESMO it showed that maybe 65% to 70% of patients with non-small cell lung cancer across the trials presented had some type of expression of PD-L1 whether it be greater than 1 or greater than 50.

But if you look at those that are just greater than 50 it's somewhere between 25% and 30% of the patients. So that just gives you a sense of the addressable population based on the data that was presented.

Roy Baynes - *Merck & Co., Inc. - SVP, Global Clinical Development & Chief Medical Officer*

And then I think the question that you were getting at was the discussion trying to basically say what does the funnel look like and where do you start and where do you end? In many ways this was I think not really truly representative of what happens.

In fact, virtually every clinical trial excludes poor performance status patients because unfortunately poor performance patients often times die very rapidly. So that's a usual exclusion.

Likewise, there is no reason at this point given an approved therapy for an ALK positive mutation or for an EGFR positive mutation not to use those as first-line therapies. So, in fact, those are very reasonable exclusions. The performance status exclusion is, in fact, usual but that generally does not make its way into labeling and indeed the control brain mets is also a usual requirement.

So it's not usual to put uncontrolled brain mets into a study. So in reality I must say I don't agree with this characterization. I think that, in fact, the majority of patients that actually are PD-L1 strongly positive will be eligible for treatment and this typically, as Adam says, reflects about 30% of all of the front-line squamous and non-squamous patients.

Adam Schechter - *Merck & Co., Inc. - EVP & President, Global Human Health*

And as to the second part of the question was how do we feel about CTLA4, maybe more broadly immunotherapy and what are we doing about that, we have an ongoing program. We've already presented data for pembrolizumab in combination with ipilimumab. And we have additional data that are coming out from the 021 cohorts that look at that as well as other studies.

But one thing to point out is that the 021G data basically provide a floor. Now that you know that chemotherapy used in combination with Keytruda is tolerable, that there are no remarkable unusual safety problems that emerged from that and that when you use those two together in the first-line setting you have this quite remarkable improvement in response rate and progression-free survival, a near doubling of response rate, that says well, gee, if I'm going to use an immunotherapy I need to do better than that and the adverse experience profile should not be worse. Ideally you would like it to be better, as well.

So those are things that we think about a lot and that affects our thinking about how a CTLA4-directed therapy whether that's in ipilimumab or one of our own CTLA4-directed molecules how that would be used and developed. I think what it tells us is that, again, pre-clinically most combinations work and what we're finding is that clinically they do too.

So when you look at combinations with TVEC or combinations with an IOD1-directed molecule or combinations with chemotherapy or combinations with CTLA4-directed therapy, combinations with radiotherapy, in all of those cases there's evidence for at least some additivity with in combination with pembrolizumab. So what means this we're going to have to think very carefully about which sorts of combinations to address and which tumor types and that's our plan going forward.

Operator

David Risinger, Morgan Stanley.

David Risinger - *Morgan Stanley - Analyst*

So I have two questions. First, what we saw in the combination 024 study was crossover of 44% and I think that was partially blamed for the lack of OS benefit in addition to the early nature of the assessment. But in 021 the crossover was pretty close, at about 32%, and that wasn't an issue at all. So could you comment on your expectation for OS durability and advantages of the combo?

And then separately, do you have any development updates in terms of how you're thinking about future trials, either adjusting trials or evaluating CTLA4 in combination with Keytruda for the frontline setting? Thank you.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

So Roy, you might want to take the issue on OS durability.

Roy Baynes - *Merck & Co., Inc. - SVP, Global Clinical Development & Chief Medical Officer*

So just for clarity I think we got those reversed. So basically on the combo arm, our combo study, we had shown that, in fact, the effective crossover rate is very much higher than that. In fact, it's much closer to 70% plus.

And really the reason for that is the number is based upon patients eligible for crossover have to progress. So if a patient hasn't progressed or it is on chemo without progression they are not yet eligible to cross over. So of the population that could have crossed over, 75% already have.

So in 021 we do believe that that is probably at this moment attenuating the overall survival curve. But, again, to be clear, the OS curves for both arms are exceptionally good. They are better than anything that's ever been seen before.

When we look at 024, the effective crossover rate there when we account for patients that are eligible to crossover, it is 54%. But despite that we still see a very significant reduction in the risk of death. So, in fact, it is a very, very positive study.

I think Roger may want to talk to the CTLA4. In terms of looking to adjust trials I assume you are referring to 042 and that trial, obviously, enrolled all patients with greater than 1% and we continue to evaluate whether there are refinements to analyses which have to be done. But essentially the whole population is, in fact, greater than 1% population.

Roger, do you want to talk?

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

Well, we had mentioned a little bit about CTLA4. Not much to update there except to say that, again, the 021 chemo combination study does provide a floor for our thinking about what a combination ought to do. It better be better than that, we should be looking at response rates better than 55% in a first-line setting.

We want to see landmarks of overall survival better than 92% at six months. Again, those are quite profound numbers. And so as we look at how to feather in CTLA4 we will want to -- or other, not just CTLA4, but other things, we will want to understand how we can do that while still maintaining the kind of adverse experience profile and tolerability that we see in combination with chemotherapy which is, frankly, very manageable.

It's probably also we're keeping in mind that oncologists have for the last 30 years used platinum doublet chemotherapy in treating non-small cell lung cancer. They are extremely familiar with how to manage the adverse experiences there.

And so there will be, that too is going to mean that, along with other considerations it is going to mean that that combination will be seen as very useful. But we continue to be interested in ways that we can improve combinations still further and bring about these kinds of revolutionary changes and outcomes for patients with non-small cell lung cancer to an even broader populations of cancer patients.

Adam Schechter - *Merck & Co., Inc. - EVP & President, Global Human Health*

The only thing I would add to Roger's comments is when I visit governments around the world they realize that chemotherapy, for the most part, is relatively inexpensive versus other therapies. So if they see this floor per se, as Roger was discussing, not only do you have to have better efficacy and at least as good tolerability but cost is going to come into play, as well. So the 021G data is very, very important for that reason, as well.

Teri Loxam - *Merck & Co., Inc. - IR*

We are going to try to squeeze in at least one, if not two, questions. And I'm going to apologize in advance, we are not going to be able to get to everyone and I recognize people have other places to go. So Anthony, can we get the next question in please?

Operator

Seamus Fernandez, Leerink.

Seamus Fernandez - *Leerink Partners - Analyst*

Thanks very much for the question. So, Adam, maybe commercially could you talk a little bit about, it seems like there's a possibility that you would actually want in this case to promote the 223 assay as a companion diagnostic rather than just being assigned broadly. Can you talk a little bit about the commercial implication of perhaps actually establishing the 223 assay as the preferred assay for Keytruda?

And then separately, as we think about the longer-term duration of the benefit in the chemo combo study, these data look actually quite similar to the data that you presented in the larger patient population. But the only discrepancy is the fact that there appeared to be previously a benefit on PFS by PD-L1 status, but no difference in response rate whereas in this case we are seeing a bit of a difference in response rate but we haven't seen the PFS differential. So can you maybe just help us understand if you think that the PD-L1 dynamics are at play here? Thanks.

Adam Schechter - *Merck & Co., Inc. - EVP & President, Global Human Health*

Yes so the first thing I would say is that we're going to remain agnostic to the PD-L1 assays. And the reason why is many large institutions are developing their own assays, doing their own work. The thing that is really important is that people measure PD-L1 and that they determine if a patient is PD-L1 positive or not.

What we're finding is about 60% of physicians in the US today are testing for PD-L1 and we believe that's going to go up very significantly. So as opposed to confusing the market and trying to promote one assay versus the other, I think the most important thing that we can do, because our labels are agnostic to which PD-L1 test is used, is to just reinforce the importance of testing.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

And, Seamus, just to make sure we're in the same place on the data, so we presented two studies in first-line lung cancer: 024 and 021. In both of those studies, the arm in which we introduce Keytruda whether it was comparing Keytruda versus chemotherapy in 024 or Keytruda plus chemotherapy versus chemotherapy alone in 021, there was an improvement in response rate and progression-free survival as a result of adding Keytruda. So the benefit was seen, for both of those measures progression-free survival was, in fact, the primary endpoint for the 024 study.

The difference was that the overall survival data for the 021 study we didn't see an overall survival difference in part because it's a small study, in part because the data are very immature at this point and in part perhaps because of the very high crossover rate of over 70%. So I hope that makes sense.

Teri Loxam - *Merck & Co., Inc. - IR*

And we're going to go to one last question. For those of you who we didn't get to, please know the IR team is available for any questions you have. So, Anthony, can we go to our last question, please?

Operator

Alex Arfaei, BMO Capital Markets.

Alex Arfaei - *BMO Capital Markets - Analyst*

Good evening folks and thanks for squeezing me in. Roger, you mentioned that Keynote-021G provides a floor for the combos. But the data shows that the overall survival after crossover is the same.

So what's in the argument for treating with Keytruda plus chemo in frontline as opposed to sequential therapy with chemo upfront followed by PD-1 in second-line patients? And basically what I'm asking is are you seeing more complete responses or deeper responses upfront like you did in Keynote-024 to strengthen the argument that combo early is better than sequential therapy?

Then the follow-up is could you please comment on the Keytruda plus IDO data in both melanoma as well as lung? Thank you.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

Yes, so it's a great question, Alex. We actually -- because the sequential test, if you will, is a test that's performed informally, so fails therapy and then at some point they are rolled over onto Keytruda or, in fact, another PD-1 or PD-L1 directed therapy it's very difficult for us to suss that out.

I would like to say that we should keep in mind that the 021 study is a small study. It's very early and the overall survival data are not mature.

We like what we see in that study because the trend is good and the numbers are quite high. And with time, given that we have so much censoring at this point beyond six months, with time we may see those curves separate. If it turns out that sequential administration is every bit as good as simultaneous administration, which we will address over time, then that's a great, too, where we are happy to deal with that.

Again, the points to make I think are, first of all, that in the first-line setting Keytruda is extremely active, extremely active and that it is very active when used in combination with chemotherapy such that the reflex should be now this is a patient with first-line non-small cell lung cancer. Let's think about Keytruda, now should I add chemotherapy to it?

That is at least a transformation in my thinking that's gone on. Obviously there needs to be, this needs to be reviewed at FDA and there have to be label updates and lots of things have to change.

But it is changing, I think, thinking here from the experience, Roy, that you and I have had talking with opinion leaders here at ESMO in light of these data. So we really can't speak to the sequential issue.

Roy Baynes - *Merck & Co., Inc. - SVP, Global Clinical Development & Chief Medical Officer*

Just as a clinical trials matter, just to say you can't really answer the question in this way either because you are not really randomizing for the crossover question. You are not randomizing for sequential therapy.

That's a very hard study to do because essentially the only way you can do that is chemotherapy and then at progression randomized to, what, more of the same or crossover? Well, more of the same is not really acceptable. So it's going to be a very difficult one to actually answer scientifically.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

Right. It will be very hard to do. And, again, with respect to the IPI combinations and what combinations can be done, what we have, as I said, the 0 to 1 cohorts that have IPI combination data in them in addition to the IPI that we've already presented, and in addition we have other combination studies going on, I would draw your attention to the interesting data that has been presented here at this meeting by our colleagues at Insight with respect to the IDO1 combination which, again, is intriguing in terms of the depth of responses and complete response data.

But that's really all we have time for. I want to thank everybody for joining us this afternoon, evening. I know it's Sunday evening, there's plenty of football going on and lots of other things to do.

But these are very exciting data and we feel so privileged to have had the opportunity to present them here at the European Society meetings. And I can tell you that the interest level among the professionals who treat cancer, not just non-small cell lung cancer but across the board, is enormously high as it should be.

There's a dramatic change going on. And we are pleased to be a part of it. Thank you very much.