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PRESENTATION

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Good morning, everyone. For those who don't know me, I'm Vamil Divan. I'm the U.S. pharma analyst here at Credit Suisse. Thank you, everyone, for joining us again this year for our Healthcare Conference, for day 1 here.

Our next session in this room, we have Merck. We have Roy Baynes, the Senior Vice President and Head of Global Clinical Development, as well as Teri Loxam, who is Vice President for Investor Relations.

Just one quick disclosure. The -- as we have our discussion, there may be some forward-looking statements made, and we just advise you to go to the Merck website or their SEC filings for further information around that.

So just to kick things off here, Roy, I thought it's -- for all of biopharma, I think there have been a pretty interesting couple of weeks kind of leading up to our conference, certainly for Merck. You guys had your earnings call a couple of weeks ago now, 10 days ago. There was the announcement made around KEYNOTE-189 and the decision to include overall survival as a co-primary, but pushing out at least the final analysis until February 2019. So for those of you who have not had a chance to speak to you directly since then, maybe you can just give a little more color on the thought process, why the decision was made. And I know there was also comments about interim analyses being made prior to the final. Any further color on timing or when those might happen and also what would be included would be, I think, very helpful.

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

Yes. Maybe I'm going to start off with just a general idea. So typically in cancer trials, when you're looking at a therapeutic intervention, progression events antedate death events. Progression comes first, and then death comes second. And there's clearly an interval between progression and death, and that can depend, to some extent, on the aggressiveness of the disease, the speed of the disease. It can also depend on other treatments that are given during that interval. So it's extremely usual in cancer for progression to occur before death. That's just how it works. When we presented the 021G study at the ESMO meeting in 2016 -- and just to remind everyone, 021G is essentially the same as 189, just a smaller trial, about 120 patients. Where there's a randomization in the frontline, irrespective of selection markers to either chemo or chemo plus pembro.

And in this trial, by design, patients were able to cross over if they progressed on the chemotherapy arm to receive pembrolizumab or KEYTRUDA. So when we presented those data in 2016, there were 2 striking findings. With relatively short follow-up, there was a dramatic improvement in progression-free survival. There was no difference in overall survival. And you may remember some of the debate back then was, well, gosh, maybe it doesn't matter whether you do the combination -- in other words, get pembro onboard early -- or whether you just use it as salvage at the time of progression. In other words, combination and sequence are the same. That was the objection. As we have followed that trial out, and we presented an update at ESMO this year or truly a year later, what you see now is that not only is the progression-free survival strikingly different, but overall survival is now trending in a very favorable direction. We can't actually do a statistical test at this time, because the final analysis was presented, but this is really a follow-up. And essentially, the nominal p-value is now approaching significance. But again, there's no alpha left to spend at that point.

So looking at those data, what it tells us is that the combination actually is really important. It's really important to have KEYTRUDA and chemo together upfront and not wait for progression for salvage. With those data, it became really pretty important to include overall survival in the analysis, and that's what was done. The trial was updated to essentially look at overall survival. I think it's important to recognize, whenever we do,

or in most instances, when we do, let's say, interim analysis, we look at PFS and OS. But depending upon the alpha weighting, you may be more likely to hit on one than the other at interim analysis.

So what we updated the plan to be was, in fact, to include overall survival as a key primary end -- or a co-primary endpoint. This was done out of a position of strength. This was basically we were so enthused by what we saw on 021G it became imperative to look at that overall survival endpoint. We will have proximal interim analyses. We don't disclose when those will occur. They're event-driven. And we will be looking at PFS and OS with appropriate alpha allocation at those proximal time points. So there are opportunities for earlier readouts, but our projection is that overall survival will meet its full information fraction at that time frame indicated as a final analysis. Is that clear?

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Yes -- no, that's clear. If anyone has question in the audience, as I mentioned, just raise your hand, we'll get a mic over to you so people on the webcast can hear the question. But just a follow-up, and you sort of touched on this. I was surprised by the stock (inaudible) other things around earnings and other announcements, if you can talk about. But it felt to us that this was actually, like you said, done in a position of strength and because you're optimistic on what you're seeing. So just to confirm that, that is the case, were you surprised by the reaction that you've seen from the market since then?

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

Yes, I'm not an expert in the markets. All I will say is, yes, we're actually very enthused about the data. We did this out of a position of really tremendous enthusiasm for the data. So I must say I'm surprised that there's any negative view of that. That's actually a -- should be a real strong signal.

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Okay. And then also related to 021G, the same day that afternoon there was the announcement around Europe and the filing being pulled. Sounds like until 189 is finished, from what -- the way I read it. Maybe you can just provide a little more color for us on what happened there at that point.

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

So again, maybe I'll start off with a general comment. As we look at regulatory agencies around the world, in the United States, the FDA has made every effort to get important treatments to patients quickly. And consequently, pathways such as accelerated approval, priority review, breakthrough designation, have all been put in place to enable medications that are important to get to patients quickly. Around the world, the movement is in that direction, but it is not necessarily as well evolved as it is at FDA. I think we filed 021G in the U.S. because of this very enthusiastic approach to bringing important medicines forward. We also filed in Europe.

I think the European filing was always a bit of a longer shot because I think there was always the notion that there's an inherently more conservative approach to smaller data sets and enabling early approval. Without getting into a lot of detail, we didn't have a formal meeting with EMA, and at the end of the day, it became clear that they were going to wait for the 189 data. We did not want to preempt the EMA in that announcement. So essentially, EMA is due to come out with an announcement that we have withdrawn the file. That is expected in the next few days. And we were going to wait for that to happen. But on the earnings call, a specific question was asked about this which forced us to essentially have a public disclosure ahead of the EMA statement. So I'm not sure if that helps.

These are 2 completely disconnected events. So moving the prime -- the co-primary endpoint OS out was driven out of a position of strength generated from 021G. Withdrawal of 021G had nothing to do with the 189 data. No one's looked at the 189 data. That 189 data remained blinded at this point. And essentially, the decision to withdraw was driven largely by the fact that the EMA indicated they're going to wait for 189.

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Okay. All right. So I do want to -- I think it's interesting from an investor perspective how much focus there always seems to be on the next data point, but there's obviously more you guys are doing in lung cancer and some studies that should be reading out early next year. So maybe you can just talk a little bit about your broader strategy in, I think, 402, 407, those chemo trials. How does that sort of fit in to what you guys are thinking about in terms of lung cancer?

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

Right. So again, at highest elevation, we have an extraordinarily broad program. We're studying KEYTRUDA across many different cancer types. We have over 40 registrational trials ongoing in different tumor types at this point. The strategy has always been pretty consistent, and that is that we try and define benefit in salvage situation with proximal lines of treatment, so that goes to second line, first line, adjuvant, sometimes neoadjuvant. And we use a biomarker-informed approach to try and select the patients most likely to benefit. And that's been the strategy pretty much all along.

To focus in on lung cancer, we have a broad suite of opportunities that we're pursuing in the lung cancer arena. As you know, we established a biomarker-driven treatment paradigm in second-line treatment with the 010 study. We demonstrated remarkable improvement in PFS and OS in the KEYNOTE-024 study, which is the biomarker-selected, highly positive frontline lung cancer setting. 021G has established, we believe, a very important data set, looking at the chemo/PD-1 antibody combination. We believe both of these have defined the floor that others have to beat to come into this market. And then we have, as we've discussed, 189 coming along behind. We have a similar type of trial in the squamous setting. And maybe I should spend a moment just explaining the differences here.

In our Phase II exploration, we found that the combination of pemetrexed and carboplatin plus KEYTRUDA in the setting of nonsquamous, non-small cell lung cancer had remarkably high efficacy. That was the basis of 021G and 189. But that is focused on non-squamous because pemetrexed already is the chemo applied to that setting. In the squamous environment, we are exploring a very similar design, but looking at the combination of carboplatin plus paclitaxel plus/minus KEYTRUDA. So it's a very similar design, also with crossover, exploring, as I say, in the squamous setting. Then we also have an ongoing study, the 042 study, which is an important trial which looks at extending the range of PD-1 positive -- PD-L1 positivity. So as I mentioned, in KEYNOTE-024, we're focused on the strongly positive patients, that is to say, more than 50% of the tumor cells expressing PD-L1. In the 042 study, to get into the trial, you had to have more than 1% of the tumor cells expressing PD-L1. The trial is stratified on greater than or less than 50% positivity. And we have the opportunity here now to look at different levels of expression, with the potential of extending monotherapy into lower degrees of positivity, potentially.

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Is there any limit to how many cuts you can take? I guess, seeing some of the other data from Bristol and others at lower endpoints. I mean -- how do you -- how can you look at that data beyond just the 50%?

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

We haven't had much discussion around that. All I will say is that, to get into the trial, you had to be greater than 1%. It's stratified on less than or greater than 50. And we have the potential to put additional cut points in between 1% and 50%.

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Just going broader than just -- well, we've been talking about lung cancer, obviously. I think 500-something trials that KEYTRUDA is in now. Many, many combinations that are being studied. Maybe you can provide your perspective based on everything you've seen from Merck, from competitors, and we have SITC coming up this weekend, in terms of some of the combination approaches that you're most excited about beyond the chemotherapy that we've been talking about?

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

Okay. Yes, so just to highlight, monotherapy has been explored across more than 30 different tumor types. We've already shown activity in at least 25 of those. And we have registrational work going on across a large number of tumors. In the combination environment, we have firstly tried to use a biologically informed approach. So we use our biomarker program, firstly, to try and select those patients for whom monotherapy makes perfect sense. We've also tried to use that approach to identify those patients for whom other opportunities might make sense to explore. And in that context, combinations become quite important. We think about combinations really based on 3 different frameworks. The one framework is to say, can we change biology? And we've reduced this down to really 3 key steps: can we prime the cell which kills the cancer? So this is called the cytotoxic T-cell or CDA-positive T-cell. Can we do manipulations to make that a more active cell? And checkpoint inhibitors are a great example of what you might do to try and enhance that, but there are other possibilities there. Next, we try and see, can we actually increase the performance of those cells moving through the microenvironment.

And this really is looking at trafficking of cells through the microenvironment, also removing the immunosuppressive elements in the microenvironment, and there are a number of possible targets there. And the third key element is can we increase the amount of antigen presented to the system to try and increase the immune response? And the mechanism here is loosely described as antigenic cell death. That is to say, that we kill more cancer cells, we should express more or have presented more antigens. So that's one framework for looking at combinations.

Another framework is to look at it through the lens of KEYTRUDA. And you can create, obviously, an analytic framework. I'll just give you one. You could look at, for example, the degree of tumor inflammation let's say on the x axis and response data on the y axis. And what we know is that the majority of responders have highly inflamed tumors. There are some cancers which are highly inflamed which don't respond. And so trying to understand what the genetic determinants of that are makes a lot of sense. And then there's a group of patients who are not inflamed and typically don't respond. And do we understand why they're not inflamed? And are there things we can do to try and increase the degree of inflammation?

The third way of thinking about combinations is to say, look, there's buckets of therapeutic options that you can combine. You can combine with standard therapies, and that would be chemotherapy or radiation therapy, and I'll go through each of these in just a moment. You can look at targeted therapies together with PD-1 antibody. You can think about combining immunologically active drugs, either other checkpoint inhibitors, molecules which modulate the degree of immunosuppression in the microenvironment or stimulatory molecules. And then you can think of another category, which is really, can we deploy a vaccine to improve the antigenicity, if you will, of the cancer? Or can we use something like an oncolytic virus to try to increase the amount of antigenicity? So those are all frameworks for thinking about it. Let's use the latter to talk about what we're doing.

So the chemo combo data, there are a plethora of important findings coming out showing the value of combining chemo with a PD-1 antibody. Obviously in lung cancer, 021G was the forerunner there. Obviously KEYNOTE-021 was the Phase II study which looked at a number of chemo combos; they all looked very active. We had data from, for example, the I-SPY program as well as an internal program showing that the combination with chemotherapy in breast cancer looks to be very active. Very nice data presented at ASCO this year looking at combined-modality chemoradiation plus KEYTRUDA in head and neck cancer showing extraordinarily high response rates. So across the board, we are seeing really important addition of chemotherapy to PD-1 antibody. And we have a very large suite of Phase III trials deployed around that.

Thinking about the targeted therapies, there are a number of potential targeted therapies that could be put together. Let's just take an example. In kidney cancer, we explored the combination of a TKI together with KEYTRUDA. We actually have 2 examples there. We looked at the Pfizer TKI, axitinib, and in exploratory trials, we saw very high response rates of the combination. That's in Phase III trial now versus standard of care. We have shown similar data with another TKI, lapatinib from Eisai, and that's in Phase III trials right now. There are other targeted therapies that one could think of other than angiogenesis factors. You can think of, for example, combinations of ALK inhibition in lung cancer. We have a small exploratory study going on there and a number of other targeted therapies.

When we think about the combinations of immunologically active drugs, there is obviously a lot of activity going on there. We have characterized these as checkpoint/checkpoint combinations, and we obviously can think of a number of examples there. You think of CTLA-4 antibody. You can think of LAG-3. You can think of TIGIT and we have trials ongoing with all of those. Some of those we have -- we own internally or are developing internally. We can think of costimulatory molecules. Here, you can think of molecules such as GATA where we have an internal program. You can

think about modulators of the immunosuppression in the microenvironment. A good example here might be an IDO1 inhibitor, and we have a suite of Phase III trials ongoing based upon activity seen in Phase II studies.

When we think about vaccines and oncolytic viruses, let's deal with vaccines first. We have a very nice collaboration with Moderna where we are looking at RNA constructs specific to the mutations observed in the cancer and seeing whether indeed that can generate a meaningful neoantigen response against the cancer. So that's a very nice collaboration that is in its very early stages. When we think of oncolytic viruses, there are a large number of these. And in fact a number of these are injected intratumorally. Good example here would be, let's say, Amgen's molecule TVEC. And what we've shown there is the combination of TVEC plus KEYTRUDA in a melanoma trial markedly increases the response rate. And based upon that, we've taken that into Phase III. There are a number of other modulators that we're really excited about, which we are developing internally. We've got over 20 molecules now in early-stage development that are aimed at improving the -- or enhancing the immune response. Just to give you a few examples here, intratumor injection of, for example, STING. That looks like a powerful activator.

You might have seen a deal recently where we acquired the company Rigontec. This is the RIG-I molecule, again a stimulator of innate immunity. And that's in trials at the moment. We have other oncolytic virus programs that we're working on. We have, obviously, a suite of internal programs, including our IDO1 program, our LAG-3 program, our CTLA-4 program. A number of our own internal targeted therapeutics are looking promising in combination. And so what you see is really a broad array of possibilities. I think, at this moment in time, we really don't have perfect clarity as to what the best combination is. It's unlikely it's going to be a one-size-fits-all. And we do think there's going to be a high degree of personalized medicine based upon use of biomarkers in patient selection to define the optimal combination.

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Okay. Maybe if you can just go beyond, I think -- we can certainly talk more about KEYTRUDA, there's obviously a lot going on there. I think one of the things investors are looking for is what else is -- in the Merck story, maybe in the mid- to late-stage pipeline or earlier. What are you most excited about? I think some of the areas you guys have talked about is vaccines, HIV, anti-infectives. Maybe you can just give us your sense of what are things that people should be asking about that we're not focusing on?

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

Well, I think, appropriately, you're asking us about the immuno-oncology activities first because we've got a lot going on there. And we always described KEYTRUDA as the sort of the pipeline in a product type of idea. So many, many opportunities there and has the potential to really reshape how we treat the cancer patient, so that's obviously a high priority. Vaccines is clearly an area that we're extremely excited about and very active in. Merck has a very proud track record in vaccines. We have sort of have been a leader in this field for many decades. I think what we are particularly excited about is our next wave of vaccine work, which is coming along. And I think we've mentioned publicly that we have a program which is aimed at pneumococcal vaccination, and this is to try and improve upon the current standards that are used for the prevention of pneumococcal disease. It still remains a very serious set of medical conditions. And increasingly, what we're seeing is that the diseases that we see are actually caused now by serotypes not covered by standard vaccines. So it's an idea of broadening the repertoire, if you will.

We also have a very active program inside of megalovirus, respiratory syncytial virus, dengue. And we're also quite actively working with Moderna on some RNA vaccines, which look like a very important platform for developing new vaccines on. In terms of anti-infectives, certainly, in the HIV space, we have some rather exciting assets. We have advanced doravirine, which is our non-nucleoside reverse transcriptase inhibitor. That has completed 2 Phase III trials. Data have been presented. And this looks like an important advance. It looks like, at least in our opinion, the best-in-class non-nucleoside reverse transcriptase inhibitor. It certainly seems to have advantages over the standard NNRTIs. It has less by way of CNS side effects. It has less by way of metabolic side effects, particularly as it pertains to lipids. And so these are exciting attributes of the molecule. And this molecule is in the process of being filed worldwide.

We also have advanced a nucleoside reverse transcriptase and translocation inhibitor called MK-8591. And this molecule has come through Phase I testing, where it showed really quite remarkable activity, very favorable kinetics, very potent. And so this is now being advanced both for full development as well as in combination with doravirine. We've also spent a lot of time trying to optimize the kinetics and half-lives of these molecules.

We have additional molecules coming along, which may lend themselves to less frequent dosing, such as weekly dosing. We're also actively building on our platform, which is used, for example, in our women's health arena, which is the implantable technology with an idea to really getting to very infrequent applications of medications that last for very long period of time. So we think this has a real potential to transform the management of the HIV patient.

Other areas that I'm quite excited about, we have a broad antimicrobial program, particularly addressing areas of antimicrobial resistance. And so those programs are moving ahead. The other area is a collaboration with Bayer that we're very excited about, looking at the sGC class of molecules. And here we're studying particularly exciting applications in heart failure. I then also want to come back briefly to oncology. You probably saw the collaborative deal recently with AstraZeneca, whereby we acquired a half share of olaparib or Lynparza, which was the really first PARP inhibitor approved. We think it's best-in-class PARP as well. I think the program that AstraZeneca has deployed around monotherapy is an extraordinary exciting program. You've probably seen approvals in ovarian cancer both therapeutic and maintenance, and initially with attention to the germline BRCA mutation, but now essentially independent of that mutation.

Also recently filed the breast cancer indication. There's a broad array of monotherapy and combination opportunities being explored. We're extremely interested in this class because what PARPs actually address is this whole question of DNA mismatch repair. And you'll recall that we really led the field in development of MSI high both for colorectal and noncolorectal cancer. That is an extreme component, if you will, of DNA repair. So this all represents a spectrum of DNA mismatch repair modulation. We think that's important in an immuno-oncology sense. We think it's very important from a PARP sense. So we think that this deal really is a very important deal in that it gives us access to a terrific asset that will be developed in a very fulsome way around monotherapy, but we think will have tremendous potential in combination also with PD-1 antibody.

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Maybe I can have one last question in, in our limited time left. It's just around what else would you be thinking about from Merck's perspective? What areas are you wishing you had more assets in? Where would you be looking to do maybe as part of business development to broaden out the portfolio?

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

Yes. So -- I mean, we have always had a broad strategy. We are in 8 therapeutic areas. I think we have good assets in virtually all of them. I've just highlighted a few. But we always -- as in any drug development company, always wish our pipeline was even stronger. So we're always on the lookout for good assets, and business development remains an important part of our strategy going forward, in addition to a very deep and abiding commitment to discovery research.

Vamil Kishore Divan - *Credit Suisse AG, Research Division - Senior Analyst*

Okay. I think we're going to have to leave it there in the interest of time. Thanks so much, Roy and Teri, for joining us. And there is a breakout session down the hall in Room 1, I believe. Thanks.

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

Thank you.
