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PRESENTATION

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

(technical difficulty)

With Dr. Roy Baynes, Senior VP of Global Clinical Development and Chief Medical Officer of Merck. And thank you so much for being here, very timely after what was, I think, a very exciting ASCO for Merck, a lot of developments in the space. So it's a pleasure again to have you. So thank you very much for coming.

Roy Baynes

Thank you, Jami.

QUESTIONS AND ANSWERS

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Before we talk about ASCO and all the exciting news that you've had this year with KEYTRUDA and some of the future development programs, there was news yesterday that -- on KEYTRUDA and 2 multiple myeloma trials put on hold or paused, as you said, to allow for additional information related to reports of death in the KEYTRUDA arm. Can you share with us a little bit more information? How big was the imbalance between the arms? What does this mean? Whatever you can share would be appreciated.

Roy Baynes

Right. Well, I can't share a whole lot. I'm -- we were all (inaudible) blinded to the data. I'll just tell you a little bit about the trials, why we were doing these trials and then what the DMC recommended. So we had showed fairly early on in myeloma research that PD-1 antibody didn't have much monotherapy activity in myeloma, but we did find an interesting phenomenon that in patients who were primarily or secondarily refractory to the IMiD lenalidomide, when we added KEYTRUDA to lenalidomide therapy, there were dramatic responses. Similarly, a small Phase II study with the combination of pomalidomide plus dexamethasone plus KEYTRUDA had very high response rates and were durable. That was published very recently in Blood. So based upon those, we had moved into some randomized control trials in 2 settings: the one was in the patient population that was relapsed and refractory, so pretty advanced population, oftentimes quite ill; and the second population was a frontline population who would transplant ineligible, and typically those folks are either very old, frail, comorbidities or poor performance set. So both were quite sick populations. The first trial, the 183 study, about 300 patients, randomized patients, to receive either pomalidomide, dexamethasone and KEYTRUDA or pomalidomide and dexamethasone. The second trial, 185, which is slated to enroll about 600 patients, was a trial of lenalidomide plus dexamethasone plus KEYTRUDA versus lenalidomide plus dexamethasone. At a routine safety data monitoring interim analysis, the data monitoring committees sourced an excess death rate on the key -- the combo that included KEYTRUDA and requested that we pause enrollment and that we gather all safety and efficacy data to try and understand this better. I don't have any more information to provide to you at this time as to what the detail of the imbalance is, and so we're moving very quickly to get those data. And obviously, FDA's been notified as well.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Are the issues related to immune-response-type issues? Or are they safety issues that have occurred that were -- I mean, you would expect a certain number of safety issues and even deaths in this population. So I'm just wondering if it's something that came kind of out of nowhere that caused this decision.

Roy Baynes

We don't know what the detail is of the excess death, whether it's progression or whether it's complications. I don't have that answer for you.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

And when you say the trial was paused, does that mean that patients already on KEYTRUDA arm will stay on the KEYTRUDA arm and you're just pausing the enrollment of patients? Or what does that actually mean?

Roy Baynes

Yes, to rapidly try and sort out what's going on. And to be clear, this is really the only circumstance where we're seeing this. So there's no other trial that's affected by this at this time.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

And when do you think we'll have more information?

Roy Baynes

Well, it's a global trial. It covers many different jurisdictions, and so we will get the data in as quickly as we can and make it available to the Data Monitoring Committee.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

That's great. I want to talk about ASCO 2017, which just ended last weekend. And just curious, you're -- as a physician, a clinician, a drug developer, what were your high-level takeaways from a broad industry, immuno-oncology perspective and specific to Merck?

Roy Baynes

Well -- so I think there were some rather remarkable stories that came out of ASCO. So firstly, updated data represented on the long-term follow-up on the patients in the early KEYTRUDA trials in melanoma, and I think interestingly, the responses are incredibly durable. Patients are now out getting on many years. A number of patients have stopped treatment because they've been on treatment for probably 2 years plus. And the good news is the vast majority have not shown any progression. So that, I think, is really quite remarkable and exciting data. There were updated data on the lung cancer 024 study continuing to show marked PFS and OS benefit despite significant crossover in the setting of monotherapy in the PD-L1 strongly positive population. So that, I thought, was a very nice data set. I think the update to the G cohort of 21 looked at the longer-term follow-up in patients who'd have chemo combo in nonsmall cell lung cancer. This was in an unselected population. And what we're seeing is maintenance of a striking difference in progression-free survival and survival curves that are now starting to diverge, and that was quite encouraging. I think the takeaway for us from ASCO was really the number of situations where combinations of chemotherapy are looking very encouraging. So

that's one. The I-SPY 2 data were presented. I-SPY 2 is a platform trial where patients are randomized to either get standard of care or to get standard of care plus the interventional arm, and it's a Bayesian design, which allows a parsimonious use of the control group to actually try and infer what combinations look particularly promising. And just at high level across triple-negative breast cancer or HER2-negative breast cancer and hormone-responsive breast cancer, roughly a tripling of pathologic complete response rate was shown when KEYTRUDA was applied to standard of care, all of which includes chemotherapy. That's a remarkable finding. Pathologic CR has typically translated into long-term benefits.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Is that a trial you're doing? Or is that some of...

Roy Baynes

Well, actually done by Laura Esserman's group, the I-SPY group. We provide the drug and, obviously, support. But here, it's an independently conducted trial. And the Bayesian statistics suggest that all 3 of these arms have a very high probability of succeeding in Phase III. So that was another chemo combo trial which was important. Another trial which are presented on the Tuesday morning when everyone was fleeing for the airport, which always seems to happen at ASCO -- the great stuff comes right at the end. This was a study by...

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

I don't pay. I was on the plane on my way home.

Roy Baynes

This was in the head and neck session, and it was an investigative response and study looking at primary treatment of head and neck cancer. And basically, what the investigator was doing was giving standard radiation, chemo plus KEYTRUDA, and the sort of complete response rate was 85% in that trial, which people in the audience first -- one of the first times I've actually heard a collective gasp from the audience. So that was pretty cool.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Radiation plus KEYTRUDA.

Roy Baynes

Chemo -- and plus chemo.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Chemo.

Roy Baynes

The other -- the exciting bit of data was the neoadjuvant data which was presented. Now this was really a window-of-opportunity study where patients with head and neck cancer that had been proven on biopsy were given a single dose of KEYTRUDA and then taken to surgery 3 weeks later. This was an independent study conducted by Wash U, and what they found was -- it's a small study, 25 patients, that had -- roughly, 50 to

(inaudible) % of the patients showed a downstaging pathology. There was a marked increase in the tumor-free margins of surgery compared to what would be expected. And the longer-term follow-up had shown no sort of local recurrences; so again, just a single dose looking to be quite promising in a neoadjuvant setting. So those were all exciting data. There's also updates to the bladder cancer trial, which continues to show survival benefit. This is the first immuno-oncology drug to show survival benefit in bladder cancer, and those results are quite gratifying. So from a Merck perspective, I think there were a lot of -- we have 50 abstracts, and a lot of these data were, I think, really quite important in advancing the field. I think the (inaudible) data were very interesting; and so all in all, I think an interesting, meaningful patients and really a lot of progress in the I-O space.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Is this, I guess, late enough in that evolution of this market to discern differences between PD-1 and PD-L1 or even differences between KEYTRUDA and Opdivo in your opinion?

Roy Baynes

Yes. So none of these drugs have been studied in head-to-head comparisons. So I think it's very hard to infer any clinical difference because you're always doing cross-treatment comparisons. So those are always fraught with hazard.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

So that's an example. Your drug did show an overall survival benefit in bladder and TECENTRIQ did not. So I don't know if you want to speculate as to why.

Roy Baynes

Not really. I haven't -- I don't know enough of their data to know why the trial didn't work. Clinical trials are difficult, and there are always going to be some risks associated with design and analysis. And I think we all just have to be pretty humble because this is really a difficult business, and trials can go wrong. So I have no idea whether that trial was...

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Do you see a difference between KEYTRUDA and Opdivo?

Roy Baynes

So there are differences, biochemically, between them. The different epitopes are covered. Clearly, they're distinct molecules. They have different affinities. They have different kinetics. There's no head-to-head comparison, and so I think it's very hard to really infer anything different, the differences in dosing, differences in scheduling, but again, whether any of that translates into a true difference in outcome...

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

And I doubt we will see a head-to-head trial.

Roy Baynes

Well, I think a lot would be driven by what effect sizes you'd have to power around. And obviously, the most (inaudible) they are, the bigger those trials become more unlikely that they'll be done.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Clearly, KEYTRUDA has just been a huge success for Merck, and I congratulate you on a phenomenal regulatory success. I think that you now have almost as many indications as Bristol-Myers in such a short period of time. So that's really quite phenomenal. I wanted to get your view on -- going back to KEYNOTE-021G, on the response rates that were seen in that data, where we saw an 80% ORR in the over 50% responders versus a 26% ORR in the under 50% responders or the 1% to 49% responders, suggesting that the benefit was really driven by the higher responders. I mean, I understand that this is a small trial, but what do you make of that? And would you conclude that the jury is still out in the 1% to 49% responders?

Roy Baynes

So maybe we should go back to the trial design. So the trial was really an all-comers study. We basically took all frontline nonsquamous nonsmall cell lung cancer. There was no biomarker requirement to actually enter the trial, and we did stratify. The stratification was based upon less than or greater than 1%. That was the stratification for the trial. So in the spirit of you get what you study, there was a dramatic improvement in PFS. And I know certain folks have minimized that, but I think it's important to recognize, we've been trying to bend that curve for forever in lung cancer, and this is really a meaningful, I think, shift in the PFS curve. OS -- initially, the 2 curves was superimposed but actually really good numbers, and there was a lot of crossover in the trial. We had fully 50% absolute number crossed over, and about 75% of those that had progressed on chemo had crossed over. Interestingly now, the survival curve is diverging. The hazard ratio was about 0.69 or 0.65 or something like that. It wasn't statistically significant but clearly moving in a favorable direction. So typically, what we do in an all-comers trial, where you've stratified your report out by the stratification variable, and in fact, the response rate between less than or greater than 1% was identical. I mean, there was really no difference. The additional cut points were really not stratification variables. They're not really randomized for that question. It's really just observing, and it's a small number. And I think the more finely you cut those subsets, the less confidence you're going to have in any given observation. I would think -- what we can say is that whether you were PD-L1 less than 1% or greater than 1%, the results look the same.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Will we get that answer with 189?

Roy Baynes

It's big enough, I think, to get a more robust assessment of it. The trial design is very similar to 21 in terms of the eligibility and operational characteristics.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Does the fact that you achieved a trend towards overall survival in this very small patient population and with a high crossover rate, does that increase your confidence that we will see a statistically significant overall survival benefit with 189?

Roy Baynes

I think it's always hard to predict what happens in clinical trials. If it's the same population, the design is the same, we would expect some of the crossover rate. And so I think we'll just have to see what the trial shows, but it's well-designed if, indeed, the assumptions pan out as expected.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Right. The primary endpoint is PFS.

Roy Baynes

PFS, correct.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

And OS...

Roy Baynes

As well.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Is that -- it is PFS and OS?

Roy Baynes

Yes.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Okay. We saw a lot of data this year from IDOs in melanoma, renal and nonsmall cell lung cancer, and I know you've initiated a Phase III trial with Incyte's IDO in melanoma. But just curious on the progress in other tumor types, we saw interesting data from Phase -- early Phase I, Phase II. You announced at the JPMorgan conference that you were going to initiate Phase III trials. And here we are in June, unless I'm mistaken, I don't think you've started yet or I haven't seen anything in clin trials, an initiation of a Phase III trial. I'm just curious how we should think about the time line because as you know, you're not the only game in town with IDO inhibitors and how we should think about the design of your trial. Anything you can share with that would be great.

Roy Baynes

So a number of presentations at ASCO looked at readouts from the screening Phase II program. And I think we're seeing what we consider to be meaningful response rates across a number of tumor types, as you mentioned, melanoma, renal, bladder, nonsmall cell as well as head and neck. We've indicated that the collaboration between Incyte and Merck seeks to explore those additional tumor types. We have announced that there will be, in addition to the melanoma trial, which is actually quite far along, an additional 6 Phase III studies conducted. We've been working very rapidly to actually develop the protocols, but as you can imagine, combination trials actually are quite design-intense. And for purposes of regulatory approval, you do have to satisfy rules of what is called the combination rule, and so this does require quite a lot of interfacing with FDA to make sure that we actually design the trial in such a way that when you get a result, that result benefits the labels of both parties. So there's quite a lot of design work going on in the background, but I'm confident we'll get these all (inaudible)

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Are you at a disadvantage not owning the IDO itself in -- for example, moving forward with the Phase III trial, meeting with the FDA, satisfying both companies' questions.

Roy Baynes

I think the companies are working very well together, and it's not our first combination with another company. For example, we have Phase III work ongoing with Pfizer in renal cell with KEYTRUDA plus axitinib. We have Phase III work -- Phase III study ongoing with Eisai related to lenvatinib and KEYTRUDA. We have Phase III work ongoing with Amgen in relation with (inaudible)

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

So this is no different from many of your other...

Roy Baynes

No. This is a little bigger that is -- it's a bigger number of trials.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Going back to the data that was presented with KEYTRUDA IDO combo in lung, the response rates were strong in both PD-L1 -- both PD-L expressors and nonexpressors. But we didn't -- I don't know, get enough of a sense of how many of those patients were frontline versus second line versus third line, if any of them were refractory patients treated previously with PD-1, PD-L1. Is there anything you can share with us about that?

Roy Baynes

Not really. I mean, these were screening Phase II trials. So basically, it is a bit of a heterogeneous population, but I think we're really struck by this magnitude of the response. But no, I don't have a lot more color and shading to provide on that.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

More broadly, how do you see the frontline lung landscape evolving over the next several years or awaiting multiple Phase I large frontline lung studies? One of your competitors, Bristol-Myers, is saying the market is likely to be fragmented and broken down by patient subgroups with no one-size-fits-all. Do you agree with that assessment? Or do you see your chemo combo regimen as being used across the board?

Roy Baynes

Yes, it's hard to predict what this will look like. I think lung cancer frontline is fragmented de facto by, for example, EGFR mutations, ALK mutations. When you take those off the table, I think at this moment in time, you'd have to say that if your PD-L1 is strongly positive, the benefits of the PD-1 antibody in the form of KEYTRUDA are unassailable. I mean, that is a very, very robust data set. And in many ways, it sets the floor for what people have to beat. So if you're PD-L1 strongly positive and you're coming along with a different combination, a pretty high bar to beat. Now granted it's cross treatment -- but I think people will look at that and say, "This is sort of where you need to be." Chemo combo does roughly the same thing in that it does set the floor to beat because it's way better currently than anything else that's been established in randomized trials. So yes, there will be a lot of readouts, but I do think the frame of reference has shifted a little bit and what the goal of therapy will be.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

I'm just curious to know your view on sort of I-O/I-O versus I-O/chemo. I think that you have been on record saying that CTLA-4 would not work because of its toxicity profile. I'll just be curious to know what your thoughts are on the CTLA-4s in combo with PD-1s. I know that you are developing -- you have an internal trial with that combination, but following ASCO, is there any change to your view on that?

Roy Baynes

So I don't think I've ever said it wouldn't work. I've said that there is a tolerability question with this combination. And I think most people would agree with that, that there is a heightened degree of toxicity. So whether it's going to be I-O/I-O or I-O/chemo, I think the jury's out at this point. I think the I-O/I-O data have been largely single arm experience. And so that has all the problems of trying to interpret what do you make of 20-, 30-patient studies, that type of idea. I think that the randomized trial that I'm most familiar with is the melanoma setting. And those data have shown -- now again, the trial has a lot of caveats on it. It's not designed for a direct comparison. The crossover rates are significant, and that's going to bedevil this field going forward. There will always be crossovers. But the magnitude of difference in -- within that trial between the 3 arms, clearly, the PD-1 antibody beats the CTLA-4 handily. The combination beats the CTLA-4 handily. But when you look at the difference between the PD-L1 -- pardon me, the PD-1 and the PD-1 plus CTLA-4, that's not so clear that there's a lot of benefit there. OS was not statistically different granted it's nowhere near the prespecified number of events. So there's a lot of crossovers, a lot of caveats to it, but I still am not sure that we have a good handle on what we can really expect I-O/I-O is to do. I think we're just going to need more data.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

You'd expect to learn much from the MYSTIC trial that's expected to report out soon?

Roy Baynes

I'm looking forward to seeing the results. I have no idea what they're going to show, yes.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

So there was a lot of discussion also on the new biomarkers at ASCO, like tumor mutation burden and LAG-3. Can you comment on how you're thinking about clinical trial design and incorporating some of these new biomarkers? As you know, PD-L1 is certainly imperfect and always changing. Do you see -- the data that we saw with MSI high is very exciting. How do you see thinking about these biomarkers in terms of developing your own trial?

Roy Baynes

Yes. So biomarker approach has been fundamental to our program right from the get-go. I think we've always taken the point of view that if we can identify those for whom monotherapy is a good option, that's a real plus. By difference, if we can identify those with whom monotherapy is not likely to be a good option, that's the group we should focus on in more detail. And then we should look at biomarker work which can help channel (inaudible) in appropriate direction for studies. So our biomarker program has had a few key pillars. PD-L1 was a very reasonable one to go after because frankly, if you're trying to interdict the interaction between the ligand and the receptor [gush], each would like to be working in tumors that have a lot of ligand around. That was a pretty simplistic view that we took, and it's actually served us pretty well. I mean, it hasn't reached the number of the trials they're made for, I think, fairly straight linear drug development. It's not perfect. Clearly, we do see PD-L1 negative patients respond, but the effects are really very large in strongly positive populations in most of the tumors we've looked at. The next key component of this has been related to the degree of inflammation in the tumor. And I think most would agree that if you have an inflamed tumor, that's most likely to respond to a PD-1 interdiction. And so we have developed a gene signature which basically looks at inflammation, so-called gene expression

profiling. And that has been quite predictive. That also has another advantage in that we can identify, in certain cases, genetic overexpression which may correlate with resistance. And so it allows us to start thinking a little bit about the combination approach. And then the third pillar has been related to mutational burden. And the idea here is that if you've got a lot of mutations, you're more likely to have more antigens, neoantigens, and that might be underlying stimulus to developing an immune response. So we have spent quite a bit of time on that. We've, as you said, developed the MSI high concept. That's a very specific mechanism-based increase in mutational burden. It speaks to a defect of DNA damage repair. We're very interested in looking at other markets of DNA repair. And then globally, at the total mutational burden -- and actually, the data are starting to amount -- increase to say that mutational burden is independent and possibly important predictor. There's a huge degree of overlap between mutational burden and PD-L1 expression and inflammation. So these things are, to some extent, interrelated. But that's sort of the totality of how we are thinking about it.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Do you think it's too late to design trials around these new biomarkers? Or will they be slowly integrated into future clinical trial designs?

Roy Baynes

Well, I think the answer is yes and yes. I think that firstly, some of these biomarkers lend themselves to tissue-agnostic approaches. So MSI high approval was really quite a breakthrough conceptually. I mean, here, basically, the agency has agreed to an indication which is defined by a biomarker and not by histology. That's a big deal. And we've been trying to do this for the better part of the last several decades. So this is a breakthrough. And there are many other potential areas that lend themselves to this type of molecular type of diagnosis and indication. So I think this is thin edge of the wedge. I think that for ongoing trials, certainly, understanding the mechanism basis of resistance will inform certain combination trials. So no, I don't think it's too late, and I think it actually behooves us to include translational measures because frankly, it's the only way we're ever going to really try to understand what's going on.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

In terms of other assets that you have in house, I think you have a LAG-3 in-house. Where is it currently in development? And do you see a broad role for it across tumor types based on what we know today? I thought the data that Bristol-Myers showed at ASCO was intriguing, particularly in the LAG-3 expressor population.

Roy Baynes

Right. So we have a very broad array of combinatorial approaches. We have, at this moment in time, about 300 combination studies ongoing, most of which are exploratory. And then where we've seen positive signals, we've ramped up Phase III work. Internally, we have a number of assets that are in the clinic. I believe we've introduced something like 10 new molecules into the clinic. And these fit into a number of categories. It's basically immune stimulatory molecules. And there, I can point to [Elgueta] molecule, which is in monotherapy and combo studies. I can point to a number of additional approaches which include, for example, STING agonist. We have cytokine agonists. We also have, in collaboration externally -- this is not our molecule, are working on some others cytokines as well as some TLR agonists. So these are all ways of inducing an inflammatory type of situation. We have a number of checkpoint molecules. So we've mentioned LAG-3. We have a LAG-3 that's in monotherapy and combination therapy work. Bristol certainly has a large program, and it'd be interesting to see what comes out of that. And the biomarker-driven part of it may be intriguing. In addition, we have -- in CTLA-4, which we've mentioned before, which is now in the clinic, and we have an IDO1, which is quite far along as well. We're also pursuing a number of oncolytic-virus-type approaches. The one that's furthest along is obviously collaboration with Amgen, but we have additional programs behind that; certainly looking at a number of targeted therapies. So for example, our ERK inhibitor together with KEYTRUDA in certain tumor types, we have a [cyclamen-based] -- inhibitor-based approach. And then we've entered into a fairly large collaboration with Moderna looking at mutation-specific vaccines, which are RNA-based vaccines. So it's a pretty rich portfolio, but we're also very actively collaborating with external partners because frankly, I don't think any one company can own the totality of opportunities.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Are there any assets or technologies that you wish you had in-house like CAR T technology, for example?

Roy Baynes

So I'm not -- yes, I think, CAR Ts are interesting in heme malignancies. I don't think we've seen good data yet in solid tumors. Hopefully, those will be forthcoming. And certainly, it's an interesting platform. The -- McKinsey, a couple of years ago, did a calculation of the total potential number of combinations. It's an enormous number. And so I don't think any one company can own them all. We have, I think, been able to target the molecules that they're most interested in.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

We only have 4 minutes, and I want to move off immuno-oncology because I know you have broader responsibility. Just yesterday, J&J announced the CANVAS data with INVOKANA and the SGLT2 class. Just I want to know your thoughts on SGLT2 versus DPP-4. I know you have your own combination of SGLT2 and DPP-4. Do you think this will be sufficient to change dynamics in the marketplace because they've actually really been quite slow to change?

Roy Baynes

Right. So I think diabetes is a progressive disease, and it's very likely that we will continue to see multiple modalities needed, and patients will probably work through additional therapies as disease progresses. The CANVAS data are quite early. I haven't had a chance to really dissect them out in great detail, but at high level, I think what you could say is that both that and the Jardiance…

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

EMPA-REG.

Roy Baynes

EMPA-REG trial broadly showed an improvement or a noninferiority at MACE and direct superiority at MACE. The trial is a little different in the components of MACE. So I'm not sure we understand what that's all about. Is that -- this trial design and populations, is it fortuitous? I don't know what to make of that, and we need to drill into that a lot more still. Both of them have shown quite significant benefits in terms of heart failure. And certainly, directionally, it looks as though there's some favorable impact on renal function. So if this is true across the class of SGLT2s, we will know because they have a number of additional SGLT2 CVOTs that will read out. And I think that's good -- all of this is good for patients. I think that -- will it supplant DPP-4s? I think DPP-4s have a tremendously good track record. They're a safe class of drug. They're certainly for a number of patients, have served them very well. And so I don't think that we're going to see a huge sea change, but I do think that there is increasing data to think about using an SGLT2. Clearly, there are some side effects that one has to look at as well.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Right, right, right. I -- just let me quickly move on. We -- I think we expect the readout from the REVEAL study for anacetrapib midyear, which would be, I guess, maybe -- we're in the midyear. Can you speak to the trial design and expectations in the context of disappointing data that we have seen from this class? I think that -- either CETPs have shown harm or have shown no benefit. So how do you think about the differentiation with your asset?

Roy Baynes

Well -- so this trial actually was designed 10 years ago. So the world changes, obviously, over time. It has survived obviously a number of monitoring -- Data Monitoring Committee reviews, and it's run to completion. So that's exciting because I think we'll be the first one that actually will answer the question definitively. We know that for the level of LDL reduction that we see, we would expect a positive trial. And so that's an important question that will be answered. As you know, this class of drugs also elevates HDL. It also changes the LDL -- pardon me, lipoprotein(a) concentration and probably has some effect on particle size; so again, lots of questions to be answered. The trial is a little different from a few of the others in that, firstly, it's a very large trial. It's about 30,000 patients, and patients have been followed for a long time. And in this world of lipid lowering, we know that whether it was statins, whether it's the PCSK9s, you don't typically see an early response. There's usually a lag period before you start to see the appearance. So certainly, we are well beyond the lag period, and hopefully, we'll not be confounded by that. Many of the others have stopped a little earlier than that, and that may or may not have been relevant. So I don't have a crystal ball. I think it's an important trial that will read out. The world has changed, and I think we don't really know what to really expect from this trial, but it will give us an answer, I think, which should be definitive.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

But are you optimistic it will be a positive trial?

Roy Baynes

I'm optimistic because I do believe in the LDL hypothesis, and I do think that the trial is powered for an outcome based upon the magnitude of LDL change.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Is it still a market opportunity for anacetrapib with (inaudible) entirely positive?

Roy Baynes

I think it will all depend on the effects. If it's a small effect size, probably not. If there's a large effect size, then I think, well, bets are off.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Right, right, right. And just one last question, and that's on your triplet in the hep C program. Given that both Gilead and AbbVie will be ahead of you with a triplet pan-genotypic opportunity, how are you going to differentiate yourself clinically and commercially?

Roy Baynes

Yes, well -- so the good news for patients is there are a lot of good drugs for hepatitis C. I mean, the vast majority of patients can be cured today, and that's just an amazing concept. I mean, that's what I get excited about. Our doublet is doing very well. I think doing very well in numerous markets. The triplet data that we showed at meetings, I think investigators and KOLs believe it's a very important molecule. The combination rule that has become applied to triplet has made the development path there a little less easy. And as a consequence, we will probably be combining triplet and then also do some doublet work as well. This is -- remains a very large population. It's getting harder to find those patients, and a lot of effort is going to have to be put into the public health aspect to actually getting people screened and tested and focusing on populations that are, in fact, at very high risk for reinfection or spreading infection.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

There was just a little bit of confusion though because I think earlier in the year, you wrote down some of the early investment from Idenix, but you're going ahead with the triplet combination, the triplet program.

Roy Baynes

Right. So I think the combination rule has made it hard to get a triplet into a pan-genotypic setting because there are a lot of doublets that actually meet the requirement. So as a result, the actual breadth of the triplet application may be a little narrow, and so that was the reason for the write-down.

Jamilu E. Rubin - *Goldman Sachs Group Inc., Research Division - Equity Analyst*

Okay. We are out of time. Thank you very much.

Roy Baynes

Thank you so much.