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MRK - Merck & Co Inc Investor Briefing at 2016 ASCO Annual Meeting

EVENT DATE/TIME: JUNE 06, 2016 / 10:45PM GMT

OVERVIEW:

MRK provided an update on its oncology strategy.

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PRESENTATION

Teri Loxam *- Merck & Co Inc. - Head of Investor Relations*

Let's get started. I'm Teri Loxam. I run Investor Relations for Merck for those of you that I don't know. So what we're going to do today, we've got a really short video that we wanted to play for you. And then Roger Perlmutter, our Head of Clinical Research, or Head of Development, Head of MRL, is that better? He's everything in R&D for us. So Roger Perlmutter is going to come up and do a short slide presentation.

We know you guys have been inundated by data throughout the past several days. So we've actually kept our slides pretty short and high level because we want to save as much time for Q&A as possible. So after Roger finishes the presentation, we're going to bring up Roger and his oncology team and Frank Clyburn, who also runs the commercial side in the oncology business, to answer all of your questions.

So with that we'll start with the video and then have Roger up.

(Video playing)

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

It's a pretty impressive legacy I think. And we made that video to celebrate the fact that this is our 125th anniversary beginning with the statement, which I assert absolutely, which is that great medicines change the world. And all of you who've been at ASCO the last few days have seen exactly what that means. It's quite extraordinary.

So thank you for coming this evening. It's great to see all of you. I'll spend a few minutes talking about where we stand with respect to our immuno-oncology program, our oncology more generally. And then we'll have a chance to answer your questions. Needless to say there are forward-looking statements in the things that we present. And this is our usual Safe Harbor statement.

So we'll talk a little bit about our strategy; the way we conceptualized it; how it's proceeding; what we're doing both in monotherapy and combination work; how we're using improved biomarkers to identify patients who will benefit most from KEYTRUDA therapy; and then we'll talk in more detail about what the future looks like.

So to begin with, our strategy really is pretty straightforward. And that is we want to translate break-through research in immuno-oncology into medicines that improve overall survival. And we want to improve the number of years that patients afflicted with malignant disease have to spend on earth in a high-quality way. My expectation has been, since I became associated with the program, that KEYTRUDA would prove to be foundational in the treatment of malignant disease. And I think we've seen over the last few days exactly the way that's evolving.

And of course we want to identify patients who are going to benefit most and then deal with the challenge, and it is a large challenge, of trying to improve, as well, responses in those patients who right now are not seeing the kind of response that we'd like.

So five years since we entered clinical development. We've done a lot. KEYTRUDA was the first PD-1 directed therapy to enter the market in the United States. It's now approved in melanoma, second-line [PD-L1] positive non-small-cell lung cancer. That is the population that benefits most from these therapies as you know.

We've demonstrated overall survival in melanoma benefits versus ipilimumab, what was previously the best therapy. It's the only drug for which overall survival improvement is demonstrated that are superior to ipilimumab. And versus docetaxel in second line non-small-cell lung cancer.

We are filed in head and neck cancer with the PDUFA date of August 9, the priority review. Launching right now in more than 50 markets; Frank Clyburn will have some more things to say about that in Q&A.

Clinical activity in a huge number of different tumor types; one of the things that we wanted to know was how broadly is immuno-oncology applicable? What can we really do with PD-1 directed therapy? And the answer is we can do quite a lot. We have more than 30 registration-enabling studies currently ongoing. And we have had four FDA breakthrough designations.

Let me put that in context for you and point out that my -- this as everyone knows is my second tour of duty at Merck. I returned to Merck April 15 2013, not to put too fine a point on it. But when I arrived in 2013 we had one ongoing study with KEYTRUDA, the 001 study.

In ASCO 2013 when I stood here at this lectern, we actually had only one abstract. And here we are now, three years later, with more than 80 abstracts and data in more than 20 different tumor types. It's been an extraordinary voyage. And it's a voyage that has benefited from the very gifted clinical and basic scientists, clinical scientists and basic scientists, at Merck who have worked tirelessly to try and make this happen.

So global launching and a really, really, really broad program. If you look at the program you'll see that it includes a lot of internal molecules beyond KEYTRUDA that we're exploring as combinations, and potentially as standalones. Some of those we developed, that is invented ourselves. Some of those we've licensed in. Many of them are in the clinic and we are pursuing them.

Then we have this very large set of registration-enabling studies which are listed there in a dozen different tumor types. So the expectation is there are going to be an awful lot of filings and ultimately, we expect, a lot of approvals across a broad set of jurisdictions. And KEYTRUDA will indeed become foundational in the treatment of malignant disease.

Have a look at this. These are waterfall plots, little mini waterfall plots, conveniently arranged in such a way that you can put it, for example, on your refrigerator. That's what I do with mine. And it's just great to look at, right? It's extraordinary. You look at this thing and you say here's where we started with melanoma. You can see these waterfall plots where when the green lines go down -- each line represents an individual patient, as you know -- and when the green lines goes down that means that the sum of linear dimensions of the tumor is shrinking. So you see that in some patients the tumor still increases in size despite treatment in melanoma. But in an awful lot of patients it goes down.

Non-small-cell lung cancer perhaps not as impressive as melanoma, but very impressive given the nature of that lesion. And then you walk across in head and neck cancer, and urothelial cancers like bladder cancer, triple-negative breast, gastric cancer, in classic Hodgkin's Lymphoma, where

we see the most profound responses overall with nearly 90% responders; in primary and mediastinal B-cell lymphoma, obviously not a huge market, neither is mesothelioma, but also responses in small-cell lung cancer, esophageal and a whole range of tumors that you could just walk through. It is really quite remarkable.

As one of my academic colleagues at the Fred Hutchinson Cancer Research Center commented to me as we were walking across that bridge that you've probably crossed a hundred times during this meeting, that separates the two different parts of the McCormick Place convention center, he said, it's really just going to be a question, in the future, of KEYTRUDA plus [X]. That's really what it's going to be a question of and there are going to be lots of different Xs, so you'll have to, each patient you'll have to evaluate, well, what is that X and on what basis do we use it?

But what we've established is, we started out and said, KEYTRUDA monotherapy, how well does it work? The answer is it works in an awful lot of different tumor types. And when you look at KEYTRUDA monotherapy in terms of overall survival, this is the comparison from the 006 studies showing two different doses of pembrolizumab versus ipilimumab, and which is unambiguous in terms of overall survival that pembrolizumab is superior. The two pembrolizumab doses are superimposable but they are superior to ipilimumab. And that is really quite durable.

How durable? Well, we presented, Caroline Robert presented, many of you were there today, this afternoon, when she presented the three-year data from the original 001 Study. It's quite remarkable how durable those responses are.

And another interesting thing to point out is that the responses, in many cases, mature late and she pointed out that there was one example of a conversion to complete response at 33 months. That is a remarkable story. So, as patients are treated with KEYTRUDA, they may have stable disease or a partial response, and then they evolve and the responses become deeper, more profound. And the durability of those responses, as she pointed out, and as Jacob Schechter pointed out for the 006 study, the durability of those responses is really quite extraordinary.

So we know that in cancer it will never be enough to rest on monotherapy. I think that while KEYTRUDA provides a foundation, there will be other combinations that will work, and we've been exploring those combinations diligently. We began from a mechanistic perspective, so the way I had looked at it was to say, look, let's look at the patients who don't respond, which, in most tumor types it's the majority of patients who don't respond.

So what's wrong with those patients? The problem in those patients could be that they have a tumor that simply is impossible to recognize. Whatever the basis of recognition is, and these days we talk most often about neoantigen recognition, but whatever the basis of recognition is, perhaps the tumor is just invisible. In which case, our job is to make it visible somehow.

Perhaps, however, instead the tumor is visible but just not in that individual. That for one reason or another, that tumor hasn't yet attracted interest from the immune system and we need to do something to give the immune system access to it. Under those circumstances, you might want to take tumor antigens that are relevant and immunize with them. That might stimulate the immune system's interest.

Yet there are other circumstances in which the tumor is recognizable, the immune system has recognized it but either has become exhausted or suppressed, or in one way or another, its effects have been abrogated. In that circumstance, you might want to do something that would relieve the additional checkpoint inhibition, whether that's by stimulation with a GITR agonist standard body or by blocking one of the many antagonist checkpoints. And all of those things are worth exploring.

In the years since we've started doing these studies, we've learned quite a lot. One of the things that we noted early on in preclinical studies was that, in general, combinations seemed to provide benefit and all mechanisms seemed to work. So, if you look in combinations in a syngeneic mouse tumor model and you look with immunization, if you look with traditional cytotoxic chemotherapy, if you look with targeted therapies, if you look with other checkpoint inhibitors, you often see at least additive effects. Never sure how that kind of stuff is going to translate in the clinic, but the answer is that in the clinic we see, in general, combinations are working surprisingly well.

So if you look at it, and this is blocked out as, what about the combinations with standard therapies? What about combinations with targeted therapies? What about novel vaccine approaches? And then, what about the immuno-oncologic approaches? It's a crude fractionation because, again, people who have been advocates of the immuno-oncology field for a long time would argue that all of these things work by immunologic manipulation. But let's just use this as a moment, for a moment.

I think, data we presented at ASCO with respect to the combination of pemetrexed and KEYTRUDA in non-small-cell lung cancer are especially profound. You're looking at 70% overall response rates by a small number of patients, it's only 24 patients, but early on, 70% response rates, top left waterfall plot. Those are very dramatic response rates in a non-small-cell lung cancer population being treated with standard chemotherapy to which pembrolizumab/KEYTRUDA is added.

One of the things it's worth recognizing is that oncologists around the world are extremely comfortable with standard chemotherapy. They understand how to use it and they understand how to manage the adverse effect profile. So that's very promising in terms of treating patients.

It's also the case that the combination in melanoma and in other settings of ipilimumab plus KEYTRUDA does work. There's no doubt, as has been shown also for nivolumab and ipilimumab. It adds a lot of toxicity and we'll have to wait and see for both of these therapies whether you actually achieve an improvement in durable, long-term survival. And that's, I think, what we need to know.

Similarly, we see really exciting, interesting results in renal cell carcinoma with the combination of axitinib and KEYTRUDA, suggesting that those two can be used very well together.

If you want to try and improve immune recognition, one way, as I said, is to try and immunize. And one way to immunize is to use an oncolytic virus. T-VEC is an approved oncolytic virus that infects cancer cells preferentially. It lyses them directly and it attracts inflammatory cells by virtue of expression of the GM-CSF cassette. And if you use that, T-VEC, together with KEYTRUDA, you see improved responses in a melanoma setting with one quarter of patients, nearly one quarter of patients having complete responses. And I would point out these are early days and if those responses mature in the way that we've seen with KEYTRUDA alone, it could be quite impressive. So that looks pretty exciting.

And then we are also pursuing a lot of other interesting immune modulators, for example, the ITA 1 inhibitor that was developed by INSIGHT. We have registration studies going on in melanoma with that combination too.

So lots of interesting combination data. You can see here that the response rate in what's called, Cohort C from Keynote-21, 71% overall response rate in the KEYTRUDA plus pemetrexed combination, as I mentioned, which is really very, very impressive.

The same kind of thing is seen in other tumor types, so if you look in the Keynote-023 study, this is a further elaboration of data in relapsed/refractory multiple myeloma patients. These are patients who really, because they've already failed traditional therapy, would have no response to lenalidomide because they already relapsed refractory.

We know that KEYTRUDA does very little in a multiple myeloma population by itself, but when you put the two together you see something that is real synergy. Completely unexpected; we really didn't think we would see this kind of response and we're very impressed and we're very, very pleased.

And we think there's an opportunity here to make a big difference because these are patients that tend to cycle though multiple therapies. Our hope is that therapy with KEYTRUDA in this combination will be more durable and, of course, that's stimulated registration [labeling phase] as well.

So, beyond the combinations that I've already described, there are the internal molecules that we've talked about, including two different GITR molecules that -- one of which is very far along now in the studies and we're doing combinations. We've finished single agent studies and we're doing combination studies with KEYTRUDA.

We also have an IL-10 directed antibody trying to relieve IL-10 mediated immune suppression. We acquired another molecule called CEACAM, which is an antibody against a negative regulator. We also have a LAG-3 molecule in the clinic and then a number of more traditional small molecules; PI3kinase delta and a CDK inhibitor, dinaciclib. And then we have an epigenetic modifier that we licensed in, which is the first advanced molecule against the BET-Bromodomain epigenetic regulators.

So a lot of work going on in combination with KEYTRUDA by itself but beyond those combinations there's the question of how best to treat each individual. And we've done a very substantial amount of work, which is presented here at the meeting, trying to identify which patients benefit the most.

I think the data with respect to PD-L1 expression in non-small-cell lung cancer is at this point inconvertible, both from us and from everyone else who studied it. It's clear that the PD-L1 expressing tumor population is the population that derives greatest benefit from PD-1 targeting and that that is an important predictor of response. It is in many other tumor types as well.

We sort of know what that is, why it works, because PD-L1 in that case is really just a surrogate for an ongoing inflammatory response. PD-L1 is serving as a read-out, basically, for the expression of gamma interferon and other inflammatory cytokines. Once you know that, then you might as well just measure those inflammatory cytokines and we chose to do that in collaboration with the group at NanoString, developing new approaches to better biomarkers.

Those expression-related -- immune-related expression signatures, rather, are potentially very powerful for identifying patients whose tumors are already undergoing a significant inflammatory response, which you can boost with KEYTRUDA by releasing the brakes, if you will, on immune function.

But maybe the most interesting and most exciting data that has emerged from this ASCO on the heels of what we presented in 2015 are the data that have been obtained looking at patients whose tumors have mutations and mismatched repair genes.

So that's really been quite a great story. It was a story that was begun at John Hopkins University by Bert Volgenstein, asking the question of whether patients who have inherited mismatch repair mutations, Lynch syndrome, whether those individuals, by virtue of the fact they have so many mutations, would have more, potentially more immunogenic tumors and that that would be, in one way or another, would dictate response in.

It was a good place to look because colorectal cancer happens be one of the tumors in which you see very poor responses to KEYTRUDA but when we looked in patients with colorectal cancer where there were mutations in mismatch repair, surprisingly there were a lot of responses. It took some time to see that but we did see it and it was quite extraordinary.

So we pursued that in a great deal more detail and data were presented at ASCO about that. Because what's interesting is that if you now say, well, let's not worry about what the tumor type is. For 50 years we've classified tumors by virtue of their cell of origin and we've directed therapies to tumors based on cell of origin.

But if instead we try and treat mechanistically, as more and more in oncology we are trying to do, and we say, anyone who has a significant mismatch repair mutation likely is a candidate for developing a high mutational burden and likely as a result they'll have an immune response directed against the tumor. And likely as a result they'll have a response to KEYTRUDA. We needn't worry about histology too much. Instead we should worry more about the status of the mismatch repair gene.

If we look at microsatellite instability as a surrogate for that, and just ask, what is the response rate in such patients? The answer is, the response rate is very high and you can see from the Keynote-016 data which we presented and discussed at ASCO, a dramatic set of responses, again looking now in the spider plot, at the percent change from baseline in the sum of the linear dimensions of tumors for patients with a variety of GI malignancies, including those of gastric and small bowel, pancreatic, ampullary related tumors. And also endometrial tumors, sarcomas, very hard to treat, and prostate malignant.

So really, this could turn out to be quite revolutionary if over time we are able to acquire more data that demonstrates the impact of analyzing tumors from this perspective. The power of the gamma interferon selection score is shown on the right hand panel.

So what are you going to see from Merck oncology going forward in the near term in 2016? We're going to be adding more programs into the clinic because we do believe that there are ways to make KEYTRUDA still more powerful in a variety of settings.

We have a lot of filings on additional tumor types that will evolve as more data become available. We are anticipating approval as I say in August; we hope anyway, that the FDA be doing that; and of course approvals for the Keynote-010 study. So approval in head and neck and Keynote-010 approval.

We do expect to get results from the first line non-small-cell lung cancer study, the Keynote-024 study. Those results should be available within weeks. We've said they would be available in June, based on our just looking at the event rate. It's event driven and we've reached the point where we think that should be available within weeks. So fingers crossed, and see how that works. And then a lot of additional combination data.

So, returning to where we began what I would say is that we started this odyssey five years ago. Three years ago we had our first abstract at ASCO. We gained registration in September 2014 in melanoma and we've broadened that registration both in the US and now soon in Europe.

But we are just still at the very beginning of showing what immuno-oncology, and in particular KEYTRUDA, can do for the world. It's really quite profound and every day I get letters from people who have had the experience of having benefited from KEYTRUDA therapy.

And much as was seen in the case of Jimmy Carter, a famous person of course who benefited and at a very advanced age, but in every case it gives individuals a chance to contribute to the social fabric of the world in a very profound way; and permits me to return to the video which you saw, just for 125 years that has been the guiding principal behind what is done at Merck.

We're in the midst of a very exciting chapter but it's just one more step along the path in building Merck as the premier research [and defensive] biopharmaceutical company, something which we've always been in the past, and a position we intend to occupy forever.

That's my plan for world domination, thank you very much. With that, I am going to invite my colleagues up to the podium. I think everyone knows them, but just in case, I'll introduce them.

Roy Baynes is our Head of Clinical Development. He's responsible for all clinical development, just oncology. He does happen to be a Board certified oncologist, a former transplant expert and a true key opinion leader in this area, so it's usually powerful to have him leading the oncology group.

He has worked for many years, as have I actually though they've worked together for a longer time together, with Roger Dansey and Roger Dansey is leading the oncology program. Roger has an enormous amount of experience in phase 3 programs and came to join us precisely because we are launching such a large set of phase 3 programs with a very, very exciting molecule. Roy, Roger and I were all together at Amgen some years ago so we've gotten used to each other, it's helpful; at least that's the way I tell it.

And then I also want to have Frank Clyburn come up because Frank is the guy who is responsible for the entire oncology business unit.

We recognized early on that KEYTRUDA and the things that work with KEYTRUDA would be so important and oncology was so special that we're going to have to have a special business unit to manage the way in which we interact with patients and peers and physicians, and Frank and his team are doing a terrific job of that.

So the commercial questions Frank can field; the clinical questions Roy and Roger can field, and anything else I'll try and deal with myself. Teri's going to act as triage here. So they'll all come up and then we'll be happy to take any questions you might have.

QUESTIONS AND ANSWERS

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

While we're getting settled, so if you've got a question, raise your hand. Amy and Justin have microphones so make sure that you ask your question with a microphone so that it comes up on the webcast. If you're on the webcast itself and have a question, you can email Justin Holko and we'll try to get to that question, time permitting, as well. So let's start here in the room, and Justin, if you and Amy just want to alternate on side.

Paul Choi - *Barclays - Analyst*

Paul Choi, Barclays. I have two questions. So first with respect to the first line [chemo] combination data you presented at this meeting.

Can you comment on how you perceive it as stacking up relative to the other chemo combination data sets that we've seen in the front line? And does it affect your strategy potentially for any other tumor type?

And then second, with respect to your diagnostic development plan, when we speak with physicians, a lot of the comments and questions we get are with respect to the tumor micro-environment. Can you comment on your efforts there and any data points or product timelines that we might see for diagnostic products within the tumor micro-environment? Thanks.

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

I'll do the triage. I am so motivated to answer these questions myself, but Roy, why don't you go ahead and talk about the combination data and then I'll say a bit about the tumor micro-environment.

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

If I understood the question correctly, it was comment on the front-line combination chemo data and how is that affecting our thinking in other tumor types.

So I think you've seen some nice initial data looking at chemo combos in non-small-cell lung cancer. The data clearly are provocative. They show very high response rates.

The big question, obviously, in all of the chemo combo work is how durable are these responses going to be? So this, we will find out over time and the key question is does it look more like chemotherapy, does it look more like immunotherapy or just somewhere in between? And we don't have an answer to that right now; we're clearly going to define that very robustly.

We've also looked at a number of other tumor types where, indeed, the tumors are, in fact, chemo-sensitive and we have a number of now chemo combination studies ongoing and, Roger, would you like to comment on the totality of those that we're involved with right now?

Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

Sure. So as Roger said earlier, chemotherapy is not foreign to oncologists. And so the concept of an add-on approach, which is to take an existing therapy and improve its outcome by adding a PD-1 is something that we are testing in diseases other than lung cancer.

So two examples come to mind: for example, gastric cancer, we have a three-arm study, Keynote-062, which is looking at front-line gastric cancer and the PD-1 positive population, comparing monotherapy to standard chemotherapy in combination with KEYTRUDA. So you can see there is a good example of us asking a number of questions and the assumption, obviously, would be that the potential for the monotherapy to work against the chemotherapy is obviously very real, but it's also possible that combining KEYTRUDA with chemotherapy will be chemotherapy as well, so we're looking forward to that. And head and neck cancer is another example. So those would be two just to give you a sense of we are doing this in other programs apart from lung cancer.

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

And with respect to how to find those patients who could most benefit, our approach was really to say we have no idea which things will be most predictive; let's try and measure as much as we can in tumor samples, recognizing that, for example, every part of a tumor mass may be a little bit different and each metastatic nodule may be different, one from the other.

Certainly, the goal would be to get to a point where you could do blood tests that would be revealing. And in many ways, if you believe that cytotoxic T lymphocytes are the things that are actually killing tumor cells, you ought to be able to see clonal expansion of those cytotoxic T lymphocytes, you should be able to see what they're directed against and they ought to recirculate. And so that would be the place you'd like to get to.

Our first approach was just to say well, gosh, if PD-1 is down regulating T-cell function, if that's really what's happening, it ought to be really advantageous for a tumor to express PD-L1 and PD-L2. And so, by looking for tumors that express PD-L1 and PD-L2, we'll be identifying those tumors that have figured out, using cocktail party conversation if you go to the kind of cocktail parties I go to, that those tumors have been selected for PD-L1 and PD-L2 expression because it was important to suppress the immune system.

That was our idea when we started these. In fact, it turns out that expression of PD-L1 and PD-L2, which are closely correlated, one with the other, that's really just reading out the presence of an inflammatory environment.

That inflammatory environment subsumes all aspects of the tumor micro-environment. It subsumes what's going on in terms of activators, it subsumes Tregs, it subsumes myeloid-derived suppressor cells, all of it is embedded in there.

Now you have to go in and say, okay, can we pick those things out that are important, either at the cell level or molecular level, and the answer is we're working on it. So we're trying to find things there that would be especially predictive by looking at signatures.

I think it's fair to say, we hadn't really thought that we would be able to enumerate mutational burden and that didn't seem like it was so important. But when the early data came out from non-small-cell, showing that cigarette smokers had better responses and that that was correlated with the higher mutational load, it was natural to go and look at those kinds of things. That may turn out to be a more powerful approach.

I'm still speaking from an immunological standpoint which is the way I grew up. I'm still interested in finding which cells actually are responsible for recognition and killing and why they work and what's wrong with them when they don't. So that's still what I'm trying to get at [as soon as we can].

Chris Schott - *JPMorgan - Analyst*

Chris Schott, JPMorgan. Two questions. The first when we think about first-line lung and the role for monotherapy KEYTRUDA versus combination. So we look at the chemo combo data you've presented, we look at some of the Bristol data with ipi or even in some of the very high expressed, there's just still seemingly seeing enhanced efficacy by adding something to PD-1. What role, over time, do you see for monotherapy? At this point, is it going to become a combo market based on what you're seeing today? Or do you still see there's going to be subsets of the population where just monotherapy is going to be an acceptable treatment?

My second question is also on the chemo combo data. You've shown some great response rate data. Can you just talk about the depth of response and the time to response that you're seeing relative to monotherapy? I don't know if you've seen those spider plots but just qualitatively, what type of responses are we seeing in the responders and is that different than what you see with just monotherapy? Thank you.

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

So first, we'll deal with the clinical data; remember, there's not an enormous amount of it, but we'll deal with the clinical data first. And then, Frank, I'll turn to you to talk about the market because I think it's important to understand that too. But, Roy, maybe you want to start with monotherapy and then, Roger, you can talk a little bit about the characteristics of the chemo combinations and what they look like.

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

So the question really goes to the issue of is there a place for monotherapy given the striking results that you are seeing reported in combination. I think that no combination is for free; every combination comes with some baggage. It's going to be in the form of toxicity.

So if you could identify the patient for whom monotherapy is all that's needed, that would be a great service to that patient because there's no question that monotherapy can induce very profound, deep responses and they are very durable. In fact, you saw today in the melanoma presentation just how durable those are. So no question there will be a place for monotherapy.

And actually, quite a substantial place. For example, if we look at our non-small-cell lung cancer data, when we select patients using PD-L1, recognizing it's not a perfect biomarker, but using that, we get a response in one out of every two patients. That's remarkable. So for about half of those patients, in fact, nothing else is probably going to be relevant.

As we look at the combination question, I'd caution about over-interpreting early readouts from checkpoint combinations. The data that you saw here were very small numbers and pretty short follow-up. We have no idea about durability or anything like that.

So I think, as a practical matter, monotherapy will continue to be very important. Where we think there might be well a place for moving quite rapidly to combinations would be in those populations that are probably not destined to have a high response rate. So, for example, those that are PD-L1 negative or patients who, by other criteria, may not fit into a good prognostic group.

And then, Roger, if you want to comment on some of the details of the combinations?

Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

So time to -- so depth of response, if you look at the waterfall plots that we generated with the chemo combinations, particularly say with Cohort [beta], they're deep and they're very impressive [visually].

Time to response is dependent on when you do the imaging. So it's a fixed period in time from initial enrollment and I don't believe there's any -- that you can make anything particularly around time to response. We see across the program, notwithstanding Roger's comment about very late responses that develop, the bulk of the responses occur relatively early and that's just monotherapy and it's the same with chemotherapy.

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

And maybe just to add one comment. The melanoma data that were presented in today's session were actually quite informative. So if you believe complete response is a good surrogate for depth of response, actually as you looked across those programs, the combination of two checkpoint inhibitors look no different from the complete response rates seen with monotherapy in melanoma.

So again, I think there's been a huge over-interpretation of this depth and breadth of response. In fact, we're very, very impressed with monotherapy depth of response.

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

Yes, I think the one-word summary from the Roswell Park discussion of the melanoma data was, wow. And that's right. It really is. Even in monotherapy it's just, wow, quite amazing.

So, two things to emphasize. The first is a lot of patients with cancer are elderly and in an elderly population. Of course you want to avoid adverse experiences as much as you can because you don't want to burden them and they often have co-morbidities. Bring back Jimmy Carter, a 91- year old, and he's a pretty healthy 91-year old, how much do you want to burden someone at that age with an adverse experience?

So, that will play in and it will be a very personalized decision, as it always has been for practicing oncologists that are working with patients, to try and figure out what the right approach is. And in many cases monotherapy will make a lot of sense, because of other co-morbid conditions.

The other thing that will play into it, of course, is the market environment. Here to tell us about the market environment is Frank Clyburn.

Frank Clyburn - *Merck & Co Inc. - President - Merck Oncology*

So, Chris, I think, to answer your question, just to follow up on Roy's point, if you're getting a high response rate based on enrichment strategy from monotherapy, I can tell you not only here in the US but as you go outside and around the world, that is very important data. There are a lot of questions with regards to the value that the combination is bringing over monotherapy as well as not only just the toxicity potentially profile that Roy talked about but also the economic aspect.

So I think there is going to be a role for a substantial amount of patient monotherapy and we've seen the high expression, [which shows] this could be one-third of your patients, this could be 40% of your patients.

I think the next question is then, for those that do not respond, as we were talking about, it's likely going to be combination. I'm actually, personally, very excited about the data we showed today or in Keynote-021. Clearly we'll have to see what happens with regards to our trial on 189 in non-squamous and then obviously our trial in 407 as we're looking at combinations there.

So to answer your question, Chris, I think you're absolutely going to see monotherapy place definitely in the US but I can tell you outside the US that's -- I really get a lot of questions around that. And I think that's the way they're going to want to really try to treat many of their patients, based on the data we've seen today.

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

Okay, thanks. We're going to take a quick question from the webcast. This is from Tim Anderson at Sanford Bernstein.

Merck continues to say that it's less enthusiastic about combining KEYTRUDA with CTLA-4, yet a couple of days ago the updated 012 data from BMS was compelling.

Can we assume Merck might rethink whether running combo trials with ipilimumab makes more sense now? If nothing else, it would be an insurance policy in the event that BMS and AZ phase 3 trials look solid once they report out.

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

So, again, I think we've sort of discussed that. We've demonstrated, as have Bristol Myers, that the combination of CTLA-4 with nivolumab, that you get actually an improved response, particularly in a PD-L1 negative population, which is in a way not surprising because of the known association response in the (inaudible) positive.

The question is what is the role for that combination. Where is it best used? It brings with it very substantial toxicity and we still don't know or understand the magnitude of the benefit. Even in melanoma, for example, we don't yet know whether the combination of nivolumab plus ipilimumab behaves better than nivolumab alone with respect to a critical result and that is overall survival.

Those data we had thought were going to be presented, actually, at ASCO this year but we're not presenting, so we don't know what's going to happen with those data. It's important to see those data and our own data, other data, but we -- of course we see ipilimumab as being one thing that could be used in combination and as the data emerges we'll adapt to it, of course we will.

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

Okay, thanks. Let's take another one from the room.

Unidentified Audience Member

Roger, just following up on 021, the Keynote combo, we've repeatedly seen that response rates can at some point become disconnected with overall survival. When you look at the OS curve in Keynote-021, it looks remarkably similar to what we've seen with PD1 [monitor]. I think the one-year OS is about 7%. So, if you could comment on what (inaudible) survival.

And a follow-up for Frank, if I may, on the market environment. How do you think PD-L1 screening will play out and if you could add color as well? [The academic institutions, so] the community, are they going to adopt all the different tests? Are they going to use their own? Are the physicians going to get a detailed report about the specific number or just yes and no? Thank you.

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

So, first with respect to overall survival, which of course is the key result. In order to get overall survival, you actually have to wait long enough to see it and what we're really interested in -- the whole logic of immune-oncology was that you were going to bend the shape of the survival curve. Because for years those of us who've been trying to develop drugs in oncology and registering drugs in oncology, have found that we would move overall survival by just a few weeks, despite the fact that responses sometimes were very impressive.

What was so remarkable about ipilimumab when it first became available was it seemed to be bending the shape of that curve and there was a tail that went out for a long time. And with KEYTRUDA it appears that there's a similar tail but it's higher up. It may have similar durability, we just don't know, but for KEYTRUDA we have in melanoma three-year data and we still don't know.

To start talking about where we are with the chemo combinations, where we have six months and follow-up, we have no idea what those survival curves are going to look like. We're hopeful that high response rates will translate. Certainly in the monotherapy data that we've seen thus far, response rates, particularly complete response rates, are associated with quite long survival but we just don't know. Time will tell.

Frank Clyburn - *Merck & Co Inc. - President - Merck Oncology*

On testing, right now we're seeing about -- and we're very encouraged, probably about 60% of oncologists are testing. The majority of that, I think, are still in the early lines of first-line therapy and that continues to ramp up.

We are spending a significant amount of time, and I think this is really what will help us as we move forward, hopefully, in early lines of therapy, we're working with key stakeholders, we're working with pathologists, we're educating them. Even this week, just in talking to a number of oncologists, they see testing continuing to increase.

So, I think what you're going to see, once you move to early lines of therapy and everyone is basically, has an enrichment-type approach, I think you're going to see very high testing. I have no doubt about that. And then as far as how the product is labeled, it's really labeled for an FDA-approved test.

To your point, some people are using lab-developed tests in some of the institutions, or academic institutions. Some, obviously in the US, are using a lot of the reference labs. But we're confident in what we're seeing, especially right now and as we move, hopefully, to early lines of therapy, that testing will become pretty standard, especially in non-small-cell lung cancer.

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Steve Scala - *Cowen and Company - Analyst*

Steve Scala, Cowen and Company. In head and neck I believe the phase 1 Keynote-012 study had eight CRs. In the confirmatory phase 2 Keynote-055 trial, I think there were no CRs. What are possible explanations for the difference in the CRs generated in those two trials?

And Dr. Perlmutter, I think you said that Keynote-024 would end in weeks. I'm just wondering, will Merck have the data in weeks and will we have the data in a similar timeframe and does Merck aspire to present it at ASMO. Thank you.

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

So, Steve, I'll answer that last question first, which is that we will have the data within weeks, we expect, based on the event rates and processing of the information, and that you will have the data within three days of the time that I see it. So you'll be the second to know. Depending on -- these things can always fall apart in these kinds of analyses, but that's our expectation. And then, depending on what the timing is, then we'll try and get it into the appropriate [site]. Pretty straightforward, no secrets here.

And with respect to the difference in CR rates, maybe, Roger, you'd like to --

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Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

Yes, it's a question of timing. So, Keynote-012 is a nice mature data set and I think we do see this. We see PRs convert to CRs and stable disease convert to PRs over time.

So, notwithstanding my earlier comment that the bulk of the response is seen early, CRs do take time to develop. So that cut of data for Keynote-055 was based on six months follow-up; it's too short to make any comment but I think we're confident that the [early mature] Keynote-012 data is likely to be recapitulated with the follow-up.

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

Let's go to Mark in the back.

Unidentified Audience Member

Based on the preclinical work, what are some of the new internal candidates that you're working on, you're most excited about as you're moving into the clinic now? Whether it's going to be a monotherapy or a combo with KEYTRUDA.

And then second of all, just on pricing of these combinations as we move forward. How is Merck thinking about it? Is there any type of strategy where we end up where one plus one equals less than two?

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

So as far as -- again the problem with the pre-clinical work is that everything seems to work okay. And then you go in the clinic and it does too. So in terms of excitement, I must say that I don't feel as if I have a lot of predictive value.

I certainly would not have guessed that a next generation folate antagonist like Alimta, in combination with KEYTRUDA, would give the kind of results that we're seeing. That's something to be pretty excited about. That's gives -- that's really important for patients.

In terms of the new therapies, all of them look very exciting. How that will play out, whether [biotin] antagonism will play out well, or LAG3, or Tim-3. Frankly the logic behind the CEACAM is really powerful and it's hard to know how those will play out. And the only thing we can do, at this point, the clinical data is so far outstripping the fundamental research that we are in this empiric environment.

One of the things that I hope you all realize is that the environment for clinical trials has changed dramatically. If you look at how quickly these clinical trials are enrolling around the world, not just for us, but for everyone. Look at how rapidly patients, even with rare malignancies, are being ascertained and brought in. In part because of the NCI clinical trial network.

But there's so much more awareness and so that means that we can get a lot more done. Particularly when we take this approach in setting a statistical threshold and saying, let's look at groups of 25 patients at a time. Those patients are relatively easy to ascertain. So we're getting a lot of information from those kinds of studies.

The next question was a market question.

Frank Clyburn - *Merck & Co Inc. - President - Merck Oncology*

Well I think it was the pricing. Just to make sure, you were thinking about our own assets, if the bolt-on one and one was two

I think if you look at it, the way in which we approach pricing is really based off of the value and the data that we're bringing forward.

So for instance, when we price KEYTRUDA, we spent a lot time looking at the current market, looking at the advantage or benefit that KEYTRUDA brought over standard of care. And then determine what the price we thought was appropriate for physicians, patients and payers.

It's no different in a combination approach. We have to look at the data, we have to look at that data. How does it stack up to standard of care? As you know, in many markets around the world, many health technology assessment bodies do cost effectiveness models etc. So you have to take all of those things into consideration.

But really as far as with the clinical data and the benefit that the combination brings over standard of care and then at that point in time we'll be able to make a more informed decision around pricing.

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

I think the only circumstance under which you actually can take advantage of the price/ volume, a trade-off that you're talking about, is if -- in the environment where you can co-formulate, and you can administer.

KEYTRUDA, for example, if something else that's formulated in the same way, then in essence, you could drive KEYTRUDA volume because you're adding benefit and packaging the things together. The likelihood of that is obviously small.

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

One other consideration as well is, you've seen a lot of these combinations work. You can imagine if generic chemotherapy as KEYTRUDA works, that looks similar to, for example, [two IOs] together. I think you know which direction that value story will go pretty quickly.

Vamil Divan - *Credit Suisse - Analyst*

Vamil Divan, Credit Suisse. Two questions, if I could. So first on the combination therapies. I think one of the messages that came on in a lot of the presentations, that it's not one size fits all (inaudible). And so in KEYTRUDA you guys are going to be putting more towards [that dose] (inaudible) tumor type. How do you think about that when you go to combination in terms of maybe to change the dosing for KEYTRUDA?

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

I don't think there'll be any different dosing for KEYTRUDA. One of the reasons is that actually the exposure doesn't actually change very much. Because you plateau in exposure and there's also so much variability.

So that if you look at just a PK measurement, forget pharmacodynamic measurement, just look at PK measurement. It really doesn't make any difference whether you're giving [10 q2 or two q3].

So that is a feature of the -- it's not uncommon by the way, that for many monoclonal antibodies they have very flat dose response curves in PK. That's been true for a very long time. So I don't expect the dose -- we've gone to a unit dose of 200 milligrams, [q3]; I think that's what we're going to be giving.

Vamil Divan - *Credit Suisse - Analyst*

Thank you. The second question is just on [radiation] therapy. Again thinking about the cost of this therapy (inaudible). I want to get a sense of how long do we need to keep [this in vision].

If you can talk about it, one, from a clinical side? Any work you're doing around how long patients need to be treated? It's been almost two years now since the product's on the market. (technical difficulty) in terms of how long (technical difficulty).

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

When we started out the program we were dealing with, obviously, people that had failed every potential modality. So very reasonable approach was to simply treat the progression.

We've had some wonderful stories that have emerged from this. Imagine being called up by someone who was in the earliest trials, now four years out and saying, I really love you guys, but do I have to get a CAT scan every six or nine weeks?

These are amazing stories. So in fact, clearly there are people having wonderfully long results. And if you actually were at the session today, as they looked at the outcomes in some of these patients, those that achieved CRs, there are a large number now that have been off treatment for 10 months, [haven't] progressed.

So that's incredibly exciting. So that's shaping our thinking now. So typically what we're doing now is basically, if anyone achieves the CR, we'll treat for a few cycles past that and stop, follow and then potentially restart, if they recur.

In most of our trials today, we're looking at two years of treatment. And in patients who are going, have begun to go in adjuvant therapy, that is to say they've had their definitive surgery, they've got minimal residual disease, there we're looking typically at a year of treatment. So those are the types of intervals that we're looking at now. Roger, did you want to add anything?

Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

No, I think that's exactly right.

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

One thing I would add about it and then I'll let Frank talk about it from what he's seeing in the marketplace.

But certainly as I've gone around at this ASCO meeting and talked with a lot of practitioners, this is something that everyone wonders about and everyone is experimenting with a little bit. And they're trying to -- because each patient management decision is unique; as you can imagine there are a lot of patients. If they are experiencing a response, but it's not as complete response, when the physician suggests to them that maybe it's time to stop, they're not so sure they want to stop.

We don't know what the right answer is. But there will be a systematic exploration of this and it's very important that we understand.

Frank Clyburn - *Merck & Co Inc. - President - Merck Oncology*

It's no different in the marketplace to what you've just heard, is that it's a question that's on a lot of folk's mind. And actually the patient plays a big role here. That's what we're hearing, is that there are patients expressing when they respond, they want to stay on. And you know the safety and the toxicity of the profile of KEYTRUDA is great.

So it's not a hard answer right now. We still need to explore it, but you are clearly seeing patients play a role here. And those that are responding are wanting to continue to receive treatment. Even two years and beyond.

Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

And I'd like to say as a comment, the toxicity profile doesn't change over time. Mostly of the events are front loaded. So it's possible to give the drug chronically and I think we don't want to miss out on maximum treatment effect.

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

We recognize that we're bumping up against time, but we still have a few questions in the room that we want to get to this morning. So we're going to go to Seamus and then we are going to go a little bit longer there to try to get a few more of these questions.

Seamus Fernandez - *Leerink Partners LLC - Analyst*

Seamus Fernandez, Leerink Partners LLC. So just a couple of quick questions. Frank, can you just help us understand how you changed the current trajectory of market share in lung cancer? What are the key dynamics that are really going to change that? Is it the Keynote-010 study and getting that in the label? Or is it really the front-line message that starts to change the market share dynamic?

Second question is for Roger. On the first quarter conference call you specifically mentioned that it takes quite a while to develop agonists. We had data for two agonists at this meeting, one of which KEYTRUDA was partnered with.

Can you help us understand your thoughts around the 4-1BB data, particularly in the context of Roy's comments that he would anticipate that a combination should have some incremental toxicity. That was, I think, something truly dynamic about that combination and almost un-understandable. So that would be great.

And then lastly, as we think about the mix of opportunities in hematologic tumors, how different is the solid tumor marketing effort versus the hematologic tumor marketing effort? Thanks.

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

Frank, maybe you want to take the two marketing questions first.

Frank Clyburn - *Merck & Co Inc. - President - Merck Oncology*

Sure. All this I think is -- we are waiting, obviously, to get the label updated with Keynote-010. And I think that will help that it puts into label overall survival. It really shows a broader [PD-1] population. It will help I think. But it's still within the second line and that's something that we're obviously building on and building upon.

As far as the shift, the way I would think about it, I do think obviously first line is very important. And who gets there first with what data set. And the thing that I think we're very excited about is the foundation that we're building with the community around testing and the benefits when KEYTRUDA is used in that enriched strategy, we're seeing real and hearing real good positive results. So as you move to front line we think that obviously is going to be a really important opportunity for us.

There was -- I think, Roy, you had one, or the other.

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

Well let me just say, with respect to how you develop these things in combination, the agonism is hard, and particularly for agonists that are powerful because the risk of anaphylaxis is significant. And you can have cytokine storm syndromes that are actually deadly.

So we've advanced those very, very, slowly. But there are agonists that have already been looked at where a lot of information is available, quite a lot of information from 4-1BB, the Pfizer antibody, just one example of that. That was talked about a little bit at this meeting.

A good example is you would actually consider the T-VEC virus to be an agonist, a [GNTSF] agonist. That's well understood. And those data too, where we were able to get those kinds of data together. T-VEC of course has almost no adverse effect profile. There's still a little bit of cutaneous reaction, some flu-like syndrome sometimes, but it's basically very benign. And so that is a particularly easy one to pair together. But there are others too. So Roy, [if you'd like to comment on that].

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

So I think 4-1BB you asked specifically about. That's quite a small early phase study. Clearly there's responses there. It's impossible from those data to know whether they're different from what you might have expected with pembro alone. So I don't know that we really can say a whole lot about that. Certainly of the dose tested, there didn't appear to be much by way of toxicity.

I think what we've seen in all of the trials that have tried to look at ipilimumab together with a PD-1, there's a heightened degree of toxicity. Certainly our early experiences with, for example, IDO-1 toxicity looked actually modest. In fact, for the most part very manageable and really not excessive. We've certainly got other examples where we've put TKIs together with PD-1 antibodies. And we've had a variable toxicity profile. So axitinib plus PD-1 looks actually quite good.

If we take pazopanib and put it together with PD-1, we actually see quite a lot of hepato toxicity, almost additive hepato toxicity. So it's not a one size fits all. And I think each one of these is going to have to be explored in a fairly fulsome way to really understand the toxicity profile.

I think to add just one other comment, just looking at the melanoma data; if you look at the experience, for example, putting ipi plus PD-1 together, or you look at putting something like IDO-1 together with PD-1, or if you look at putting T-VEC together, all of them have -- now again, these as a cross-treatment comparisons that we'll obviously caution don't read too much into them, but actually, broadly, the efficacy looks similar but the toxicity looks actually very different.

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

So summing overall, no shortcuts. We're just after the data. It takes a while to figure it out.

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

Tony, we'll go to you in the front.

Tony Butler - *Guggenheim Partners - Analyst*

Tony Butler, Guggenheim. Dr. Baynes, just remind us what is a platinum doublet in first line look like with respect to duration and response so that we have -- we're all on the same playing field when we do see the 024 data?

Roger, let's go back to the agonist question and I maybe was at the cocktail party you were alluding to earlier, but I really thought we'd see GITR this past weekend and maybe -- clearly we didn't --

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

I told you we wouldn't.

Tony Butler - *Guggenheim Partners - Analyst*

Here's the real question, is it because of this agonist comment around 4-1BB and what you may see on cytokine storm? Or is it one of the lesser side effects because -- [if it's] dosed correctly and then -finally --

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

We've just gone very, very slowly. That's all. We did that. And you won't see anything until we're [combination] (technical difficulty)

Tony Butler - *Guggenheim Partners - Analyst*

And, Frank, really non-US, you've done a good job in melanoma. What are you seeing with respect to the payers there in pushing back with respect to other therapies that may be available, clearly not as good as using pembro alone in combination with other [umbrella] combinations [direct]. I want to understand non-US. Thanks.

Frank Clyburn - *Merck & Co Inc. - President - Merck Oncology*

There was another one you had, Tony, as well, the doublet.

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

Roger, you're close to] those data you talked to.

Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

Sure. So it's probably 35% response rate. Medium PFS, five months, six months, something like that. And OS around 12 months. Those would be sort of reasonable doublets. Duration of response I don't think chemotherapy trials report out that type of data. They focus on PFS, OS.

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

The PFS data though are well understood. I think if you look at the doublets in front line, median survival is on the order of 12 months and the medium PFS is on the order of about (technical difficulty).

Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

That's pretty typical.

Frank Clyburn - *Merck & Co Inc. - President - Merck Oncology*

And just on ex-US, Tony, we're very pleased with the early progress with regards to reimbursement, the value proposition that we're seeing. We're seeing actually not only the product getting registered in regulatory [teams]. We've done a tremendous job in getting the products registered. We're seeing very quick reimbursement and reimbursement decisions around the world.

That is, I think, also the beauty as we talked about, and sometimes we don't spend enough time talking about the slide Roger mentioned on 006. So around the world, KEYTRUDA is replacing ipilimumab in melanoma right now. They see the value. They're reimbursing it. And it's being used, which encourages us as we go forwards.

So we feel good, Tony, about what we're seeing. And I think it speaks also to Merck's capabilities and footprint globally. We have significant footprint, significant relationships, with Ministries of Health, with the HTA bodies. This is something that we do very well. And we're very encouraged by what we're seeing.

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

We're going to squeeze one more in here, let Jay ask a quick question before we close this out, because I know there's other events going on.

Jay Olson - *Goldman Sachs - Analyst*

Jay Olson on Jamie Rubinstein, Goldman Sachs. Congratulations on all the data you've presented here. And thank you for taking my questions, I have three of them. But they're quick. Regarding Keynote-164, which we understand is registrational phase 2 in colorectal cancer with high microsatellite instability, do you need both cohorts from that study to file? Or since Cohort A is already fully enrolled, could you potentially file sooner with Cohort A alone?

And second of all, Roger, you spoke about the predictive value of various biomarkers. Can you help us to understand the rule of HPV positivity in predicting response to KEYTRUDA for the treatment of head and neck cancer?

And then finally with regards to Cohort D and Cohort H in Keynote-021, conducted in second-line non-small-cell lung cancer, when Cohorts A, B and C, were conducted in first-line non-small-cell, why didn't you study KEYTRUDA with ipi first line? Was there some pre-clinical or other data suggesting that there would be particular incremental benefit to adding ipi to KEYTRUDA in the second-line setting? And, if so, how should we interpret the results which suggest that there was no benefit? Thank you.

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

Right, so the first question is related to filing strategy with respect to microsatellite instability. And the reality is we, I can't speak for the FDA, all we can do is pull the data together, look at the responses and go and have a meeting with them and say does this make sense or not. So we don't -- I can't tell you the answer to that. But obviously depending upon the magnitude of benefit, we want to have that kind of discussion with them. If it's necessary to have more data, then we need more data to understand it better. That's kind of where we get to on that.

Let's see, what were the other questions? The role of HPV. There is no role so never mind. Because it works on HPV positive or negative. And they can't really tell the difference. So there's no role.

And then the last question was why second line as opposed to first line. There's actually -- there are several stories to that. But Roger, maybe you want to pick that one up.

Roger Dansey - *Merck & Co Inc. - SVP, Global Clinical Development Oncology*

It pre-dates me somewhat. But I certainly can give the story, if you like. So ipi, to the point of evaluating patients with therapies that are unknown in terms of the toxicity profile, and at the front line, patients will benefit from chemotherapy. It's appropriate to begin a chemotherapy pembro combination in front line and then evaluate the other more experimental investigations (technical difficulty).

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

Chemotherapy is already approved for front line. So pretty straightforward.

Roy Baynes - *Merck & Co Inc. - Head of Clinical Development*

Maybe just to highlight that if we select front-line lung cancer patients, the response rates of monotherapy are actually exceptionally high. And the durability of those responses are again quite exceptional. So we've actually presented those data. And I think, gosh, if we could recapitulate that in the pivotal trials, that would be a home run.

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

Sure would, would be great. Huge effect for patients. I think we're done?

Teri Loxam - *Merck & Co Inc. - Head of Investor Relations*

Thanks to everybody in the room and on the webcast for joining us. I know we went a few minutes long. But we had a lot of exciting data at this meeting, a lot more to come. So thanks to the Merck team as well for answering all those questions. And we look forward to the next several years as KEYTRUDA continues its journey.