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OVERVIEW:

Co. provided an update on oncology.

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PRESENTATION

Teri Loxam *- Merck & Co., Inc. - Vice President, Investor Relations*

Good evening, everyone. Do you want to take a seat, if you want to get some food or drinks? Thanks for joining us tonight. I'm Teri Loxam, Head of Merck IR. Joined with me tonight is Roger Perlmutter, President of Merck Research Labs; Frank Clyburn, President of our Global Oncology business unit. We plan on going through a few slides, followed by Q&A.

And with that, we'll get started with Roger.

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

Thanks, Teri. Welcome. Thank you all for coming. We're going to spend just a few minutes reviewing some of the material that has been presented here, taking into account the fact that we had quite a lot of data that came out in advance of ASCO 2017. It's been a really exciting meeting, I think, for many of us, kind of breathtaking the scope of data that's been presented. So this, of course, is our forward-looking statement.

Our strategy really has been the same from the very beginning, and that is, to me, it was extremely important seeing the early results from the 001 study that we had to establish what monotherapy looked like, what was the spectrum of activity of KEYTRUDA monotherapy. Keep in mind, as you all know, that, in KEYTRUDA, we're treating the host, not the tumor. What we've learned across a variety of studies is that, that results in meaningful responses and a whole variety of different tumor settings. But evolving from that monotherapy platform, we always knew that it was going to be essential to understand exactly why it was that patients didn't respond to KEYTRUDA and to search for combinations that would improve that still further. And the basis of doing that is, in part, to understand at a very deep molecular and cellular level what's happening in tumors, what exactly happens in a patient with malignant, and particularly metastatic disease, when you introduce KEYTRUDA, activate an immune response or permit it to be re-elaborated. And that immune response then, once revealed, eliminates a lot of tumor cells. What happens at that interface? What is the recognition event? How does that tumor destruction take place? And that, as some of you have seen, maybe personally, and you certainly have seen in photographs, very large tumor masses can shrink very fast as a result of KEYTRUDA administration. It's quite extraordinary. But thereafter, though most responses are durable, there are some people who fail and there are some people who are also resistant. Why is that? And how can we address that scientifically?

So we have now, having begun this program 5 years ago or so, the broadest program directed at understanding exactly how PD-1 blockade reveals the preexisting immunity against malignancy in cancer patients with more than 500 trials at ClinicalTrials.gov. At this point, more than half of those trials are combination studies. And that 500, of course, includes registration-enabling studies, a small number of registration studies, by comparison only about 40 or so at this point, as well as a large number of other studies that are being done with collaborators. I think you all recognize the accomplishments that have been made. And I want to point out that those accomplishments have depended so much upon the very, very gifted team of oncologists who work in Merck Research Laboratories and led by Roger Dansey, who's in charge of the late-stage oncology, and Eric Rubin, who is in charge of our early-stage, and overall by Roy Baynes. And all 3 of them are with us here tonight in the front seats so they can provide additional perspective on the program. But we have breakthrough designation for KEYTRUDA, as the slide says, in 8 different tumor types, approved in 10 different indications, that's with tumor types and lines of therapy, and ongoing launches that are being carried out by Frank and his colleagues in more than 60 markets for melanoma, more than 50 markets for lung. We believe, we are delivering on the promise of KEYTRUDA and bringing the benefits to an awful lot of patients around the world.

So just to give you a feel for this, this is a slide that we update as we obtain more data. It's a set of waterfall plots where we're looking at a variety of different tumor types, in this case 20 different tumor types. We have more than 30 tumor types under study. And you can see circled are those tumor types in which we have gained registration in melanoma, in non-small cell lung cancer, head and neck cancer, and bladder cancer most recently, and also in classical Hodgkin lymphoma. We also have gastric cancer under review. Each one of these waterfall plots shows you the set of responders, where the green lines are going down, as well as those in whom the tumors progress. And you can see the variability in responses that occur. For example, if you look at classical Hodgkin lymphoma, in those people who have failed all therapy, rigorously failed all of the therapy, including stem cell transplant, the response rate to KEYTRUDA is over 90%. So most -- the vast majority of patients respond in terms of tumor shrinkage. And we see something in the order of 75% tumor shrinkage, not all of those meet RECIST criteria, but 75% tumor shrinkage in a melanoma setting.

In contrast, if you look at some other places, we have very low responses. In colorectal, you'll see that there are very few responses, that's the second line farthest over to the right. And virtually, all of those responses are in patients who have DNA repair defects. They have microsatellite instability. And we recently received approval for the first time for the FDA for the treatment of patients who have DNA repair defects as evidenced by microsatellite instability, which results, we believe, in a higher mutational burden. And we can demonstrate that, but we believe that's the mechanism that results in responsiveness in those solid tumors that otherwise would not respond terribly well to KEYTRUDA.

These data that you see here in terms of responses are, of course, also supported by very impressive improvements in overall survival. That's true, for example, in the first-line in the melanoma setting, comparing 2 different doses of KEYTRUDA with ipilimumab. It's also true in first-line non-small cell lung cancer in the PD-L1 high population from the KEYNOTE-024 study. Of course, we showed in second-line, in non-small cell lung cancer versus docetaxel chemotherapy and also in second-line bladder in the 045 data that were just presented today and for which we recently achieved approval -- FDA approval. Very impressive improvements in overall survival that are actually having a big impact already. One of the things that I heard many times in the course of the meeting today was -- today and yesterday, was having academic oncologists, whom I knew over the years, come to me and say that they actually are in a situation now where their practices are so busy, particularly in pulmonary oncology, that they need more hands, more oncologists. Because more patients are returning, more people coming back, and they're being managed by oncologists. So I think there's an impact already that we're seeing as a result of the advent of immunotherapy, and it's an important impact when people are surviving longer.

So we have many registration-enabling studies underway. I mentioned the number, 40. The list includes those that you see here, across a very broad range of interesting and important indications. So for example, asking the question whether patients who have resection, definitive resection for melanoma but are at high risk for recurrence, whether an adjuvant administration of KEYTRUDA can prevent recurrence in that population. And that adjuvant study is obviously a very important advance, moving up the lines of therapy in melanoma and offers the promise of taking, in many cases, are very young people who have many years of life ahead of them and ensuring that they can actually live those lives. The reason why we can do those kinds of studies, it's not lost on you, is that KEYTRUDA is very well tolerated compared to many other kinds of therapies, and so you can administer KEYTRUDA in that kind of setting to patients who have undergone definitive resection and are otherwise healthy. Many, many other studies to point out, in head and neck cancer, obviously in lung cancer, GI, and bladder cancer, triple-negative breast cancer. And there are some interesting data that was presented here about breast cancer, which we'll talk about in just a minute.

So at ASCO, there has been a huge number of different presentations. We, ourselves, had more than 50 abstracts across 16 different types of tumor. That's just from our own presentations and doesn't include presentations from many of our collaborators who use KEYTRUDA. Some of the highlights, of course, the extended data from KEYNOTE-024, our first-line non-small cell lung cancer study done in the setting of greater than 50% tumor proportion score PD-L1 positivity, an oral presentation. We presented updated data on KEYNOTE-021G, which is the chemotherapy combination study for which we received first-line approval in non-squamous, non-small cell lung cancer just a few weeks ago. We also presented data from the bladder studies, as I've mentioned, data from our third-line gastric study, and the breast cancer data, both our own KEYNOTE-173 data, early data, and also the I-SPY 2 data, which has been done as part of a collaborative effort with a government-funded agency.

So just to look at the KEYNOTE-021G. You'll recall from the initial presentation of these data, back at the European Society for Medical Oncology, that there was a near doubling in the response rate as a result of adding KEYTRUDA therapy to the combination of carboplatin and pemetrexed, which is a very common chemotherapy regimen, as you know, which -- and that was associated with a very impressive improvement in progression-free survival. At the time, the data were immature, it was not yet possible to see an overall survival benefit and also there's substantial crossover in the population. Despite this crossover, which is now about 75%, despite this crossover, you're beginning to see a trend towards improvement in overall survival. So that's demonstrated in this slide, and that trend is, if continues to improve ultimately, I think will get to a point where people recognize that indeed the same kinds of benefits that we saw with KEYTRUDA low and the PD-L1 high will inure to this population as well. Importantly, these responses seem to be durable, as they typically are with KEYTRUDA treatment.

So beyond that, the KEYNOTE-024's data, as I mentioned, continues. And it's very gratifying to look at these overall survival data and see as we look out the past nearly 2 years now that we still haven't reached median overall survival in this patient population. And keep in mind that these are patients who, prior to the advent of chemotherapy, had median survivals that were much closer to 1 year. So that's a huge improvement. Again, the responses tend to be durable, so really quite impressive.

The bladder data from KEYNOTE-045 and KEYNOTE-052 were presented today and you can see the overall survival data comparing KEYTRUDA to chemotherapy in the second-line bladder setting. It's unambiguous with a hazard ratio of 0.7 and a p-value with 3 zeros to the right of the decimal point. Really a very strong result and gives us a lot of confidence going forward in the bladder cancer setting. And if you look at the first-line setting, there, the data of course is substantially less mature. First-line is actually looking at the population that's cisplatin-ineligible. So that's the reason that we can go forward in that first-line setting and in that cisplatin-ineligible population response rate of nearly 30%, which is, again, very gratifying.

We also had the opportunity to present data today from the KEYNOTE-059 study, cohort 1. This is looking at advanced gastric cancer progressing after at least 2, and often, more lines of therapy. This is an extremely difficult tumor to treat, nearly 12% overall response rate, which is not perhaps what we would have hoped for in our wildest dreams, but again, these are patients who really having exhausted 2 lines of therapy, have little in a way of effective options that they could look for. And I would point out that there is an effective PD-L1 positivity in this population. The PD-L1 positive patients have nearly double the response rate that PD-L1 negative population does. So this is a population in whom we have Priority Review and PDUFA date is September 22. So really quite enthusiastic about bringing the benefits of KEYTRUDA to gastric patients more generally.

And finally, with respect to breast cancer, I think, the interesting thing is when we look at the pathologic complete response rate in breast cancer, which is a demonstrated surrogate for more favorable outcomes, in the pathologic complete response rate in patients who are receiving neoadjuvant therapy, so that's using chemotherapy prior to surgery in order to -- as it was described, debulk the tumor, but it probably has many other effects. In this case, we're using KEYTRUDA chemo combo therapy in order to look at the pathologic complete response rate, which, in the triple-negative compartment, as you see from the I-SPY 2 trial, is tripled. And in the hormone receptor positive HER2 negative compartments, these are very aggressive breast malignancies. There too, more than doubled, nearly tripled. So quite dramatic improvements in pathologic complete response rates. And though this study, which was run by the I-SPY group, the study is done in such a way that they try many different combinations and depending upon the results, using a Bayesian analysis, the therapy can graduate into a more definitive study. We received the news from them that KEYTRUDA had graduated. We're proud of our new graduate.

So breast cancer, I think, is a really important indication. There's a lot of opportunity here for us to do a great deal of good in patients who really have very few options, particularly in the triple negative breast population, as many of you know.

So tremendous progress in establishing KEYTRUDA as a fundamental foundational cancer treatment across a broad range of tumor types. Lots of opportunities to combine it with other therapies using a very scientific approach to try and identify those things that will improve lymphocyte activation, improve priming, improve durability and increase the representation of recognizable epitopes on those tumor cells that the immune system must attack. So the waves of therapy are shown on this slide. We never really envisioned them in waves, but they seemed to be arriving that way. And we are investigating, as I say, more than 30 lines of therapy. It's a terrific opportunity. But beyond that, the combinations promised to be extremely interesting. Some of them that we have developed internally are outlined here on the slide. Those that we've developed internally that are in the clinic are shown. I would point out, that includes, as I said, things that our direct immune agonists, the GITR and STING agonists, for example. We have others in the works. Things that act to relieve the antagonism that may be present in the tumor environment. And we also have a variety of approaches to the tumor microenvironment. And in addition, we're doing a lot of studies in collaboration with, for example, Incyte, on epacadostat for IDO and in the development of vaccine technologies, which could be viral-based vaccines and could also be RNA-based vaccines, our collaboration with Moderna. An extremely broad program, an extremely powerful program, and one that is yielding results that make a real difference for patients around the world.

So we started with this strategy slide. It's been the strategy for a very long time and continues, in general terms, to be our strategy, and we continue to execute.

Thanks very much, and we'd be happy to take any questions you might have about our approach in oncology, in general, and KEYTRUDA, in particular.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Yes, thanks. And I just wanted to mention to everyone, I should have mentioned before, the slides are available on the website. So you can download those. We'll move on to questions. From the front here, to Dave.

QUESTIONS AND ANSWERS

David Risinger - *Morgan Stanley, Research Division - MD in Equity Research and United States Pharmaceuticals Analyst*

Dave Risinger from Morgan Stanley. I have 3 questions. First, for Frank, could you just comment on the opportunity to promote KEYTRUDA to all oncologists for all cancers as a result of the MSI high indication? Second, I guess, maybe this is best for Roger, but many of the thought leaders that have been committed to CTLA-4 I think have been surprised at the 21G results. How do you see the thinking evolving among thought leaders with respect to the chemo combo? And then third, it'd be great to get your thoughts on opportunities and challenges associated with tumor mutational burden and LAG-3 biomarkers.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Let's start with Frank.

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

Sure. Hi, Dave. For us, now, you can imagine this tremendous excitement that's happening in the market place with the number of indications that we receive. So the MSI high indication, to your point, basically, can take you to all oncologists. But we're pretty broad, obviously, based on our lung cancer approvals in the number of these patients that -- or number of physicians that treat lung cancer. So we're very well positioned, very well resourced in the marketplace. We have added sales force and other resources to support the number of indications, but overall, the oncologists have been very receptive and they really do, I think, start to see KEYTRUDA's foundation because of now 10 different indications across multiple cancer types there.

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

And Dave, the -- they're -- the chemo combo data, I think, did surprise a lot of people. The magnitude of the treatment, in fact, is impressive. But it also -- it went a little bit against the grain. I think all of us who've been involved with this for years have wanted to come up with therapies that would eliminate traditional chemotherapy. The toxicity of traditional chemotherapy is something that patients live in fear of and that physicians live in fear of managing at least those who aren't doing it all the time. And so the thought was that the new immunotherapies would eliminate chemotherapy and that we wouldn't need that anymore. And it was natural to think that, although the spectrum of activity of PD-1 directed therapy is so much broader than see CTLA-4, since there's reason to believe that they act at slightly different points in the lymphocyte recruitment spectrum that maybe the 2 of them would work very, very well together. Notwithstanding the very meaningful immune-related toxicity of see CTLA-4. So that said, I think, there's -- people realize that the combination of chemotherapy clearly works as we've done it in not just the 21G, but the prior earlier cohorts, single-line cohort study. And there are good immunological reasons to believe that it would work. Broadly speaking, although we all worry about the psychopathic effects and toxic effects of chemotherapy, in part what happens with chemotherapy, we believe, is that there's a pretty substantial antigen burden that is introduced into the immune system locally, as result of tumor destruction, and some even speculate that a lot of the activity of chemotherapy traditionally is immune-mediated. So at this point, I think, the jury is out on exactly why it works, but it certainly appears to work and people are becoming more comfortable with it. And meanwhile, a lot of work is being done to try and see, is it possible to introduce see CTLA-4 antagonists into treatment regimens, at least in certain tumor types in certain doses of schedules in a way that would provide additional benefit. And we've been doing those kinds of studies too. And then the last questions had to do with the scientific approach, really. What about tumor mutational burden and what about things like LAG for your other related biomarkers? For tumor mutational burden, it's very clear that when you measure tumor mutational burden, if we -- when we look at the totality of our data, and we've done a lot of this work. When we look at the totality of this -- of our data, what we would say is that the 2 principal determinants of immune responsiveness, the things that have most predictive value are the presence in the tumor of an inflammatory response, which we can measure in part with PD-L1, but we can measure usually better using a gene expression profile approach, and that's number one. And number two is the mutational load. And so the question becomes just as you asked it, well, how are you going to measure mutational load? By what criteria is mutational load important? And I would mention here that, in preclinical settings, only a few mutations seem to matter. And if we go back to the kind of work that Bob Schreiber did many years ago with methylcholanthrene-induced tumors. It appears that it really comes down to 1 small epitope that is introduced as a result of methylcholanthrene mutation, despite the many mutations. That's really important. So how do you measure which ones are really important? And I think there's a lot more work that has to be done. One of the things that we noticed, and others noticed as well, is the narrow clonality and in terms of the expansion of T lymphocyte populations when you're treating the patients with KEYTRUDA. Suggesting, again, that there may be a small spectrum of mutations that are really important and that are recognized by the immune system. Well, time will tell. And similarly with other agents, we've been studying a LAG-3 antibody in the clinic as well and other things too. And in parallel, we developed reagents that permit us to identify the expression of the target. And we are looking at all of those things as we try and advance combination therapies to more patients.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

We've got over here.

Unidentified Participant

Perhaps one for Frank and one for Roger. Frank, perhaps for you to start, do you think a potential approval for Astra with the PACIFIC trial impacts the potential eligible patient pool for Merck using KEYNOTE-021G, and potentially 189, down the road at all? And then, for Roger, was there any data point for any of your competitors at the ASCO this year that made you think, well, I know KEYTRUDA data is different in some shape or form. Any differentiation that you've seen in your trial versus the type of data they were able to produce in their own trials.

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

So on the first question, not really a significant impact from the trial that you referenced, obviously, with AstraZeneca because those were more stage 3 patients, different patient population. And we'll wait and see how the data obviously reads out, but not a significant impact to where KEYTRUDA is currently positioned in first-line.

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

And with respect to differentiation from other agents, of course, it's very -- it's always very risky to try and differentiate across studies because the differences in patient recruitment are -- could have an enormous effect. There has been a general trend, which has been pointed out, in a number of different tumor types for the PD-L1 directed therapy to have response rates that look a little bit lower than the PD-1s. But I don't know whether that's real or not. And obviously, since there haven't been any head-to-head studies, there's just no way to say.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Let's go to Jami in the middle, and then [Mike] (inaudible)

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

Just a couple of questions. When I look at the data from KEYNOTE-021G, it seems that most of the benefit is being driven by the over 50% expressers where we saw an 80% ORR. And then the under 50% expressers, we saw an ORR of 26%, the 1% to 50%. So does that not suggest that the jury is still out in the under 50% expressers? Can you explain why we saw such a dichotomy? And then, secondly, if you could talk about your IDO development plan with Incyte. When do you plan to initiate those trials? That market is getting more competitive. And then, thirdly, we haven't seen an update on your GITR. And I think you were the first company to talk about a GITR, and it's been slow to materialize.

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

Right. Okay, thanks, Jami. First of all, with respect to the PD-L1 subsets within 021G, it's a small study. And once you start fractionating them into those small groups, I think it's pretty hard to reason through it and say, well, these are better than those. So I think we'll wait for a larger data set to say I'm not convinced that we can say from that data set which patient population responds best. 60 patients is a small number for the -- sorry, what?

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

(inaudible)

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

Oh, yes. I know. We've put the data in because people are obviously going to ask about it, but it's not something that I feel very comfortable commenting on, as far as that's concerned. I think, with respect to the epacadostat studies, we went -- we've gone through study designs. We announced, as you know, back in January that we're going to go forward and bring -- we've already -- we've put the epacadostat study into a Phase III in melanoma some time ago and that will be the first one that reads out. We announced that we would go forward with another set of Phase III studies based on just the -- we've looked at a lot of small Phase Ib/II studies and seen sort of a consistent improvement in terms of breadth and depth of response. There's no way to tell without doing a randomized Phase III study. We've gone through and done a lot of work on designs, what those designs should look like. We've had a chance to review those designs with the FDA. We're ready to get started. So we're just moving along on that. And with respect to GITR, we've done a lot of work with GITR. We actually have 2 molecules in the clinic with GITR. We've done a lot of work with it. Thus far, we're not in the position where we can say that GITR adds a great deal. A lot of what we did first was kind of look at single agent

studies. And now we're doing much more combination studies. Again, combinations -- as we've seen throughout the last couple of days, combination studies are really hard to interpret unless you have a very, very big treatment effect because the magnitude and treatment effect for KEYTRUDA or for other PD-1, PD-L1 directed therapies is significant. And so when you just see a difference in response rate from 20% to 30%, it's a little hard to know in a small study.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Right up front to Tony, right up front.

Tony Butler - *Guggenheim Securities, LLC, Research Division - MD and Senior Equity Analyst*

Roger, 2 questions. I recognize, in answer to Dave's question, your notion of mutational burden. And that's very clear in 30 tumors you have. There's no mention of colorectal cancer where you don't have very good mutational burden. And I guess, the question I have is one more of thinking through do you just toss it out and don't try anymore or is there some combination or some thought or some biology that you all have been working on that says that, that may be able to be tackled despite the fact that there's not high mutational burden in that histology. And then the second question really on IDO because you -- it triggered a thought when you were alluding to GITR and that is that -- correct me if I'm wrong. Let's take single agent IDO. You don't have activity, but yet you clearly do -- something is going on when you add it to pembro. So was the question really then I've got to clean out all the Tregs and MDSCs or whatever may be in the way in that tumor-marked environment that then allows pembro to work. So I'm just trying to understand the notion of no activity then you get it when you use it in combo versus not. This also actually goes to the first mutational burden question.

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

Right, right. So as far as the mutational burden is concerned -- first of all, maybe it's worth sending back and saying, preclinically, in syngeneic tumor models, everything works in combination with PD-1 blockade. So that's true of cytotoxic chemotherapy, it's true of CTLA-4 directed other immunologic manipulations, it's true of immunization, it's true of targeted therapies, it's true of radiotherapy. All of those things will work. And in part, we've gotten a sense, as I said, that if you just kill cancer cells a little bit, you can dump enough DNA out and you dump enough antigens out so that you get both direct MK stimulation and you also get antigen stimulation if there's any antigens that we recognize, and you may not need very many. I mean, if you can direct an immune response against a KRAS codon 12 mutation as a recent publication suggested, then a lot of those tumors, including colorectal cancer, have codon 12 mutations. So you ought to be able to get at it. So there is an approach that says, hey, look, we can irradiate those tumors or we could use other kinds of mechanisms. Just cytotoxic chemotherapy by itself might be enough that would help you there. It's just necessary to do the studies. And of course things that would interfere with DNA repair might be helpful too in that regard, provided you can give them enough time to accumulate mutations. I would just say, as a side issue, we should recognize that we haven't established any of these mechanisms. So there is the idea that cells that have a lot of mutations in them. They're not happy cells and generally not so healthy cells. They might be just easier to kill. So before we get too far down the road of thinking that the whole business is you've got more antigens to recognize, it's important that there are other things that are going on in those tumor populations that we need to pay attention to. As far as the issue of what do you do with an agent that has no single agent activity but is used just in combination, that's always been a problem in the field. It was such a problem, and in the past, that we wouldn't -- we simply wouldn't look at combinations of agents that didn't have a single-agent activity. It was always an initial criterion. It had to have single-agent activity. Now what we've seen is that there does appear in a preclinical setting to be at least additive and sometimes more than additive activity with things that don't have single-agent activity, IDO being the example par excellence. So that means that we do have to study things like GITR that appear to have a very similar characteristic.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

[Mike], do you want to go to Chris (inaudible)

Christopher Schott - *JP Morgan Chase & Co, Research Division - Senior Analyst*

Great. Chris Schott from JPMorgan. Just 2 questions here. First, coming back to lung combos. I'm just interested, as you look at the 21G data versus some of the IDO data we saw at this meeting, how do you compare and contrast those data sets? I know the different lines of therapy. I know it's early, but you obviously have a lot of experience with IDO and chemo, so I mean, like the depth of response, breath of response. I mean, do you have a bias, one way or the other, of chemo is looking better, IDO is looking better. Just any more color on that would be appreciated. The second one is on the commercial side post the 21G approval. I know it's early, but based on initial feedback, et cetera, you're having from the market, just talk a little bit about the use of patients who traditionally would have otherwise received ALIMTA. Or could we see a broader use beyond that? Is there anything that you're hearing in this first month since approval that's kind of better helping size that initial opportunity?

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

Frank, why don't you take the first...

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

Sure. I'll start and we'll come back. So a couple of things with what's happening in the marketplace first and I think as Roger just went through the data with regards to KEYNOTE-024. So the feedback early on is that physicians are still wanting to test, and we absolutely support that. We think it's the right thing because, I think, we explained -- or actually we shared on our last call that about 1 out of every 4 new lung cancer patients in the front-line are going to KEYTRUDA monotherapy in the high expresser patient population. And that has not changed. So many of the physicians we engage where testing is important. It's also important because remember KEYTRUDA monotherapy is available for both non-squamous and squamous patients in that high-expressed population. So then, as you now look at 21G and bring it to the marketplace, I would say, overall, the feedback has been very positive. Many of the community physicians, and it's really early on, but early feedback is those that are comfortable using ALIMTA carbo, see the major step up in response rates, very strong progression-free survival, and obviously we've gotten some positive feedback on now the updated OS curves. So I'd say overall, very positive. As far as using it in other areas beyond where ALIMTA and carbo is, it's probably too early to comment on that right now. Most of the feedback is where they are using ALIMTA and carbo, they see KEYTRUDA as a very nice complement to that and obviously the data that we shared on 21G is helping -- for 21G is helping. So there'll be a lot more obviously to come over the next several months, but we're very encouraged about what we're hearing early on with, not only the monotherapy approval obviously, but now the expansion of a number of patients with 21G. I would not expect a bolus. So as you think about it, this is for new patients coming into the market. But obviously being first to market with the first randomized trial is very important, and we're very excited about the opportunity. Roger?

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

Yes, and thanks, Frank. So building on that, I would say that, understandably, a physician practice, if you see a patient who's elderly and has many comorbidities and has PD-L1 greater than 50% proportion score, KEYTRUDA monotherapy seems like a good choice. If you're seeing somebody who's in their late 40s and has no other medicine, takes no other medicines, for that patient, there are many people look at that and say, well, maybe we ought to be going with a combination with chemotherapy. And I mentioned that because we can't say anything really about chemotherapy plus KEYTRUDA in terms of the efficacy versus IDO. What we can say is chemotherapy is a lot more toxic than IDO. I mean, IDO is a very -- is really quite benign intervention with some rash associated with its use and a few other things. But the expectation is that we can get a meaningful improvement in response as we learn more about how to use it together with KEYTRUDA. The fact that it's so well-tolerated will turn out to be really important, particularly in the younger and healthier patient population.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Want to get Greg right here on the left side.

Greg Gilbert - *Deutsche Bank AG, Research Division - MD and Senior Analyst*

It's Gregg Gilbert from DB. Roger, I was hoping we'd have some MYSTIC data to ask you about. But what's the next step for KEYTRUDA plus CTLA-4? And what depends on MYSTIC and what doesn't? And then for IDO plus KEYTRUDA in lung, can you talk about the responses in treatment-naive patients versus those in second or later lines? And lastly, for Frank, I think you mentioned that uptake's going pretty well in 21G, but we've heard some feedback among physicians that 21G wasn't big enough, robust enough, et cetera. Is anyone really hiding behind that now? Or sort of are physicians caving as they're confronted with the real-world decision of do I treat with this or not in this population?

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

(inaudible) Frank...

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

Right. Well, Frank, do you want to do that one and then I'll do...

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

Okay, sure. Just as a follow-on on 21G, I think, as I mentioned, overall positive. There are some opinion leaders in the academic centers that would like to see additional data. They're waiting for the Phase III trial. There are some physicians that would like to get to a chemo-sparing regiment if possible. So there are clearly KOLs that are maybe going to take a wait-and-see or use it for a select number of patients, not broadly, but like I said, for the majority of patients that we -- or physicians that we've been engaged in here at ASCO, and then obviously we're just a couple of weeks into the launch. It's been overall positive. So we're encouraged by that.

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

And Gregg, with respect to CTLA-4, clearly, the preclinical data, there's no doubt, you can combine CTLA-4 directed therapy with PD-1 directed therapy. There's reason to believe that you can see some improvement as a result of combining the 2 based on data that we and others have presented. The question is sort of is the [juice] worth the squeeze? I mean, you get enough response to justify the quite significant increase in toxicity, which includes Grade 5 toxicities in many cases as a result of combining those 2. And we've been asking the question ourselves with ipilimumab, wondering about dosing schedule, and also with our own molecule, which has slightly different properties. That the next step for us isn't, in any sense, dependent upon whatever happens with MYSTIC. MYSTIC has its own characteristics known to the AstraZeneca team and we won't be able to reason from that to ours that there -- it will not be dispositive. It is not the case that if they fail then we won't continue to study the combination, or if they succeed wildly that then we're going to do 12 combination studies. We're systematically trying to understand how best to use the combination together because we're concerned about the toxicity. Oh, I'm sorry. The outer response rate in treatment-naives. Again, I don't think we have enough patients to be able to fractionate that out. I don't know if Roy...

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

I don't think we disclose that...

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

Yes, we don't have that. I don't think we can do that.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Do you want to come up to Alex here?

Alex Arfaei - *BMO Capital Markets Equity Research - Pharmaceuticals Analyst*

Alex Arfaei, BMO Capital Markets. Roger, just following up on KEYNOTE-021G. When you look at Roche's data, they updated their poster with that doce chemo. PFS was lower than yours, but they had about 19 months' median survival, survival rate of 1 year, were very similar to KEYNOTE-021G. Celgene had an interesting data with 23 patients, but still similar with your survival rates. So the question is, are you -- does that give you increased confidence? Are you seeing more kind of things pointing the same way, supporting chemo PD-1 combo?

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

I'm very confident. I mean, I'm extremely confident. I think that the 021G data speaks for themselves and we had prior 021 cohort single-arm data that were actually even stronger for the combination that's allowed us to do the 021G cohort because we saw those data. And we said, "Gee, we better do a controlled study here." The reason why it looks -- we did 60 patients in each group and it was not difficult to tell the difference, right? So when you have a very high treatment effect, then you don't need giant studies to see it. If we're going out and looking at penicillin and then we talk of pneumonia, I don't have to do 1,000 patients to see the result, right? So it's very impressive in terms of the combination. I've got a lot of confidence in it. What the actual number is in different settings, I'm sure there'll be quite a lot of variability as these data accrue over many years.

Alex Arfaei - *BMO Capital Markets Equity Research - Pharmaceuticals Analyst*

Right. And a follow up, if I may. So in light of the MSI high indication, and I'm sure you probably heard about the Glaxo 101 study with -- which seems to be another situation where you might have a treatment that's going to be targeted to a mutation regardless of where the tumor is. Do you see that as an indication of where we're going? Or is that the exception?

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

Oh, I believe in that completely. Completely, Alex. I've been a champion of that for decades. My view is when you do a hematoxylin-eosin stain of a tissue sample, yes, you are, in sort of an aggregate kind of way, getting some phenotypic information about the tumor. But to really treat tumors, we need a lot more specificity. And our hope really had been, back at the time when the original driver mutations, now what we now we call driver mutations, (inaudible) to gene activation, at the time when those things were identified, we really believed -- I certainly believed at the time when we showed that the PDGF sequence in (inaudible) , the acutely transforming retrovirus sequence were the same. It seemed like there was a countable number of mutations that would be responsible for a lot of malignancy. And if we could just address those, we could treat patients. And when you go back and look at it -- Gleevec was developed for chronic myelogenous leukemia. But the reality is, you could have developed it for anybody who has an able activation event. Because it works. It works in anybody who has an able activation. We couldn't have done it that way, it just happened we were so conditioned, I'm getting up on my soapbox here, but we were so conditioned by the fact that, Philadelphia chromosome associated and drive (inaudible). That's the way it was done. And it was a sensible way to approach at the time, take nothing away from Brian and Nick Lydon who did the work. It was terrific work. The reality is you could have just said, "Let's go out and look for able activation, whether it's by breakpoint cluster region translocation or by something else." You could have done that. And so suffice it to say, I'm convinced that this is the way the field is going.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Why don't we just go to Vamil right there (inaudible)

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

Great. Vamil Divan, Credit Suisse. So just 2 questions. One, the I-SPY 2 data that you touched on here. Just curious, I know you talked about moving into Phase -- just graduated to Phase III, given the way the stats was presented, 99% chance of Phase III were positive. Is that something that just goes directly to filing what you have right now? Or does it need a full (inaudible).

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

I don't think so. It's just not enough patients. I think we really need to demonstrate that we actually can do a controlled study with a pathologic complete response and in a large number of patients and see the result. They're -- it's funny that you mentioned that because there has been some speculation internally about that, but I think it's -- I think, there's more data required.

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

Okay. And then other question. You're getting close, I guess, close to the 3-year mark when KEYTRUDA was first approved. So Frank, just curious on if could you talk a little bit about the duration of therapy you're seeing in the real world. Is there any move for patients being pulled off therapy if they're doing fine, tolerating it fine, but just wanting to stop paying or whatever it might be where people are limiting the duration?

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

Yes. So we're still not really seeing that data (inaudible) robust data set yet. You noticed many of our studies now basically are about 2 years when a lot of our studies are actually the duration for those. So as far as the real world, we are seeing a number of patients that are continuing beyond 2 years. So if a patient is actually getting a good response and also because of the great toxicity profile that this product has, patients are continuing well beyond 2 years, and as you mentioned, into 3 years. It's hard to give a specific answer because it's in real-world data that points to that yet. But that's how I'd respond at this point in time.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

(inaudible)

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

Oh, yes. One of the comments that I wanted to make sure, I think it was clear as far as where KEYTRUDA is being used in lung cancer today. So in the front-line setting, upon testing when patients are being tested, which is about 3/4 of new patients are now are being tested, if they are high expressers, 15 above, the majority of those patients are going to KEYTRUDA.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Yes. I think there was just a misunderstanding earlier when Frank had said that 1/4 were going to -- it's 25% to 30% of non-small cell is high expressers.

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

Right. And we're getting the majority of those upon testing.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Yes. I just want to make sure that, that was clear for everybody.

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

Yes. Thanks, Teri.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Let's go to Seamus.

Seamus Fernandez - *Leerink Partners LLC, Research Division - MD, Major Pharmaceuticals and Biotechnology*

Seamus Fernandez at Leerink Partners. So I just had a couple of questions. Roger, can you just help us -- you guys have a STING agonist in the clinic now, but you're also studying TLR agonists as well, I think, in 2 separate studies. So can you just give us a general sense of how you're thinking about the science behind the TLR agonists and your enthusiasm for them. And then, second question. Frank, are there -- uptake in second line indications has been extremely swift. As we think about other first-line indications, what are you seeing that's different? And how would you have us think about the uptake in first-line? Because I think some folks may have kind of mismodeled the pace of uptake to some degree when you think about second-line versus first-line to some degree in some of the various tumor types. And just the last question. Roger, you mentioned approaches to LAG-3 and interest in tumor biology-type approaches. For -- as you think about LAG-3, is that sort of a transiently expressed target that will only really be useful in the refractory setting? Or is this a type of target that's more useful? So PD-1 refractory setting, meaning -- or do you see it as something that moves forward? And again, maybe you can comment on, is this something that crosses tumor biology as well?

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

Right. Okay, so let me -- first of all, with respect to STING and toll-like receptor agonists, there's a variety of intra-tumoral agents. We've done quite a lot of studies with TVEC, as an example, the oncolytic virus administered intra-tumorally. And in addition to STING and TLR9, in collaboration with our colleagues at Dynavax, also work that we've done on IL-12 and other virus. In all of those cases, there are intriguing signals. What we can't tell yet is the magnitude of that. Of course, these agents do, by themselves, particularly for the well-studied ones like TVEC, have an abscopal effect. To see action at a distance, you inject a tumor mass here and you see shrinkage of the visceral mass. And it does appear that you can accelerate -- improve that process with -- on a background of KEYTRUDA pretty dramatically and the 2 work together, and that the data from TVEC, I think, are pretty strong. So that's intriguing for us. I think, one of the advantages of the intra-tumoral administration of these agents is it's really quite benign. It's extremely well-tolerated. So again, you go to those individuals where you'd like to be able to give a greater response on a background of KEYTRUDA without suffering the ill effects that might come from cytotoxic chemotherapy. So I think, that's -- we're looking at all of those and we're interested in them. With respect to LAG-3, of course, like many of these elements within the immune regulatory network, it's cytokine-regulated as a gene. So you're going to see an effect of inflammatory responses in different cell types as a result of the fact that there are cytokine response elements at the transcriptional level. Exactly what those mean and whether those can help you pick out which tumors you should treat, it's a little bit unclear. But that's clearly one of the things that you want to study.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

And Frank, do you want to comment on the ramp, first-line versus second-line?

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

Sure. So in first-line, I'll just use, I know you mentioned, I'll use lung as the example. So if we take a step back globally, there's probably about 400,000 drug-treated patients in many of the major markets around the world. If you take that and look at the U.S., it's on the order in an annual basis of about 110,000 to 120,000 patients. So if you start there, and these are new patients coming in, right? So unlike second-line where patients have already been treated, these are new patients coming in every month. And then if you look at where KEYTRUDA currently is now indicated, obviously if they are PD-L1 positive high expressers, as we talked about and they've been tested, that's about 20% to 25% of that opportunity. So if you've been looking on a monthly basis, it might be 8,000 to 9,000 patients per month that are eligible. So you have the high-expressed population. You then have to obviously take out of that equation patients that are EGFR-mutated positive or ALK positive. So that's about 25% of the population that's not eligible. And then the rest is now become available to non-squamous population, obviously with the approval of KEYTRUDA plus pem/carbo. So that's really how I would think about the patient flow on an annual basis and then obviously every month as new patients come in.

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

I think the point that you made is an important one. I mean, everybody gets it that in the later lines of therapy, once it gets approved, there's a large addressable population. Whereas in the first-line therapy setting, thankfully, people accrue slowly over time because it's unfortunate people get cancer, but fortunately they don't all get it at once.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

I want to try and squeeze in one final question. Let's go to Paul here.

Paul Choi - *Barclays PLC, Research Division - Research Analyst*

Paul Choi with Barclays. My first question is for Frank, please, and it's with regard to the bladder data, which was presented here, and specifically with regard to the KEYNOTE-045. Now KEYTRUDA's the only agent with an overall survival claim that you can make, whereas your competitors were approved on either overall response and so they can't make that claim or their trials have failed to show overall survival. So can you maybe comment on how you're thinking about pressing your potential advantage here? And if we use, let's say, the second-line lung market as a potential market analog where survival did result in your competitor getting meaningfully a higher percentage of share, is that the right way to think about how you're approaching the bladder market?

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

So one, we're very encouraged obviously by the KEYNOTE-045 data and I think actually one of the sessions here today, they actually showed and started to highlight the fact that KEYTRUDA being the only one at this point in time to demonstrate overall survival and to get a Category 1 NCCN rating obviously is very important. So we are in the bladder field, obviously, with a number of other competitors, but we clearly see having overall survival. And the strength of the data that Roger just showed you, we think that is going to help us to be well positioned in bladder. In addition to that, we've got approval now for the first-line cisplatin-ineligible patient population, which we think when you combine the strong results and survival with KEYNOTE-045 with the KEYNOTE-052 data in that population, we think we have a very good opportunity in bladder. Crowded. Many of the newer agents have been approved in bladder, but we feel very good about our data. And in fact, while we are here, one of our key customers just announced that they are going to add KEYTRUDA for bladder into their regimens based on the strength of KEYNOTE-045.

Paul Choi - *Barclays PLC, Research Division - Research Analyst*

And my second question is for Roger. Over time, you've certainly emphasized exploring KEYTRUDA as carefully as possible as a monotherapy before advancing to combination approaches. But at the Bristol investor update yesterday, they're emphasizing more of a portfolio approach and advancing some of their next-gen agents into the registrational stage. And I'm just curious at what point -- or what sort of philosophical shift or strategic shift

do you think is necessary to take more of a portfolio approach and think about advancing some of the other agents that you highlighted today into the next stage or registrational stages?

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

Well, Paul, I can't obviously speak to what the Bristol-Myers strategy is. Our own strategy is systematically to dissect out the components of responsiveness and to understand why it is that people don't respond in order to broaden that response base. I mean, if you think about it, on average, something over a huge number of different studies, response rates are typically in the 20% range or so. So what's wrong with the other 80%? Why is it that they don't respond? And in principle, there are 3 kinds of reasons why they might not respond. The first reason is that they have a tumor that no immune system could see, that, that tumor looks so much like a normal tissue and has no recognizable epitopes. You just can't recognize it. There's no way. And obviously, that means that you're going to have to do something to introduce new epitopes to that tumor. Maybe that's radiation, maybe that's something else. Alternatively, it could be that they have a tumor that actually could be seen by some immune system but just not that person's immune system, because they have a hole in the repertoire, the right cells weren't stimulated or whatever. Well, that changes your approach quite a lot, because under those circumstances, then immunization seems to matter and things that permit access of lymphocytes to regions that might other be sequestered otherwise be sequestered seems kind of important. And the third possibility is that, yes, the tumor is recognizable and it's recognized by that person's immune system. But some other kind of regulatory mechanism, let's call it a checkpoint, has been engaged. It's not PD-1 but it's something else. And there you'd want a different approach. As we begin to be able to evaluate patients and to assign them systematically to these mechanistically quite different reasons for nonresponsiveness, we'll understand how best to apply new mechanisms. And we're exploring new mechanisms that address all of those different areas. Thanks.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

Yes. I think, we'll close it out there. I know there's other events that people need to go to. But thank you for spending some time with us.

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

But our food is best.

Teri Loxam - *Merck & Co., Inc. - Vice President, Investor Relations*

And feel free if, you want to chat with anybody from the broader team or Roger and Frank, feel free to stick around, have a drink and we'll be here. Thanks, everyone.
