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MRK - Merck & Co Inc Investor Event at the AACR Annual Meeting

EVENT DATE/TIME: APRIL 16, 2018 / 11:45PM GMT

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PRESENTATION

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

All right, everybody. We're going to get started. All right. We'll get started here. All right, we are webcasting this event tonight, so thanks for joining everybody at our AACR event. We have Dr. Roger Perlmutter, the President of Merck Research Labs, as well as Frank Clyburn, our head of our Oncology Business units here tonight. Roger will go through a few slides, and then we'll open it up to Q&A. And so we'll go through -- do you have the slide clicker?

Roger M. Perlmutter - *Merck Research Laboratories - President*

I'm going to do at the podium. No, I'll do it up there.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

Okay. So we will get started.

Roger M. Perlmutter - *Merck Research Laboratories - President*

Okay, good. Good evening. Thank you, everyone, for joining us this evening. This is an opportunity for us to talk about the -- where we stand with respect to our oncology program. Of course, focusing a lot of attention on KEYTRUDA and the data that came out today. But in addition, talking

more generally about the oncology programs that are evolving at Merck and have been evolving over the last few years. We do very much appreciate you coming in this evening.

So the forward-looking statement is, as before, every bit as interesting and exciting as you know it to be. The important point to remember is that we began this odyssey a few years ago with the idea in mind that KEYTRUDA, pembrolizumab, would be a foundational treatment in the interventional therapies for cancer. And it was very clear back then that KEYTRUDA had very special properties. And it was important for us to understand how well KEYTRUDA, directed against PD-1,would behave as a monotherapy. And many of you will recall that these studies in monotherapy were the first and primary commitment for us. But we also recognized that despite the fact that we had embarked on a very broad program looking at monotherapy and a broad range of malignancies that we also wanted to explore 2 other things. One of those was to look at combinations of therapies that could improve on KEYTRUDA's effects based on a new understanding of the role of immunotherapy and the treatment of malignancy. It was very clear from our work and the work of others that PD-1-directed therapy had a minimum or more generally immunotherapy represented a fourth pillar in the treatment of cancer after surgery, chemotherapy and radiotherapy. And indeed, I've said in other settings that the advent of PD-1-directed therapy and immunotherapy generally is the most important advance in oncology since the advent of radiotherapy. And KEYTRUDA is the first truly broad-spectrum antineoplastic agent that's been introduced into clinical practice as a therapy.

So beyond the exploration of combinations -- we'll have a little bit to say about that tonight, we also thought it important to understand in a mechanistic level how KEYTRUDA was actually working and to be able to select patients who would benefit both from monotherapy and also from combination therapies. And more recently, we've added to our portfolio a very large number of compounds that we're pursuing that are derived from our own laboratories or from licensing. And in addition, we've formed 2 very large collaborations, 1 with AstraZeneca, taking advantage of their leading PARP inhibitor, LYNPARZA, and the other with Eisai more recently, which is a collaboration on their multi-kinase inhibitor, LENVIMA or lenvatinib. In addition, very recently, we've announced that we are acquiring a small company in Australia, Viralytics, whose Coxsackievirus, oncolytic virus, has shown very interesting results both as a stand-alone therapy and also in combination with KEYTRUDA. So we've been adding to our internal pipeline with very precisely selected combination therapies.

So where do we stand? Over the last few years, we've made a great deal of progress. I checked on the way in, if you look at clinicaltrials.gov, not a fair measure of progress by any means. But nevertheless, we have 759 trials listed right now in clinicaltrials.gov, treated more than 200,000 patients with KEYTRUDA around the world. We are studying -- more than 400 of these 759 trials are in combination. And we have multiple trials that have demonstrated improvements in overall survival. Some of those improvements are really quite dramatic, and we'll talk about one of those in just a minute.

We've had 12 Breakthrough Therapy Designations, of which the most recent is in combination with LENVIMA for the treatment of renal cell carcinoma where we currently have an ongoing Phase III study. And we have shown activity in more than 25 tumor types. And here's an example of what that looks like. These are waterfall plots that you've become familiar with, in which we're just looking at individual patients and tumor size. When the tumor grows, the line goes up. And when the tumor shrinks, it goes down. And they're just ordered from right to left, from greatest shrinkage to least shrinkage. And you can see the activity was originally pursued in melanoma and non-small cell lung cancer as it was by others who had similar molecules directed against PD-1 or PD-L1. But in addition, we broadened our studies to look at head and neck cancer, urothelial cancers, more generally gastric cancer, hematologic malignancies, particularly classic Hodgkin lymphoma. And you'll note actually, if you look at the shape of these waterfalls, that the most profound responses are seen in the relapse refractory classical Hodgkin lymphoma trial. It's really quite impressive with typically on the order of 90% of patients responding. And in all of those areas we've gained regulatory approval, we have currently 2 indications under review in the United States for -- one for primary mediastinal B-cell lymphoma, a small but important tumor type and another for refractory cervical cancer and those for cervical cancer, we recently obtained a priority review. So a lot of progress being made in the understanding of the breadth of tumors to which KEYTRUDA could be applied, and there's still more going beyond this. And that I think is -- speaks to the process that we have gone through, referred to here as waves in which we began in melanoma and non-small cell lung cancer, but realized fairly quickly that we had to pursue other indications because of the extraordinary results that we were seeing as we added cohorts to our earliest multi-tumor salvage study, the 001 study. That led to a second wave which includes those tumors that I've mentioned, and as well triple-negative breast cancer where we've done quite a lot of work. And the third wave, which includes things like esophageal malignancies and combination studies, in particular, in renal cancer and as well hepatocellular malignancies. So a lot of progress being made and a lot of important malignancies in an extremely broad clinical program. And as we've said before, we demonstrated overall survival in multiple different studies.

The combination studies that I've referred to have benefited from our recent partnerships with AstraZeneca for LYNPARZA and with Eisai for LENVIMA. And these are full partnerships in the sense we have -- we share 50-50 in the cost, the expense and also in the revenue that's generated from these entities. LYNPARZA, of course, is the first PARP inhibitor that was introduced. It is now in a tablet as opposed to capsule formulation, which has made it much more useful. It's gained approval in mutant -- BRCA mutant breast cancer. There's the OLYMPIAD trial, there was quite a lot of discussion of that. Today, in fact, a whole session devoted just to the OLYMPIAD trial, which is I think a really exciting trial for maintenance therapy in individuals who have failed -- who have been treated successfully and wish to be sustained following traditional therapy for BRCA mutant breast cancer. And there's a significant long-term opportunity across multiple different tumor types. I think the important thing to remember about this is that a PARP inhibitor in principle should have its biggest effect by virtue of the fact that it interferes with DNA repair mechanisms. So the same DNA repair mechanisms, if interdicted, should permit fixation of mutations that will increase mutational burden and, we hope, the representation of neoantigens, which should improve responses to KEYTRUDA. We've generated some evidence along those lines, and we're eager to test that more directly with LYNPARZA, and combination studies designed to do that are currently either underway or soon will be.

For LENVIMA, we were extremely interested in the question of whether a multi-kinase inhibitor, in particular one that blocked VEGF receptors as LENVIMA does for VEGF receptors 1, 2, and 3 could be beneficial in combination with KEYTRUDA. But we were very impressed with the results that we obtained from our Phase II studies in renal cell carcinoma, and that led to a registration enabling study which compares LENVIMA with everolimus versus LENVIMA with KEYTRUDA in that population. And that will be, I think an extremely important study to watch over the next couple of years.

And in addition, LENVIMA, as a stand-alone monotherapy, is approved in differentiated thyroid cancer. It's approved in advanced renal cell carcinoma and in hepatocellular carcinoma. Just recently in Japan, filed in hepatocellular carcinoma elsewhere, and we believe there's an opportunity there in combination with KEYTRUDA. In fact, we're launching soon 11 potential combinations in 6 different tumor types. So a lot going on in that area.

Those partnerships are the most advanced programs beyond combinations with traditional chemotherapy that we'll talk about in a minute. We also have a very, very large set of internally derived assets that cover the waterfront in terms of immune agonist directed at innate immune function, blocking negative immune regulators, a very big personalized cancer vaccine program and programs that are directed against the tumor microenvironment. In those cases where we believe the microenvironment may have an immunosuppressive effect. I would call out among all of these things that we are already seeing interesting results with molecules like LAG-3. We're not the only ones, but there's certainly promise there. We have advanced a STING agonist that looks quite attractive as an intratumoral agent. There is -- we and our colleagues, have published data on intratumoral agents, including toll-like receptor agonists and also cytokines. But the combination of STING and also the Rigontec-derived RIG-I molecule is -- looks extremely interesting. And we also have oncolytic viruses, both those that we've generated internally, partnerships, for example, with T-VEC, with Amgen. And we are going to acquire, as I mentioned, Cavatak, the coxsackievirus from Viralytics, which has been studied in Australia and for which there are very interesting combination data already available.

And within the tumor microenvironment, some fairly conventional molecules that inhibit signaling pathways, including those that we ourselves have developed as well as those developed by others, look very promising. So this is an extremely broad program in oncology and we think, over the next decade, will yield real benefits.

To give you a sense of how we think about that, let's just review very quickly data that were presented yesterday and today here at the American Association for Cancer Research.

The KEYNOTE-189 study, combination study in first-line, non-squamous, non-small cell lung cancer. And the KEYNOTE-054 study which is an adjuvant study in melanoma.

For KEYNOTE-189, this is the slide that I have pinned up to my refrigerator door. It's unbelievable, actually. I mean, so you look at this slide and this is overall survival in a population with advanced non-small cell lung cancer. And these individuals were either given traditional chemotherapy, platinum-based chemotherapy plus pemetrexed, which is standard of care in much of the world for these people or the combination of that chemotherapy along with KEYTRUDA and the hazard ratio of 0.49. So you have half the risk of death across the intervals of the study. P value has 4 zeros to the right of the decimal place in a study that had just 620 or 616 initial participants, randomized 2:1. So this is a very powerful effect. The effect was seen at the first interim analysis. We have almost 10.5 months of follow-up in this study. But the expectation is that, as we've seen so many times, KEYTRUDA PD-1 directed therapy is associated with a long tail, it's a long plateau in terms of overall survival in particular. And so we're

optimistic that we're going to be able to hold that line up for quite some time as additional data are accrued from this study. So an extremely important result. And it's a result that confirms the result that we had from the KEYNOTE-021G study. And you'll recall, when we talked about KEYNOTE-021G. KEYNOTE-021G was a very small study, it was the G cohort of the KEYNOTE-021 study which is the first set of combination studies that we did with chemotherapy in non-small cell lung cancer. And we -- intrigued by the result that we had seen with this chemotherapy regimen, we expanded this in the G regimen. And with just 60 patients per group, we were already able to see a very impressive result in progression in terms of response rate and the durability of that response. That is what led to registration of this regimen when we obtained these results at the end of 2016, for registration in 2017. Because the effect size was so large and many people questioned me after that about why I had confidence in the 189 study, which was essentially the identical study for KEYNOTE-021G just about 5x larger. And the answer was those kinds of effect sizes typically should be reproducible. If you've seen that kind of an effect, you can see it was 60 patients per group, you certainly should be able to see it with a larger group size. And of course, we did and we saw it immediately in terms of overall survival. One of the questions that was asked about 021G was, "Gee, what do you know about the populations of individuals with respect to PD-L1 expression?". And the concern was that those who had high PD-L1 expression were really driving the results of the study. It was impossible to tell with just 60 patients per group, but you can get more information about that when you look at the KEYNOTE-189 study. And here is what it looks like if you look at tumor proportion score, which is the measure that we've typically used, that we arrived at after quite a bit of study and evaluating cut points. If you look at tumor proportion score, for the tumor proportion score of greater than 50% which is the population, as you know, where we registered from KEYNOTE-024, we registered KEYTRUDA as monotherapy in the first line non-small cell lung cancer setting. Tumor proportion score of greater than 50%, the effects size looks even larger with a hazard rate of 0.42. And it's clearly very impressive. But as you step down to proportion scores of 1% to 49% and even to the total proportion score of less than 1%, you can see in every instance, there is a hazard ratio that does not cross unity for overall survival. Irrespective of the PD-L1 expression pattern, the addition of KEYTRUDA to standard chemotherapy provides benefit in terms of overall survival. And the benefit is actually quite impressive. So these are extremely encouraging data, and these data set a new standard, we believe, for the treatment of non-small cell lung cancer and will, I believe, and we'll talk about that some more, become standard of care.

KEYNOTE-054, similarly but in a different tumor setting, looked at the question of whether one can use KEYTRUDA as adjuvant therapy for individuals who've been -- undergone definitive surgery for cutaneous melanoma. This is an EORTC study. The study had an early interim analysis, based on what was believed to be the power of the treatment effect, and there's no question. It's extremely powerful. Here, we're looking at recurrence-free survival, a traditional endpoint in adjuvant studies. And you can see that the hazard ratio was 0.57 in this study. And it's a reasonably large study that included more than 1,000 patients who have been treated, will continue to be followed so that, ultimately, we can gain overall survival data. But recurrence-free survival is a -- has predictive value for survival overall. So we're confident that, over time, we're going to see a survival benefit. And recurrence-free survival by itself is an important benefit to patients. So this is really an important finding that was presented yesterday at the plenary -- opening plenary by Lex Eggermont and published in the New England Journal. Beyond those 2 studies, which are extremely important, there are a lot of key data readouts over the next 18 months. This is a selected list. We have a lot of studies. And as a result of that, we have a lot of data that will be coming through. And some of these clearly are going to be practice-changing.

The first, of course, is to look at the question of whether KEYTRUDA by itself can be used in non-small cell lung cancer in patients whose tumor proportion scores are less than 50%. We've toplined that data last week and said, in fact, yes, KEYTRUDA can be used in patients whose tumor proportion score is equal to or greater than 1% for PD-L1 expression. And we'll have an opportunity to present those data at an upcoming scientific meeting. We're hopeful that we'll be able to present it in a room very much like the room that we presented the data on 189 today at ASCO in June, but that's to be seen.

We also have data that are coming up with squamous cell non-small cell lung cancer, the KEYNOTE-407 data. Those are going to be really important. The KEYNOTE-048 data first-line head, neck, mono in combination with chemotherapy, which should look, I think, really exciting. We're really very interested to see that big study that has many arms, but still looking at a very simple set of outcomes. So I'm enthusiastic about where that will be. We're having a chance to look at our triple-negative breast cancer data, which we're very enthusiastic about. First-line gastric data, expanding our bladder indications to include first-line and non-muscle invasive bladder cancer. So all of that very important. And of course, the SOLO-1 study for LYNPARZA.

So a lot of things that are going on in our studies. We're very enthusiastic about it. We've come a long ways in the last few years, and we've built an oncology program that's adding a lot of benefit for the patients whom we serve.

Fortunate to have Frank Clyburn here who'll be prepared to answer all of your questions. And thank you very much for your attention. Thanks again for coming in this evening. Thank you.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

All right. We'll move on to some Q&A. Just so everyone knows and for those on the phone, the slides are available on our website. So you guys can download those. We will not be able to take questions on the phone today. It will just be in the room. So we'll move to those questions. And we'll start. If we can go to Alex Arfaei here in the front.

QUESTIONS AND ANSWERS

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

Roger, congratulations to you and your team on all the progress including the KEYNOTE-042, look forward to seeing that. Wondering if I could get your thoughts on TMB. Not (inaudible) high but TMB as discussed at this conference. It seems to be a new format of biomarker that's independent on PD-L1 just thoughts about there and whether or not you plan to include that in your studies going forward. And then Frank, maybe you could comment on commercial considerations on TMB. And then a follow-up, if I may, Roger. Could you comment on your adjuvant strategy? Obviously, a very impressive melanoma data, but what else can we be looking forward to in the adjuvant setting?

Roger Dansey - *Merck & Co., Inc. - SVP of Clinical Research - Oncology*

Right, so on tumor mutational burden, of course, we and many others, academic colleagues, colleagues at Bristol-Myers, et cetera, have been working on tumor mutational burden for some time. There was a lot of reason to believe beginning back in 2014 that if you are -- let me put it this way, KEYTRUDA is exciting and PD-1 blockade is exciting because it reveals the pre-existing immunity in a substantial fraction of cancer patients directed against the tumor. It reveals the pre-existing immunity. It's not -- you don't prime. It's not that you're priming immunity. It's not like you de novo establish T cell clones to react to the tumor. They have to be there. And that's why things like PD-L1 work because they show you -- give you a measure of intratumor inflammation, which is a partial but incomplete surrogate for an antitumor response. So what could that tumor be recognizing -- and it only made sense to think that the tumor was recognizing the results of genomic instability in the tumor itself, both the mutational load that arises from cosmic rays and environmental exposure, but as well because of defects in DNA repair that occur in tumors. And there was actually kind of wonderful data published in several sets, looking at the large set of tumors and trying to correlate tumor type histology with the frequency of non-synonymous mutations. And everyone's familiar with those plots that have been published. They look pretty good, but they're not completely right because you find that there are tumors that don't have much in the way of mutations that nevertheless respond and others that have a lot of mutations that nevertheless do not. But they seem like they might be important. And so we've gone about doing these studies in a very serious way across our clinical program, and we have a paper in press that it describes that experience, which in 1,000 patients. I mean, it's a very large population across many tumor types. And what we can say is, first of all, somewhat surprisingly as everyone has said, and everyone says it's somewhat surprising, the PD-L1 expression and tumor mutational burden are orthogonal. They are not correlated. And that doesn't really make a lot of sense because you would have expected that if the tumor mutations are the things that the T cells are recognizing, then you really would expect that if they recognize it, there ought to be more inflammation and there you go. But I get back to the point that when we look at baseline samples, what we're looking for is the pre-existing immune response. And if that immune response has been suppressed sufficiently, then you may not actually be able to see evidence of that inflammation, which PD-L1 is a surrogate for PD-L1 or gamma, interferon, or any other gene expression profile that looks at inflammatory signals picks up the same thing. And those things do not correlate well with tumor mutational burden in most studies. So that gives us the promise of using those 2 things together. I think everyone agrees that if you use those 2 things together and you pick tumors that have both high tumor mutational burden and have an inflammatory response, the frequency of response to KEYTRUDA or PD-1 blockade more generally is much higher in that population. And that stands to reason for -- given what I've just said. I mean, if you have both evidence of a pre-existing inflammatory response and you know that there are mutations there towards which that response could be directed, that tends to give you a lot more confidence. If you look at either one, either tumor mutational burden or PD-L1 expression, they are both flawed biomarkers, and they're flawed in more or less the same way. So if you just look at tumor mutational burden, it doesn't have more

predictive value than PD-L1 has. It's really only with the 2 of them are together. And the problem is that for both PD-L1 and tumor mutational burden, if you use them by themselves or together, you miss an awful lot of patients who could respond. And that's understandable for the reasons that I've said. Mechanistically, it's understandable. So tumor mutational burden is interesting. But in order to understand how best to actually use it or whether we can use it in the current environment, that's going to take some time. Those of you who attended the session this morning heard a lot of concern raised about TMB as a -- from an operational point of view, that is in the clinical laboratory setting because there's so much variation how we score mutational burden. And the cut point of having 10 mutations per mega base is different on different machines with different sampling -- oversampling rates and in different settings. There's still work to be done to standardize that. Okay, there was work to be done on PD-L1 standardization too -- still is, some would say. And so there are things that can be done to improve that, to improve throughput and to understand how to get a firmer idea about it. At the moment, I think it's still a research tool. I think there's hope that it could turn into something that had real value in terms of patient management. So that's a long-winded answer to your question, but it's an important question, I think, to understand. And Frank, if you can remember what the other part...

Frank Clyburn

Well, the only thing I would add is that we established PD-L1 testing at Merck. And our experience -- and if you think back to when we first launched in second line lung, it took us a while to really establish that testing in second line as we all discussed. When we moved to front line, what we saw in the community -- and I think this is very important, the reason why people really wanted to test was the magnitude of effect from an overall survival perspective of what they saw with KEYNOTE-24. So I think to Roger's point, there are a lot of questions that are discussed and posed, but I think we'll see how things play out from a TMB perspective. But from a community perspective, turnaround time as well as the overall survival benefit of the actual intervention, I think, is really important for testing to be adopted.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

And do you want to mention quickly the other part of the question was on adjuvant?

Roger Dansey - *Merck & Co., Inc. - SVP of Clinical Research - Oncology*

Adjuvants, yes. We have a lot of studies that are looking at the adjuvant and particularly neoadjuvant question. You'll probably recall that the I-SPY results that came out in hormone-receptor-positive breast cancer that in neoadjuvant treatment from Laura Esserman which -- and her team -- which looked really very exciting. And we've seen a number of examples of what we think are really exciting studies, pilot studies that we've done in head and neck cancer and others. I'm going to guess that we probably have more than 30 such studies now ongoing in a whole variety of different settings. And there's -- I think that it's worth remembering -- it's worth remembering that surgery is a pro-inflammatory intervention, right? The more I look at these data, and we get to look at a lot of them, the more I look at the totality of data, anything that dumps antigen into the system improves responses with KEYTRUDA. And of course, that's one of the exciting things about the active immunization programs that we're pursuing largely with our colleagues at Moderna using mRNA-based immunization because I think the opportunity exists as we come to really understand which clones are represented in a typical response, which ones are important that we can actually direct our therapy at improving antigen delivery in those settings and expanding the right clonal populations. And that will have a big effect.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

You want to go over to Geoff Meacham there in the middle on the left?

Geoffrey Christopher Meacham - *Barclays Bank PLC, Research Division - MD & Senior Research Analyst*

A couple of questions, I guess one for Roger -- maybe 2 for Roger. But in the greater, in 50% expression level, how do you see chemo combos versus KEYTRUDA monotherapy playing out, is it just patients with more symptomatic disease that will ultimately need a chemo combo? And then the

presenter talked in the presentation about low crossover rates. And this was below the level seen in 024 and 021G. So how much of a role do you think crossover played in the ultimate treatment effect that you saw with 189?

Roger M. Perlmutter - *Merck Research Laboratories - President*

Yes. So first of all, what do you do with a patient who comes in with non-small cell lung cancer, has not had systemic therapy. This is their -- they're clearly not receptible, and they have PD-L1 greater than 50%. I think the treatment of those patients will be very personalized and depend upon a dialogue between the oncologist, the medical oncologist, and the patient. And in a -- a patient who is frail, who has many comorbidities, those patients you may say look, I'm uncomfortable with the idea of having to manage chemotherapy which has genuine toxicities, particularly in suppression of hematopoiesis. I'm uncomfortable with that. And in this population in which monotherapy is quite effective, why not go with KEYTRUDA by itself. On the other hand, I think for patients who are younger, more robust and where you really want to go for broke, gosh, that curve I have printed up on my refrigerator is pretty impressive. I mean, that hazard ratio of 0.49 in an all-comers environment is really very impressive. And I think that would probably tip the scale. Oncologists are pretty comfortable with delivering platinum plus pemetrexed in these populations. And I think that, that's probably what they would do.

And the second question was with respect to crossover. And crossover is -- of course, has an interesting and imponderable effect, right? I mean, you never know exactly what's happening. What we've said before is that, on balance, patients in our study, in 021G for sure, where we had a much higher crossover rate, patients were either receiving the combination simultaneously or serially. So they're receiving chemotherapy followed by serial KEYTRUDA as opposed to the combination. And there was good reason to believe that the combination would be better than providing serial therapy. We didn't formally test that. But in a way, that's what we're looking at. I still think that's likely to be true. I think mechanistically, from a scientific perspective, that's likely to be true. And as we develop more data, we'll come to understand whether it is true. I don't think that the crossover had really any meaningful effect in this particular study because of the timing of it.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

You want to come up front here to Dave? We'll try to get to everybody.

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

Dave Risinger from Morgan Stanley. So I have one question for you, Roger, and one for you, Frank. With respect to TMB, could you just talk a little bit more about what you've seen when you've looked at KEYTRUDA plus chemo in TMB high patients? And then, if you could just shed some more light on what you may potentially be sharing in the future with us. For example, should we expect to see TMB high data out of 189 or is that to be determined? And then Frank, if you could comment on the timing for the rollout of 189. Obviously, it's not in your control. But I'd like to think the EMEA would move pretty quickly now that you have the 189 data in hand that you could share with them. But if you could talk about potential timing for ex-U. S., that would be helpful.

Roger M. Perlmutter - *Merck Research Laboratories - President*

Right. So Dave, there is -- we have a lot of data on tumor mutational burden. We don't have a lot of data on tumor mutational burden in the combination studies. Most of that is stuff that was queued up as part of monotherapy studies, and that's virtually all of the data. For 189, it would be very difficult to do a good study. You'd end up with the sort of thing, I mean, frankly that they ended up with in CheckMate 227 with a very small subpopulation that -- where you have the data. And that was -- just sort of leaves you with kind of wondering what you're looking at. If I'm going to do a tumor mutational burden study, I'm going to do a tumor mutational burden study where we randomize with tumor mutational burden in mind. And that's not what we had in 189. If you go back now and try and take 8 slides if we've got them and see if we can scrape up enough DNA off of them, I don't think we get much out of that. And so I don't want to do it. I think if we're going to do this study, we should do it carefully, so we would do it differently.

Frank Clyburn

And the filing, Roger, I think was...

Roger M. Perlmutter - *Merck Research Laboratories - President*

So with respect to filing in Europe, obviously, we're hopeful that the European agency will move swiftly. That said, they have a process. And their process involves a supplementary BLA that goes through the usual set of hurdles. We like to think that they'll say, "Gosh, we should have approved 021G but actually, they might have other ideas." So they'll look at it in their own way, and they'll make their decision about what the timing is.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

[Courtney], you want to come up here right in front to Vamil?

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

Vamil from Credit Suisse. So 2 questions. One, you've mentioned the breast cancer. There was some data from Roche at this meeting in breast cancer. Just curious if you can comment on what they showed and kind of your enthusiasm for that opportunity which then gets a little bit -- you can tell with all the focus on lung cancer. And then the second question actually relates to 042. I'm not sure if you can comment on this or not. But we've gotten some questions as to whether that study was enrolled and if there's any sort of strategy in place where this could be more than you'd expect patients with 50% expression or above the 20% expression or should we assume that it was sort of a all-comers 1% and above and what we see in the general population is generally what got enrolled into that trial.

Roger M. Perlmutter - *Merck Research Laboratories - President*

Right. So first of all, with respect to breast cancer, breast cancer is not an especially responsive tumor. And as you know, breast cancer is complicated because you have to break it down to all of the different subtypes. We began to see signals in the triple-negative breast cancer environment and have pursued the triple negative breast cancer studies. The response rates in triple negative breast cancer are certainly not the best that we've ever seen. But we're hopeful that they'll be sufficient to add benefit for those patients. And we have ongoing registration enabling studies that we'll see. We're very enthusiastic about what we can do in breast cancer in combination, particularly because of the very impressive effect of LYNPARZA in maintenance therapy and because of the known importance of -- I mean, scientific importance that's now been demonstrated clinically of poly ADP-ribose polymerase as part of the DNA repair mechanism in individuals who have a pre-existing either somatic or germline BRCA mutation. So all of that plays into our thinking about how best to use KEYTRUDA in that population. As far as 042 is concerned, the study was designed such that we enrolled a population of individuals who had greater or equal to 1% PD-L1 positivity. In that population, we began first by looking at the patients who had greater than 50% PD-L1. This is again part of my view that if there's a scientific finding as in 024, it ought to be reproducible. So we ought to be able to reproduce an 024-like finding. Sometimes, I terrify my colleagues when I say that stuff. But we should go out and do it. So we did that, and then stepped down from the 50% to 20% down to 1%. And as we indicated, the study met those primary endpoints, and we'll have a chance we hope soon to show exactly how that happened. And that's the way the study was done.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

You want to go to Steve Scala right here in my side.

Stephen Michael Scala - *Cowen and Company, LLC, Research Division - MD and Senior Research Analyst*

Steve Scala from Cowen and Company. Two questions on KEYNOTE-189. First, what is your plan for EGFR expressing in ALK patients? And secondly, in PD-L1-negative patients, the PFS was borderline statistically significant. Should those patients who are also TMB-high be treated with I-O/I-O in your opinion or perhaps not based on your thoughts on the strength of that data?

Roger M. Perlmutter - *Merck Research Laboratories - President*

Right. So first of all, the general question of what to do with individuals -- if I think I've got your question, Steve, correctly is what to do with individuals who have pre-existing EGF receptor mutations?

Stephen Michael Scala - *Cowen and Company, LLC, Research Division - MD and Senior Research Analyst*

Right, so even the Roche data which...

Roger M. Perlmutter - *Merck Research Laboratories - President*

Right. I think that, that we are asked that question a lot about prior EGF receptor and ALK mutations. And I think there's reason to believe based on preclinical studies that therapies that are targeted against cells that have mutations in EGF receptor or in ALK actually, the combination works pretty well. And this is just generally the -- again, if you dump Anderson in the system, things go better. So I think there's reason to want to do a study like that. And we have queued up a number of studies that begin to address that question. I think that's a useful thing to explore. And if those things can be used in combination, then I think there may be an opportunity there. So we'll seek to translate those kind of preclinical results into clinical results. It just takes a while to get all the data sets put together. And then, the question is well, how are we supposed to feel about individuals who are PD-L1 low based on a PFS result which -- a cross unity. And the problem is, I think, we really need to focus on -- remember, these are all exploratory endpoints. You have fairly small populations. And what we showed you in the manuscript as we should, is we showed you the subpopulations with respect to overall survival and progression-free survival.

For overall survival, it's very clear that those hazard ratios do not cross unity. You benefit from receiving combination therapy irrespective of your PD-L1 expression level. And again, the reason why you would is understandable because PD-L1 is simply telling us that there's inflammation present by virtue of killing more cells with chemotherapy, you stand a better chance of stimulating an immune response which might not have been so evident in the population at the time you did the initial PD-L1 measurement. And so there's every reason based on that overall survival data to give the chemotherapy combination. With time, we will understand whether tumor mutational burden measurements and other measurements too provide a means of better selecting patients for a different cadence or a different combination of therapies. We're just not there yet. Right now, what we know is, if we give platinum pemetrexed and KEYTRUDA in that population, in non-squamous, non-small cell lung cancer, the benefits are dramatic and the hazard ratio overall for the total population for overall survival is 0.49. I mean it's just a powerful result.

Frank Clyburn

And if I can just add one point to that, Steve. And we've met with a number of key opinion leaders since the data has been out. And that was probably the biggest question that we were receiving with 021G, in all honesty, was that patient population. And since they have now seen the updated data from 189 and that subset that Roger just mentioned. I mean, we're talking about a 0.59 hazard ratio in that patient population for overall survival. And the KOLs, to each person that we met, really thought that, that now does warrant clearly the combination of chemotherapy plus KEYTRUDA.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

Let's go to Andrew Baum here in the front.

Andrew Simon Baum - *Citigroup Inc, Research Division - Global Head of Healthcare Research and MD*

Andrew Baum, Citi. Three questions, please. Your competitive trials in the PD-L1 low, TMB high, the treatment effect they saw was greater than in patients with PD-L1 high, TMB high, which runs contrary to the science. Do you think it's just the small sample size or do you think there's anything interesting going on there mechanistically? Second, an active topic of discussion is whether the different data sets that we see with monotherapy in non-small cell lung between pembrolizumab and nivolumab is a function of molecular differences in activity or whether it's patient selection. So on the first point, could you tell us both for KEYNOTE-24 as well as for 189 the time between enrollments and first dosing and Bristol obviously addressing the other. Just to help us understand whether there could be some patient selection as a function of your requirement for fresh biopsies versus their archival acceptance? And then finally, and this is really getting to the nub of it. You've obviously started nivolumab I'm sure intensely as you have obviously pembrolizumab in, in vitro assays as well as in vivo. Do you have any belief that these agents have differential activity in a clinical setting given the differences between the molecules, the binding time, and on the (inaudible) and so forth?

Roger M. Perlmutter - *Merck Research Laboratories - President*

Right. Thank you, Andrew. So nivolumab and pembrolizumab are different antibodies. They bind differently. They have different binding affinities. They can behave differently. If you ask me to gin up a preclinical experiment that showed that pembrolizumab was better than nivolumab, I can get that done for you. But preclinical experiments don't have a lot of predictive value for clinical results. And it's kind of an imponderable. And randomization is always your friend. And the only way to really understand this would be to do a large randomized study and try and see whether you could distinguish between pembrolizumab and nivolumab. I have no idea what the outcome would be. At the moment, what we can do is use pembrolizumab to try and advance the therapy of patients. And frankly, I'm optimistic that with nivolumab, that they'll do that, too. Because we all care about the same thing which is that patients get the best therapy. So that's all I can say. I have no idea whether or not clinically those things are different. I have told the story before. I will say it again that when the KEYNOTE-024 study came out and CheckMate-026 came out. And the first time I saw those data was at ESMO in Copenhagen. I, for the life of me, couldn't figure out how in the world they could've gotten that result with CheckMate-026 given what we had seen with 024. I actually had the opportunity to speak, as it happened, in Copenhagen with the Bristol-Myers team, whom I know well. And I have to say, I hope someday when the shoe is on the other foot, I'll be even half as gracious as they were. And they couldn't figure it out either. My first concern was whether or not, in one way or another, the randomization table got screwed up or something because it just didn't make any sense to me given the strength of the KEYNOTE-024 data. We will see over time exactly how these molecules behave, and ultimately, there will be some desire to compare them, I suppose. But there are 2 molecules that are directed against the same target and both have a similar therapeutic effect. There may be differences that are important, I don't know. One of the differences that I don't think is important is the time of -- from screening to actual first dose. There may be many subtle aspects of patient selection. But I don't think that will turn out to be an important one. The -- I like to think that in the KEYNOTE studies that we've done, we've tried to articulate very simple testable hypotheses, and we've adhered to a very simple structure. And we've tried to make sure that we didn't have missing data. And I think that those things are important. So the clinical trial execution, which has nothing whatsoever to do with me and everything to do with my colleague, Roy Baynes and Andy Lee, and the others in the team, that I think is very important and permits us to feel very comfortable about our results. And I think over time, we'll learn more about how these different therapies behave.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

Let's do a cluster back there. We'll do Jason and then Jami and Chris.

Jason Matthew Gerberry - *BofA Merrill Lynch, Research Division - MD in US Equity Research*

Jason Gerberry at BofA. Just a couple of questions. Just in the frontline lung cancer setting, can you quantify what the rate of adoption is in the non-KEYNOTE-024 population or indication? Basically the non-50% expressers. And then just second question from a timing perspective for KEYNOTE-042, can we get that data before ESMO? Just curious.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

You want to start, Frank?

Frank Clyburn

Sure. So in first-line non-small cell lung cancer and non-squamous and also squamous, remember in KEYNOTE-024, it's both populations or both histologies. That adoption has obviously been very rapid. We have pretty much every patient that it is expressed in the TPS score 50 and above is, for the most part, getting KEYTRUDA in some form, either monotherapy or combination. As you step down into the 1 to 49 segment, you are seeing the combination of chemotherapy plus KEYTRUDA be used in that patient population. Obviously, there are some clinicians that are waiting for the 189 data. And then in the TPS 1, below 1, we're seeing some adoption of the combination, but that's really where I think a number of oncologists have been really waiting for our KEYNOTE-189 data set.

Roger M. Perlmutter - *Merck Research Laboratories - President*

And for KEYNOTE-042, again, we'd be thrilled to have the opportunity to present the data here in Chicago in June. But the folks at ASCO will have something to say about that. So we'll wait and see what they have to say.

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

Just a few questions and related to KEYNOTE 42. Obviously, a very compelling trial with a surprising result. Frank, where do you see using this commercially? Where will it fit in? And also my understanding is that the trial was done outside the U.S. and outside Western Europe where PD-1 is not yet available. Just curious to know what the crossover was in this trial versus KEYNOTE-024 and if the FDA would accept label -- this is as a label expanding trial when the trial didn't include U.S. patients? Secondly, just on KEYNOTE-189, I may have missed this, but what were the treatment related deaths? I know that you gave all cause but I don't think I saw treatment related. And then just lastly, more theoretically for you, Roger, on IDO. What do you think happened with the combo in melanoma, and what are you -- what, if any, are your future plans?

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

So Frank, why don't you start on the KEYNOTE-042 and the potential patient and commercial opportunity there, then we'll go to Roger for the others.

Frank Clyburn

Sure. So Jami, with 189. Obviously, this is now an all-comers trial across a broad set of patients with -- as you have seen, with a very significant effect size and overall survival. So we think that for the appropriate non-small cell lung cancer patients, non-squamous, 189 is going to likely be the overall treatment choice for many oncologists. KEYNOTE-042 just expands the monotherapy option that we have in KEYNOTE-024. And as Roger mentioned, there's clearly going to be some oncologists that are going to want a monotherapy option as they look at individual patient selection. KEYNOTE-042 obviously broadens that opportunity. As you look outside the U.S., obviously, we do not have 021G approved yet outside the U.S. except in some other very small markets. As you go outside, monotherapy could be very important, especially as you look at Asia and some other markets like Japan. So we're excited about having the opportunity of potentially bringing KEYNOTE-042 to those markets as well. The thing I would highlight though I think that's important is that when you take a step back, you now have a KEYTRUDA option that pretty much can potentially cover, almost 90% of non-small cell lung cancer patients, if you exclude ALK and EGFR mutated patient populations. So for us, as we think about it, we've demonstrated overall survival with KEYNOTE-024. We now have demonstrated overall survival with KEYNOTE-189. And obviously, we'll look forward to sharing the results with regards to KEYNOTE-042. But we think we are very well positioned in first-line lung cancer patients as I look both in the U.S. and as I look outside the U.S. Roger?

Roger M. Perlmutter - *Merck Research Laboratories - President*

So Jami, on KEYNOTE-042, I'm not going to provide really any detail beyond the top line. We are going to have the chance to present all of those data. But it's a very robust study. And I actually wasn't surprised by the results. I actually -- was what -- kind of what I expected. But it's a very robust study. And I think it will -- people will find it very, very compelling. So I'm not so concerned about that. For the IDO question, as I said in a variety of different places, what we liked about IDO was that it seemed like the responses were broader and deeper. Remember, we only had single arm studies with IDO in combination with KEYTRUDA. And it had such a good safety profile. And faced with that, with the responses seeming broader and deeper and such good safety profile, it was something we really felt we had to pursue. On the other hand, epacadostat does not have single agent efficacy in any setting. It doesn't. And it's very worrisome to try and do combinations of things that don't have single agent efficacy. And so it was always to me quite a wild card. I liked the safety profile, but it wasn't so clear we were going to be able to get enough leverage. I think there are people who look at the data that we gather together with our colleagues at Incyte and say, "Well, melanoma is such an inflamed tumor anyway. You really couldn't get much leverage out of epacadostat in that setting, but it could work better in other setting." And there are other people who say, "Well, actually blocking tryptophan metabolism and kynurenine generation really is -- there's just not enough leverage there." And we'll be looking carefully at the data along with our colleagues at Incyte and asking the question, "What should be done about the existing studies?" But there's -- I think clearly, it's not good news. It's not good news for patients. We would prefer that there had been a big treatment effect. But obviously, there wasn't. And I think there are lessons there. Until you do a randomized controlled study, you really just don't know in these settings. And then the last question I think was for 189, overall deaths versus treatment-related deaths. And I don't have the numbers off the top of my head, but we can look at the New England Journal paper and see. I can't remember, but it's not alarming. It's not alarming.

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

Chris Schott, JPMorgan. Just 2 questions here. Maybe coming back to on the commercial side following the KEYNOTE-189 data, can you just remind us when you look at those 3 baskets you were talking about of the highs, the 1 to 49s and the below 1s. Just your latest thoughts in terms of where your -- as far as you can tell your share stands there, so always think about the incremental opportunity? And just a quick follow-up to that. Given that you're already approved in front-line with the combo, how quickly can you get out in front of physicians and start talking about the OS data, in particular? Do you actually have to wait until this gets on label or label update or can you kind of immediately get out there with that? My second question was a broader question just on -- as we get standard of care developed in some of these larger tumor types and you get data sets like 189, that seem like they're very high hurdle, how do you think about developing combos? Can you go head-to-head against these data sets or does, increasingly, the combo work -- is it going to be triple? Is it going to be looking at frontline failures? I'm trying to understand as we think of these kind of next-generation agents you're working on, how that fits into the paradigm in some of these larger tumor types, again, where standard of care is being evolved.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

Frank, you want to start on the commercial side with 189?

Frank Clyburn

Sure. So the way I would look at the overall what's happening in the marketplace. I mean, KEYTRUDA right now, if you look at new patients, it is leading in new patient starts and first-line [lung], small cell lung cancer. It's hard to really get really good reliable share data as you start to cut the segments down to the 1 to 49s, the less than 1s, the above 50. What I can tell you is that we're seeing really good progress in our overall share. As I mentioned, we are seeing good progress with the combination, but it's primarily more in the PD-L1, above 1 population. So it's either at the 50 or above or 1 population is where we're starting to see or what we've seen with regards to the introduction of 021G. And as you think about it, the market that I just described as segment from an easy perspective about 1/3, 1/3, 1/3. So in about 1/3 of the patients that are TPS score less than 1, we've seen some use but we haven't seen significant use in that population for the combination. And then, obviously, 1/3 of high expressers where we clearly have a significant share. And most of those patients are being used with KEYTRUDA either monotherapy or combination as I mentioned. Roger?

Roger M. Perlmutter - *Merck Research Laboratories - President*

So Chris, you asked about next generations and how those are going to be developed. I do think it's always the case that as you're able to, if you're lucky enough to be able to introduce therapies that have a meaningful effect, it becomes harder to get the next generation of therapies. It's a lot harder to develop. Cholesterol lowering agents or anything that affects cardiovascular risk. We had an agent, an anacetrapib, that lowered cholesterol pretty well and optimally treated people. But not well enough. I mean, it's just hard to move on from that. And we're also talking about a fatal disease there. So in the end, I think what we have to expect that we are -- we are willing to take on the challenge of developing truly better therapies. And inevitably, those better therapies will have to be differentiated against the best available combinations. That's why I think that the combination of platinum pemetrexed plus KEYTRUDA, that's a high bar now. I mean we hope to surmount it completely because there an awful lot of patients who don't respond. And we need to get better. But this is so much better than what we have been getting from chemotherapy alone for 2 decades. That the next step, it could take a while to get there. I am optimistic that some of the things that -- particularly the innate immune activators could turn out to add a lot to PD-1 blockade. But that's just sort of gut reaction. It's not because I have the data to support it. Time will tell how good those are.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

We are over time. We're going to try to get a couple more. We're not going to get to everyone, so apologies. So let's go to Greg really quickly here, and we'll go to Jon and close it out. Just apologies to those who are trying to ask questions. We'll make sure that we're around afterwards as well to answer questions.

Gregory B. Gilbert - *Deutsche Bank AG, Research Division - MD and Senior Analyst*

I'll be quick. Greg Gilbert from DB. Roger, how would you characterize your interest and enthusiasm in exploring KEYTRUDA with CTLA-4 now that you're seeing some more data? And then a broader R&D strategy question, you've been clear that it's your responsibility to fully explore I-O and KEYTRUDA. But how much room financially and operationally does your organization have to explore [BDDLs] with an R&D emphasis with all of the resources you're deploying into I-O, so outside of I-O?

Roger M. Perlmutter - *Merck Research Laboratories - President*

Yes. So first of all, with respect to CTLA-4, we have generated data of course in combination with ipilimumab. And some of those data look interesting. But we don't have critical data where we really show that KEYTRUDA plus ipilimumab behaves better than KEYTRUDA alone does. Those data are not easy to get in any setting and they're not -- a lot of those data [within nivolumab] frankly. So it's just hard to get the -- get down to how much more you get out of CTLA-4 blockade. We like to think of them as being complementary because CTLA-4 acts at an earlier stage in the differentiation cycle. But we really need to nail that down. We also have our own internal CTLA-4 program, 1308, which seems to have quite desirable properties. I'm not sure it's distinguishable from ipilimumab, but that's another one that we could pursue. We sort of have been looking for the right place to deploy those 2. And we continue to look at that, and we possibly might do it. And then with respect to business development, I think it's just true, and everyone knows, there are no undervalued late stage assets period, okay? And generally, they're all overvalued. We have a lot of programs going on. We have -- we're very robust beyond oncology. We didn't talk about any of that stuff. I mean, our vaccine team program is just extraordinary and there'll be some announcements coming out in the next week or so that's relevant to that. The combination of pneumococcal conjugate vaccines multiple, the CMV vaccine which is unique and really special. Some of our other vaccine programs, what we've done with the mRNA vaccine. Vaccine is a big business for us as you know and it's getting larger all the time. But we also have a lot of really interesting opportunities in cardiovascular medicine. Of course, we continue to pioneer a lot of work in antimicrobials including antivirals, and our HIV program, 8591 is always the belle of the ball. And I probably get more calls about that than any other program that we have. So we've got a lot of things there to pursue. We firmly believe, and I would say, I speak for Frank, I speak for Ken Frazier, I speak for everyone that we get the most leverage in terms of business development by getting in early at a time when we recognize something has value and can deploy our full clinical development expertise, and also the really skilled people we have in process development and formulation. So that's the place where we get the most value and those are the

things we tend to look for. We're not very interested in -- certainly not in transformational transactions, and we're not really trying to do a revenue-based deal. That's not really what we look for at the present time. And I think we're in a reasonably comfortable place to do that.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

(inaudible), do you want to come up here really quick? We'll do Jon really quick here in the front. And then, I apologize, we are overtime as well.

Jonathan Miller - *Evercore ISI, Research Division - Associate*

Jon Miller, Evercore ISI. So your choice of chemotherapy to combo with, obviously, (inaudible) it's a widely used in non-squamous, but it's not the only chemo backbone you can imagine and certainly, we saw some data from Roche today with the addition of [elotuzumab]. So what do you think is going to drive the use of different chemo backbones in the first-line setting and especially with regard to anti-antigenics.

Roger M. Perlmutter - *Merck Research Laboratories - President*

Yes, great question. I think a lot depends on having some -- if we could have some insight for the system and what we're trying to manipulate. I -- unfortunately, it's the case that a lot of chemotherapeutic regimens are relatively poorly characterized in terms of their immune effects. So we actually don't know that much about them. There's some provocative data on pemetrexed which certainly influenced our thinking, but it's not certain at all. With respect to Tregs. So I think that it is possible that many other chemotherapeutic regimens could be used in combination with KEYTRUDA and could deliver similar kinds of results. I think it's going to be hard to beat the results that we've got because they're just really -- it's very impressive. But there are others to think about. We are interested in what we're seeing with VEGF receptor antagonism from the work that we've done in combination with lenvatinib. Every single one of the VEGF receptor directed molecules [remember] those antibodies or small molecules has different characteristics. And of course, you affect not only what's referred to as angiogenesis, although I think it's fair to say that it has a lot more to do with vascular permeability than anything else, but as well what goes on with lymphatics. And then some of the molecules like lenvatinib have other kinases in the FTF PDGF receptor family that they hit. So those things are going to turn out to have interesting characteristics. It's a field I used to work in for years. It's really hard to -- it's sort of in the midst of a Goldilocks argument all the time, too hot, too cold. How do you get it just right? I don't know that lenvatinib is just right, but it has some pretty interesting properties, and we're pursuing those pretty carefully as a way of trying to understand that particular chemotherapy to (inaudible) in combination with KEYTRUDA. But these are hard problems.

Teri Loxam - *Merck & Co., Inc. - SVP of IR & Global Communications*

All right, folks. I think we're going to end it there. I know we're way over. Apologies again for the people that we didn't get your questions. We'll be around for the next few minutes if those of you who have extra questions that you want to have answered. But otherwise, thanks, everyone, for joining us tonight.

Roger M. Perlmutter - *Merck Research Laboratories - President*

Thank you for coming.

Frank Clyburn

Thank you.
