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MRK - Merck & Co Inc Investor Briefing at 2018 ASCO Annual Meeting

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OVERVIEW:

Co. provided an update on its current studies and data.

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PRESENTATION

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

So similar to our AACR presentation, Roger Perlmutter, our head of MRL is going to provide a few words and go through a few slides. And then, we're going to open it up to questions with both Dr. Perlmutter as well as Frank Clyburn, who runs our oncology business unit. So with that, let's get started, so we can try to stay on time.

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

Right. Thank you, Teri , and welcome, everyone. And thanks for coming to this Investor Meeting. We recognize that you have a lot of meetings to attend and there are many more tonight, stretching out into the wee hours. We're eager also to make sure that those who are joining us on the webcast have the opportunity to hear this general a summation of the data. So of course, this is our forward-looking statement. And preceding, I want to emphasize again that we have taken a very systematic approach to exploring the importance of immunotherapy and particularly KEYTRUDA in the treatment of malignant disease. KEYTRUDA, it was clear to us years ago, when we first have the opportunity to look at it, could prove foundational in the treatment of malignant disease. And those of you who were around at the time will remember what things were like 5 years ago when we had our first presentation here 5 years ago at ASCO. At that time, we had 1 abstract, just 1 abstract. It was a good abstract but it was 1. It was an oral presentation and just a couple of handfuls of patients really. But even then, it was very clear that the results that we obtained with KEYTRUDA treatment at that time, MK-3475, the results were really very special. And for that reason, we charted out a course for its development that we needed first to understand how it behaved in monotherapy in malignant disease. And it was necessary to understand that in order to pursue combination therapies intelligently. And at the same time, we would be performing mechanistic studies with the goal of being able to select those future combinations because there really was never any doubt that if you want to treat malignant disease successfully, you're going to have to use combinations of active agents. We've explored those combinations now having nearly completed our monotherapy studies. We still probably have 1 year, 1.5 years to go on those. And we have also gained access to 2 important new drugs through our partnerships with AstraZeneca on LYNPARZA and with Eisai on LENVIMA. And we've also taken advantage of something that was very evident back then in 2013, which was that we could develop biomarkers that would enable us to identify patients who were especially likely to respond and to have a favorable result from monotherapy treatment with KEYTRUDA. So that's the approach that we've taken over the last 5 years. 1 abstract for presentation in 2013 for KEYTRUDA alone, 112 abstracts this year. So an awful lot of work that's taken place. And those of you who tried to keep track of all of the

material during this meeting recognize just how difficult that is, an extraordinary breadth of data from this very expansive clinical program. We have demonstrated activity for KEYTRUDA in more than 25 tumor types. Most of those, of course, in single-arm studies, but more recently we've been developing randomized control data for a lot of those. Overall, including our abstracts related to other molecules, 140 abstracts in this ASCO presentation, so really quite a large set of presentation. And we're going to focus most of our discussion this evening on lung because so much lung cancer data was presented. And I'd like to try and place that in context for you.

At ASCO 2018, the KEYNOTE-407 data chemo combo in squamous cell and KEYNOTE-042, which was the monotherapy data in non-small cell lung cancer reproducing, in essence, our KEYNOTE-024 data and extending it to patients who had lower levels of PD-L1 expression. And then, of course, there's the updated data on 021G. And we'll draw in and compare that to some of the results that we've had from other studies.

So KEYNOTE-407, as you'll recall, it was presented just a day ago, is a study in which we ask the question as to whether or not patients with squamous cell malignancy, non-small cell lung cancer to be treated in the first line with the combination of KEYTRUDA plus chemotherapy and whether that would be beneficial as compared to chemotherapy alone. And so the standard of care at the time, chemotherapy, we add KEYTRUDA to that, and we look to see what the result is. What we're showing is overall survival, and KEYTRUDA reduced the risk of death by 36% compared to chemotherapy alone, hazard ratio of 0.65. And that result was very significant. There are 3 zeros to the right of the decimal point. So the chance of this having obtained this result simply by repeatedly doing studies as a matter of chance will be sort of like the chance of flipping a coin and getting heads 10 times in a row, probably pretty unlikely. Did that at my head, I think that's about right. So at any rate, that's a pretty powerful result, and it broadens the utility of the chemo combination because, of course, 407 is making reference to the KEYNOTE-189 data that we had the opportunity to present at AACR.

407 showed that there was an overall survival benefit that was present across all PD-L1 subgroups. And that is not so surprising. A couple of things to look at on these slides. First of all, sometimes there's evidence in monotherapy studies of non-proportional hazard risk because early on, chemotherapy has a benefit in a lot of patients. And that benefit may, in neural laser, to patients receiving immunotherapy and, as a result, the survival lines may cross. But in this case, of course, everyone's getting chemotherapy. There's the early benefit you see right away. But the benefit persists and extends as a result of the concomitant administration of KEYTRUDA. And that's true whether you look in patients who have a tumor proportion score of less than 1% or tumor proportion score of greater than 50%. So PD-L1, in that context, really doesn't make any difference.

If you look at the KEYNOTE-189 data that I mentioned, which is the data that we presented at AACR, this is data looking in the nonsquamous non-small cell lung cancer population in the first-line therapy. Again, overall survival data, the gold standard. And what you can see is in this setting, just to remind you, once again, we showed a dramatic improvement in overall survival that was true across all PD-L1 subsets. Here, you can see something important, which is that, in the tumor proportion score greater than 50%, that the benefit looks exaggerated as compared to that in less than 1%. And when I look at that, what I'd say was that's provocative and interesting. It's not 100% clear that we could reproduce that, in fact, over and over, but it's certainly consistent with what you see in the non-squamous population as opposed to the squamous population and that is the treatment effect of KEYTRUDA is greater. And that perhaps is what we're visualizing there, comparing 189 to 407. It would have to be studied in more detail.

We also presented the data from KEYNOTE-042. This is monotherapy. Again, it is recapitulating data that we obtained from KEYNOTE-024. And KEYNOTE-024, which we presented at ESMO back in 2016. What we showed is that in, all comers, patients with non-small cell lung cancer. And by all comers, I should say we exclude patients who have EGF receptor mutations or ALK translocations that would mean that those patients would be much more successfully treated at least early on with the tyrosine kinase inhibitor directed to their particular lesion. That, excluding those patients, here, we take all-comers, squamous, non-squamous, and in that population, we look at the totality of the population that has PD-L1 tumor proportion scores greater than or equal to 1%. So what you see in that study is with a hazard ratio of 0.81 for overall survival, the result is really very significant with a p value of 0.0018.

The study is designed as a step-down study where we look first at overall survival in the population of individuals who have a tumor proportion score of greater than 50% then a 20% then at the entire population. And so you can see what those curves look like here. And you can see that the benefit in the greater than 50% is demonstrably based on this Kaplan–Meier curves is demonstrably greater where there, the hazard ratio is 0.69. And it's important to recognize that this study, as I say, precisely recapitulates what we had done previously in the 024 study, looking at a similar population but a much smaller study. And once again, looking at overall survival.

I should also point out that if you look at the 021G results from some time ago now, the 021G results which we also had the opportunity to present a couple of years ago, when they were much less mature, this was a study from an early study, a single cohort, representing only 123 patients who are randomized to receive either chemotherapy or KEYTRUDA plus chemotherapy. And this was the first data that demonstrated to us in this setting that there could be an improvement, first of all, in PFS but also in overall survival, these data are now becoming much more mature. And although they're descriptive data, you can see that the 24-month overall survival data looks very powerful in this very small study. And so it is recapitulating now what we know very well from the larger studies that we've done, 189 and 407. So if you sum over the totality of all of this data, what you can see is if we take out that set of individuals, about 20% that have mutations in EGF receptor or ALK translocations have a driver mutation that should be treated with a tyrosine kinase inhibitor, across the remainder of the non-small cell lung cancer population, which includes a small set of squamous cell cancers and these days a much larger cell of non-squamous cell cancers, we look across the totality of that. There is reason to prescribe KEYTRUDA in every segment. Sometimes, most often, that will be KEYTRUDA in combination with chemotherapy. The appropriate chemotherapy for a squamous or for more common non-squamous. In some individuals who are, as a result of comorbidities or advanced stage, one worries about the adverse effects associated with chemotherapy, single agent KEYTRUDA may be the appropriate choice. So the important thing to mention is that we have demonstrated improved overall survival in the single agent setting as well as in combination with chemotherapy across these different subsets and with different chemotherapy regimen.

So we've also expanded this in lung cancer beyond non-small cell lung cancer and have the opportunity to present the small cell lung cancer data, small -- a small data set at this point. But I think for those who saw it, representing it in totality about 100 patients that we've looked at, you can see the clear effect of PD-L1 positivity there, and the improvement in response rate and durability of response, I think all goes well for what will be ultimately an overall survival signal. So we'll have the opportunity to look at those data in additional studies, some of which are outlined on this slide. And ultimately, I think we'll be able to treat those tumors as well.

Beyond those of course, we've had the opportunity to present a lot of data at this meeting, more to come. It's really an extraordinary effort on the part of the Merck Research Laboratories team. And I can only begin to approach some of them. But an example of a combination study with lenvatinib, LENVIMA from Eisai. This is data that we presented in second-line renal cell carcinoma treatment, an overall response rate of 70%. The waterfall plot is very impressive and Phase III trials in first-line renal cell are underway. We are very optimistic about this as a new means of providing improved survival for patients who are suffering from renal cell carcinoma. Almost all the patients in this study experienced tumor reduction per baseline. And that probably reflects again the activity of lenvatinib which is a multi-kinase inhibitor that affects a VEGF receptors which, of course, are very important in the pathogenesis of renal cell carcinoma and as well other growth factor receptors that probably play a role later in the progression of disease.

And beyond that, we also had the opportunity to discuss study 08, which is a combination of LYNPARZA plus abiraterone in patients with previously treated metastatic castrate-resistant prostate cancer. This is an event-free survival plot. This is not an overall survival plot but event-free survival. And it's provocative and interesting but early days. Note that there are only 70 patients per arm. And what it suggests is that the combination of LYNPARZA plus abiraterone is superior to abiraterone alone with a hazard ratio of 0.65. The strength of the study, of course, is it is a randomized study. But it's small, it's early days and clearly needs to be confirmed. And it offers the promise of being able to begin to use LYNPARZA beyond the settings of treatment of mutated -- BRCA-mutated ovarian cancer maintenance therapy in patients who've had a response to treatment chemotherapy treatment for ovarian cancer and also in the treatment of breast cancer which was recently approved. So a lot of work going on with our colleagues at AstraZeneca on LYNPARZA and ultimately, a lot of work that will be done looking at LYNPARZA because of its activity as a poly ADP ribose polymerase inhibitor in combination with KEYTRUDA.

So when we think about what to watch for in the next 18 months, we just pick the numbers out of the source of all truth which is clinicaltrials.gov and just lay them out there. You could do this yourself. And the important thing to note is we've just listed the dates for some of the important studies. But keep in mind that these trials are event-driven. So the event rates may vary, and we may not actually see them exactly when we want to. But we try to keep you informed of that as best we can. We also have some important action dates that are coming up very soon, this month. We expect to hear from FDA with respect to our cervical cancer accelerated approval. We also have a primary mediastinal B-cell lymphoma file which is under review. Additional data were provided and the PDUFA date was extended. But that's currently July 3. We will have a chance to look at the hepatocellular carcinoma approval which we are doing in concert with our colleagues at Eisai on LENVIMA in some time towards the end of August. And then, at the end of the year, our second-line head and neck cancer KEYNOTE-040 study for which there are now overall survival data. We also will have, we hope, the opportunity to gain approval for non-small cell lung cancer, KEYNOTE-189, in September. And so a lot of stuff going

on, a lot of important work being done, a lot of important work that's been presented here. And now we'd like to have the opportunity to take your questions. Thank you very much.

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

Before we get started, I just wanted to let everyone know, these slides are already posted on our Investor website. So if you want to download them. Let's start with Chris over there in the left.

QUESTIONS AND ANSWERS

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

Maybe 2 questions here. First, help us put a little bit of perspective around the 042 data versus the competitive data set from a few years ago whereas you didn't see a benefit. So just interested in any perspectives that we've seen in that data set. How are thinking about very different outcomes with your monotherapy versus your competitor?

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

The world is full of competitors, but I guess you're talking about Bristol-Myers?

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

Yes.

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

And so you're looking at the 042 data versus the CheckMate-026 data. And again, it's impossible to do satisfactory cross study comparisons. I have never understood the CheckMate-026 data. I don't understand it because even if you look at the high tumor proportion score, PD-L1 high population using the Bristol-Myers assay, and this is their data. And their assay performs very similarly to ours, to our 22C3 assay which we've done together, so we know it's similar. So that should be a similar population. The hazard ratio in their study was 1.07. So a cross unity on the wrong side. And it would be very difficult for us to have gotten a result like that. But at another Investor Meeting, I remember, before CheckMate -- before KEYNOTE-042 came through, people said, why in the world did you do this study when there's so little likelihood of it working because of CheckMate-026. And my thought was, well, how can I not do this study given KEYNOTE-024? And I even -- I got a lot of pushback about the 50%. They didn't want to do it. Why do that because you put your results at risk but I said my gosh, I can't reproduce that. That kind of p value. I got to find out about it. It is -- it would be very, very difficult based on just statistics to have the results bounce in the wrong direction. And as it turned out, of course, they didn't. They were very similar to what we had before. Nearly identical. So I think we feel pretty confident about our results. They're reproducible. They look very substantive. I really can't speculate on the CheckMate-026 data or why they look as they looked. I just don't know.

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

And my second question was just on renal. You also presented in this conference some monotherapy data that had some very nice ORRs obviously early data. Can you just talk a little bit about your perspective on combo versus monotherapy in frontline renal and the roles they could play and kind of next steps as we think about what we do with monotherapy.

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

Yes, it's a great question, Chris. And I must say we talk about this quite a lot because the monotherapy data in the first-line renal cell population looks really quite strong, and I believe the discussion point is that's out yesterday. And that's a pretty well-tolerated therapy. And the question is well, should you hold, for example, VEGF targeted therapies and multi-kinase inhibitors in reserve given the power of those data? We just need to spend more time looking at it and thinking about it. The reality is that while there was plenty of toxicity associated with VEGF receptor antagonist particularly small molecule, nevertheless, if my instincts in well I think you also feel the same way is to try and get as much traction on the tumor early on as you can rather than permitting additional mutations to accrue that may make it difficult to treat. It's tough, I agree.

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

Let's go to Jamie here.

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

(inaudible) 189 and the label. What is the reasonable expectation for a timing of when prescription trend start to reflect the significant opportunity for KEYTRUDA?

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

Jami, thanks for the question. And if you go back to what we talked about even at AACR, if you look at how the patient flow happens within non-small cell lung cancer, there's really not a bolus of patients. What is happening right now, and I can tell you, we are hearing very encouraging feedback. We are seeing guidelines especially in many of our integrated systems be updated to now (inaudible) the combination of ALIMTA carbo KEYTRUDA. We are, even at this meeting, have met with numerous KOLs and they're basically saying which you heard even this afternoon from the discussions that the 189 combination in non-squamous, non-small cell lung cancer is moving to a new standard of care. I think to answer your question what we'll have to see is now as new patients start to come in, we do anticipate that we will start to see an acceleration of KEYTRUDA. But it's not a bolus. It's as new patients get diagnosed, get tested, remember that patients are being tested now for EGFR ALK mutations as well as PD-L1 status. As that happens and it comes through, you'll start to see expressly new patient prescription start to pick up, very confident about that. So right now, if you think about it today, we already have approval based off of the 021G data set, we are actually sharing in New England Journal of Medicine publication with clinicians as we speak. And then ultimately, obviously, Roger just highlighted in September there hopefully will be an update on the label for 189.

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

Thank you. And go to the back to Dave.

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

Dave Risinger from Morgan Stanley. Two questions. First, Roger, could you just talk a little bit about TMB? Obviously, Bristol was really trying to push TMB adoption. But the data sets were not prospectively defined in terms of how the trial was originally constructed. Just love to get your thoughts on TMB more broadly. And then I guess, specifically how Merck plans to evaluate TMB in the future. And then second, could you discuss the time line for adjuvant lung for KEYTRUDA?

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

Yes. I mean, first of all, with respect to tumor mutational burden, clearly, that's an area that we've done a lot of work in and have pioneered this with microsatellite instability program that enabled us to get a broad registration. Our view of it of course has evolved over time. Initially, it seemed

just sensible that as more mutations accrue, there was a higher likelihood that those mutations would be represented in the set of proteins that might be presented to T lymphocytes and hence, there would be a more vigorous immune response. Imagine then our surprise, and I think the surprise of almost everyone, when you find that tumor mutational burden is actually as a biomarker is orthogonal to PD-L1. So PD-L1 is a way, as an imperfect biomarker, but it's a way of measuring the existence -- the pre-existing immune response. If there's a pre-existing immune response at the tumor site, the results in gamma interferon release, for example, that will up-regulate PD-L1. It's gamma interferon responsive. And you would expect, gee, if there are a lot more mutations in there, there's a much higher chance that there's immune response. When I biopsy the tumor, obviously PD-L1 go up. But in fact, the two are orthogonal. And we and everyone else in the study found that, which raises questions about what you're actually studying there just as a possibility with our very high mutational burden these high cutpoints that people are looking at, maybe just that those tumors are easier to kill. Cells are just easier to kill. One of the interesting things is that when you look at tumor mutational burden and this number of people have done this including ourselves, you look at tumor mutational burden and you plot receiver-operating characteristics, it's a very similar kind of imperfection as a biomarker to PD-L1. They look very similar. So that permits you to establish 4 quadrants which have been described. There is the tumor mutational burden high, PD-L1 high, tumor mutational burden low, PD-L1 high, and et cetera, et cetera. And -- but what's clear is that even in those patients who are low for both, there are meaningful responses to KEYTRUDA. They're much less common. They're much more common when you look at the high, high population. The question is how do you integrate that into clinical practice? First thing that has to be done is you have to do a series of test sets to establish a cutpoint. And then you have to take those cutpoints in and prospectively analyze whether or not they actually contribute. Distinct data sets that have looked at this have been unfortunately not -- they don't result from randomized data because they were, in essence, introduced post (inaudible). And so particularly because there's so much missing data with only a little over half of the materials sufficient to enable you to score tumor mutational burden, you can't really tell what's going on there. But we and everybody else are doing those studies, and we will come to find out how useful that marker is and in which tumors. Ultimately though, what we really need, what the entire field really needs and what we've spent a lot of time working on is a mechanistic understanding of the activity of KEYTRUDA. And the reason we need that is since the goal is to take the majority of patients who don't respond to KEYTRUDA and make them responders, what do we have to do? What's wrong with those people who don't respond? And we're sort of searching around for markers that would help inform that. But ultimately, we need to understand it at a very deep cell and molecular level in order to be able to make the right compounds to combine with KEYTRUDA. We have a start with chemotherapy. We have various speculations on why chemotherapy might work in that setting, but we'd like to do better and improve the therapeutic indices for the drugs that we're using. That's the goal.

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

Do you want to comment on adjuvant lung?

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

Oh, adjuvant lung. Well, you have to wait a while. I mean, it's ongoing but it will be a while before we have a chance to see those data. I think that they're -- I must say that we are impressed with the adjuvant data, for example, the melanoma adjuvant data that we have obtained that we described at AACR. And we're quite impressed with the very small studies that we have helped to prosecute in neoadjuvant settings. There are reasons why one might think neoadjuvant might be an especially good place to be using KEYTRUDA, and that's something that we'll be pursuing in the future.

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

Let's stay in the back with Andrew.

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

Andrew Baum, Citi. A couple of questions. First, on the LYNPARZA abiraterone trial that you presented. There's an imbalance of cardiovascular deaths. How are you thinking about that as you proceed to Phase III? And then second, have you characterized the patients by DDF status in terms of progressive versus non-progressive? And then the second question. Learnings from your Epacadostat experience. One, you've highlighted and

calling out single agent activity as being nice to have for future combination trials. The other is gauging your interest in other TME-modifying approaches. How is that impacted? And we touched on it before but I'd be interested.

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

Yes. So first of all, with respect to the abiraterone kind of combination, there was an imbalance. And again, it's a very small study. We have to be careful in looking at it and trying to find safety signals. We don't really have an understanding for any differences that might occur, and I'd say a lot more analysis has to be done, including the analysis of progressive subtypes that you mentioned. So there's more work to be done and looking at that data set. Then the lessons from epacadostat. Again, I think -- epacadostat was an interesting story. Is an interesting story still, because there's an agent in which the underlying mechanism whereby epacadostat might work is a little mysterious. You inhibit IDO1, and that blocks tryptophan metabolism. It's unclear whether or not tryptophan is limiting in a certain setting or whether the products of tryptophan metabolism, particularly (inaudible) might interact with a particular receptor. And whether that could have an effect. But if you look at combination studies preclinically, you can clearly demonstrate a combination with PD-L1. So you use a KEYTRUDA analog and a mouse study with (inaudible) tumor population and you can clearly see that introduction of epacadostat or a similar IDO1 inhibitor, we have many in-house, will pair with that effectively. Preclinical studies don't always have predictive value for human disease. We know that. All preclinical studies are by their nature contrived. So it was hard to know what to do with that. We decided initially that we would just do combination studies of single-arm and look at them. And our impression of those studies was, gee, as I said, to this group and other places, it looks like the responses are broader and deeper. And that's -- the only way to know that is to do a randomized controlled trial. We set up a randomized controlled trial for melanoma, and then announced and set up the other randomized controlled trials. But we wanted to proceed slowly on those trials to make sure that we have the melanoma data to look at. That's exactly what we did and together with our colleagues at Incyte. When the melanoma data came in and we had a chance to see those data, they're clearly negative. The question then became, well what do we do. There's an argument that people have made that well, melanoma might not be the worst place to look because it's such a KEYTRUDA responsive tumor. How about others? So with some lung cancer -- 2 lung cancer studies were downgraded to Phase II, changed in terms of size and endpoint. And we'll have a chance to look at it and we continue to explore it mechanistically. But I think it is important to note, and you and I have talked about this before, that epacadostat and other IDO1 inhibitors do not have single-agent efficacy. And it is -- it makes it much more difficult to study clinically if you're pairing something that has no efficacy by itself but must be used in combination. That's the sort of thing that one can to effectively in the antimicrobial space, usually mechanistically driven because you're typically improving the half-life of the active drug. But it's very difficult to do in a cancer study. And so that is a cautionary note. We knew that and it's even more a cautionary note now. I think the other point that you asked me to comment on is tumor microenvironment and how important is it. And I think it's important that we not be caught up in [shibboleths] about how immune recognition of tumors actually takes place. As an example, I would say there's been a long-standing view that lymphocytes can't easily penetrate pancreatic cancer because of the vigorous desmoplastic reaction, which excludes an immune response. Well, maybe so, but in MSI high population, you see responses in pancreatic cancer. So the inference that was drawn from the histology of that tumor may be not so helpful. And I think the same is true for many of the places where we look at inflammatory responses just with hematoxylin with inspections or special stains in colorectal cancer and other settings. So we should be a little bit careful about trumpeting the tumor microenvironment as an explanation for nonresponsiveness. There may be many other reasons. And it's a complicated systems problem. We just need to get down to molecular and cellular levels in understanding this.

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

(inaudible)

Unidentified Analyst

A couple of questions. I thought Dr. Leena Gandhi had an interesting concluding slide yesterday where she segmented the first-line lung cancer market and basically said that pembrolizumab was (inaudible) product of first choice in most settings. But she did say that in the low PD-L1 high TMB populations, (inaudible) was the drug of choice. And in patients with liver (inaudible) pembrolizumab would be the drug of choice. And I'm just wondering if you agree with Dr. Gandhi or not on this. And secondly, maybe it's a better question for Frank, but when you think about the Merck lung cancer franchise over the next 5 years, do you think it's settled ground and Merck prevailed or do you lie awake at night worrying about the next data readout maybe in [power 132] is going to change everything?

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

Well, so first with respect to Dr. Ghandi's commentary. I think it's -- we really have to be pretty careful about rules of inference here. There are now 5 overall survival data points with KEYTRUDA in non-small cell lung cancer. Their -- the overall survival data are extremely consistent. The thing I guess I would say about KEYTRUDA is so remarkable is just how consistent the data are, time after time, study after study. But we don't -- we're not surprised by the consistency but I'm not surprised -- I don't find myself saying, look it doesn't work. You can almost dial in the numbers. We don't have any post actively defined data on tumor mutational burden. but I have trouble using that as a way to decide what I would treat a patient with when I have data that tells me I can improve overall survival with the combination of KEYTRUDA plus chemotherapy, for example. And I guess, I will return back to where I was before, which is that in an all-comers population, many of whom have liver metastases, many of whom have a low and high tumor mutational burden. In that population, what you see is that the combination of KEYTRUDA plus chemotherapy adds real benefit over chemotherapy alone. It's what -- the bedrock that we have to stand on. And I think it does set a bar for future studies in terms of what everyone else has to reach. Obviously, there -- we've heard many different perspectives on this. But I think in general, most people have come to that conclusion so that's kind of where I'm, and Frank, you can talk about the market.

Frank Clyburn

So if you take a step back, I think that right now clearly, we know there's a lot of competitive data still yet to be read out. The way I would think about it though is where Roger started with the data. I mean, right now, if you look at the bar that's been set with 189 and the combination setting, and we're talking about reducing the risk of death in half. We think that bar is pretty high for our competitors as well as even ourselves as we think about even additional studies we may want to do in those patient populations. I think when you come to the meeting and you see KEYNOTE-407. And we're now talking about a hazard ratio of 0.64, you're talking about across all squamous non-small cell lung cancer patients, there's a very significant benefit. We then look at our monotherapy opportunity and option, and obviously around the world right now we have established in the high patient -- PD-L1 high [express] patient population pretty much KEYTRUDA monotherapy as the standard of care in most markets now around the world where we have approval and reimbursement. And then you can now look at the expansion of a monotherapy opportunity, depending upon regulatory approvals of a broader mono-opportunity for patients and physicians depending on what they may choose. And then lastly, when you round that out and think about the breadth of our overall program, we collect the [physicians] very well. I can tell you that being first with overall survival matters. And what we're establishing right now is a very, I think, high bar with KEYTRUDA, monotherapy and combination for the future and being able to address almost 80% the non-small cell lung cancer patient population, we feel we're positioned very well for today and into the future.

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

And if I could add just one thing today, all I would say is that if you had told me 2 years ago we got the 024 data that showed improved overall survival as monotherapy versus chemotherapy, if you had told me that 2 years later nobody else could have demonstrated that with the PD-1 directed therapy, I would've thought crazy. And it's not for want of trying. Because there's lots of studies that have been done. So right now, we just have to be careful because these data that we obtained with KEYTRUDA, as I say, are very predictable. But it's -- we're the only ones who have it.

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

Let's go to Jason and Vamil.

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

Jason Gerberry from Bank of America. First question just on KEYNOTE-042. Just trying to make sense of the ultimate utility of the broader role potentially of future monotherapy and the 1 to 49. I think both the discussions over the last 2 days really did not indicate there is an expanded role

for KEYTRUDA monotherapy. So the signal that we saw in the 1% to 49% expressers was on the weaker side. I was just curious if you can kind of comment on how you see that playing out.

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

Well, first of all, I think it's important to recognize the way the study was done. So the study was designed to look at the total population and did so by looking at the 50% population first, as I mentioned, and then stepping down. There was no prespecified analysis that looked at the individual components of this. And so we should be very careful about looking at those because from a statistical point of view, we were never powered. We weren't in power to do that. But what I would say is, all of that said, I think in general, the strength of the 189 data and the 407 data are such that most people look at this and say, "Right, the issue isn't whether I use KEYTRUDA, I'm going to use KEYTRUDA. The question is do I add chemotherapy." And in most cases, that's going to be yes. There will be some individuals in whom for a variety of reasons, there's some concern about the toxicity, and there is meaningful toxicity that's added as a result of the additional chemotherapy. But these are agents that oncologists have been using for decades. They know how to manage them. And I think as a result, in general, and Frank, you may want to comment on this, but I think as a result a very large percentage of patients will receive combination therapy because people view those results as superior.

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

Let's go to Vamil.

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

Vamil Divan from Credit Suisse. So just building off of that question, just following up. Do you expect any difference in the academic (inaudible) around.

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

You mean in terms of sales?

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

So the [1% to 49%] group (inaudible) having a (inaudible). My actual question was around beyond lung or is it just -- are you seeing any indication that this [revenue data] in lung is having an impact [for the] use, for indication for better data set? Similar again I'm wondering especially about the academic setting for -- with the simpler regimen and the (inaudible) with the (inaudible) by drugging?

Frank Clyburn

In the community, I think what we're seeing in here, they're very familiar with the combination of (inaudible) and carboplatin and they've been using it for years. So what we're seeing is not really a difference between the academic or the community when you think about monotherapy or combination. Very comfortable with the combination. I think it does go to the point that there are decisions that will likely be made primarily on an individual patient basis. If you have high PD-L1 expression, and you have comorbidities or if you have some concern about the toxicities with chemotherapy as Roger mentioned, maybe it's monotherapy. But we don't see a difference between academic and community with regards to the use of combination [effort] of using KEYTRUDA plus OLYMPIAD, plus carboplatin. And as far as some of the other indications, I would say that we do feel as though the breadth of our data continues to help us overall. And I will give you some examples, in second-line bladder cancer as an example. We have established in new patients a leadership position in new patient share. Now, we have overall survival in that indication, so we have very strong data. We launched fifth into that indication now. So I think as physicians start to become more comfortable with using KEYTRUDA not only in lung cancer, but in bladder cancer, in melanoma, in head and neck, we think that, that does help us in the long run.

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

Maybe just one, a second one for Roger on first-line data you went through is very impressive. The second-line lung seems to be [worse for this] issue. Maybe if you just want to comment on Merck has here or what you see (inaudible) the meetings. What do you think are the most exciting opportunities for patients?

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

You're talking about the evolving practice. Once KEYTRUDA has been used as a first-line setting in individuals who failed -- I mean, it is a characteristic, of course, of KEYTRUDA therapy. In general, of PD-1 directed therapy, the responses are often durable but they're not perfect, and people do relapse. There is a question as to whether or not in those individuals, retreatment can sometimes provide a mechanism. In individuals who never have a response to KEYTRUDA, in that setting, clearly, at the moment, we do not know how to treat those patients. And there are lots of ideas. We are certainly very interested in mechanisms, or maybe I should say this differently and say, I'm very interested. I'm very interested in how one improves priming of the immune system, because largely, the reason for failure, I believe, is that there is no satisfactory priming that's taken place. And again, I'm basing this on far too little data and far too little understanding. But to the extent that one can get satisfactory immune responses generated early, I think the likelihood that you'll see a good response from KEYTRUDA is high. And so the question is how can we ensure that, that happens. And some of that may be achieved by simultaneous administration, for example, via vaccination. And we're engaged in a whole variety of those kinds of studies. First of all, taking advantage of oncolytic viruses and today, I believe our transaction with Viralytics just closed in Australia, whatever time it is there. And that's a pretty interesting implementation of the coxsackcie A21 virus for which the data are really quite, quite surprising. And we'll have a chance to share some of that data with you soon. And there may be other opportunities beyond that, that could be quite exciting too. So to the extent that we can improve the priming process absent recovery of KEYTRUDA, I think we might be able to drive better responses. Some of that may be applicable to a second-line setting too.

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

Let's come up to Alex, up front here.

Alex Arfaei - *BMO Capital Markets U.S. - Pharmaceuticals Analyst*

Alex Arfaei with BMO. Roger, a couple of questions. First on KEYNOTE-042, given that the survival benefit was primarily driven by (inaudible) patients. Is there any risk getting KEYTRUDA approved at a 1% (inaudible) since we already have (inaudible)? That's the first question. And then on the timing comment. There were some suggestions that the chemo (inaudible) 189 was (inaudible) arguably more (inaudible) of (inaudible) KEYTRUDA. Just wondering if you've seen any of that or if there was a [status quota with] rationale for selecting their chemo (inaudible) 189?

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

Well, for the second question first, I mean really that wasn't part of the rationale. And I think at the moment, I mean, in general, we know that chemotherapy is proinflammatory generally. There's always been this argument -- and have lots of discussions about this to the extent to which chemotherapy suppresses replicating T cells et cetera. But the point is that it also [kills] a lot of cells and dumps a lot of (inaudible) system, it dumps (inaudible) the system and as a result, accumulates a lot of innate immunity via 2 independent pathways. So this -- so there is a pro-inflammatory response. And that would be true for a lot of different therapeutic regimens. The decision to work with the (inaudible) carboplatin was really based on its use pattern, whether it's (inaudible). As far as approval with respect to 042, again, we have not had regulatory discussions about this. But we certainly went through a statistical analysis plan with the agency when we designed the study. The step-down approach was an approach that provided a basis for looking at, in a population defined in this case by 1% or better PD-L1 expression, was this a satisfactory way to treat that population. It does not answer the question for an individual with 12% versus 24% versus 64%, what do you do there. That's a different study. I don't actually feel like that -- to me, the study stands on its own.

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

Can we grab Greg over here.

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

Greg Gilber from DB. Roger, do you plan to pursue KEYTRUDA for unresectable lung in Phase III study? And if not, what's your strategy there? And for Frank, are there any countries in which you are a seeing price competition between PD-1 inhibitors or PD-1 and PD-L1s, whether driven by industry or payers?

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

So Greg, with respect to unresectable lung. I mean, it's important to keep in mind that we did have some of those advanced patients represented in small numbers in 042. And we, in addition, are doing other studies, multiple other studies that define better how to treat that population. So the answer is yes.

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

You mentioned (inaudible)?

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

No.

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

Okay. It's on our slides.

Frank Clyburn

And Greg, as far as any countries with regards to [slicing within] the PD-1s or PD-L1s et cetera, we're not seeing that. Really, what we're seeing is a technology assessment that are really based off of the current data that one has. And they're making their assessments on what does [U.S.] product bring compared to standard of care, not necessarily within the class and trying to necessarily compare one price of a PD-1 to another price. It's really the data being submitted and then how do you fair versus their current standard of care.

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

Jon?

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

Jon Miller, Evercore ISI. Great data, or meeting, I suppose. I might as well split some hairs. So the 042 data in greater than 50% expressers looks a little bit different from the 024 data. Not a lot. But especially, with regard to the early progressers, the hazard ratio was a little bit lower. How do you view the variability between those 2 patient populations, especially in light of your earlier comments, Roger, about how consistent the data has been?

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

I think it's still pretty consistent. I mean, one of the issues is the timing of the analysis, which is different for the 2 studies. And I think, as these data mature, I think they will converge in any case. But they are different populations as well and they're different patient sub-groups that are represented. So there will be a certain amount of variability. But I actually feel pretty good.

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

One other question. Just to get back to EGFR and ALK mutated patients where we haven't seen a lot of data in what we see with those patients either ahead of the TKIs or even in TKI failures, with the exception of course of R150 your competitor. What are your plans about moving forward there, and do you think that's a meaningful subgroup?

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

Well, every patient is meaningful, first of all. They're all important. We care about all of them. I think it's very hard to get much good discussions about this just today, this afternoon at the presentation of the -- our data. There is a lot of reasons we want to treat patients who have (inaudible) EGF receptor mutation (inaudible). With the tyrosine kinase inhibitor first or with the dose you have of (inaudible) arrangement. It's pretty hard to get away from that as it's difficult for me to imagine that one would pretreat those individuals with KEYTRUDA, but it's something that one can think about as we talk about issues related to adjuvanted therapies, it will be an opportunity to look at that. But I think those -- there's a sense of urgency about treating these patients who (inaudible) often fairly advanced, need to be treated by young people, et cetera. They're after the question of how to treat individuals once they relapse, and they do relapse essentially invariably, is an unknown. It's a (inaudible) at this point and only time will tell.

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

Any other questions before we (inaudible).

Unidentified Analyst

Roger (inaudible).

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

It's been such a long time. I saw you in the back there and I thought what a wonderful familiar face.

Unidentified Analyst

Nice to see you too. Well, it's wonderful (inaudible) you just answered, which is you're going to have a host of post PD-1 therapies coming through after all the exposure they get in, the adjuvant, neoadjuvant even. What are you thinking about in terms of second-line, later-line treatment strategies that might involve immunoncology approaches? And then secondly, could you tell us your lessons about some of the pitfalls of add-on second I/O programs given what you've seen at the meeting?

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

Yes I mean, so again we talked a little bit about the problem of trying to understand how to manage patients who have failed therapy. And I'm eager to see what the readout is from a lot of the innate stimulation studies that we're doing with, for example, STING agonist, [RIG-I]. And I think there may be some lessons that will come from that, that will be helpful in understanding. Certainly, our goal is that we would like to improve, as I say, the therapeutic index for the treatments that we give. And that means ultimately trying to be more incisive about immune manipulation than we're able to be right now. So I'm eager to learn some lessons from that. And we'll see about that. I also think that the lessons that we have learned to this point relate to clinical trial design and execution, to be honest. And this is something very important to me and also very important to Roy Baynes who is sitting in the front row and who's really the architect of the totality of the clinical program that you've seen here and the person to whom all credit is due. Thank you, really. What we have said over and over and over again is that simple trials, clear endpoints, single endpoints, ask a single question and make sure that the statistical analysis of that is bulletproof in the primary endpoints and make sure the primary endpoint matters and just after that from an execution point of view, we want to make sure that our studies are monitored, monitored, monitored and that we exclude protocol violators and we exclude [variabilities] as much as we can to better understand what our drugs are doing. And that approach, I think has been very powerful. I'm not saying that nobody else does that either, but I am saying that there are some studies that we see and many that we have presented here, in which an attempt was made to test multiple questions in a single study and many commentators have gotten up and said that about some of these studies here, it seems like there were 2 questions that were asked here. And we try not to be in that situation. And I think that would be even more important going forward given the large amount of data that's now being produced by us and by others emphasizing the importance of immunotherapy in the early treatment of (inaudible).

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

Okay, I think we're at the end of our hour. I want to recognize that there are other events that people might want to get to. So thank you for everyone for joining us here for our ASCO event. And we appreciate your attendance.

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

Thanks, everyone.

Frank Clyburn

Thank you.

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

Thanks, everyone.
