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QUESTIONS AND ANSWERS

Seamus Fernandez - *Leerink Partners - Analyst*

Okay, thanks very much, everybody. In the interest of time, we're going to go ahead and get started. Good afternoon, I'm Seamus Fernandez, Leerink's large form analyst. We're really pleased to be joined here today by Dr. Roy Baynes, he's the Senior Vice president of Clinical Research at Merck. He's immediately to my left, and Terri Loxam, Vice President of Investor Relations -- many of you know Terri -- is just to Roy's left.

So, we're going to go ahead and get started. Folks, if you can quiet down, really appreciate it, thank you. So, first off, Roy, I know we're not going to go through a presentation of any kind, we're just going to jump right into Q&A, but I have to congratulate you and your team and Merck for really impressive clinical execution with Keytruda. As we sort of look at the lung cancer market, you guys appear to be pulling off quite an upset in lung cancer, and you're advancing a lot of new clinical indications across what you've called the foundational medicine. From here, frankly, how do you sustain and kind of capitalize on the momentum that you've created so far?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Well thanks, Seamus. I think the first comment to make is, you know, this is a tough business and I think we're very humble and very grateful that we have been able to get the trials done in a good way. You're right, we have a number of approvals under the belt for Keytruda. We've got approval in first- and second-line melanoma, first- and second-line lung, head and neck. We've also indicated we have a number of files under review at the moment. We have a file under review for MSI high malignancies, we have a file under review for Hodgkin's Disease, and we have a file under review for both second-line and first-line cis-ineligible bladder cancer. I would point out that the second-line bladder cancer file is the first randomized trial in bladder cancer that actually shows survival advantage, so we're very excited about those data.

Those are all under priority review, they've got PDUFA dates in March, May and June, if I remember correctly.

We have an enormously large program, and we've taken a very deliberate strategy of trying to define monotherapy activity in tumor types that we think will be responsive, and to do it by lines of treatment. We then try to identify those patients for who monotherapy is more than adequate, and to also identify patients who may need more, and that involves a fairly comprehensive biomarker program to try and select specific patient groups for hopefully specific combinations. We have a very broad combination program underway, and in that regard we have 21G under review at the moment, again with priority review for chemo combo in lung cancer. And, we have a very broad chemo combo program across many different tumor types. We also have a number of other combos which are in Phase 3. So, when you look at the breadth and depth of the program, there will be a very rich data stream for a number of years to come. So, I think the momentum hopefully will build off that.

We also are moving into a number of less common tumors as well. So, a very exciting time at Merck.

Seamus Fernandez - *Leerink Partners - Analyst*

Great. And as we think about the opportunities to expand the label, you just went through five or six opportunities that are already at the agency. As we think about the next opportunities, at least in terms of data that you guys have discussed could be coming. What could we see, potentially, in the next 12 to 18 months that's of particular interest to Merck?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Yes, it's a broad list, and obviously when trials read out is event-driven. So, the degree of specificity is always quite imperfect, and we do tend to stick with what's in clintrials.gov, but these do have to be revised from time to time depending upon event rates.

Just in broad strokes, I think it's pretty much the major tumor types. It's lines of treatment. And without getting terribly specific, I would say that we have an enormous number of near-term filing opportunities in the next 18 months. Happy to discuss any one of these that you may be particularly interested in, but it's a broad array.

Seamus Fernandez - *Leerink Partners - Analyst*

So, let's say, take for example liver cancer and the approach in liver cancer. How are you guys attacking it by line of therapy? And what do you see as the opportunity, the unmet need, in liver cancer in particular?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

So, liver cancer is obviously a complicated circumstance. We have, for example, liver cancers which are related to Hepatitis B infection, we have liver cancers which are related to Hepatitis C infection, and then there are liver cancers which are unrelated to viral infections and related to other fibrogenic hepatic conditions. So, it's not necessarily a homogenous group of conditions. We are exploring both a third-line and second-line opportunity, and we'll move forward in proximal lines as data read out. And you know, the focus is global so it's a mixture of those various etiologies, and we try to control for the individual specific disease groupings.

Seamus Fernandez - *Leerink Partners - Analyst*

And what about the -- we see a mix of approaches when it comes to biomarker strategies, even within Merck's own development strategy. So, how should we think about that? Is it a reflection of things like mutation burden? What are we learning on the biomarker front? Obviously, you guys have really established your PD-L1 -- or are establishing, but are establishing quickly your PD-L1 biomarker as a preeminent biomarker in the space. But, where do we go from here, and why is it so different by tumor type?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

So, as we thought about how to approach patient selection, we thought about it in a couple of ways. Mechanistically if we believe PD-L1 and PD-L2 are the ligands that you're trying to block, it makes sense to look at tumors that have a lot of PD-L1 and PD-L2 around. So, hence the initial focus on PD-L1 expression. And I think that has served us actually very well. I think we've been able to enrich in certain disease types, quite meaningfully by using PD-L1.

When we actually set out to explore which tumors were responsive, we used really a two-dimensional matrix that was mutational burden as well as PD-L1 expression. And using that matrix, we explored initially 30 different cancers, and I think to date we've declared positive results in 25 different cancers. So, it's actually a pretty high hit rate. So, that was following the science around the biomarkers.

I think the other component of this that we've all recognized, is that PD-L1 in many ways is an inflammatory marker and it is an immunohistochemical test. Are there other ways of trying to define an inflamed milieu? And in addition, even if there is inflammation, are there specific genes which are expressed which might modulate that inflammatory process? So, that's led us to really a third platform which is a gene signature, which looks at a number of genes which mark for inflammation and a couple of other parameters. So really, at the moment, the platform is a three-component one. It's ligand-based, gene expression largely through the RNA-based assessment of signatures, as well as mutational burden. And it's a complicated matrix, but it actually is working out quite well. We have actually published on the gene expression signature showing very nice predictive value.

It also gives us the opportunity to look at classification, if you will, of responsiveness through the lens of Keytruda. So, if we look backwards, let's take patients who respond to Keytruda. What does their gene signature look like? We've got a very good idea of what that looks like. But, there are a group of patients who have inflammation in their tumors who don't respond. We can now start dissecting out what genes are over-expressed, or under-expressed, what patterns we see. And then there's a group of tumors which don't respond and have no inflammation, and there again, we can start trying to dissect out the biologic components of that.

Now, it's early in that journey, but we're using that type of matrix to inform our approach to the combination strategies.

Seamus Fernandez - *Leerink Partners - Analyst*

Great, and then as we think about the combination strategy, one specific choice that Merck really seems to have made is not necessarily to own all assets. And I guess interestingly, looking back, it's a way of basically sharing the burden, not frankly -- you know, one company boiling the ocean is a pretty challenging dynamic. So, was that a big part of the strategy, because you saw the breadth of the opportunity for Keytruda in that way? Or, has it just evolved in that way?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

I think when we set out on this, we came at it from really two different directions. The one was just as -- based on mechanism of action, are there sort of broad categories? As we think about it, we think about ways of increasing antigen presentation. So, that refers to essentially cancer cell death, or antigenic cancer cell death. And there's a group of approaches which will increase cancer cell death, thereby increasing antigen presentation, and hopefully recognition. There's a group of approaches which are aimed at enhancing the T-cell response, priming the T-cell. Then there's a group of strategies or approaches which might focus on, how do you improve trafficking of the activated T-cell into the cancer. So, mechanistically, that's how we've thought about combinations.

Then, we've also thought about it in terms of just categories of modality. So, for example, standard of care such as radiation chemo, increases antigenic cell death. That would be the basis for example of why we pursued chemo combo in lung. It turns out, that has worked out quite well and we have a very broad array of chemo combinations across a number of tumor types. We're also looking at combinations with radiation as I mentioned.

Then we think about targeted therapies, and we have a number of approaches where we're looking at targeted therapies in a way to both increase antigenic cell death and potentially also further modulate inflammation. I'll give you a couple of examples, here. We've shown very nice combination data with the TKI axitinib in renal cell. We've shown very nice combinatorial activity with another TKI, lenvatinib, from Eisai in renal. And, we've actually spooled up two Phase 3 programs in that setting.

Surprisingly, in a disease like multiple myeloma, we saw very little activity of Keytruda monotherapy. When we put it together with an IMiD, we saw remarkable responses. This was in patients who were refractory to IMiD, so this includes pomalidomide in advanced myeloma, lenamidomide in early-phase myeloma, sorry. So, that's a series of Phase 3 trials which are ongoing.

Then, we are looking at combinations with other immunologically-active drugs and here we're looking at combinations with, for example, other checkpoint inhibitors. We're working with CTLA4. We have looked at CTLA4 in the form of ipilimumab across various tumors, and we have programs ongoing there. We have our own in-house CTLA4 program. We have worked very closely with our partners or colleagues at Insight around an inhibitory molecule in the -- the microenvironment space, this would be IDO1. That's gone forward. We've got one Phase 3 ongoing, four more planned in additional tumor types.

We've looked at a series of co-stimulatory molecules, we have a large number of assets internally that are moving forward in the space as well. we've got over ten immuno-oncology drugs now that are public domain that are actually in the clinic, in early-phase trial. And then, we're obviously looking at ways, another way, of increasing antigenic cell death using for example, oncolytic viruses, and there we have a collaboration with Amgen around their T-Vec molecule.

So, in summary, we have an approach here which we don't believe there's going to be one-size-fits-all. There's going to be almost certainly combos for tumors and combos for specific patient characteristics, and the trick here is also to try and get to a point where you've maximized efficacy but have not massively increased toxicity. And so, we're trying to all the time look for the combinations that meet those criteria. And again, we're pretty sure this won't be a one-size-fits-all, and there'll be a pretty high degree of either precision or customization by patient groups.

Seamus Fernandez - *Leerink Partners - Analyst*

Great, and maybe just my last question before we dive deeper into the first-line lung opportunity, do you believe there is a credible, or even a growing case, that Keytruda is uniquely differentiated from other PD-1 agents like Opdivo in its clinical activity as a PD-1 antibody?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

So, these molecules are clearly very different. I mean, they bind different epitopes. They have different binding affinities, they have different rate constants. So, they are clearly different molecules. Having said that, both of them, we believe, act by preventing PD-L1 and PD-L2 from interacting with the PD-1 receptor. And so, on first principles, we would not expect big differences, but there are different molecules and you can be surprised sometimes. But again, there's been no head-to-head comparison, and so we really can't make any sort of statement around that.

Seamus Fernandez - *Leerink Partners - Analyst*

Okay, great. So, we're going to move to lung cancer specifically. Maybe we'll just start with the strategic choices that you've made to first explore monotherapy in PD-L1 high patients, and then advance the chemo combo over an IOIO strategy. So, really, we know -- we already know the outcome of the biomarker-driven strategy, and that was successful. But I think really, the story that's up in the air is the combination strategy. So, just from a clinical perspective, let's talk about the efficacy benefits of chemo combo. But then also, I think there's a bit of a regulatory choice that's built into that, as well, that may help us understand the opportunity for chemo combo as well.

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Right. So, as you rightly state, we started off with monotherapy, biomarker-driven, initially highly positive and then walked into the less positives in second-line, highly positives in first line, and we're exploring less positives as well. In terms of the combination strategy, we had done some early work -- and I'm not going to go through all of the categories of combo that we looked at -- but one of them that looked quite interested was chemo combo. And, we explored a number of chemotherapy combos with PD-1 antibody. This led us to conclude that in non-squamous non-small-cell lung cancer, the combo of pemetrexed platinum looked increasing with Pembro. That was the basis of doing an expansion cohort in the 21 trial, so-called 21G, a fairly small trial, but it was a very clean trial which essentially -- and by the way, it's one of the first randomized IO studies in the lung space. It's also important to note that most of the IO -- there's no real, at this moment, IO combo that's actually shown outcomes benefit. So, that's another important point to bear in mind.

In this trial, it was very clean design, it was essentially chemo, versus chemo-plus-Pembro. And if you progressed on the chemo arm, you crossed over to Pembro. When we presented this at ESMO last year, we had shown already something which had been very hard to achieve in lung cancer. That is to say, to bend the PFS curve, and to improve response rates. And actually, when you look at it, we doubled the response rate and just about halved the progression rate. So, quite impressive results.

We have fortunately been accepted for review by the Agency. It's under priority review, it has a PDUFA date in May, and we're very grateful that they are looking at these data. We have a larger trial coming along behind, 189, has the same design. We've also shown a very nice set of activity in the combination of Taxane and platinum-plus-Pembro in the squamous setting, so that's the 407 trial which is ongoing at this point.

I should mention that it's not peculiar just to lung. We've taken this approach broadly across a number of different cancers as well.

Seamus Fernandez - *Leerink Partners - Analyst*

Great. And as we think about the regulatory dynamic, I think it's been a bit of a surprise to investors and in fact some of your competitors. Can you just help us understand why or how the factors that would influence the NCCN's decision might differ from how the Agency could approach something like this?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

No, NCCN, I can't really comment on. This is an independent process that looks at data and makes a determination. You know, we are pretty impressed with the 21G data. As I said, you know, we've been trying for decades in lung cancer to try and bend the PFS curve, and this actually did achieve that. So, it is a big deal. You know, living longer without progression is an important endpoint and we're very grateful that the agency is looking at this and reviewing the file. So, I can't really explain the NCCN position but again, it's an independent process, and they're probably in a better position to speak to their decision making.

Seamus Fernandez - *Leerink Partners - Analyst*

And then in terms of just sort of the process as we approach the PDUFA date in May, do you need to provide additional data to the Agency before the file is officially complete? And frankly, can you comment on whether or not a planned interim efficacy look has occurred or not in the 189 study?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

So, what I will say is that when we file with the Agency, the Agency may have many requests and we do our best to honor all requests and provide answers. We filed based on the data that was shown at ESMO, and the 189 study is an event-driven trial. It continues at this moment in time. On clintrials.gov it indicates completion in a roughly September time frame, but again, this will be event-driven and at this moment in time we're all blinded to the data and our trial continues.

Seamus Fernandez - *Leerink Partners - Analyst*

Great, and in terms of the consideration of your own monotherapy data versus the chemo combo data, what would you say are the differentiating characteristics and perhaps even the types of examples that you would provide as the way the agency has addressed labels in that way? I think the one that I'm thinking about is the monotherapy PD-1 versus IOIO combination in the melanoma space. So, just wondering how you think about that distinction?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Yes, I can't really comment on that label. I think that the -- that particular label is a three-arm trial of IOIO versus monotherapy versus Yervoy monotherapy. That is an accelerated approval. It's based upon a PFS curve that to my knowledge, there's no statistic even shown about that. So, my assumption is that that will have to be confirmed with an outcomes measure.

How the Agency will think about our file is hard to predict at this point. I think we know that the monotherapy front line is approved in PD-L1 strongly positives. That's a full approval and it frankly sets the bar for that group of patients. I think anyone who's looked at those data will say those are really pretty impressive data, and it does set the bar for anything that comes along afterwards. For the chemo combo data, again, it's the first randomized data in the setting, the chemo IO combo. We certainly believe it does set the floor for what's needed for a combo, remembering that that combo was studied in all comers. So, there was no PD-L1 requirement, and in fact the responses were very similar whether you were PD-L1 negative or positive. So, it suggests that chemo can override to some extent, PD-L1 negativity.

The highest response rates were the PD-L1 strongly positives, obviously. And how this will get used in practice, I think, is another question, but we would anticipate that the trial really looked at PD-L1 all comers.

Seamus Fernandez - *Leerink Partners - Analyst*

Okay. If there are questions from the audience, please just go ahead and shoot your hand up and I'll -- go ahead, [Prem]?

Unidentified Audience Member

How would you (inaudible) with only six months' data? Let me show you the Phase 3 and I'll (inaudible) -- how will you convince them to use (inaudible)?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Right.

Seamus Fernandez - *Leerink Partners - Analyst*

So the question is on convincing physicians if 21G is approved, how do you convince physicians on the basis of six months of data? Obviously -- when it's approved, but obviously the 189 study follows onto that.

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

So, I think -- you know, in non-small-cell lung cancer we've been trying to change PFS now for forever, and we've tried all sorts of doublets and triplets and you know, nothing has really moved the needle. This PFS result won't change. I mean, the PFS is the PFS, because basically once someone progressed, they crossed over, there were still a few patients that hadn't progressed. Over time, we expect there will be some progression. The prediction that the PFS will change or -- absolute numbers may change, but directionally, very unlikely that that will change.

The OS curve reflects obviously a significant crossover rate, and in fact, the OS numbers at that early point were rather good for both. In fact, while they were overlapping they were really quite exceptional OS results. So, again, I can't predict how physicians will react to let's say if this is approved. I think that most oncologists have used chemotherapy for a very long time, they know how to use it. Many of them have used IO drugs and know how to manage those. There's no combination toxicity. You get the toxicity of chemo and the toxicity of the PD-1, there's no additive toxicity. And so again, I think there will be quite a lot of individualization of care. I can imagine a circumstance where if you're PD-L1 strongly positive and you are frail, that monotherapy may be the way you go. If you're young and fit and you're looking for an even better response rate, you might try the combo.

Unidentified Audience Member

Relatively healthy patients?

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Healthy patients, that's right. So, I think, you know, there will be some individualization but whether that will be reflected in label or not, I couldn't comment.

Seamus Fernandez - *Leerink Partners - Analyst*

I apologize, we do have to wrap up because of the webcast. So, if I could just follow up with one last question, in terms of the dynamic of some of the questions that thought leaders ask us is about CR rates. What can you tell us about CR rates in the 21G study at this point? Because if there's a criticism of the 21G data, it's that the CRs, the complete responses, may be coming in at a lower frequency rate than what you may even see with monotherapy.

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Yes. So again, early data. We do know that CRs can build over time. I think we've also got to be a little bit more sanguine about what does CR actually mean. So, I'll just give you one little explanation, here. If you look at the melanoma trials, the early trials, they're now out many years. And you probably saw Carolyn Robert present data at ASCO last year where she looked at a number of folk who had been in PR for a long time, and had been on treatment for more than two years, sometimes approaching three years. The notion was, can you stop treatment? And actually, they did, and virtually none of those have progressed.

There have also been anecdotes now where people have operated on to remove residual tumor, where everything looks well-controlled, and actually found no cancer in it. Just finding scar tissue. So, it's very hard to know what's a CR, what's a PR. I think we're very early in this journey. I think what we know is that many durable PRs behave incredibly well.

Seamus Fernandez - *Leerink Partners - Analyst*

Great. Well, with that, we are going to have to wrap up. If folks have additional questions, I would ask that you allow the Merck team to move to the back so that we can basically have the next presentation begin. So, out of respect for the next company coming in, I would appreciate that. Thank you so much, thank you Roy and Terri for joining us today, look forward to speaking -- again, folks, if you can walk with the Merck team as they move to the back of the room, I would very much appreciate that.

Roy Baynes - *Merck & Co. - SVP, Clinical Research*

Thank you, Seamus.
