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PRESENTATION

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

To introduce our next session, we have Roy Baynes who's the Global Head of Development at Merck and the Chief Medical Officer. We have Teri Loxam, who, as you know, runs Investor Relations. So not much to talk about then.

Roy Baynes

No, slow day.

QUESTIONS AND ANSWERS

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

Slow day, quiet day. So why not -- given the news flow this morning, and I know that it's not your drug, so I understand that your comments will be well chosen. But why not just give us some gestalt comments of the data and things that you think we, as investors, should look at, particularly in terms of the commercial impact as it relates to the drug selection versus the alternative, which is obviously KEYTRUDA.

Roy Baynes

Great. Well, as you rightly said, it's not our trial, it's not our data. So you probably know about -- as much about the data as I do. I saw them just in the abstract this morning and there've been a couple of slides floating around. I think the first important concept is that the trial is a quadruple combo versus a triplet, if you will. In the treat -- or experimental arm, 2 biologics are added to chemotherapy in the nonsquamous non-small cell lung cancer setting compared to obviously a biologic plus chemo. The biologic that's common to both is Avastin. This agent has not been a prominent feature of non-small cell lung cancer treatment for a variety of reasons. So in many ways, this is a more complex regimen, hard to know how the practicing community will evaluate this. From what I've seen of the data, it looks as though the progression-free survival looks positive. Overall survival did not meet its statistical endpoint, but I believe they've shown a graphic and it's directionally favorable. And then, the third arm of this trial, Arm A, was not presented, as I understand it, because there's a hierarchy of testing, which -- because OS was not successful, they did not get to test. I don't know if the data were actually shown directionally this morning, but I have certainly not seen that. So that's really the key question is, do you actually need Avastin in this? So in other words, is the combination of chemo plus the PD-L1 antibody better than chemo? Or is it better than chemo plus Avastin? We don't know that as -- I don't know that answer right now. But that, to my mind, is a pretty key question. I think the important part of this is it sort of validates the idea of chemo combo plus a PD-1, PD-L1 type approach, which is what we had demonstrated, I think, fairly convincingly with our 021G study. And just to remind everyone, 021G is already approved in the United States. So a chemo combo is already approved and this is a nice validation of that.

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

So thinking from a clinical perspective, if we segment the patients into PD-L1 high versus low, the treatment algorithm which physicians are going to have to think through right now, it's going to change and probably change again over the next few months. But certainly, in the next 12 months, it will be, do I stay with monotherapy or do I throw in chemo? And given the patients who have the highest PD-L1 expression levels seem to be driving most of the benefit or significant, disproportionate amount to the benefit, it would seem that the adoption in the PD-L1 high is -- of chemo combination is going to be relatively low. Does that sound consistent? Or are you seeing, in your existing physicians, that even in patients with PD-L1 greater than 50%, you're getting the increasing use of chemo used in combination?

Roy Baynes

Yes, it's a great question. So I think from the KEYNOTE-024 study, where we had a highly positive PD-L1 population, where we looked at monotherapy versus standard chemo, I think the results were unequivocal. I mean, there's a dramatic improvement in progression-free survival, overall survival despite very significant crossover. And based on that, there's been very rapid uptake of KEYTRUDA in the front-line setting in that population. 021G showed very clearly that the chemo combo provides a very marked improvement in progression-free survival. And certainly, the subsequent data have shown a trend in favor of survival, although we couldn't test that formally because [Alfred all] been spent at the earlier part of that trial. And as a consequence, chemo combo's a very reasonable option for all-comers, whether you're PD-L1 positive or negative. Informally, what I've heard is that within the practicing community in the PD-L1 strongly positives, there is a little bit of patient segmentation that is done. So in other words, for an older, frailer patient, very often, monotherapy looks very reasonable. For a younger, fitter patient, certainly chemo combo is certainly offered. It's important to recognize that in the -- and I know there's been some controversy around this, so I'll just spend a moment on it, 021G basically studied all-comers, and there was a stratification based upon positive or negative. In other words, less than or greater than 1% positive. There was no difference in outcome, pardon me, as a function of whether you were positive or negative. So indeed, it does appear to be a very reasonable approach for all-comers. But again, the monotherapy looks like a very reasonable approach for those in the PD-L1 treatment proportion score greater than 50%. We have additional data that will be coming from the 042 study, which is looking at, again, monotherapy. And to get into that trial, patients had to be greater than 1% positive, stratified [of] greater than 50% and clearly, we have the opportunity to interrogate other cut points below 50% to explore whether indeed there might be additional biomarker selected patient groups which may benefit from monotherapy.

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

So going back to KEYNOTE-024, where the data was remarkably impressive. It's a landmark trial. So there was a review or analysis of the paper from some statisticians, and I can't remember the center but Goldstein was one of the names and I can't remember the 2 others. And their contention was while, however you looked at it, the trial was a positive trial, the magnitude of the benefit was inflated because of the very, very heavy censoring within the patient population. I think there was about 50% of patients who were censored from -- this is their commentary. And because of the application of censoring rule, the data that was reported reflected really a best case representation of the treatment benefit. Is that -- would you push back against those observations?

Roy Baynes

So I guess, the -- I'm not familiar with the particular work that you're quoting. I think the -- was this for progression-free survival that, that argument (inaudible)

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

I think they did it for both PFS and for OS.

Roy Baynes

Well, it's hard to imagine what the OS argument is based upon because, essentially, this complete (inaudible) of OS.

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

Yes. Again, I can send you the paper but it was definitely for PFS and I think it was for OS too, but...

Roy Baynes

Yes. So remember, PFS, the trial allowed for crossover. So indeed, there was an analysis that was done both with and without censoring for crossover, so I don't know if that's the part that they're referring to. Anyway, happy to look it over and I'll get back to you on it.

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

Yes, that's absolutely fine. So the other -- aside from the Roche data set this morning, the other recent news flow item is obviously the posting of the EMA analysis for the explanation behind why they declined to recommend 021G for approval in Europe. So given you're here, given there's certainly investor interest on that, perhaps you could explain your take on it, particularly the alleged misclassification or potential misclassification of the histology of patients. And whether you think there's a scope for it to have any commercial impact because one would imagine that your competitors will be enthusiastically educated physicians on that and whether you think there has any relevance or impact whatsoever.

Roy Baynes

Yes, I'm familiar a little bit with the article, with the note that you're referring to and the posting. I'm not sure that actually the interpretation is accurate. So maybe I'll comment on a few items there. I understand there's been some swirl around the notion that there was histologic variance within the group. So just for clarity, everybody on the trial was non-squamous. You had to be non-squamous to get on the trial. Most pathologists would recognize that within non-squamous histology, there is some heterogeneity of cell type. And so I know that the article, that, if I'm quoting the one that you're thinking of, mentioned that there were, I don't know, a small number of patients that were unknown. That's actually not correct. They were non-squamous, not otherwise specified. That is a recognized histologic category. So in fact, 100% of the patients on the trial are non-squamous. So that really is a bit of a red herring. I don't think there's any relevance to that particular observation. Then there was quite a lot of swirl around PD-L1 status. So again, for clarity, the trial was an all-comers trial and was stratified on 1%. So any valid comparison is the less than 1s versus the greater than 1s and the outcomes are virtually the same with that. So there really is not a PD-L1-based argument. The analysis to break this out by subgroup is an improper analysis because you're not randomized for the question. It's not uncommon that regulators may do exploratory analyses as hypothesis-generating exercises, but it is an improper analysis and in fact, the only valid analysis is the less than or greater than 1%. And we made that case pretty strongly. I see a hand waving.

Unidentified Analyst

This is a follow-up to Andy's question. I just want to confirm we're talking about the Tim Anderson note where he suggested earlier this week that there was squamous patients in 021G. You're confirming there were no squamous...

Roy Baynes

No squamous patients.

Unidentified Analyst

No. Non-squamous?

Roy Baynes

Correct.

Unidentified Analyst

As hypothetical as incorrect?

Roy Baynes

Incorrect.

Unidentified Analyst

Do I have a chance to ask a second question, if you don't mind.

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

[Prem], could we just take -- could we take it at the end? Is that okay?

Unidentified Analyst

Right. On the earnings call, the company said that there'd be 2 interim analyses in -- one in KEYNOTE-189 in 2018. Is it possible for you today to confirm or, say, state anything if you have any interim analysis on KEYNOTE-189 by midyear next year? Is it possible that you have KEYNOTE (inaudible)

Roy Baynes

So it is certainly a possibility there might be an analysis by midyear, it's an event-driven trial. And so as events occur, interims will occur, so it's certainly a possibility.

Unidentified Analyst

Around ASCO?

Teri Loxam - *Merck & Co., Inc. - VP of IR*

And maybe, getting back to 021G, maybe Roy, you can talk about the process that we went through with the EMA and their general desire for Phase III data and how that came to us.

Roy Baynes

Yes, maybe we could...

Teri Loxam - *Merck & Co., Inc. - VP of IR*

That's part of your question, right?

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

So my -- when the news broke, my initial -- I was very surprised that knowing the EMA and being based in London, I thought the probability that you were likely to get approval on that Phase II seemed remote. And it struck me again they would find whatever reasons they could in order not to approve. So that's the way I read it. I was trying to raise the [ASCO] without naming a particular source but that's kind of in the past now. But anyway, so why don't you address Teri's question?

Roy Baynes

Sure. So I think there is a distinction between regulatory group -- or regulatory agencies. The FDA has been very clear that they see it as an important missions of the agency to get important medicines to patients expeditiously. So there is a process which involves certain designations to allow this to happen. So just to remind everyone, 021G had rather remarkable findings. Those findings supported breakthrough designation, priority review and an accelerated approval. And it happened in a fairly brisk time frame. We didn't expect that EU would have the same type of enthusiasm because, frankly, EU has not frequently exercised the opportunity for conditional approval with confirmatories to come and have a preference for outcomes-based measures on larger Phase III trials. It didn't occur in a vacuum. There was a dialogue with the agency. There was a willingness to review the file. And it wasn't a straightforward process. In fact, it went through review. We don't generally share the content of what those reviews are but this actually ultimately went on all explanation because clearly, there was not complete agreement at the EMA level. At the end of the day, the EMA elected to wait for 189. And we, at that moment, then decided to withdraw the file. That adequately cover it?

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

So on 189, a couple of questions. You've set yourself a high bar. You could have set yourself a much lower bar. You could have recruited a bunch of patients from Ukraine or another country with less access to second-line PD-L1. And yet you decided not to do so. So what I would like to understand is whether that is because of the magnitude of confidence that you have in the treatment benefits seen in 021G will be replicated, or whether your sense of the, I was going to say real world experience of pembrolizumab plus ALIMTA, has changed that now actually you have more concern that this particular patient population in 021G was actually not representative, but it's really too late to do anything about in terms of adding patients. I'm assuming it's the former rather than the latter, but if you could talk to that, that would be helpful.

Roy Baynes

Right. So just -- again, recapitulate the history of this. So we did an initial exploratory Phase II single-arm experience of chemo combo using a number of chemo regimens, one of them chemo plus Avastin. And certainly, we saw a rather high -- strikingly high response rate in the combination of pemetrexed and carboplatinum plus KEYTRUDA in the non-squamous non-small cell lung cancer setting. Based on that, we did an expansion cohort 021G, which was a randomized study, which basically allowed crossover. And I think we've been very clear that crossover was pretty complete. In fact, the vast majority of patients who progressed on the chemo arm, because that was the comparator, actually crossed over and got KEYTRUDA. Despite that, we have had a very striking trend towards a favorable survival pattern. And I think we -- as we put the confirmatory trial together, it was very clear to us that indeed if 021G was as favorable as we thought it was going to be, it will be extraordinarily difficult to complete that trial if indeed there had been a striking benefit of the combination, if you did not allow crossover. So it was always intrinsic to the plan. So in fact, 021G and 189 are really the same design.

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

But in terms of optimizing clinical trial outcome and creating a greater buffer for confidence, it would be much easier to have a larger cohort of patients O.U.S. where there was no crossover?

Roy Baynes

Yes, that's certainly a possibility. I think the data are really quite strong, and we feel pretty comfortable that we would likely be successful with the design that we came forward with.

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

When you're -- obviously, you model very carefully all your trials, including 189. You have your total number [events], you have an idea of what the historic control arm is going to do, and you can back out within confidence intervals some idea of what the arm is. In light of the delay of the PFS and the inclusion of OS, what -- in terms of your expectations of how those curves have evolved on those modeling exercises, is it in line with your expectation?

Roy Baynes

Yes, I think when we saw the very striking favorable direction for survival in 021G despite the crossover, we thought it was really important to elevate overall survival to a co-primary endpoint. That really occasioned the -- or dual-primary endpoint. That occasioned a later date for the completion of the trial, but we will have opportunities for interims before that. And certainly, those modifications in the trial really born out of confidence of the data and the strength of the data that we saw in 021G.

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

Can I ask -- we're going to segue slightly to tumor mutational burden, which has long been a topic of interest in the academic community, and is likely intrinsically related to how these drugs work. We've written very excessively in relation to one of your competitors who we think is maybe jumping the gun, maybe the pioneer, we believe, in using TMB potentially as part of their primary analysis to select patients to show a benefit. They have, in addition to prospective trial; Roche has a prospective trial. Merck, as far as I know, does not have prospective trials. It strikes me, given your work with MSI high patients, that you have more than a passing familiarity with the potential role of TMB. So therefore, I assume that within your trial program, this and other markers play an important point. So what can you share with us in what you think the environment is going to look like in the near future? The reason why I'm focused is I see lots of things happening concurrently. FDA hosting a meeting in September to standardize TMB testing. 2 gene panels approved using a new pathway, including TMB assays and a whole conversions of additional TMB data. So looking at the footprints in the snow, I don't think you have to be a genius to see that things are moving faster rather than slower. So where is Merck on that journey?

Roy Baynes

Well, it's a great question and I appreciate it. So just by way of reminder, at the time that various competitors were pursuing very strongly non-precision medicine approaches to immuno-oncology, Merck was actually pioneering the precision medicine approach. I will start off on the journey by just mentioning, when we saw initial, really striking activity in melanoma and in some non-small cell lung cancer patients, the immediate question was, "Gosh, how do we explore the totality of this?" So we, in a very deliberate way, using large data sets, basically identified the cancers that had either high mutational burden, high PD-L1 expression or both. Using that matrix, we set out to screen in Phase II 30 different cancer types that met those criteria. Lo and behold so far, of those, 25 have turned up unequivocal activity. So without doubt, we recognize the importance of tumor mutational burden very early on. We have really all along been very committed to a precision medicine approach, and our precision medicine approach has

had many components. The most visible has been PD-L1 staining and at least in our hands, has served us remarkably well. I think we've been able to increase probability of success in a number of the development programs. We've been able to achieve fairly rapid registration. And indeed, we think it's the right thing for patients. So I think if we look at, for example, PD-L1 negative versus positive patients in second-line lung cancer, first-line lung cancer, it's very clear there's a big impact. And so it's certainly been our position all along that precision medicine, using that approach has served patients well and has served the enterprise well. Next key component of our biomarker strategy was to explore genetic signatures which might portend responders -- responses, and we started off with a very large gene signature. We've pared it down to what we call our gene expression profile, which is, essentially, a number of inflammation markers, genetic markers and, indeed, that performs very well. It predicts also very well, full response to PD-1 antibody. What we have found is that there's a high degree of overlap between PD-L1 and gene expression profiling. So in our hands, gene expression profiling, while it's a very useful tool, does not add a whole lot to PD-L1. Next component has been essentially related to defects of DNA repair as well as mutational burden. Obviously, those 2 are intimately linked. We have -- just may not be recognized, one of the first publications of TMB actually came out of a Merck trial. So yes, we've been firmly committed to it. We interrogated in a large number of our trials and data have been forthcoming and will continue to flow in relation to this. The most extreme form of DNA mismatch repair finds its expression in the specific mutations of a number of repair genes that end up with the microsatellite unstable situation, also called mismatch repair defective. And as you know, we had rather remarkable results as such that indeed, we ended up with a successful FDA approval for a tissue-agnostic MSI, high-based tumor type. So obviously, that's the most extreme form of mutational burden. You get the very highest numbers of mutations in that setting. So to reassure you, completely committed to the field, I think completely committed to precision medicine approach is to optimizing results. The FDA meeting that you've mentioned, I think FDA is eager that there'd be commonality of approach to tumor mutational burden. PD-L1 was an interesting time because a number of companies developed their own assays. And after the fact, there was obviously a need to try and harmonize these because it gets very complicated with a number of assays being deployed. There was a project conducted called the Blueprint Project, which showed a very high degree of concordance between Bristol, Merck and AstraZeneca's PD-L1 assay. The Roche assay seemed to be a bit of an outlier and certainly didn't seem to be measuring the same thing as the other 3 assays. So that's an observation that came out of Blueprint. I think FDA's eager to avoid that and it's trying to get to a point where there's agreement on what a cut point would likely be for tumor mutational burden to try and avoid that notion of trying to harmonize after the fact.

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

Sure. There's lots of directions one could go on mutations and burden. So one, on a sort of clinical near-term perspective, where you have a biomarker that is not -- the trial's not stratified for that biomarker from get-go. But let's say, you were running 189 and you determined that you would like to include an analysis after patient recruitment had begun for a sub-group of patients who may have high TMB, greater than [20%, 60%,] whatever and the [half] was allocated appropriately. Aside from the risk of imbalances and paring that you'll be taking as a function of putting out a subpopulation. In the current environment, how do you think the FDA would perceive that?

Roy Baynes

Well, I think, generally, the approval of these drugs has been based upon frequentist-type trials; in other words, randomized controlled clinical trials. And so really to have a firm conclusion, one does need to be randomized for the question. So what do I mean by that? Well, let's take, for example, 021G is a good example. Here, we took all-comers who have non-squamous histology, randomized them with stratification based upon a 1% cut point. So in essence, you are randomized for that 1% question. You're not randomized for other questions that might be explored. So generally, once you are applying retrospectively an analysis that you were not initially randomized for, it becomes important data. It certainly could be important hypothesis-generating data but generally will not be seen as strongly supportive.

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

So when we have explored this and obviously, it's pertinent to one of your competitors, we were looking at other examples, and betrixaban was one where the FDA didn't sign off on that. And in a slightly different way with olaparib in terms of supporting data that was certainly used. So I take your point, it's not ideal, but if the signal is strong enough...

Roy Baynes

If it's strong enough, yes. I think that's right. And if it's strong enough and sufficiently un-confounded. But having said that, the gold standard is the randomized trial.

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

I understand. And then, whether we can do better, and I'm sure you will do better. We, as an industry, will do better in identifying patients who are likely to respond. There's been a number of papers on insertion deletion mutations that's actually giving more endogenic neoantigens and maybe a better predictive biomarker. Is that a subject of your attention? And does that add too much complexity above and beyond TMB to look for insertion deletion because you're forced to do whole exome rather than using a gene panel?

Roy Baynes

Yes, I mean, I think these are all important questions. I don't believe they've ever been adequately addressed in a true randomized fashion. So these are all interesting hypotheses and obviously merit testing. We are very intrigued by trying to identify the most immunogenic neoantigens. And in fact, you're probably familiar with our effort with Moderna, where we are, in fact, taking specific mutational sequences generating the RNA construct and then, using those as a vaccine to actually explore whether indeed there are very significant enhancements that can be made to the neoantigen profile that you're trying to interrogate. So absolutely, these are important concepts but I think they're concepts at this point.

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

So you've mentioned earlier, we discussed your pioneering work and approval in MSI high patients. Given the precedent of the FDA setting, the tissue-agnostic approval, and given increasingly, the ability to identify patients with either very high baseline tumor mutational burden or pathologic germline DNA damage repair alterations, isn't there an opportunity that could be done very quickly to replicate the MSI experience using either of those patient populations with a checkpoint inhibitor? And I'm curious why no sponsor has initiated that to date.

Roy Baynes

I wouldn't make that assumption. They may well be trials addressing that type of approach. I think there are basket trials that had -- maybe interrogating a pretty broad array of possibilities.

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

And could they be used for registration in the same way as...

Roy Baynes

I think it would depend on the strength of the data.

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

But do you have a trial ongoing that could be used as a registrational trial within those patient groups?

Roy Baynes

We really haven't speculated on that. We do have basket trials which interrogate a broad array of biology.

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

Okay. Can we move to your PARP deal in LYNPARZA? So conceptually, I can see why, aside from selecting out sub-populations with germline mutations, for example, but conceptually, I can see why there may be merit in combining a PARP inhibitor with a checkpoint. Although I'm struck by the data that I've seen at least in the public domain is ho-hum. I mean, it's okay, but it's not mind-blowing. When I think a little bit deeper about the biology, I wonder whether different from a germline DNA damage repair mutation, where you're getting sort of clonality of mutations. If I'm just giving the combinations of these 2 drugs in a non-germline setting, I'm going to get a ton of sub-clones, which may not set me up for optimal response to checkpoint inhibitors. So is that the right way of thinking about it? Or am I being overly judgmental on something where maybe you'll have to test it empirically and I shouldn't think too much mechanically?

Roy Baynes

So even in circumstances where we have robust biomarkers, for example, PD-L1, it's not 100% respond. There's always going to be some heterogeneity response based upon other factors, which may or may not be understood. What was intriguing about, for us, the PARP program is that AstraZeneca, our partner in this or collaborator, has done a wonderful job of really dissecting out the components of DNA repair. Obviously, the single-strand break effect, which you've seen and magnified, for example, in certain circumstances, sets itself up well for PARP introduction because, frankly, then if the cell, in any way, is defective in homologous repair, because remember, once you've got a single-strand break, you then ultimately, with an extra application, end up with a double-strand break. You're then dependent upon a homologous repair for that. So essentially, when you think about this, you have obviously defects of single-strand breaks, you got defects of double-strand breaks, you've got defects of end-to-end repair and then you have defects of specific repaired mutations with all mechanisms, which ultimately lead to the MSI high situations. So there's a continuum across that. I think there's been remarkable work done on this in that the BRCA I/II mutations have clearly established very nicely that you can enrich significantly for PARP response. Obviously, work has to be done to see whether indeed that enriches for an immuno-response as well. Does that lend itself to combination work. That's true for each one of these mechanisms across DNA repair. I don't know if you're familiar with the work from de Bono's group, which is...

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

In the U.K.

Roy Baynes

Yes, lovely results where they took a prostate population, and using a 15-gene signature of homologous recombination response mutants, and that's obviously looking at 15 specific mutations that affect homologous recombination response or repair response. They were able to segregate the prostate population into a group where virtually everybody responded if they had the mutation, a mutation or virtually nonrespondent if they lacked the mutation. Now whether it will play out as cleanly as that, we'll see as the programs go forward. But you can imagine that's another whole spectrum of possibilities that open up for I/O and for combinations. So we're pretty early in this journey, but I think there's enormously powerful biology here to be interrogated both for monotherapy, for immunotherapy and for the combination. And that is really why we're so interested in this deal.

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

And I understand the patient selection and the broader portfolio options that may exist. I guess, what I was thinking about was, from an investment point of view, there's a very relatively straightforward jump to, you can put a PARP together at Mayo and everyone, more mutations. And I guess,

I was influenced by the [Swanson] paper on subclones and suboptimal responses, hence the question there's more subtlety to it than just either [how it's relevant] and throwing 2 drugs together in nonselected patient population.

Roy Baynes

I think that's true though for whatever mechanism you approach. I mean, if you think about, just take I/O approach alone, we have a preponderance of patients in any given category that don't respond. It's not like we're getting the majority of patients are responding. So there's clearly a mechanism base for resistance there. And we're spending a lot of time in our biomarker and precision medicine world trying to understand that. There's also a group of patients who, over time, may lose their response. Now fortunately, it's been a relatively small number but if that happens, you could infer that it actually is a subclone that's grown out. That's always the argument about secondary resistance. Is secondary resistance driven by mutations? Or is it by selection pressure? And that's always a question that's sort of -- it's bit of a chicken and egg argument. But I think the overwhelming belief today is that most of those secondary resistances are in fact selection pressure rather than submutation and that again speaks to subclones.

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

So one area which, from the outside, the industry has shifted, is a pivot away from overcoming tolerance through blocking inhibitory checkpoints to moving towards intracellular mechanisms along mutation interferon-gamma pathway, be it neoantigen vaccines such as Moderna or DNA damage repair but also TNR, STING, RIG-I. And you have both a STING and a RIG-I license, one I think you own organically, that require, right now, [intramoral] injections. Could you talk through your relative level of optimism on both? I've -- I was initially very encouraged by STING in the early preclinical data. But I've read more papers on there may be unwanted effects of STING, which may work the other way. And I'm also aware that Novartis seems to be going rather slower with their Aduro and I'm not sure they've seen enough scope of responses in humans yet, which makes me a little bit concerned about STING. So anything you could update us on because I know you're dosing patients right now with STING and I'm not sure you've done anything with the RIG-I, but I'd be interested in anything you can add.

Roy Baynes

Yes, so these are important questions. Obviously, the Holy Grail here is can you take a tumor that's destined not to respond and make it into a tumor that's likely to respond. And so all of these mechanisms that you're referring to are really attempts to either increase immunogenicity or to essentially boost the innate response. And you're absolutely right, we're extremely active in this space. We have brought forward STING. We have brought forward, obviously, the in-license, the RIG-I molecule. Both of these are doing exactly as you described. We haven't shared any of the data yet. We are in (inaudible) and we're actually quite excited by the prospects. Would also comment that we have had presentations of a number of similar such approaches, TLR9, TLR4; obviously IL-12 data looked quite good. There's some constructs of the oncolytic virus together with IL-12. So I think in general terms, we are quite intrigued by the possibility of the specific modulation of the interferon pathway as well as a number of cytokines as potentially being important in this regard, and we're very active in that area.

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

I think in the interest of time, I can see a (inaudible) the door. We should probably stop, but I'd like to thank Roy. Thank you very much for coming today. Much appreciated. Thank you for your insights.

Roy Baynes

Thank you so much.
