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PRESENTATION

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Good evening, everyone, and welcome to Moderna's ASCO 2023 event. We're so happy to welcome you here. Today, we have both Stephen Hoge, President of the company; as well as Kyle Holen, Head of Therapeutics -- Oncology and Therapeutics, here to review some of the data that we presented at ASCO. As a reminder, this is an IR event, and we will be making forward-looking statements. Please refer to the Slide #2 on the webcast relating to the risks associated with everything we're about to say today. And with that, I will hand it over to Stephen.

Stephen Hoge - *Moderna, Inc. - President*

Great. Thank you, Lavina. So I'll make some brief remarks -- that's going to be a problem -- and then turn it over to Kyle to walk through the data. So first of all, thank you for everybody who's come here to hear this. We're really looking forward to completing the picture of our first primary analysis in this mRNA-4157, previously called PCV, now called individualized neoantigen therapy, Phase II trial. This trial, as you all know, we announced the first top line results on relapse-free survival last December. And what we've been doing since then is completing the analysis on that first primary analysis of about 40 cases. It's now 44 cases that we have in this data set.

Looking at the secondary endpoint from that, which is distant metastasis-free survival. And that will be the focus of our presentation today. But we've also been looking at biomarkers to help us characterize that responses, the response that we've seen. And I think what we'd like to do is share a little bit of our perspective of how we're interpreting those biomarkers and why it continues to leave us very bullish on the potential for 4157 to have an impact in melanoma and other cancers very quickly.

I'm going to turn it over to Kyle now to walk through the data from both our presentation today (technical difficulty) -- I will come back while we're going to have to get that -- sorry about that.

Kyle Holen

I'll present from here. So we don't damage anyone's ears. All right. I think we're good. Am I still on? Okay. Great. So I'm going to walk through the slides that were presented earlier. So my apologies to those of you that were at the session this afternoon. I'll try and give a little bit more context

to what was discussed earlier this afternoon. But for those of you that weren't there, I'll try and hit the highlights and describe what we observed in our P201 study.

So just a little bit of a background on melanoma on this slide. RFS and DMFS are really important endpoints in this disease. They have been correlated with overall survival, and RFS has been a regulatory approvable end point for quite some time, including from KEYNOTE-054, which was approved -- was a study that approved pembrolizumab, and pembrolizumab was approved with a hazard ratio of 0.60 and the KEYNOTE-054 study. The KEYNOTE-054 also showed an improvement in DMFS, which was statistically higher in patients who received pembrolizumab than patients who received placebo, and this was a highly statistically significant result. So this led to the approval of pembrolizumab. However, I will point out that even in the patients that had pembrolizumab, there was still a significant unmet need, with 65% of the patients who were alive and distant metastasis-free. However, there were still 35% of the patients that had recurrence. And so we would hope to improve upon that recurrence rate with the use of 4157.

We designed this study, the 4157-P201 study, to include patients with high-risk melanoma, that meant patients who had Stage IIIB, IIIC, IIID or even Stage IV disease, all these patients, however had had complete surgical resections. Even in the patients with Stage IV, they had no evidence of disease at the time that they initiated treatment and were randomized into the study.

Patients had an ECOG performance status score of 0 to 1, and they had tissue available for next-gen sequencing. They were randomized in a 2:1 ratio with 107 patients in the combination treatment and 50 patients in the pembrolizumab control arm. And you can see at the bottom that the analysis -- the primary analysis was triggered at 40 RFS events and at least 12 months of follow-up.

In the analysis -- statistical analysis, we had a secondary endpoint of DMFS, and it was hierarchical testing, meaning that we would be able to transfer alpha from RFS to DMFS should we have a positive RFS signal. We also had endpoints around safety and tolerability. I'll walk through this very briefly. I think most of you by now know how we create the 4157 individualized neoantigen therapy. At the bottom on the right -- I'm sorry, on your left, you can see that a schematic where we take tissue from patients, both tumor tissue and normal tissue. We sequence with whole-exome sequencing, and we do RNA-seq. We then take this information, we put it into our algorithm. The algorithm then selects for 34 neoantigens. We then -- after designing the mRNA, we manufacture the RNA and then we ship it back to the patient for administration.

So these are the demographics for our 201 study. They were generating balance between the 2 arms with equal amounts of men and women on both arms. The age was fairly comparable between the 2 arms. We also had comparable ECOG performance status -- staging LDH and lymph node dissections. There have been some comments regarding our PD-L1 and tumor mutational burden, slight imbalance. However, we have done sensitivity analysis on these, and we don't believe that, that modest imbalance led to any difference in the outcome.

And as a reminder, these are the data that we presented at AACR back in April. And at AACR, you can see at the 18-month RFS endpoint, we had a hazard ratio of 0.561, with a p-value of 0.0266. This was a one-sided p-value, and that was what we had designed as part of our statistical analysis plan. We met our endpoint with that one-sided p-value, and therefore, we moved on to our next endpoint, which was DMFS.

These are our DMFS data. So whereas we had a 44% decrease in the risk of recurrence or death with RFS, here, we're seeing a 65% decrease in distant metastasis-free survival with a hazard ratio of 0.347 and a p-value of 0.0063. Again, this is a one-sided p-value, but still even with the 2-sided p-value, considerably -- statistically significant here. There's really no question about that statistical significance at this p-value. And here you can also see the difference in DMFS between the combination and the pembrolizumab arm. And you'll also note that the pembrolizumab arm performed similarly, in fact, probably slightly better than some of the other studies that were -- have been performed in the melanoma space.

We've also looked at the recurrence patterns, particularly the distant metastasis-free recurrence patterns. And we've highlighted the different organs that were impacted by recurrence events, and generally, the patterns were similar from the 4157-containing arm and the pembrolizumab control arm. Some of these, of course, are significant events, which are clearly not curable, including the recurrence in the brain where you see a 6% recurrence from the pembrolizumab arm and approximately 1% in the brain. And in the lungs you see a much higher percentage of patients recurring in the lungs. However, these numbers are pretty small. So you have to use some cautionary interpretation. But generally, the trends show favorability with the 4157 treatment arm.

We also have some swim lane plots here on the actual events. And I'll just remind you that in this swim lane plot, it's a 2:1 randomization. So we had doubled the number of patients in the 4157 arm that we had in the pembrolizumab arm. And as I walk through this, I'll show you that the treatment is signified by the gray bar of pembrolizumab as well as the combination therapy is the red bar. Each 1 of those red dots is a local recurrence, whereas the black squares are distant recurrence and then death is signified by a blue square. Here, you can see there were quite a few consistent and early recurrence events, and the distant recurrence is both in the 4157 arm and some early events in the pembrolizumab arm.

Now we also have done DMFS by ctDNA status, and I will show you some more in-depth results from our poster on ctDNA. But what I'd like to highlight are a few things here on ctDNA first. In the solid lines, those are the patients that had ctDNA-positive results at the time of the patients enrolling in the study. And then at the top, you see the dash lines, those are patients that were ctDNA negative. The ctDNA-negative patients all performed much better than the ctDNA-positive patients. And you can imagine that this would be true because ctDNA positivity just means that there's likely residual disease at the time of surgery. We just couldn't see it with any type of imaging or by the naked eye. So it's a very highly significant prognostic factor.

And unfortunately, for the 4157 arm, we had a significant imbalance of patients that were ctDNA positive in the 4157 arm, with 13 patients being ctDNA positive in the combination arm and only 2 ctDNA positive patients in the pembrolizumab arm. You can also look at the Kaplan-Meier curves. The patients on pembrolizumab, who had ctDNA positive disease, recurred very, very quickly. Patients did slightly better with the combination arm, although these numbers are quite small. But then when you look at the ctDNA negative population, you're taking out all the imbalance of the 13 to 2 patients, you can see the Kaplan-Meier curve separate pretty quickly. The Kaplan-Meier curve separate before 20 weeks and then they continue to separate as you follow these patients out long term. And here, we saw a hazard ratio of 0.048 with the ctDNA negative patients.

Now I'd like to talk to you a little bit about safety and tolerability. This is the same slide that we presented at AACR. Essentially, the types of events that we observed in the combination arm that were related to 4157 were what we would have expected with any type of vaccination process like a COVID vaccine where we saw patients with fatigue, injection site pain, some chills and some fever, rarely were this severe. Most of these events were mild and very limited in the first week or 2 after treatment. And then if you look at the pembrolizumab adverse events, very, very consistent with what you'd expect from pembrolizumab, and you don't see a significant imbalance between those who are in the pembro arm and those who are in the combination arm, suggesting that we did not increase the toxicities of pembrolizumab with the addition of 4157.

Some of the safety and tolerability that were immune-related adverse events that you'd expect from checkpoint inhibition therapy. Similarly, we did not see an increase in the immune-related adverse events with the addition of 4157.

Now I'd like to do a little bit of a deeper dive on the ctDNA results. So the ctDNA, positive or negative, the assay was done using an amplicon-based next-gen sequencing RaDaR assay by NeoGenomics. We used this assay on 2 of the core biopsies and whole blood samples to identify some of the variants that were most suitable for MRD. Now unfortunately, there were some patients that we could not identify enough of the variance to determine whether or not there were ctDNA negative or ctDNA positive, but the majority of patients, we were able to assess whether or not they had a ctDNA result.

These are the curves I showed you before where we had a significant benefit in RFS from the patients who were ctDNA -- or actually, I showed you DMFS' data. This is the RFS data. And with RFS, again, we see a pretty significant change in the curves. Now this is even earlier than what we saw previously. And also impressive here with the RFS data is that we have a hazard ratio of 0.225. The numbers, again, here are pretty small. So because the numbers are so small, we haven't calculated a hazard ratio, but we're really excited about the results in the ctDNA-negative population.

Now this is a depiction of the prognostic value of some of the markers in this population. So here, we're comparing ctDNA negative versus ctDNA positive, and the hazard ratio is remarkable at 0.149 when you compare the ctDNA negative and ctDNA positive populations, meaning that this is a significant prognostic marker for recurrent disease. If you look at other markers like TMB-high, TIS status and PD-L1 status. They still show some benefit in helping prognosticate patients, but not at the same degree as ctDNA status.

So we are continuing to follow up patients. And the 1 thing I just wanted to mention very quickly because I know that there are some questions about censoring. So in a Kaplan-Meier curve, any time a patient does not have an event that those patients are censored. It does not necessarily mean they're lost to follow-up. So we actually have no loss to follow-up patients in our study. They're censored because they just haven't had an

event. And each 1 of those tick marks means how long they followed up. And so those are the censored events. We are continuing to follow patients in adding more events as they occur. Our next protocol-specified analysis will happen after 51 events. When we have 51 events, we will redo the RFS, DMFS and see if maybe even OS is mature at that time, and then we'll release updated results at the time of the 51 events. That will help us with the durability of the treatment effect with a long-term follow-up.

As you already know, we are initiating a Phase III confirmatory study, which we hope to have open in the third quarter of this year. And then we'll have many, many other studies that we're planning to initiate in additional tumor types, including another study opening up again this year in non-small cell lung cancer.

So 4157 with pembrolizumab had a clinically significant improvement, and I would argue a clinically meaningful -- clinically significant and meaningful improvement in RFS and DMFS compared to standard-of-care pembro, with 44% reduction in RFS and 65% reduction in distant metastasis with 2 years of follow-up. It's the first randomized trial to demonstrate an improvement over pembrolizumab and the first vaccine to show an improvement in a randomized setting. The combination was well tolerated without an increase in immune-related adverse events. And the combination received the breakthrough designation, as you're aware, from the FDA and a prime designation from the EMA just this last April. So I just want to thank all the people that participated in the study, the personnel, the collaborators, the scientists, all the clinical research staff and, of course, the patients and their family, and all the people at Merck as well as our Moderna colleagues.

And I think that was the last slide. I think we have time for questions?

Stephen Hoge - *Moderna, Inc. - President*

Yes, we're going to -- so we're trying to quickly do Q&A because we know you probably have seen some of this before. So -- just as a closing couple of comments, and then in the mean I will start that. So what we're looking at now because I try to say up front is the initial -- the primary analysis. And what we've seen is statistical significance to the RFS primary endpoint and now dramatically more significant benefit in the DMFS endpoint. What was a 44% reduction is now a 65% reduction in the rate of those events.

And as we look to the biomarker data, we start to actually have a pretty clear understanding, we think, as to why, which relates to ctDNA positivity. So people who've had ostensibly curative resection, but before they start their treatment, there's still evidence in their blood of circulating tumor DNA, and therefore, a higher risk of progression. But when we stratify for that subpopulation, what we see is, we think, in the RFS curves and the DMFS curves, very strong evidence of a benefit in both populations and actually a trend that starts to look pretty consistent between them, which is that the DMFS benefit, hazard ratio is 0.347, that is a dramatic number. And the DMFS and the RFS ctDNA benefit is 0.227, again, a dramatic number. Those curves are separating early, and they're not coming back.

That is part of why we are really looking forward to the next analysis, the 51-event analysis, which will move us past the 2-year median follow-up, perhaps towards 3 years. And really, we believe, start to demonstrate the maturing benefit of this immune neoantigen therapy in preventing relapses, be they distant or local.

So with that, I'm happy to take any questions about any of the data we've covered today or anything else. I'll let Lavina (inaudible). I'm also going to stand here so I don't get to...

Kyle Holen

Yes. Yes. We're going to probably...

QUESTIONS AND ANSWERS

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Okay. Great. We're going to bringing microphones [to notify] if I can just ask for the benefit of folks listening in on the webcast, please identify yourself before asking the question.

Edward Andrew Tenthoff - *Piper Sandler & Co., Research Division - MD & Senior Research Analyst*

I think I have a good 1 to start off. This is Tenthoff from Piper Sandler. So I've always kind of wondered this. Are there always 34 antigens? Are they all unique antigens every time you develop or create the personalized cancer vaccine? Are there ever any multiple antigens within a given vaccine, depending on the patient's tumor? And is there an ability or value now that this data is maturing to really analyze the responses based on these individual antigens? Do you have that level of fidelity or it doesn't even matter? And I think I have a second follow-up just with respect to showing the difference between ctDNA positivity and negativity, obviously the benefits on both, but it seems to make sense to stratify maybe in the Phase III, curious if that's something that you're thinking about?

Stephen Hoge - *Moderna, Inc. - President*

So I'll let Kyle take the second one, but I'll start with the first. So these are private mutations, truly neoantigens at an individual level. And so for the 34 neoantigens that are in each of those 107 people's product, they're almost exclusively private. Now the 1 exception to that is there are certain driver mutations that if they showed up, let's say, a KRAS mutation, they would get prioritized because there are some recurrent driver mutations. There may be a few instances of those showing up in the vaccines. We haven't published that, but it'd be very, very small numbers. And so truly, these are personalized private mutations for the new antigens.

That gets to your second part of your first question, which is, yes, we are also now looking across those to understand is there anything we can do to feed that data back into our algorithm. Because we're now starting to see real benefits, not just in terms of immunogenicity, but potentially in terms of relapse-free survival or distant metastasis-free survival. And in that case, again, we have not -- we have the data, we have the ability to do that. It's still a relatively small sample size at 107 people and will get richer as we do the Phase III trial. And what we'll be, of course, looking for, are there opportunities to see recurrent epitopes in certain populations of disease that would allow us to move towards more of an off-the-shelf approach in some instances.

But all that said, this is, we believe, to our knowledge, the first statistically significant trial showing neoantigen therapy. We do think that what is differentiated with it as opposed to other vaccine approaches is that it is neoantigen and private, and there as opposed to sort of overexpressed. And those as mentioned today at ASCO and that discussed in the slides, we do think that's a differentiating feature we don't want to lose as we move forward for now.

[Why don't] you comment on the other.

Kyle Holen

Sure. So obviously, ctDNA is the most important prognostic factor in this population. So we were assessing ctDNA for every patient in the Phase III study. What I cannot confirm yet is whether or not that will be a stratification factor because we're still under negotiations with the agency about the final design. So -- but hopefully, we'll be able to share that information with you soon.

Stephen Hoge - *Moderna, Inc. - President*

And if I could maybe just 1 other thing on that, which is as you get to the microphone. At a larger study, some of those eccentric randomization, things will just controlled [afterwards]. So I think we would all recognize that it's better not to be trying to stratify upfront, let's take patients based

on stage and just allow a slightly higher powered study not to see an issue there. It is really encouraging them to see a benefit in both populations. It just speaks to the strength of the result. And then again, DMFS, it overwhelms that because of the importance of distant metastasis. So we feel confident.

Tyler Martin Van Buren - *TD Cowen, Research Division - MD & Senior Equity Research Analyst*

Tyler Van Buren from TD Cowen. The first 1 is related to your comments on censoring. You noted that they're still being followed, obviously, but that's where they are currently on the DMFS curves a lot of ticks right around where pembro starts to drop off. So can you just elaborate on that and the probability that a bunch of DMFS events occur and kind of close that gap? And you showed that slide where there's kind of no late DMFS events and the combination. So maybe that's part of your answer, but I'd be curious to elaborate on that.

And then the second question I want to ask is, have we shown this data to the FDA yet? And regardless, have they given any color on what would be needed for an accelerated filing?

Kyle Holen

Okay. Why don't we start with the censoring. So yes, each 1 of these ticks is how far someone has been followed. And so there is a drop off here that means people had an event. These people have not yet had an event, but they passed that area where there's a big drop off, and we're continuing to follow patients. So there's quite a few patients that are in follow-up. You can see, however, that as you go out further, the number of patients at risk are very, very small. So at the very end of these curves, it's very unstable because we just don't have enough people that are out 140, 160 weeks for us to have stability in this curve. But are these the patients that you're talking about in the pembro arm that are post the...

Tyler Martin Van Buren - *TD Cowen, Research Division - MD & Senior Equity Research Analyst*

(inaudible).

Kyle Holen

So we have probably -- about equal numbers of patients here that we have in the follow-up, but I will say that there was a short period of time when we're unable to make 4157 due to the fact that our manufacturing facility was making about 1 billion COVID vaccines. And so there's a short period of time where patients were getting pembro and not getting DMFS. But I think as long as we continue to follow these out, I don't think that there'll be any changes in the outline of the curve because the curve is pretty flat all the way out. And once you start seeing flattening of that curve, it's unlikely that you're going to see a significant change.

Stephen Hoge - *Moderna, Inc. - President*

Maybe the best way to address that is, if you look at the exposure numbers in the bottom, you can see that there's a pretty much a 2:1 balance as you move left to right, right? So there's no -- while the censoring can look a little bit thick in certain places, the truth of the matter is that, if you look at the overall balance between them, it looks pretty much balanced, certainly through that day 80 or that week 80.

The other thing is that when you see those groupings, people come in for scans and screening. And that's actually really what's happened is people haven't just gotten to that point yet or in a window in which they're supposed to, but maybe haven't come into, which is what would cause somebody to be "censored." They just haven't made their appointment yet. And so they can't be contributing beyond, which is why that kind of looks like it's every 3 months as a periodicity. So it's...

Kyle Holen

Oh, you're talking about the grouping of scan. Everyone is getting a scan here and then they're all getting their scans.

Stephen Hoge - *Moderna, Inc. - President*

And then they have a window in which they come in. So we're not seeing any imbalance in that censoring as we look at that data that would cause us to have suspicions about these results. Certainly, what we're looking forward to is if you fast-forward that curve a year, which is about where we think, we don't know when we're going to see the 51 events and we rerun these curves, a lot of that will have progressed to the right just naturally over time.

Kyle Holen

And then your question about the regulatory path.

Tyler Martin Van Buren - *TD Cowen, Research Division - MD & Senior Equity Research Analyst*

Have they seen the data? And regardless of that -- or have you submitted it to them? And regardless of that, with the prior conversations, have they said what is required for an accelerated filing?

Stephen Hoge - *Moderna, Inc. - President*

Yes. So I'll take -- I'll let Kyle comment a little bit in a second. So generally, we won't comment on the specific conversations we're having with regulators for obvious reasons, so we're just trying keep this confidential with them. However, we have not had a chance to discuss the most recent DMFS data. And obviously, we're incredibly encouraged by the way. And we will, at the appropriate time, have that conversation. I think what I would just say is, independent of those conversations with regulators, we've tried to say over the last few months, from our perspective, what would we want to see for us to believe that it was time to seriously consider [accelerated] approval. The RFS data by itself alone, as I said before, wasn't quite there, right? It just didn't feel like for us, it was quite there. But as we start looking to DMFS and some of the biomarker data and the enrichment of these responses and hazard ratios like 0.347 and secondary endpoint with all of the alpha coming through in the p-value there, some of the residual uncertainty seems to be going away on that potential benefit.

I think we want to see that mature for all the reasons we were just talking about. This is still the first, right -- this is the primary analysis, but we'd like to see those slightly more events. And the last thing that we've said, for our benefit and ultimately for the public benefit, and we think regulators are increasingly expecting this, is before we move towards accelerated approval, we think we have an obligation to start confirmatory study and being rolling in it, to demonstrate real conviction on not just relying on that accelerated approval. And we've seen some of the attention around that even in this country more recently. So those are the things. If you ask me my personal opinion, we're getting to the point where the thing left to do is actually to enroll that Phase III study, get it up and running. Because, at that point, everybody will know that the confirmatory results are around the corner. And then I think it might be appropriate for us, for our own purposes, to consider pushing that way. Now I don't know if you want to add anything to that?

Kyle Holen

Well, just -- I'll just say that what regulators like to see is consistent trends across all the endpoints that you're analyzing. So we now have trends in RFS. We have the trend in DMFS. We have a trend according to ctDNA. We've presented TMB data that also shows a trend towards improvement in both TMB-low and TMB-high. So I think when you see trends across every single data cut showing very positive hazard ratios, then it leads more belief both from us and generally from regulators' standpoint that these are data that are compelling. Now the nice thing about breakthrough

designation and prime designation is we have an open door policy now with the agencies, and we can talk to them about new data as it comes in. And so it allows us to have lots of discussions with them about the regulatory path.

Stephen Hoge - *Moderna, Inc. - President*

But we're excited -- we are excited to share some [news there].

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

So before we go back to the questions in the room, can I just ask a clarifying question that came through on the webcast, which is, on the censoring, can you confirm that those patients were not lost to follow up?

Kyle Holen

Yes. We have no patients that are lost to follow-up.

Mani Foroohar - *SVB Securities LLC, Research Division - Senior MD of Genetic Medicines and Senior Research Analyst*

Mani Foroohar, SVB Securities. A couple of questions. One, clarifying the statement around a brief period were manufacturing was directed as 1 would expect, overwhelmingly towards COVID vaccine production. Have all these patients gotten the 9 doses that are designed -- that are mentioned in the [slides. Are] there still additional doses coming for anyone who kind of mixed it doing that manufacturing disruption?

Kyle Holen

So during the manufacturing disruptions, patients were manually allocated with pembrolizumab. They did not get COVID. And then once we were manufacturing again, then we were randomizing again. So there was no disruption in anyone's 4157 treatment that was already randomized to 4157. It was just a manual allocation during that time.

Stephen Hoge - *Moderna, Inc. - President*

Yes. And I can say -- Kyle wasn't here and lived through that. Folks have received their treatment. And we announced the complete enrollment of the study well over a year ago, 2 years ago. So -- and it's 9 doses, as you know. So all of that has proceeded through. And I think that's more of a historical artifact of just some -- a couple of months of disruption a few years ago in terms of enrollment.

Mani Foroohar - *SVB Securities LLC, Research Division - Senior MD of Genetic Medicines and Senior Research Analyst*

And is that 9 dose regimen about -- what we should expect in other tumor types? Or should we expect a different dose number -- sort of different regimen and other tumor types?

Stephen Hoge - *Moderna, Inc. - President*

It's a great question. I wish I knew the answer because there's not a great scientific way to answer it. And so I think we're in the -- it's not broken, so don't fix it category. This feels like it's generating strong immune responses and evidence of a benefit. So we'll likely proceed with this. Now as you move earlier stages, you might consider different regimens. This was designed because it's concurrent with people coming in for their infusion of KEYTRUDA, or just getting what is essentially a booster in the arm. And so for that reason, we go every 3 weeks here, it's very convenient. In the

future, we might pursue other regimens. But for the near term, I doubt we will change that because we intend to be principally working in the near term as on top of adjuvant and KEYTRUDA.

Mani Foroohar - *SVB Securities LLC, Research Division - Senior MD of Genetic Medicines and Senior Research Analyst*

And a question on behalf of a colleague of mine. Do you agree with the hypothesis that the late separation of the curves could be due to the slow ramp-up of T-cell immunogenicity vaccine. And if so, are you evaluating any technological approaches to speed the T-cell response?

Stephen Hoge - *Moderna, Inc. - President*

I mean I'll -- I can handle the technical question for you as well. So if you look at the RFS curves, stratified by ctDNA status, which is, as we just talked about, the single biggest prognostic factor for progression in this study is whether or not you still were had tumor DNA circulating post-surgery pretreatment. And if you look at the dotted lines at the top here, those dotted lines are for the ctDNA negative populations, as you can see that 77 and 33, that's the overwhelming majority of the study, right? It's 110, 150-odd folks at baseline. Those curves are separating, as Kyle pointed out about, give or take, week 10. So patients are being randomized. We're getting the drug on board, usually that third cycle, 6 weeks, 42 days. We actually start to see evidence that curve separation is happening pretty quickly.

Now we do believe, based on our vaccines work, COVID, CMV, RSV, that prime boost and maybe even as we saw with CMV, a second boost, you're going to get stronger and stronger T-cell responses. So it's perfectly logical. In fact, I would endorse the idea that you probably want to be boosting those T-cell responses for a while, a couple of months minimum. And so although we do see a little bit of separation after 10 weeks here, I think we've got to be careful. It's very small numbers and very small deflections. What really is obvious when you look at these curves is that, that deflection that separation just continues and matures over time. And I would think that, that's related to deepening T-cell responses across the neoantigens. So the short answer is, I think we see earlier separation than we had previously reported, but we do think that multiple boosts are going to be necessary to get T-cells [that need to] go.

Luca Issi - *RBC Capital Markets, Research Division - Research Analyst*

Luca Issi, RBC Capital Markets. I want to circle back on Mani's question, maybe ask different -- slightly differently. Is my understanding that patients are receiving up to 9 doses?

Stephen Hoge - *Moderna, Inc. - President*

Correct.

Luca Issi - *RBC Capital Markets, Research Division - Research Analyst*

So I wonder if you know what percentage of patients actually receive all 9 doses versus a fracture or 9 doses and whether you see any correlation between a number of doses and clinical benefit? That's the first question. And the second question, circling back on the imbalances of baseline. Obviously, you have more patients that are PD-1 positive as well as more patients that have higher tumor (inaudible). Can you just expand a little bit more on what gives you confidence that this signal is actually not driven by that imbalance of baseline?

Kyle Holen

So the vast majority of patients had 9 doses. I don't happen to know the exact percentage of patients that had all 9 doses, but I can get back to you with that, if that's okay. And then the second part of the question was...

Luca Issi - *RBC Capital Markets, Research Division - Research Analyst*

(inaudible)

Stephen Hoge - *Moderna, Inc. - President*

Best way to answer that question, Kyle mentioned before, is to stratify and look for the benefit in each of those subpopulations. And as we presented AACR, we actually see benefits for PD-1 in both high and low, and TMB, both high and low, and the gene inflammation scores both high and low. And here, ctDNA both high and low. In fact, it's remarkably, if I would observe, it is remarkably resilient that the benefit seems unrelated to PD-1 status, unrelated to TMB status, unrelated to ctDNA status it's showing up everywhere, which suggest as a novel mechanism of action, right? But all of these are known stratification factors that you look for.

So from our perspective and Kyle, as we look at this data, we have not yet found the place where we don't have a high degree of confidence in the biological effect we're seeing. And it probably matches the biological hypothesis of what you're doing. There's really no reason why a vaccine, a neoantigen therapy that's trying to improve T-cell, expand T-cells and activate them independent of PD-1 status, why it would be dependent upon PD-1 as an example or why it would be responsive to ctDNA, independent of the risk of progression. So...

Kyle Holen

And the magnitude of that benefit is pretty consistent as well. So when you start seeing consistent magnitude of that benefit across all these subpopulations, it's hard to argue that, that was really a factor and the inbounds as a factor in the overall outcome.

Huidong Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Gena Wang from Barclays. I have a few questions. First, I think you mentioned that there is some patients did not reach 9 doses. What were the reasons for those patients did not reach 9 doses?

Kyle Holen

Yes. I don't -- do we have -- I don't have that information.

Stephen Hoge - *Moderna, Inc. - President*

I mean, here is an example of a reason, which is patients that progress inside of the initial 27 weeks, as an example, may come off study and not receive for the doses, they may stay on study and receive them. That's an example.

Kyle Holen

We did not have significant treatment discontinuations either. And I think on the safety side, as we go to discontinued due to adverse events.

Stephen Hoge - *Moderna, Inc. - President*

Oh, on safety.

Kyle Holen

On safety before. We don't have that on that slide. But we didn't have any treatment discontinuations because of 4157 treatment. There were some treatment discontinuations because of pembrolizumab, but not because of the 4157 adverse events. But some patients did come off 4157 because of recurrence. But I can get back to you with those exact numbers. I don't have that percentage with me.

Huidong Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Okay. Great. My second question is the DMFS secondary endpoint. You did a stats analysis on ctDNA-positive and negative. Would these where prespecified, or was the post-hoc analysis?

Kyle Holen

That was a post hoc analysis. We did not prespecify a ctDNA subset.

Huidong Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Okay. But the secondary endpoint, DMFS, that's prespecified?

Kyle Holen

That was prespecified, yes. That was the first ranked secondary endpoints right after RFS then we had our DMFS-ranked endpoint evaluation.

Huidong Wang - *Barclays Bank PLC, Research Division - Research Analyst*

My third question -- last question is the 51 events based on the current update. What is the estimate? I know it's very difficult, but what could be the possible time range for the event?

Stephen Hoge - *Moderna, Inc. - President*

I'm going to say, Kyle, we don't control the rate of these real lapses, nor do we want to guide beyond saying we will as soon as we have the 51 events, you can be damn sure we're going to turn around that announcement real quick.

Kyle Holen

It's really hard to speculate when that would occur. Honestly, we hope it never occurs, right, that nobody has this recurring event. But unfortunately, there's not a consistency in these events occurring that we can safely say it's going to happen next month or in the next 4 months. We're still waiting for those events to come in.

Stephen Hoge - *Moderna, Inc. - President*

If I could give you a little bit of insight in the 1 way, I would look at that if I were in your shoes. So the events are relapses, right, not distant metastasis-free, or not distant metastasis. And what you can see, these are the populations, right? And so the ctDNA positive populations, people will have their tumor removed, but even after the removed and their lymph node removed, they still had circulating tumor DNA. Essentially, you can see that those have all progressed. The monotherapy arm moved very quickly in the black saw -- black line. They've all come down. Everyone

had an event. We were positively surprised by what we saw with the ctDNA positives on the red line, as you can see. A large number of them did last quite a while without a relapse, which is good news.

But what you can also note is that the top red line, our ctDNA negative, combination therapy has essentially flattened out. And we'll see how that plays over time. But if you believe that, that line is not contributing, and you believe that the 2 solid lines are no longer capable of contributing, and really what we're dependent upon is accruing events in the pembro monotherapy arm. And as you can imagine, that's a smaller portion. And as you can see about half of those have happened. So it is good news, we think that any patient is not progressing. It also might bode well for the performance of 4157 that in fact its taking longer and longer for us to see this event, because looking at those curves, it appears that they were like -- becoming out of the monotherapy ctDNA negative line.

Kyle Holen

Yes. One of the things that was particularly exciting for us is to see that, if you're ctDNA negative, and you were randomized to the 4157 pembro arm, you're essentially at a 90% cure because these patients are not recurring at 140 weeks. They're flat line Kaplan-Meier curve. So we'll continue to follow up and see if there's any changes in that curve. But once you start seeing Kaplan-Meier curve's go flat, then it's unlikely you're going to see significant more events.

Stephen Hoge - *Moderna, Inc. - President*

So that's a hard question to answer, Gena, we can't...

Kyle Holen

Likely from these folks.

Stephen Hoge - *Moderna, Inc. - President*

But rest assured at the moment, we have it, we will very equally look at it because it will allow us to update the maturity of all of these curves. But the latency here, the delay is maybe not bad news.

Unidentified Analyst

(inaudible) from Salveen Richter team at Goldman Sachs. In your view, how do the results from this study inform the translatability to other indications such as non-small cell carcinoma. And then could you help quantify what success would look like for you at the 51 event analysis?

Kyle Holen

Sure. So I guess I'll handle the other tumor types. So I&T is not a therapy that is created for a specific cancer. So unlike other cancer treatments where you are creating a treatment antibody or a small molecule based on that histology and what makes that cancer grow uniquely different than other cancers, we're creating I&T 4157 in a way that is tumor agnostic, meaning just looking at the variant calls between the tumor and the normal tissue. Because of that, we believe that there's really -- there's no reason why I&T will not work across all these different cancers. And in fact, it makes our job a little bit harder because, basically, the world is at our fingertips with all these different cancers.

Now we'd like to start in places where we think there's immediate adjacencies to what we've observed with melanoma. And what that means is cancers that we think are more immune responsive and cancers that have been shown to have efficacy with checkpoint inhibitors. So that's our first step. But we have ambitions beyond just the pembrolizumab combinations going to earlier settings, late settings and across a whole variety

of different cancers. We don't believe that there's really a limitation to I&T. And another reason why we believe that is because if you look at TMB status from our AACR presentation, we had efficacy in TMB-high and TMB-low, which suggests that even in patients that aren't typically responding to pembrolizumab, they'll still respond to I&T. So we're excited about the possibility and we really don't have a limitation right now in what type of cancers we think we can go after. Would you like to add anything to...

Stephen Hoge - *Moderna, Inc. - President*

No, you covered it well, particularly that we want to move outside of the combos, but the obvious place to start is in the adjuvant, where there's headroom as there is we've shown here to improve. On the question of success at 51 events. Look, I think we've talked about the fact that we believe the curves are going to continue to mature as you just look at them in a favorable direction. Certainly, the separation is, whether it's early or late, it's sort of sometime in the middle of that first year. But then what really starts to happen over time is those curves start to really differentiate, whether you're looking at DMFS or RFS. And that means that, if that holds true, the hazard ratio will improve over time.

Now to some limit, in this case, we're seeing the hazard ratio in DMFS is already at 0.347, the p-value is 0.006, I mean that's a dramatic 65% reduction. And so perhaps some of those things won't keep going. But in the case of RFS, we talked about it has a hazard ratio of 0.56, that's 44% reduction. But when you start looking at things like the stratified by ctDNA status, you could start to believe that actually that might drift down towards the number of like we're seeing here in the stratified analysis, 0.3, 0.2. And so what we'll really be looking to understand is more than just those 51 events and where they happen and hopefully, they don't happen, but if they do, we expect them to happen in the same way they have been.

The question is, as we mature another year on those curves, and you start to have more and more of the exposure risk, be on the right-hand side of these graphs, the hazard ratio just start to approximate what the right-hand side of the graph look like and go down. So success from our perspective would be continuing to see really strong statistically significant hazard ratios, both DMFS and RFS. A big success would be continuing maturation of those curves and actually an improvement in those hazard ratios, particularly the RFS one as we start to understand where we think it's trending.

Kyle Holen

And I'll just add, as a medical oncologist in the field for 30 years, I would challenge you to find many studies with a better hazard ratio than 0.225. I mean this is...

Stephen Hoge - *Moderna, Inc. - President*

Or the DMFS primary the per protocol analysis, a hazard ratio of 0.347.

Kyle Holen

It's something that is just not common in the field, and really exciting. So I'm thrilled with these data. I'm not sure it gets that much better, but we'll see what happens with the 51 event analysis.

Michael Jonathan Yee - *Jefferies LLC, Research Division - Equity Analyst*

It's Michael Yee from Jefferies. A couple of follow-ups on the patients who progressed in your arm, was the takeaway that most of -- all of those patients were basically the ctDNA positive patients? Or what else do you know about those patients, including immunogenicity data? And I thought there might be an analysis or some information on that. So that's question one.

Question 2 is, what are the gating steps to starting the Phase III melanoma in lung study? And question 3 is, what is your view on metastatic given that you continue to see a lot of positive things about where pembro works. I feel like there's a mixed commentary and body language around metastatic. And I thought there's actually a head and neck Phase I ongoing, so [where we have] any information on that?

Stephen Hoge - *Moderna, Inc. - President*

I may take the first, do you want to take the second and third. Does that work?

Kyle Holen

Yes, that works.

Stephen Hoge - *Moderna, Inc. - President*

Okay. So first on the question, I can just point to the day that we've released on the curves. But if you look at the DMFS by ctDNA status, so I'm going to look first at distant metastasis today's data. What you can see there is, there's only 1 event out of 77 that was in the ctDNA negative population. I'm looking at the table at the bottom. And so clearly, in the combo arm, only 1 event is, I think the most direct answer to your question.

As you go look at the RFS data, and again, they're, in the RFS case, it's a little bit different, but you see that there are more events in the RFS case -- I'm trying to find really quickly -- 8 out of 77 in the RFS case in the bottom of the table. In both cases, clearly more in the ctDNA positive. And I think in the distant metastasis, which is from the primary analysis, as we've been talking about. Sorry, I went pass it. That ratio is 1 versus 8. Now. Sorry second question.

Kyle Holen

Remind me the second question.

Michael Jonathan Yee - *Jefferies LLC, Research Division - Equity Analyst*

(inaudible)

Stephen Hoge - *Moderna, Inc. - President*

Immunogenicity data. Do you want to take it (inaudible)?

Kyle Holen

Sure. So we have immunogenicity data that we've generated from the Phase I study. We have analyzed some samples from the Phase II, but unfortunately, we didn't have apheresis for the Phase II study. So we don't have much data to share, unfortunately from the Phase II data. But we will be presenting immunogenicity data from the Phase I data, and that's under analysis right now.

Stephen Hoge - *Moderna, Inc. - President*

And we are expanding in our Phase II some translational endpoints and continuing to enroll some patients to build out some more of that. But immunogenicity wouldn't necessarily inform this data, we think, on the ctDNA positive versus negative side.

Michael Jonathan Yee - *Jefferies LLC, Research Division - Equity Analyst*

(inaudible).

Kyle Holen

We hope to have third quarter this year melanoma and fourth quarter non-small cell lung cancer.

Stephen Hoge - *Moderna, Inc. - President*

Again, subject to things beyond our control, consultation with regulators, our partners. So that's not guidance, but we are -- as we've talked about with our previously -- and I think Merck has talked the same, our goal is to start those 2 histologies and to studies this year.

Michael Jonathan Yee - *Jefferies LLC, Research Division - Equity Analyst*

(inaudible).

Kyle Holen

Yes. And I think what we need to do is find the right setting for us to test in the metastatic population. We wouldn't want to try and have our first study beat in the small cell lung cancer population where they progress so quickly that they couldn't wait 6 weeks before you had your first dose of vaccine. So we need to find an area where we think either we can control them initially with some treatment prior to getting 4157 or they have a slow enough growing tumor where we think we might be able to have them wait until we can give them their 4157. So that's really the biggest limitation in my mind about a metastatic setting is you just don't have as much time to create 4157 for them. But I think it should work, and we just need to find the right tumor type in the right setting.

Stephen Hoge - *Moderna, Inc. - President*

Well said. I think, hesitation is not about the biologists about the operational questions. And in the adjuvant settings, we do think we've got to talk about the tail here. We think this is exciting data. Our partner, Merck, does as well, doesn't believe that we need to go here quickly. And I think what we're trying to do is stand up as much of the trials -- as many of the trials across the many histologies we can in the adjuvant setting because we already have the operational system to do that as fast as we can. And that's probably if you see body language, it's just, this is -- we believe this is working and deserves to move forward quickly across our wide range of histologies. Let's get that going and get focused on that first.

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Okay. We have time for 1 last question.

Boran Wang - *Guggenheim Securities, LLC, Research Division - Associate*

Evan Wang from Guggenheim. I just have a few questions. I guess, clarifying the differences in ctDNA positive versus negative. I know it's a pretty small subset. But wondering how you're competing those results and potential expansion again to more advanced settings? And then contracting that maybe some of the speed of response that you're seeing now when you presented at AACR, does that actually provide encouragement there?

And then third, in terms of some of the immunogenicity data, I know you said it's maybe a small subset of that, but how should we be thinking about timing and exploit exactly that (inaudible).

Stephen Hoge - *Moderna, Inc. - President*

I'm glad you're writing this down. I'm going to try and do the first one. So there were 125 participants have ctDNA baseline status out of 157. So it's -- I think it's over 80% of the population. And the others, it was just you couldn't, at baseline, maybe get all of their -- get the assay validated for them and so NeoGenomics are partner that didn't produce it. So we'll keep pushing to do that. But it is actually quite large subset. I mean the study itself was 157, but it's well over 80% of the study. Was -- did you -- was that the wrong question?

Boran Wang - *Guggenheim Securities, LLC, Research Division - Associate*

Just to interpret some of the ctDNA positive patients in terms of...

Stephen Hoge - *Moderna, Inc. - President*

Oh, I'm sorry, the rapid progression. Yes. So the 13 versus the 2. So let's point to those numbers. It's 13 and 2. However, obviously, the benefit that we're seeing in the separation in the 13, the red line, those that were on combo is pretty encouraging and does look different. We want to be careful about overinterpreting that. We need more numbers to go much further than that. However, I think this is the part of your second question. When you see that kind of separation relatively early, you could start to see quite dramatic effects at, let's say, that 60 weeks, that's 1 year if those red and black lines -- the solid red and solid black lines held up. So we are looking at those things as potential study populations for the future.

In the near term, it is not our focus. In the near term, we're focused on melanoma by stage and trying to get that enrolled as fast as we can. But we'll continue to think about biomarkers and how they might be used to stratify risk or identify signals more quickly in the future.

Kyle Holen

And can I just add a little bit. So this is 1 of the reasons why we're excited about potential in metastatic setting because these patients with ctDNA positive disease, they're essentially metastatic patients. We just can't find it. So if it works here, we think it's likely going to work in the metastatic setting, too. And this is what gives us that early signal that a metastatic scenario might be feasible.

I think the next question you had was the comparison between AACR and the data that we presented here at ASCO. It's the same data cut from November, just to remind everyone. We didn't have a new data cut that we did just for ASCO because we are following our statistical analysis plan that triggered that data cut after we had 40 events. Now we ended up having 44 events included, but we triggered the analysis at 40 events. And by the time we had cleaned all the data, we end up having 44 events. So this analysis, the MFS, is from that same data cut from RFS. What we're excited about, however, with this data cut, as I mentioned before, we had a 44% decrease in RFS, and yet we saw a 65% decrease in DMFS. So the trend and the improvement over that RFS was exciting to us for this ASCO presentation.

And then the last, I think you asked about immunogenicity. We're in preparation to be able to release that immunogenicity data. I can't give you a time line because it's a little bit out of our control based on the journal and the editors and getting back and forth comments and trying to get that published. But we hope to have that published in the not-too-distant future. But I can't give you a time line when we're publishing the immunogenicity data. Unless, Stephen, you've heard anything that I haven't heard about?

Stephen Hoge - *Moderna, Inc. - President*

No, we're looking to publish as soon as we can. Lots of comments back and forth and reuse.

Kyle Holen

We might be able to give you a heads up if we find out that it's going to be coming out. But right now, we really don't know when that data is going to be published, unfortunately.

Stephen Hoge - *Moderna, Inc. - President*

[It's not for review].

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Excellent. Thank you so much to both Kyle and Stephen for walking us through that data, and for everyone who had questions. Have a great evening, everybody.

Kyle Holen

Thank you.

Stephen Hoge - *Moderna, Inc. - President*

Thanks all.