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OVERVIEW:

Company Summary

REFINITIV

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PRESENTATION

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

(technical difficulty)

Some time with us. We're really excited about sharing with you some new data that we just shared earlier today on one of our assets, 4359 that's quickly becoming one of our newest late-stage assets similar to INT, which you've heard a lot about. I'm going to walk you through some of the INT data. And then we're just pleased to have some experts in the field that have joined us tonight to talk to you about melanoma and to talk to you about the data that was presented, the 4359 data, and that's Dr. Sullivan and Dr. Pinato.

So we'll bring them up shortly. But before we do, let me just talk to you about our pipeline. So at Moderna, we use mRNA in many different creative ways. We use it for personalized therapies, which is our Intismeran autogene program, and I'll talk to you a little bit about that. We also have some off-the-shelf therapies. Those are our cancer antigen therapies, which we affectionately call our CATs, C-A-T.

We have T-cell engager program, and I'll share some preliminary information about where we are with our T-cell engagers. And then we also have some cell therapy enhancing an in vivo cell therapy programs, which are also really exciting for us to advance into the clinic. All of these programs have, we believe, the promise of potential efficacy across a broad range of indications as well as a broad range of different settings from early-stage disease to all the way to metastatic settings.

And what I'll share with you this evening is that if you had looked at a pipeline slide like this a couple of years ago, it would have been about half the size. So this is a testament to the hard work that our clinical development colleagues have done as well as our research colleagues to bring all of these new programs in the clinic and to expand those programs in clinic to so many different indications.

So as an example, our Intismeran program now is evaluating efficacy across melanoma, lung cancer, renal cell, bladder, we have metastatic melanoma study. So many different indications that we believe INT could have the potential for efficacy. And then across our cancer antigen therapies, we have both our 4359 program as well as our 4106 program.

And then our T-cell engager, as I mentioned, 2808, which we have our sites open and active. And then lastly, we have our sites open for 4203, which is our cell therapy enhancing program. I'll walk you through Intismeran. So many of you may be familiar with Intismeran, but in case you're not familiar with it. Very quickly, it's a program that is extraordinarily unique in the field and not just unique in terms of the oncology field, but unique overall.

There's never been a medicine that is quite so individualized as Intismeran. So Intismeran is a program where we start with understanding the patient and the patient's tumor. We take that biopsy from the patient's tumor as well as blood sample. We look at and sequence the tumor DNA as well as normal tissue DNA, we HLA type.

And then we do an assessment of the mutation status and compare that to normal tissue and tumor tissue. We look at the different mutations. We decide what the unique mutations are in the tumor. We use that information to put into the algorithm along with their HLA typing. This algorithm then predicts which ones of these mutations maybe more immunogenic.

We also, as I didn't mention, do RNA seq to understand how many of these mutations may lead to RNA and eventual proteins. The algorithm predicts the antigens that are most likely to cause an immune response. And then we encode these into concatemer. We encapsulize this into an LNP. And then we ship this back to the patient who can then receive Intismeran.

And we do all of this in less than three weeks -- less than six weeks. This is our three-year follow-up data that we presented at ASCO, and this data comes from our randomized Phase II trial. This is P201. P201 Was a randomized trial looking at high-risk patients with melanoma who had their tumors resected. These patients were then randomized to receive Intismeran plus pembrolizumab, the standard of care, or pembrolizumab monotherapy.

We followed them for a recurrence-free survival, distant metastasis-free survival. And we are also following them for overall survival. Our five-year follow-up is expected to mature later this year, and we hope to have data to share either at the end of the year early in 2026. These are the data that we presented on RFS. We reduced the risk of recurrence or death by 49%, which was super exciting.

And this is the data that led us in an earlier snapshot to proceed with our randomized Phase III study. RFS was not the only end point, however, where we saw some benefit. We saw a 62% risk reduction in distant metastasis or death, and then we also saw a trend towards an improvement in overall survival. These are the safety data from our randomized Phase II trial.

Importantly, we did not see any increase in immune-related adverse events. And overall, it was very well tolerated. There's some pain in the arm, some fevers and fatigue, but those were self-limited and went away over a couple of days. And this has been very consistent across our platform. So these type of safety data or data that we've observed now with 4359. We've also observed this with Intismeran.

And frankly, it's similar to our other products in our platform, including our ID vaccines. As I mentioned, it was these data that led us to mount the randomized Phase III trial. This is called INTerpath-001. This study has already finished accrual, and we're following up for events and we hope to be able to assess these patients next year.

The study is very similar to our randomized Phase II with the one exception is that we're allowing some patients with earlier stage disease to enroll, and those are stage two patients. And as I mentioned, we're now in the midst of a whole series of different trials, some Phase III trials, some randomized Phase II trials and we even have an ongoing P101 study that's assessing pancreatic cancer and gastric cancer in single-arm studies. We hope to have data from some of these studies over the next year or so.

Okay. With that overview of Intismeran, I'm going to turn things over to Dr. Sullivan, who'll talk to you about the melanoma landscape, in particular, the metastatic melanoma landscape and that will lead us into the results that we observed with 4359.

So Ryan, thank you.

Ryan Sullivan - *Moderna Inc - Director - Commissioning, Qualification and Validation*

Thank you very much. So my task is to talk about the advanced melanoma treatment landscape, which will make more sense when Dr. Pinato talks about the update that he presented earlier today. So this is a busy slide that we've been making busier over the last 15-years, which is a wonderful story in and of itself. I'm not going to go into the details. But just to say that in the advanced space, we have a lot of things at work.

We have the first immune checkpoint inhibitor approved in advanced cancers and Ipilimumab, we got to try and do that. We can read. We had the first anti-PD-1 antibody approved for any indication in 2014, followed soon after by -- with pembro then nivo, we had the first BRAF targeted therapies. We had the first combination checkpoint inhibitor, the first oncolytic virus.

We've done well. We've had a lot of success. But remarkably, despite all of success, we still have more work to do. I'm not going to take you through all of the data supporting this slide and the statements I'm going to make on the slide. But needless to say, if a patient arrives in our clinic, remarkably armless. Even if they have arms, we have three options.

We can give single-agent anti-PD-1, we can give the combination of an anti-PD-1 antibody and anti-LAG3, which would be Opdualag for single agent that the approved agents are KEYTRUDA and Opdualag. And then we can combine anti-PD-1, anti-CTLA4 with ipi/nivo. Even if you have a BRAF mutation, this is better. And that's been shown in a number of studies.

And here's a summary of that work. Basically, if you look across the agents, you see varying response rates, but combination therapy is typically more effective than single-agent therapy, both from a response rate, progression-free survival, overall survival, melanoma-specific survival. And while the CheckMate-067 study was not powered for overall survival, which is the ipi/nivo trial versus nivo versus ipi, the 10-year OS and the 10-year melanoma-specific free survival are higher than for nivo alone.

And the nivo data and the pembro data are actually fairly comparable. And so it likely is true that a patient who has one of two options, if you were ipi/nivo or single agent PD-1 has a similar chance of being alive 10 years if you get either of the single agents, but a little better chance if you got ipi/nivo, we don't have 10-year data with nivo. Rela, we have three-year data.

The first three years look pretty good and comparable to ipi/nivo, but there's a long way to go there. All of that said the majority of our patients don't respond or if they do respond they recur. And so despite we have with ipi/nivo slightly more than 50% melanoma-specific survival. The majority of our patients die from melanoma -- from metastatic melanoma.

And of course, the patients that are not candidates for trial who almost always die from metastatic melanoma were not enrolled on to these studies. So in the scenario where we have PD-1 resistance, we have also a few options if we're just not very clever and just say, well, we gave this, let's try that. And so there's actually now data from all of these scenarios where there's arrows.

So if you were to have received anti-PD-1 single-agent and receive combination anti-PD-1, anti-CTLA4, there's an approximate 25% to 30% response rate for that population of patients. If you've got anti-PD-1 single-agent -- or sorry, anti-PD-1, anti-LAG3 and then received a combination of ipi/nivo, response rate is less, it's about 11%.

And although there's now data that's just being published about anti-PD-1 or anti-PD-1, anti-CTLA4 pretreated patients receiving anti-PD-1, anti-LAG3 which looks better than this. But ultimately, the current data that is published and available is about 11% response rate, although the updated data that was -- so this is from a prospective study of nivo and Rela following anti-PD-1 either single-agent or a combination treatment.

There's a real-world publication that got published last week, so I didn't put it in, but it's actually about a 25% to 30% response rate with anti-LAG3, anti-PD-1 following a frontline PD-1 single agent or combo. So that's what exists. That's the actual standard of care, but for one additional thing, which is in a scenario where a patient has received checkpoint inhibition, we have one additional option certainly in the states anyways, which is tumor-infiltrating lymphocyte therapy with Lifileucel or we have clinical trials or we can recycle checkpoint inhibitors.

So if that patient has a BRAF mutation, that patient can go on to a BRAF MEK inhibitor combination and almost always, that treatment will fail that patient within 6-months to 12-months. So there's still an awful unmet need here because -- well, TIL looks promising and obviously received approval, it's not perfect. This is just a summary.

I decided not to show you all the clinical trial data with Lifileucel, but needless to say, response rates in the early days of TIL, which was developed at the National Cancer Institute in Bethesda, 25% to 50% response rates that was included pre-PD-1, post PD-1. With Lifileucel, response rates of

30% to 35%. And for the first time, seeing durable responders not just in complete responders, but in patients who had partial responses, which was never seen at the NCI. It was either CR robust.

There's randomized data from Netherlands Cancer Institute, randomized trial of their TIL approach, which is very similar to Lifileucel and the NCI compared to ipilimumab and mostly previously anti-PD-1 previously treated patients, which showed an almost 50% response rate and a clear improvement in progression-free survival.

Lifileucel was approved in February 2024, and there's a randomized ongoing study in the front line. What I'll say about Lifileucel, it's not for everybody. It requires lymphodepleting chemotherapy, it requires then receiving your TIL, which you see isn't the big deal and then receiving IL-2 following that. It's a big ask for a patient. It's about a three-week hospitalization.

It can be amazing, and it's associated with durable responses. And so we totally believe that this is the right option for some patients, but it's not the right option for all patients who are in the setting of PD-1 resistance for melanoma and clearly, suggests that the more approaches are necessary, both in cell therapy and beyond. There are some additional data that's emerging with other TIL products.

It's a very interesting study that was updated at ASCO. This year with OBX-115, it actually avoids the IL-2 because there's conditional expression of membrane-bound IL-15 that actually gets activated when you give a carbonic anhydrase inhibitor. And the early data suggests that there's a better toxicity profile if you like, figure out when you should give the carbonic anhydrase inhibitor, which was sorted out and may have equally good efficacy. It's a big statement. There's a randomized trial that's happening.

And there's also a randomized trial with a PRAME-Specific T-cell receptor, T-cell that is looking at, again, the targeting PRAME, and that data has been presented and is in now a definitive study in patients with anti-PD-1-resistant melanoma. So that's where we are with -- that's the state of the field. I don't know, Cory, should I take questions now or just get all the data and then take questions. How would we like to do it? After.

Then you're up -- sorry, Kyle.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

Okay. So thank you, Ryan. A great overview of the melanoma space. We're going to move on to the next mechanism. After Intismeran, we also now have some cancer antigen therapies including our most recent presentation, which was 4359. So 4359 got a mechanism slide.

Here is -- targets both PD-L1 and IDO. This is important because it can help with immune evasion and help get rid of some of the tumor suppressor T regs, but it also may target the cancer cell itself by activating T-cells against the target when the tumor may be expressing PD-L1. So it may work in multiple different mechanisms. We presented our safety data last year at ESMO in 2024.

And today, we had our first presentation of our efficacy data. We presented that was safe and well tolerated last year with toxicities that Dr. Pinato will describe in detail. But we're excited about seeing some preliminary evidence of antitumor activity and where this may lead for further development options for 4359.

So with that, I'll hand things over to Dr. Pinato and you can walk through the data with us. Thank you.

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

Thank you, Kyle. Good evening, everyone. The first advantage of me being able to give this presentation tonight is that I can do it a little bit more relaxed way without having just five-minutes to concentrate all the data and for a non-native English speaker, you can imagine that every time you stress, you lapse back into your regional language. For me, it's Italian. So my accent might not have sounded exactly British earlier on.

So thank you very much for the opportunity to represent this data to you, which basically go and show how mRNA-4359, which is a lipid nanoparticle mRNA molecule that is characterized by its ability to enhance T-cell responses against two key fundamental actionable drivers of anticancer immunity. PD-L1 does not need an introduction.

But I think IDO specifically is one of those targets that was actually -- one of the first that created the bubble of anticancer immunotherapy to birth, especially when the enzymatic inhibition of this enzyme, which basically catalyzes the transition between tryptophan and kynurenine. So deprives the T-cells from a nutrient, tryptophan and catabolizes the kynurenine, which is a toxin for the lymphocytes themselves was actually attempted to be targeted.

But unfortunately, the data in lung and melanoma were a failure by targeted inhibition of this enzyme. So 4359, at least it's a different mechanism of action, uses these two flags, as I describe them, to my patients whenever they come to clinic and get these type of treatments, little flags outside of the tumor cell or the microenvironment as a specific target.

And the way I tell my patients about how this drug works is that it gives the immune system a sort of an instruction booklet to try and identify a better and more tailored, the more precise way to treat cancer as a result of a specific and targeted approach. So the data that we presented today stem from an ongoing Phase I/II clinical trial, where the objective initially was to describe the safety as we always do in drug development.

But then one of the features of Phase I trials in oncology is that we give these molecules to patients with active disease and the most legitimate question that we have is are the drugs working? What is the efficacy? And although the data that we presented today are essentially preliminary in nature without control arms. I think it's very important to go through the data with you, particularly in the CPI resistant refractory melanoma cohorts. So this is the patient distribution with 29 patients.

And specifically, there were two different sub-cohorts to the group of patients that we're talking about tonight, 14 that received the dose of 4359 of 400 micrograms and 15 that received the dose of the 4359 at 1,000 micrograms. Together with this, the backbone PD-1 therapy of pembrolizumab was continued. We have seen what the expected response rate is for these patients who are basically challenged with the PD-1 inhibitor.

And the median follow-up was in the region of about 20 weeks. You can see on the right-hand side that there is a bit of a difference in terms of duration of follow-up between the 1,000 micrograms cohort and the 400 micrograms cohort. Reason being that, as you can imagine, the study was done in a dose escalation manner. So patients treated with 400 micrograms are the ones that were treated first, patients treated with 1,000 have got necessarily a shorter follow-up.

Another important aspect to say these patients are the classic early phase clinical trial population. So good organ function, good performance status, heavily pretreated. And the unifying factor though, for this population is a definition of CPI resistant refractory, which stems from clearly defined criteria by the Society for Immunotherapy of cancer.

So these include patients that might have either had a response, an initial response, to anticancer immunotherapy and then have developed resistance as a secondary mechanism or those that had primarily refractory disease, so those where there has never been a response and basically patients progressed later on.

So these are the safety data, which as we said, it's one of the primary objective of this study is the treatment, potentially going to be deliverable in these patients. And whenever I look at safety data, I do this little scanning in my head, so I always go to the type of adverse events that would concern me as an oncologist. And there is a formal way of grading adverse events.

Grade three events are the events that cause patients to turn up to hospital, are those events that especially in the setting of anticancer immunotherapy alarm as for the concept of synergistic toxicity. So if you combine more immunotherapy agents together, and it's certainly been the case of ipi/nivo, you have a certain likelihood of increasing the chances that the patient will have an adverse event.

So what we can see here is that we had to divide events on the basis of relatedness to either 4359 or the background therapy, pembrolizumab. And as you can see, the 4359 associated adverse events, which are listed here. First of all, they are not particularly different across the cohorts. Those that are characterized by an incidence above 20% are essentially fairly well manageable.

So we're talking about tiredness, injection site pain, which is expected from any of these therapies, a tiny bit of fever, erythema, chills, flu-like symptoms. But there is nothing that really speaks for the high-grade immune-related adverse events that can be either systemic or organ specific. We do have a few of those, but those are classically related to pembrolizumab.

And the ones that I would like to basically point out are the ones that were specifically labeled as immune-related so the ones that require steroid therapy, et cetera. Those are in the region of 13.8%. So it is what is normally expected as a result of exposure to PD-1 monotherapy only. This study because it's an early phase study, look at DLT.

So dose limiting toxicities, if there are any events in the follow-up of the patients through subsequent dosing lead to the treating clinicians to say we must stop the treatment. Or this is a serious event that does not warrant us continuing in that individual patient. And for this particular group, there were absolutely no events that were labeled as DLT, which is also quite important as well as very strong and debilitating or potentially little adverse events were not registered in this cohort.

Moving on to the efficacy. So we have a stratified efficacy data on the basis of each individual sub-cohort per single level of dosing. In looking at the differences between 38% and 8%, you have to consider that the maturity of the data across the two cohorts is unbalanced and so are the characteristics of the patient population.

So if you were to read the Phase III randomized clinical trial, you can infer differences across the two columns here. We have to read the data descriptively. We have an overall response rate of 24%, which in the setting of a refractory patient is notable, and you can see the description of each individual response. Mostly, we are talking about partial response.

There is a complete response and some stability of the disease. The disease control rate is a measure that encapsulates also the proportion of people that have got disease stability, not just shrinkage of the tumor. And that is actually quite good considering that we have a lot of patients that were very heavily pretreated, including the responders over 50%.

So the idea of having stability of the disease in the majority of patients across the different arms as well as in the totality of patients is fairly encouraging at this stage. But one of the things that is perhaps differentiating this specific molecule compared to others and was also picked up by the discussion is the fact that we do need biomarkers.

We need to know whether or not there is scope for this specific treatment to identify a subset of patients, which is the holy grail of oncology, precision, trying to pre-identify who are the patients that would benefit. And I think it's fair to say that overall response rates are early surrogates of what the natural course of the disease would be.

But in a study of this kind, seeing a difference based on the PD-L1 TPS, so the number of tumor cells that are picking up one of those flags, the PD-L1 flag is actually quite encouraging. And you can definitely see an enrichment in all the patients that score more than 1% of 67%, which is compared to data in the PD-L1 negative extremely encouraging.

Here, you can see the waterfall plot. So this is the unidimensional view of how the response looks like in the individual patient, expressed as a percentage change compared to baseline. You can see that one patient obtained a complete response. A lot of patients had partial responses, but there is definitely a differentiating factor, which you can see in the color red versus blue, which is the PD-L1 status.

And if you're not convinced by this, you can also look at the other aspects of the data which is this spaghetti plot, which looks at essentially the characteristics of the reduction in size over time. So this is important because it enables us to understand what is the durability of the response throughout the course of treatment. A

And some of those responses are highly durable especially in the red patients, the PD-L1 positive. This data are, to me, particularly important because when we try to develop new drugs, especially in early phase clinical trials, we have to ask ourselves whether there is enough support for the predicted mechanism of action of the drug that we are developing.

This is important because it enables sponsors to make go/no-go decisions, enable clinicians to understand how we're using these drugs, what is it that we are targeting. And so on the left-hand side, there has been a meticulous collection of peripheral blood mononuclear cells. So we've been asking our patients to donate extra samples for research to try and understand how these drugs work.

And some of these patients donated a sample at baseline. The sample of treatment is at the point of maximal response to the treatment. And in these two assays, basically the T-cells as well as the peripheral mononuclear cells are basically incubated against the very antigens that actually compose the treatment itself. So IDO1 and PD-L1 and there is an imperfect, which was pointed out by the team earlier, relationship between the responses as measured as an immunological readout compared to the responses measured radiologically.

So there is not a perfect correlation. You can see that some of the patients have a trend towards -- an upward trend, both in the IDO1 and PD-L1 responses irrespective of whether they have a response, but the trends are actually quite important more to see whether or not there is any form of immunogenicity, not as a predictor of response in these patients, which I think is very, very important here.

And then on the right-hand side, you have something that to me was even more appealing. So one of the key characteristics of anticancer immunotherapy is to expand T-cell clones. And in this particular graph, you can see that across the 2 dosing cohorts, in patients, particularly that achieved a CR or a PR, you can definitely see that there is an emergence of new clones, so T-cell clones that were not present before.

And again, this goes to support the fact that these patients may not have had an intrinsically present immunogenicity to the antigens, but they acquire such immunogenicity and the clones expanded thereafter. So I actually personally like these images very much, perhaps even more than the response data because they go and support the mechanism of response, which is ever so important in early development.

And with that, I thank you very much for the attention, and I'm happy to answer questions.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

So thank you for that overview. The data are exciting enough for us to expand our current protocol where we have now amended the study to include different treatment arms. So we have Arm 2a, which was the arm -- was the pembrolizumab frontline with 4359. We have Arm 2c, which is the frontline melanoma arm that includes 4359 in combination with ipilimumab and nivolumab.

Arm 2d is an arm where we're looking at melanoma patients, but this is an expansion of the previous data where we're expanding upon CPI refractory patient population. And we're -- because of the data that we've observed, we're restricting that arm to patients who have some evidence of PD-L1 expression. And then we're also looking at 4359 in non-small cell lung cancer patients.

This is in combination with pembrolizumab in the patients that have a TPS score of greater than 50%. Moving on to our next product in this class of cancer antigen therapies, which is 4106. This is a program that we're rapidly advancing through our Phase I trial. This is a cancer antigen therapy that has antigens that are across a broad range of different targets in multiple different tumor types.

It's, again, an off-the-shelf program so that we can manufacture large batches of drug and administer this to patients. So far, we've escalated through dose level 1, dose level 2. We're now enrolling in dose level 3. And I'll share with you that we're seeing so far, similar types of safety and toxicity events that we've seen with our other programs.

In terms of our T-cell engagers, I'll move on to our 2808 program. This is a program that we're evaluating in patients with multiple myeloma. The T-cell engager program has sites active. We haven't enrolled our first patient yet, but we hope to have that happen very soon. This is a multi-targeted program that targets different targets on myeloma cells, including GPRC5D, FcRH5 and BCMA.

And the study design is similar to other study designs that you might expect from a Phase I trial, where we have multiple dose levels that we're escalating and then an expansion cohort to evaluate efficacy. We also have plans to expand on our T-cell engager program in other tumor types with other targets as well as looking at targets not only that are displayed by the cancer cell but also targets that are displayed by MHC.

And those allow us to target then the internal antigens that may not be expressed on the surface of the cell. So it opens up a whole new range of different targets that perhaps haven't been used in the past. And then lastly, I'll walk you through our cell therapy enhancing an in vivo cell therapy programs, so mRNA-4203. This is a collaboration with a partner called Immatics.

They've been an outstanding partner, and Ryan talked a little bit about this program earlier where they're seeing exciting results with their IMA203 program, which is a cell therapy program. One of the challenges, however, with cell therapy in solid tumors is that the cells are unfortunately not something -- don't have a long lifespan.

And so by administering an antigen through the use of a vaccine type approach, we can expose the antigen to these modified and engineered cells and therefore, make it more potent and durable and hopefully improve the clinical efficacy of IMA203. This study is open at a few different sites. We have patients that are consented and enrolled, and we hope to be able to present data hopefully, in the next year or two on this program. But it's an exciting new way to evaluate our platform.

And then lastly, another exciting new way to evaluate our platform is looking at in vivo cell therapy programs. So as Ryan mentioned with TILs, but also with other cell therapies, it can be very difficult to administer cell therapies to patients because it involves my ablation. It involves then engineering these cells with shipment, which is very difficult to manufacture and then reinfusion protocols by delivering an in vivo cell therapy, we can achieve similar results without the manufacturing challenges and without the toxicities of myeloablation.

Okay. That's a review of our oncology pipeline. And I think with that, we probably can go ahead and begin with questions both me and Dr. Sullivan and Dr. Pinato. Thank you for your attention.

QUESTIONS AND ANSWERS

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Great. Thank you so much. And a special thanks to Dr. Sullivan and Dr. Pinato for sharing their expertise with us. So we'll start with any questions from the room. (Operator Instructions)

Gregory Wiessner - *TD Cowen - Analyst*

This is Greg, TD Cowen representing Tyler Van Buren. Can you please elaborate on the mRNA-4359, PD-1 and IDO mechanism in particular in the flags outside the cancer cells? And how it is differentiated from the IDO inhibitors that did not succeed.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

I can -- do you want to go ahead? Well so the small molecule IDO inhibitors targeted the mechanism inside the cell for -- as you mentioned, reducing that cell therapy -- the T-cells from being active. Unfortunately, it wasn't very effective, but we target IDO in a very different way. We target it using cell -- a direct effect on the cell, either through reducing the T-regs, which helps with the immune evasion techniques or we use it also for T-cells to attack the cancer cell itself by using that as you mentioned, a flag, to directly affect the cancer cells.

So we're having a direct effect on the cell as opposed to an effect internally at reducing the metabolism from IDO. Anything you'd want to add to that?

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

IDO is a fascinating target, but I think if you think about blocking it from the perspective of its function, rather than using it as a flag to identify cells that have it or don't have it, I think there is still a lot that we don't know about how IDO really works enzymatically. There are a lot of other enzymes that, like IDO, support that process of depleting the T-cells from the nutrients.

And so as part of the failure of the old programs, I think we've been left with a lot of questions as to why, for instance, other enzymes could have overcome the blockage of IDO specifically. But with 4359, the mechanism is completely different. So we're not using IDO inhibition, but we're using IDO as a flag that pertain the characteristics of the tumor microenvironment.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Our next question?

Salveen Richter - *Goldman Sachs Group Inc - Analyst*

Salveen Richter, Goldman Sachs. I have a couple of questions for 4359, the discussion today mentioned that they -- or yourself that you need to see T-cell response at the tumor site to validate efficacy. Have you seen any data there or any early indications?

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

So my answer was relating to the fact that in a Phase I trial of this kind in an expansion cohort with limited patients, imagine having paired biopsies of pre- and post-treatment. Technically speaking, is what we would all want to have. But practically on an individual patient level, it's actually very difficult to prove those changes in the tumor microenvironment prior to and after treatment.

So it's challenging to rebiopsy the same lesion. It's challenging to also standardize the evaluation of the changes in the tumor microenvironment. And although I believe that this data are in support of the mechanism of action. Ultimately, whether or not a drug makes it and I put my own academic drug developer hat on is whether or not they actually change the natural history of the disease from a response perspective.

So I believe that those data are important. And together with Moderna, we're working on a lot of additional translational endpoints in the biopsy materials. Some of this will be presented at other meetings later on this year. But I do believe that the key differentiating factor is whether or not a drug of this kind is capable of shrinking the disease. That's an early indication. We did mention the IDO1 program, the old one.

I mean, drugs of the likes of Epacadostat, for instance, which was one of the IDO inhibitors, which unfortunately didn't make it, had a 0% response rate. So they didn't have any form of single-agent activity. So you can imagine that in absence of any surrogate evidence of the drug changes in natural history of the disease, it becomes very difficult to support the ongoing development.

Whereas, on the other hand, the biomarkers are absolutely interesting. They're very, very important. In this case, we have one that is perhaps placed at the early beginning of the patient's journey, which is PD-L1 status as opposed to the dynamic changes across different biopsies, which would also be very difficult to propose from a clinical perspective. I'm not sure?

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

I will share though that we have been asking patients to have biopsies because it is important. And so we have captured some tissue and that analysis is ongoing. So hopefully, we'll have some data, but as you mentioned, it's difficult for patients who don't have accessible tumors and even patients who might have really great responses, we no longer have tissue to be able to biopsy. So it's not easy, but we're going to try our best to capture that tissue and then analyze it.

Ryan Sullivan - *Moderna Inc - Director - Commissioning, Qualification and Validation*

And the only thing I'd add is, with all due respect to the question, not yours, but the question that was asked, the most -- we're not, I guess, to the discussion, the most important thing is do you actually have clinical benefit. So we've been able to show that if you -- I mean there's a 35-year history of tumor vaccination data that shows that you can immunize but not actually therapeutically advance -- the care of that patient.

So if you're actually able to immunize, that's great. If you're able to get the proof that the T-cells are in there, that's even better, if you're actually able to show that the tumors shrink in the setting of the therapy, that's actually more important. They're all important. But the end point is are what we're seeing clinically better than what we'd expect if we're giving pembrolizumab alone.

And so that's the question that's out there. In the absence of a randomized trial, all we can say is it looks like a higher response rate than we would expect if we were just giving pembro to those patients.

Salveen Richter - *Goldman Sachs Group Inc - Analyst*

And just a question on the INT program here. Can you speak to the mechanistic rationale for going after metastatic melanoma versus adjuvant melanoma? And also just given the number of programs you have ongoing, if you could give us a sense of the timelines beyond the Phase II, five-year data.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

Sure. So for INT, we've always wanted to explore the metastatic setting. And in fact, the 4359 data gives us more confidence in this approach for Intismeran. Now most people in the field have stated that this approach with antigen therapy is likely only to be effective in adjuvant settings because you have a very small amount of disease.

But 4359 taught us that it can be effective even outside of the adjuvant setting, and that gave us confidence that maybe Intismeran could be effective in that setting as well. I will also share with you that in our P201 study, we had patients who had stage IV disease, who did well on therapy with preventing their recurrence. And we had patients who had ctDNA positive disease.

And I would argue that they were close to metastatic as close as could be and still had benefit with clearance of their ctDNA. So that also gave us confidence that maybe we'd have activity in the metastatic setting and why we wanted to explore it further. So we're excited to see the results of that 012 study. And I'm sorry, you had another question, I think, right?

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

The Phase III readout in 2026, I think.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

Yes, 2026, yes, we'll get it next. And I wish I could give you an exact date on that, but unfortunately, it's an event-driven study, and we have to wait for the events to mature before we can run our first analysis. So I can't predict when patients will have their recurrence, and I hope no one does. Maybe we won't have a result until 2027. That'd be the great news for patients, right? But we're thinking the way events are tracking, it will be some time in '26.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Okay. Next question?

Martial Descoutures - *Oddo BHF SCA - Analyst*

Martial Descoutures, ODDO BHF. The duration of the response was not reached, however, could you give us maybe the first feeling on the trend that compared to the standard of care? And is it possible to come back on the nature and the persistence of the new T-cell clones receptor, what could we learn for the future on these aspects?

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

I'm not sure I followed the first part of the question.

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

So how -- if I understood correctly, how the duration of response for 4359 compares with the duration of pembro on its own?

Martial Descoutures - *Oddo BHF SCA - Analyst*

Yes.

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

Yes, so there is an advantage from adding not just on the response rate, but on the durability of the responses. I mean, to be honest, in the setting of rechallenge, when we rechallenge patients and I don't treat melanoma patients.

Ryan Sullivan - *Moderna Inc - Director - Commissioning, Qualification and Validation*

Yes, I can take that one. So in melanoma patients, mostly when you get a response, it can generally lasts -- not always, but the majority of patients, if you have a -- if you see a curve like this in the frontline setting or in the -- sorry, front-line setting or even second line setting with the checkpoint inhibitor single-agent or combo, if you see a response, it tends to look like this. That there tends to be durability.

Now not everybody's response tends to be durable, and this is going out certainly 1-year, 1.5-years for many of those patients. It's hard to know what to expect in years three through five or two through five. But I think it looks like we -- it looks like a melanoma response curve in patients who are benefiting from immunotherapy, which is a good thing.

I don't think that cheapens the impact of 4359. I think it sort of suggests that if you can trigger this response in a patient with melanoma, even if they're PD-1 resistant, you might be able to have that durable controlled disease.

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

What have you learned about the T-cell responses. Well, maybe we could move the following slide to the back to the graph. So what do I think when I see these graphs. So two things: First is whether or not there is a difference in people that have or don't have a clinical response. So looking at these curves versus these curves. And being mindful of the small numbers, we have to allow for the fact that these are exploratory analysis, so they're not definitive on hundreds of patients.

But I think it's very important to look at the trends and to look at what happens to these patients. So the T-cell clonality is a readout of whether or not there are existing clones or new clones. A new clone is expected if we think that there has been a new immunization in the patient. So if the patient's immune system has been exposed to something new that wasn't seen before because let's say, the cancer had their own ability to hide that information from the immune system itself, seeing an increase over time.

So we are thinking here is cycle one, two, seven, so over a protracted duration of time enables me to be more confident that what we are seeing is due to 4359 as opposed to pembrolizumab. So it goes back to your original question around the durability of responses. The vast majority of immunotherapy agents that we have, they work against what we call anonymous antigens.

So we know that something happens in the patient. We know that we announced the capacity of the immune system to see something, but what that something is remains a mystery and it can be different from one patient to another. When, however, you see a clonality -- a clonal response of zero at baseline, it means that, that patient did not have that capacity to recognize that specific stimulus, but then it becomes educated later on.

And that education can only really and truly come, especially in a patient that has been refracted to immunotherapy, stop responding before and can only really come if you give that instruction booklet to the immune system. Am I making sense? What is this making me learn about -- yes. This is, to me, is some of the most exciting data, to be honest, because it could be that these immunotherapy agents might not work the way we think they are.

But actually, presenting this data so early and also having done the experiments gives you a little bit more credence as to what is it that you're seeing because the responses are a blind readout. You know the cancer has shrunk, but you need to understand why. And I think this is actually particularly important.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

Maybe I'll also share my comments on this slide. From the T-cell-specific responses. If you look just at the patients who had partial responses, those are the purple patients, those patients all had T-cell-specific responses either to IDO or PD-L1. And you can see the increase in the purple lines. Now there were some patients who had stable disease or progression and still had the responses.

So I think that T-cell-specific response may be necessary for a response, but not sufficient. You can have T-cell responses but still have progression of disease. But what we're seeing here is that the patients who had partial responses had T-cell specific responses to the targets.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Great. I'll take some questions from online. Dr. Sullivan, you just spoke to potentially potentiating IO therapy in these highly refractory patients. Can you also speak to the safety profile of the combination of 4359 and pembrolizumab and if there's anything remarkable there?

Ryan Sullivan - *Moderna Inc - Director - Commissioning, Qualification and Validation*

It's a good question. I think the most important thing that we can -- there's a few different things you can look at with tox. Are you seeing additive toxicity that are independent of the two agents together. And then are you seeing synergistic toxicity. We're certainly seeing toxicity from 4359. It's injected intramuscularly, people's arms hurt, there's fevers, people feel a little ill for a day or two, but generally get over it pretty quickly.

And then there's the toxicity from anti-PD-1 and the rate, as Dr. Pinato mentioned, was about at least significant immune-related adverse events was about 14%, which is about the rate we'd expect with single-agent anti-PD-1. It certainly doesn't look like there's an additive immune-related adverse event or synergistic immune-related adverse event rate with the combination.

And ultimately, those are the toxicities that we worry the most about. You don't love that patients have a sore arm and are not feeling great for a day or two after receiving treatment. But that's very different than a combination therapy that dramatically increases the rate of colitis or pneumonitis or myocarditis or any of the other entities that we see and call immune-related adverse events.

So I would say that each agent causes toxicity. They don't potentiate the toxicity, but may potentiate the efficacy. And so if that's actually what's happening, that's an ideal combination for this because as much as an immune checkpoint inhibitors have transformed the way we treat this disease, one of the major issues that we struggle with is the development and the management of immune-related adverse events.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Another one from online. Dr. Pinato, you mentioned differences in follow-up between 4359 dose cohorts. What was the median follow-up for 4359 at the 400-microgram dose versus the 1,000 microgram cohort?

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

It was close to 20 weeks, if I'm not mistaken, the 400 micrograms, I think it's one slide earlier. We can -- one earlier again, there we go. So it is -- probably one slide earlier. There we go, yes. So the follow-up is here at the top of the table. So it's 22.5 weeks for the 400 micrograms and 10.4 weeks for the 1,000 micrograms. So that's the difference.

The overall median follow-up time is 20 weeks for the whole cohort. So when we're looking at the overall response rates, we should take into account the 20 weeks. But then when you look at the different cohorts, there is that difference.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Okay. And is there monotherapy overall response data for 4359? And can you recap that, please?

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

Monotherapy.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

We have not published that data. I believe have we published the monotherapy data? Oh, that was part of the ESMO presentation, yes. So the monotherapy data, which we don't have in this slide, but it's hard to interpret the responses because we had multiple different dose levels in that program, and we did not see any partial responses or complete responses in that cohort in those escalations.

But again, it did -- it enrolled a whole variety of different tumor types, including colorectal cancers and other cancers that maybe you wouldn't expect an immune therapy to have an effect on.

Ryan Sullivan - *Moderna Inc - Director - Commissioning, Qualification and Validation*

Well, there are definitely some stable diseases that lasted longer than we would have anticipated, particularly in MSS colorectal cancer.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

And for the key opinion leaders, can you remind us what you think pembro retreatment gives you for ORR in PD-L1 positive patients specifically?

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

As a single agent?

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

As a single agent.

Ryan Sullivan - *Moderna Inc - Director - Commissioning, Qualification and Validation*

In PD-L1 positive, there's zero data that's been presented or published or probably even been looked at in that population. We can say with good confidence that the anticipated response rate of single-agent anti-PD-1 after patients have had progression on an anti-PD-1-based therapy is less than 10%. And I don't anticipate that it would be substantially higher than that in PD-L1 positive patients. But there's actually no data on that.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

One other question from online, and this may be our last question. Can you speak to competitor data with a similar mechanism of action with a peptide approach and why they are seeing higher PD-L1 negative response.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

Yes, happy to do so. I think they're probably referring to the IO Biotech data, if I would take a guess, which will be presented on Monday. There's a couple of critical distinguishing factors between the IO Biotech data and what we've presented here with 4359. One is they're very different populations. So we're studying a refractory -- CPI refractory population, which is very different than the population that they're studying, which is a frontline patient population.

The other important factor here to consider is that they're looking at different endpoints. So their assessment was on a PFS endpoint, our assessment is on a response rate endpoint. And in fact, if you compare response rate to response rate, IO Biotech showed a higher response rate in frontline melanoma in the PD-L1 positive patients. So they actually had a similar type of efficacy that we've observed in 4359.

So I don't honestly think that they might be that different. But we'll see the response rate data on Monday, hopefully, they'll present that. And then the last thing I'll just mention, when you're comparing the two is that there's a different scoring method that was used between how we're scoring patients for PD-L1 positivity and how they're scoring.

So they use the MELD score for their Phase III study, and we're using TPS for our scoring method, which has some nuance on how you declare PD-L1 positive, and that could amount to some differences between the two.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Are there any differences between an mRNA approach versus a peptide approach?

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

Yes, for sure, there are differences. So we believe an mRNA approach is very effective at amounting an immune response for a couple of reasons. One, there's a natural processing of the protein that is created intracellularly that then is displayed on the surface of the cell. And I think that can mount a particular heightened immune response.

We also are seeing both the CD4 and CD8 response in our platform, and this is true for Intismeran that we published. We've also seen both the CD4 and CD8 response across our ID vaccine portfolio. So we would expect the same to be true for 4359, and I think that may lead to increased efficacy for 4359. Early days, and we haven't assessed the difference, the CD4 and CD3 population in our T-cell assessments, but we will be doing so. And I think -- I would expect we would see the same for 4359.

Lavina Talukdar - *Moderna Inc - Senior VP & Head of Investor Relations*

Okay. Great. And that exhausts all the questions, both online and in the room. I want to just thank our speakers, again, thank you so much, Dr. Pinato and Dr. Sullivan and Dr. Kyle Holen.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

Thank you, Lavina, and thank you all for coming.

David Pinato - *Imperial College London - Clinical Senior Lecturer in Medical Oncology*

Thank you.

Kyle Holen - *Moderna Inc - Head of Development, Oncology and Therapeutics*

We'll be around for questions.

Editor

Portions of this transcript marked (technical difficulty) indicate audio problems. The missing text will be supplied if a replay becomes available.
