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OVERVIEW:

Company Summary

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PRESENTATION

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Good morning, and good afternoon for those of you that are following us from overseas. Thank you so much for joining us today. On behalf of my colleagues and I, welcome to Moderna's Science Day 2026. Before I start, let me remind you that we'll be making forward-looking statements. You can find those online at your discretion.

Moderna's mission is to deliver the greatest possible impact to people through mRNA medicine. And since the beginning, we built an mRNA platform based on three key pillars of science: mRNA science, which is the mRNA molecule itself; delivery system, how we get the mRNA molecule into cells; and very importantly, also manufacturing processes where there's a lot of know-how that we developed over the years.

But because mRNA is an information molecule, what is very exciting about this platform is we can create modalities, families of medicine that use exactly the same technology features so that we can replicate very quickly. As you can see on the pictogram on the right, we basically start with a leading product to go into the clinic as a sentinel programs to learn about the modalities. And when we have clinical signals, we can scale very quickly because we use exactly the same technology components. And that's what is exciting about the platform.

And of course, you are all very familiar with three established modalities that we built over the years, an infectious disease vaccine modality with approved products, products under review and also products that are in the clinic. Intismeran modality going after cancer and a rare liver disease therapeutics modality, all coming from the same mRNA platform.

That established modalities is what we consider Horizon Number 1, is driving the business today and in the coming years. But of course, we're working hard with the team to invent the future. And today, we want to talk to you about Horizon 2, the modalities that are today in the clinic, dosing patients that we want to share with you some of those programs and what's coming next. And the other piece we want to talk about as well is Horizon Number 3, the future modalities that the team is working hard at that we believe should be testing in human by the end of 2027 in the next 18 months.

But we're not stopping there. David will also spend time talking to you later this morning about what we're doing with AI to keep learning faster and faster to invent the next generation and the next generation of modalities. And our AI strategy in science is based on basically two vectors. One is an mRNA technology vector that we will describe and talk about. And of course, there's a biology vector where we can leverage models that exist outside in the industry.

So in a minute, David and Rose will come up to talk to you about mRED. And then Kristine, Professor Church and Sarah will talk to you about the cancer-antigen therapy modality. We'll take a small break, and then we will come back. Lin will talk to you about our T-cell engager modality. Then Sumana will talk to you about our EBV therapeutics in multiple sclerosis.

Lin will come back to talk about in vivo CAR-T for autoimmune disease. And then David will try to wrap it up to talk about what are the exciting science he and his team are doing to invent the future modalities. I'll come back with a few slides to close and then David, Rose and I will take your questions.

So with this, let me turn over to David and Rose.

David Berman - Moderna Inc - Chief Development Officer

Thank you very much, Stephane. So I joined about three or four months ago. And I think today, you'll begin to see why I joined the company, why I'm really excited about the potentials here at Moderna. But first, why are we creating an mRED, Moderna Research Early Development?

The riskiest stage in the drug development continuum is the early clinical phase. And why? It's because we need to adapt to data that emerges quickly, number one. And number two, teams need to be able to stop drugs that are not going to work to accelerate drugs that have potential. And it's very hard in the traditional scheme for teams to do that on their own. And this is compounded when you have multiple layers of governance and levels between them and senior leadership.

So based on my tenure of working at four companies, two large pharmas and now two biotechs, I think there are two major levers that can be done structurally to enhance rapid innovation.

Number one here is creating an mRED leadership team, which is comprised of research, development and CMC. And by the way, we include CMC because mRNA and lipid nanoparticle science is evolving as rapidly as our biology understanding, and we need to have CMC at the table as well. But we're having this mRED leadership team with no barriers or connections. The teams directly report into the senior leadership.

And what this will do, as you see here, is it connects the senior leaders to the data directly. It allows us to accelerate decision-making that is fast, data triggered, and very clear with no guesswork by the teams involved. It ensures that we have a dedicated focus on bringing innovation in this next generation. And very importantly, it enables us to make science-driven decisions to accelerate where necessary, but also to stop drugs that are not going to be promising.

The second major structural element that should be done is to marry early clinical research -- early clinical trial development with research. And I think there are two major reasons why it's important to do this.

First, early clinical research is actually closer to basic science research. We're getting data based on patients. We need to interrogate the data, and we need to adapt based on what the data is telling us as well as external data. In late phase, you don't want to do that. You design a Phase 3 trial and you do not want to react and change rapidly in a rapid fashion.

The second reason, and I think this is inherent to the modality discussion that you heard is, we have these modalities with sentinel programs. And these sentinel programs are in the clinic, and you'll hear about them today. And these sentinel programs inform the other programs that share the same modality, whether it's T-cell engagers, cancer-antigen therapy, you'll hear about it today. And so it's very important to make sure that the science that the clinical insights we're making in early phase are rapidly translated into the research and vice versa.

The new insights we're making in research are embedded into the early clinical stage. So I think this mRED structure, which we are now rolling out will help Moderna accelerate where necessary, but also stop programs that are not going to be promising.

And with that, I'd like to call up Rose, who will talk more about the mRED portfolio.

Rose Loughlin - Moderna Inc - Executive Vice President - Research

Thank you, David. So we wanted to share a little bit of insight into how we actually craft this early portfolio. And so the first thing to say is that we want every asset in our pipeline to start out with a competitive advantage. So we, as a portfolio strategy, look for applications where the use of mRNA and LNP platform technology offers a competitive advantage to start. That helps us advance differentiated programs.

So for example, you'll see that we utilize multiplexing in our pipeline. And we specifically say multiplexing and not combination because from a regulatory perspective, we are able to encode and deliver multiple proteins in one therapeutic, and it's not considered a combination. It's considered one potential drug product. You'll see this in the infectious disease vaccines that we already have licensed, and you'll see it in our early pipeline today in the form of our T-cell engagers.

We also have an advantage in being able to express intracellular and transmembrane proteins, which, of course, are not truly accessible, for example, if you have a recombinant protein platform. Now you'll see demonstration of this already in our rare disease pipeline, which has advanced all the way through pivotal studies, but you'll also see it applied today for our in vivo CAR-T program.

And then, for example, on the T-cell response front, we know that our platform can generate very robust CD8 and CD4 T-cell responses. That's been well demonstrated through our INT, our individualized neoantigen therapy program. And you'll also see it today in multiple applications, both in oncology and now in autoimmune therapeutic space. So that's the first pillar of how we think about crafting the portfolio.

We also think about how we're going to get the most leverage out of the investment that we make in R&D. And so we look for modalities where we can see multiple follow-on programs where the learnings that David mentioned that we're generating in the clinic can help derisk those follow-on programs. That lets us get the best return on our investment.

So what you'll see is we'll start a modality. We'll bring an initial program into the clinic. We often use the term sentinel program for that first program. We learn about how our technology performs and whether the biology that we were hoping to access is performing the way we anticipated. When we see that, we feel like that modality is more derisked, and we're willing to advance more programs behind it at a faster pace.

And then finally, this is the pretty early part of the funnel for our pipeline. So we like to keep quite a bit of diversity and balance. So you'll notice that we have multiple different modalities that utilize different types of our platform technology and are also looking at different therapeutic applications.

And this is somewhat intentional. We want the very early part of the pipeline to also have uncorrelated risk in many ways so that we have multiple independent shots on goal as we're building the pipeline through that funnel.

So we won't talk through all of these modalities today, but to give you a sense, Horizon 2, these are the modalities where we have a program already in the clinic, generating that clinical data and moving toward clinical proof of concept. Horizon 3 that you'll see here is earlier. These are the programs that we're looking to take to first in human by the end of next year. And then while we don't talk about programs that are earlier than that, you will hear some about the technology that we're continuing to advance, and that's critical to make sure that Horizon 3 stays robust and diverse.

You can also see across Horizon 2 and Horizon 3, how we gate our investment. So in Horizon 2, in some areas where we've seen early encouraging clinical signal, we're willing to advance multiple programs in that same strategy, whereas in Horizon 3, we're typically looking at one sentinel program to move into the clinic, generate data, give us that confidence, and then we will bring in more programs behind it.

So with that, I'm going to hand it over to the brilliant, Dr. Kristine McKinney, who's going to talk about our cancer-antigen therapies.

Kristine McKinney - Moderna Inc - Vice President and Head, Cancer Vaccines and Bioinformatics Research

Thank you so much, Rose. And yeah, I'm delighted to be here today to share with you a little bit about the emerging cancer portfolio, including our Horizon 2 that are entering and in clinic. So yeah, my name is Kristine McKinney. I lead the Cancer Vaccines and Bioinformatics Research team here. And I'm going to walk you through a few of these cancer-antigen therapies. Sarah will also walk you through another one.

First two that we are developing in solid tumors, mRNA-4106 and mRNA-4200 as well as our first foray into the preventative space with mRNA-4194. Okay. So as Rose has been highlighted, we're very excited about the data coming out of the Intismeran program. We were really happy to share those -- the five-year update of the Phase 2 at ASCO recently as well as showcase some of the data demonstrating the depth and breadth of the immune response that this drug is able to inspire in the form of a translational poster.

And as Rose highlighted, this means that we've de-risked this concept, and we're investing very steadily behind it to make sure that we bring this technology to the greatest impact in patients.

And so just to orient you to how we're thinking about developing the next-generation cancer antigen therapies, I wanted to highlight that there are different opportunities in different tumors in terms of targets. And here in the red boxes are the ones we're going to talk about today.

I'm going to first start with the tumor-associated antigens. And just to reinforce that these -- this class of antigens are actually non-mutated, they're shared, and they are either misexpressed or overexpressed in malignancies. And so yeah, again, these constitute Horizon 2.

So to start off, let's talk about 4106 and 4200. And you'll see these design principles flowing through the entire portfolio. So I wanted to take a second to double-click on those, how we're designing these cancer antigen therapies.

So first of all, we are optimizing for population as well as individual level efficacy. Here, we're leaning into the aforementioned ability of our platform to multiplex. This really allows us to inspire the broadest immune response across broad populations. Second

of all, we're managing the biology risk. As I highlighted, there are different classes of tumor antigens, and we're really thinking about prioritizing validated antigens and optimizing for immunogenicity.

Third, of course, safety is first and foremost in our mind. We're making sure that we're safely exploring that design space, again, in a data-driven manner. And fourth, in order to enable the portfolio strategy that Rose walked through, we are enabling optionality. So we are including targets that are also expressed -- that are expressed in a wide variety of tumors that allows us the ability to expand into different malignancies should the data indicate that would be wise.

Okay. So now -- sorry. Okay. So just to talk again about the design and mechanism of action for 4106 and 4200. On the left, you'll see the hypothesized mechanism of action, which is the mRNA encoding the antigens that we select. These are multiplexed, are formulated into LNPs, which are then administered intramuscularly just like in Intismeran.

Those LNPs are taken up by antigen-presenting cells, translated, processed and presented on MHC Class 1s, which you see the little Y-shaped molecule that's sitting on the surface of the APC there. That serves as a signal to activate T cells in an antigen-specific way. So those are now armed to go find and kill tumor cells anywhere in the body.

Okay. So in particular, how do those design principles I just highlighted play out in 4106, so and 4200. So the targets are validated across many human tumors as well as we look at both expression in tumor tissues and normal tissues in humans. That is RNA protein as well as peptide presentation using immuno-peptidomics mass spectroscopy technology.

In addition, we generate preclinical data that confirm successful antigen processing and HLA presentation as well as immunogenicity in the particular -- once the antigen is formatted. And we -- and just to reinforce that we're using whole antigens here. So these are entire protein sequences that gives us many, many possible peptides that can bind across many HLAs across populations.

Also, these are multiplexed products. So we -- this, again, reduces the risk of tumor escape through single antigen loss as well as improves the coverage in case of intratumoral and/or inter-patient heterogeneity, really trying to cover a really broad space here.

In addition, they are applicable across multiple tumor types. So we have selected targets that are expressed in multiple tumor types. Again, as we de-risk and prove immunogenicity in humans as well as efficacy, we will be able to expand these rapidly into other histotypes.

So to show you how we're entering clinic with these. So 4106 entered clinic last year in a single monotherapy dose escalation. It's been progressing very well and without any safety findings. And 4200 is coming close behind. We are developing these two in tandem. So 4200 will enter and importantly, we'll leverage the data that we've generated in 4106 to start the monotherapy dose at a safe and efficacious dose. So we don't have to go through the whole dose escalation.

After the first dose, we will then combine with pembrolizumab in cycle 2 and continue dosing the combination. And of course, as all Phase 1, safety and tolerability are first and foremost, but we will also be exploring, of course, efficacy as well as immunogenicity in these studies.

Okay. Now to switch gears and talk a little bit about 4194, which again is our first foray into the prevention space. And in this case, these antigens are actually exquisitely tumor-specific, very much like Intismeran, but they are derived from frame shift mutations. And I'm going to talk a little bit more about the provenance of those antigens and why they come into play in the following slides, maybe.

Okay. And like 4106 and 4200, this has a similar mechanism of action. So the only difference here is that the mRNA is encoding frame shift antigens, right? So that the T cells that it activates are then activated to kill any cell that expresses a frame shift peptide. So that could be a tumor cell or importantly, a premalignant cell. And that really is the biggest difference for 4106, right, is that it's opening up the prevention setting.

So in order to help you understand the context of Lynch syndrome as well as the patient journey and what patients live through, we have the opportunity to hear Dr. Church explain that to you all. David Church is an esteemed collaborator. We're so lucky to have him on this program. He's really a world-renowned expert in this field.

He's a physician scientist with numerous titles at Oxford, which you can see listed here. But I think I really want to reinforce that he is a person who's not only pushing the technology and the science, but he's also making sure that those are integrated into clinical practice in NHS and has multiple appointments to do that in a regional way.

So without further ado.

David Church - Nuffield Department of Medicine, University of Oxford - Professor

Thank you, Kristine, for the kind introduction and the invitation to present on Lynch syndrome. My name is David Church. I'm a Professor of Precision Oncology at the University of Oxford, and I'm a Cancer Research UK senior Cancer Research fellow. In the next several minutes, what I'd like to do is talk you through Lynch syndrome, give you an overview, update you on epidemiology, how we diagnose it in the UK and its management and then cover the trial that we're really excited to be starting in partnership with Moderna.

So Lynch syndrome, is a condition that many of us have not heard of, but in fact, is a common condition. It affects more than 300 people globally, that's 175,000 people in the UK, more than 1 million people in the US. And at the molecular level, Lynch syndrome is caused by germline defects and inherited defects in one of several genes which are responsible for DNA mismatch repair.

This is a process that ensures our DNA is copied accurately when our cells divide. And the failure of that due to the defects in Lynch syndrome causes error-prone DNA replication. And errors in genes that regulate cell growth, cell death can lead to cancer. And so people with Lynch syndrome have a grossly increased risk of colorectal, endometrial, and other cancers, as you see in the schematic here on the right.

And also, as a consequence of that error-prone DNA replication, they're also prone to getting these stereotypical frame shift mutations. So mutations that change the sequence cause insertion to lesion encoding DNA and cause a frameshift and to novel open reading frame, which is important as we'll come to in a second. Management for Lynch syndrome relies primarily on surveillance with aspirin used by some people after the CAPP2 study to reduce the risk of colorectal cancer and possibly other cancers.

But coming back to those frame shift mutations, these are important, particularly as we talk about the clinical trial that we're starting because they can create potentially targetable source of cancer-specific antigens. These are predictable alterations, which are present only in pre-cancers and cancers and people with Lynch syndrome other mismatch repair deficient tumors.

So to focus on the epidemiology of Lynch syndrome, there are four main mismatch repair genes that are defective causing Lynch syndrome, MLH1, MSH2, MSH6, and to a lesser extent, PMS2, and then rarely deletions in EPCAM, which cause silencing of MSH2. And the cancer risk varies according to gene.

As you see here, the risk of cancer is highest in MLH1 and MSH2 carriers. This is reflected in surveillance guidelines. MSH6 carriers have a lower risk of these tumors and overall, but a particularly high risk of endometrial cancers for women that carry these variants. And you see here at the bottom, the takeaway, the lifetime risk of cancer, very high in these individuals. And clearly, despite surveillance, despite aspirin, a huge unmet need for reducing cancer burden in this at-risk and common population.

So recognizing the need to identify Lynch syndrome to reduce that cancer burden in this population over the last decade, we've put a number of steps in place in the UK to identify Lynch syndrome from cancer diagnosis and then more broadly.

Going back to 2017, NICE, the National Institute for Health and Care Excellence in the UK, recommended that all colorectal cancers were tested for Lynch syndrome using either immunohistochemistry, so protein staining for the proteins where the genes are defective in Lynch syndrome, or microsatellite instability. This is a genomic readout of mismatch repair deficiency and consequently potentially of Lynch syndrome.

And so we've been doing that to identify the 4% of colorectal and endometrial cancers or colorectal cancers that are caused by Lynch syndrome. In 2020, the guidelines were updated to also cover endometrial cancer. So here, the testing is only immunohistochemistry because mismatch repair deficiency caused by Lynch syndrome doesn't always cause microsatellite instability in endometrial cancer.

And in 2021, NHS England published guidelines to help clinicians streamline Lynch syndrome testing pathways as follows.

So we do reflex testing on all colorectal and endometrial cancers where the testing suggests that it could be caused by Lynch syndrome. The follow-on step is to do germline testing to see if there's a pathogenic variant present in the germline. And then if that's confirmed, the index case is managed by putting them on a national registry.

We now have more than 13,000 people on our UK registry of Lynch syndrome. They're registered for surveillance to reduce their colorectal cancer risk. And then after discussion with the index case, a cascade testing of at-risk family members with the intention of identifying them, hopefully before they ever get a cancer and preventing cancer in these at-risk family members.

Management of Lynch syndrome, we've covered some of it already, covers both colorectal and extracolonic cancers. It should be noted that at the moment, there's no evidence -- high-level evidence for screening for extracolonic cancers for people with Lynch syndrome. So we focus on colonoscopy, reflecting the different risk of cancer, colorectal cancer, MLH1, MSH2 carriers compared to MSH6 carriers have a different age of onset or recommend starting surveillance. But the recommendation in the UK is it's done every two years.

Aspirin based on John Burn's CAPP2 data shows that high-dose aspirin reduces the risk of colorectal cancer. The unpublished CAPP3 study, which is just about to be published, shows that actually the reduction in cancer risk is the same as low-dose aspirin, so opening up to more people with Lynch syndrome to take this and reduce their cancer burden.

For some people, risk-reducing surgery, both colorectal -- both the colon and also women who have completed their family may consider removal of the uterus tubes and ovaries. H. pylori eradication reduces the risk of gastric cancer and also lifestyle changes to reduce cancer-causing dietary and lifestyle factors.

So despite all of those steps, as we said, there's a huge unmet need to reduce cancer risk and cancer burden in people with Lynch syndrome. It's a common condition. And so we're delighted to be able to announce that in partnership with Moderna, we've developed and about to start this INTERCEPT-Lynch study.

So a Phase 1/2 study of novel Moderna vaccine for Lynch syndrome. This vaccine leverages the fact that Lynch syndrome causes predictable frameshift mutations, which are recurrent across cancers, colorectal, endometrial, gastric, ovarian cancers caused by Lynch syndrome share these potential vaccine targets. So Moderna developed a vaccine and was going to be opening the study to test it.

The study is divided into two parts. First part will test safety, tolerability, and define immunogenicity of the vaccine to identify two doses to take forward into the second part, which will focus on identifying whether the vaccine has evidence of activity in the tissues in which we want to see it. So just to look at the first part in a little bit more detail. This is a fairly standard dose escalation study with endpoints of safety and tolerability.

It will define two doses to take forward into Part 2. And then Part 2, people with Lynch syndrome who are scheduled for colonoscopies will be identified. And the final stage of the screening is to do the colonoscopy. And what we're going to do here is we're going to leave small polyps, adenomatous polyps, which we know are the subtype of polyps that become microsatellite unstable and develop the target frameshift that we're looking to target with the vaccine.

We'll be leaving those in situ, measuring them very carefully at baseline and then vaccinating at two doses defined by Part 1. And after 28 weeks, we repeat the colonoscopy. We remeasure the polyps to see if there's evidence of response to the vaccine and then the polyps are removed. And then the standard of care colonoscopy at two years will be done, and we'll also be looking for polyp burden at that time point.

So endpoint of the study, safety, and tolerability and then the secondary endpoint in Part 2 of the study is a percentage change in the MSI-high, the microsatellite-unstable adenomatous polyps post-vaccination. We'll be looking at immunology, both circulating and in tissue. And we're really excited to be starting the study imminently in Oxford with the second part of the study recruiting from additional UK sites.

And what's really motivating about this is not just the clinician engagement. We've had a huge interest from clinicians, but also directly from patients. I've presented the work leading up this study over the last three years to Lynch syndrome carriers at Lynch syndrome UK annual meeting. And since we released the press release putting out the study, there's been a huge amount of interest and had many e-mails from people keen to recruit, keen to participate in the study and also just commending us on the effort that we're making to reduce the cancer burden in this common condition.

So thank you very much for your attention. I'm really excited to take this study forward and look forward to updating you at a future meeting.

Kristine McKinney - Moderna Inc - Vice President and Head, Cancer Vaccines and Bioinformatics Research

Okay. So David, obviously, I would just like to underscore a couple of different pieces that he mentioned as well as tell you a little bit about the design of this vaccine.

So as we've discussed and David highlighted, Lynch syndrome carriers have polyps over time. And those polyps, over the course of their lifetime, can develop into microsatellite unstable cancer. So to design this product, what we did was take precancerous polyps and look with all of the same technologies I already highlighted. So protein expression all the way through presentation at the MHC level of the peptides from the frameshifts.

And we've also looked at MSI-high cancers from sporadic cases. So as the same genes that cause the germline defect and the germline sensitivity to developing frameshift mutations, those mutations can be acquired sporadically as well. And so we do find them in cancers that have no -- like did not have any germline susceptibility here. Those have a lot more samples.

So a lot more samples from the MSI-high cancers across different malignancies and across broad populations. And we compared the frameshift peptides that we saw expressed and presented in those cases. And we were able to find many, many that overlapped.

We selected specifically from that overlap to make sure that the cancer -- sorry, that the -- that 4194 would address all the relevant stages of disease, everything from polyp to frank malignancy. And in particular, we actually were able to incorporate 194, hence, the name, 4194, 194 different frameshift peptides into this vaccine. So we really have extremely broad coverage, again, not only intertumoral heterogeneity across disease, across histologies, and across populations.

Yeah, I think that's -- and then I also just wanted to take a second to pause. I know Dr. Church reviewed the Part 2 of the Phase 1 and how it's constructed in great detail. So I won't take you through all of the steps.

But I just want to highlight that this is quite an innovative design. And the goal here is really to make sure that we are learning fast, right? And that we are de-risking upstream of pivotal investments and that we can iterate in data-driven ways.

This sort of mindset is taken through all of the [cats] trials, and we're leveraging these ideas across the cat trials more and more leaning into the translational data because we know that if we can get this to patients, as Dr. Church said, they're hungry for it and they -- and this could transform their lives.

So with that, I'm going to pass off to Sarah, who's going to walk you through 4359. Thank you.

Sarah Keidel - Moderna Inc - Executive Director, Program Leader, Oncology Development

Hello. My name is Dr. Sarah Keidel. I'm the program lead for mRNA-4359. And it's my pleasure today to walk you through our program, including the exciting data that we presented over the last year at ESMO and earlier this year at AACR.

So going back to this cancer-antigen therapy schema that Kristine talked us through earlier, we're now going to be focused on the top right-hand side of the figure at the tumor-associated antigen therapies. So mRNA-4359 employs the same mRNA and LNP technology base as the other cancer antigen therapies, but applies it to immune evasion proteins. And importantly, 4359 is the first of our cancer antigen therapies for which we'll have the opportunity to really unpick that product concept, looking at the scientific and clinical data as they emerge.

So what is 4359? It is a lipid encapsulated mRNA-based cancer antigen therapy, encoding antigens of PD-L1 and IDO1. And these are proteins that are intimately involved with immune invasion by tumor. And we know that PD-L1 and IDO1 can be expressed by tumor cells, but importantly, they can also be expressed by immunosuppressive cells. And this gives 4359 a dual concept.

So not only can it have the potential to induce T cell responses to direct tumor cell killing, but it can also direct immunodepletion of the immunosuppressive cells that are protecting the tumor. And because this immune evasion mechanism is common to many solid tumors, it is possible that this product can be applicable across multiple tumor types, although we're starting with melanoma as a very rational first place to test the mechanism given the intended backbone of IO.

So you'll recognize this schema, this mechanism of action from the talk that Kristine gave earlier on the cancer-antigen therapies. And broadly, we have the same mechanism, but there is one point of difference due to the specific antigens that are encoded by the mRNA, the PD-L1 and IDO.

So kind of skipping through, you know that the protein is translated and they get expressed. The T cells that are specific to IDO1 and PD-L1 then get activated. These mature, they expand, they go into the circulation and then they enter the tumor microenvironment. And it's at this point where you get that potential of that dual mechanism.

So those T cell -- those tumor antigen-directed T cells will then look to destroy the tumor cells expressing these antigens and also those immunosuppressive cells also expressing these antigens. And so over time, we would expect a rebalancing of that tumor microenvironment to a more immune-permissive state.

Now this also gives us that impetus for the idea of the backbone of the checkpoint inhibition. So the idea of 4359 is that it really works as a target to induce those target-directed T cells. However, the idea of the checkpoint backbone is to release further brakes on the immune system to maximize the potential of the mRNA-encoded product.

So now to the data. On this slide, you've got our Phase 1/2 study design. We started off pretty typically with dose escalation and confirmation cohorts. And at the moment, we're in the Phase 2 portion of the study at dose expansion. We'll come back to that in a minute because what I'd like to focus on the next few slides is on arm 1b, which is our dose confirmation cohort in patients who are treated with 4359 in combination with pembrolizumab and who had checkpoint refractory advanced melanoma.

So starting with the ESMO presentation here. We've got here listed the patient disposition and the baseline characteristics for the 29 patients who are included in this cohort. They were treated at two different doses, but the main takeaway from this slide is that these were refractory patients. All of them were checkpoint refractory, and there's a median of three prior therapies with a maximum of eight prior therapies in this group of patients.

Now first and foremost, in this Phase 1 study, safety. So mRNA-4359 in combination with pembrolizumab demonstrated a manageable safety profile. The majority of adverse events considered related to mRNA-4359 by the investigator were low grade, and they comprise of injection site reactions and localized self-limited systemic adverse events such as fever, fatigue and also chills. There were no dose-limiting toxicities or grade 4 or 5 adverse events considered related to 4359.

Now switching to the pembro-related adverse events. These were very typical for the adverse events seen in the checkpoint inhibitors with irAEs. But the overall, what we saw from this cohort is that it looks possible to combine 4359 plus pembrolizumab without getting unexpected safety signals. And this is something that, of course, we're watching out for as we expand our Phase 1/2 study.

So here, we have the efficacy, and this is the part that really started to get us very excited. So what you'll see here on the left side of the slide is the efficacy table, and we're going to focus on all patients pooled across the dose levels.

So you'll see that we had 25 patients who are valuable for their tumor responses and 6 of these patients responded, giving us an objective response rate of 24%. We even had one complete response. The median duration of response was not reached for these patients, and our disease control rate was 60%.

So we're encouraged by these results already. As we mentioned, this is a heavily pretreated population, but we were really interested in understanding, are there any signals or any biomarkers that could help us point to which patients have a higher chance of response.

So on this slide, you'll see the spider plot looking at the tumor responses over time. And what we've done here is color through the patients by their tumor PD-L1 expression. So in the red, we've got the PD-L1-positive and in the blue, we've got the PD-L1-negatives. And what you can see really clearly here is that all the responses occurred in patients who were PD-L1-positive. And indeed, these responses were enriched in that PD-L1-expressing population.

So six out of our nine patients responded, giving us an ORR in this subgroup of 67%, which we were very encouraged by. But of course, we wanted to understand a little bit more who are these patients? Are they on the lighter end of the treatment spectrum? What's going on with them and what treatments have they had before?

So on this slide, we've got the six patients treated who responded on the -- in each row. And we've got their prior treatments listed in chronological order and including the disease setting as well as their best overall response to that drug. In addition, on the right for reference, you'll also see the results that they had on our drug in the combination of 4359 plus pembrolizumab once they came on to our study.

But I'd really like to focus on the middle part of this slide because looking at it to me, what I take from this is that these were a heavily pretreated group of patients genuinely. So almost all of the patients were treated previously with anti-PD-L1 monotherapy as well as IO combinations with nivo/rela or nivo/ipi. And half of them had prior exposure to TILs or TCR therapies.

In addition, when you look at the best overall response to each of these therapies, the majority of patients had the best response of disease progression to the majority of these prior therapies. And so again, these are patients that, in the real world, would have exceptionally poor prognosis and see any responses in this group of patients to us was encouraging, but particularly important when you look back at that spider plot that we had in the previous slide of the durability of those responses that we saw. So for us, again, very, very promising.

Last but not least, for this checkpoint-refractory cohort, we have the translational data. We are very interested in understanding, is there a proof of biology for this drug based on its mechanism of action. So on the left-hand side there, you'll see some ELISpot analysis looking at for the development of antigen-specific T cell responses between baseline and after treatment. And what you'll see here is that indeed, there was an increase in the PD-L1 and IDO-specific T cell responses in the periphery for the evaluated patients and that this was seen across best overall response categories.

On the right, we are then interested in looking at whether the patients develop novel expanded TCR clones once they're exposed to therapy. So again, looking from baseline and across the treatment cycles and as we go through the diagram, you can see that there, again, there is an increase in these novel expanded TCR clones after starting 4359 and pembrolizumab. And this does seem to be directionally higher in those patients with responses versus those patients with either stable disease or progressive disease.

So together, these data were important for us because it really helps to underpin mechanism of action. We see that proof of biology, and it helps us to understand some of the data that we're seeing clinically as well.

So based on these data, we expanded into another multiple treatment expansion cohorts. And so we're looking at a couple of first-line melanoma cohorts with combinations of checkpoint inhibitors. We have further expanded our second-line and beyond melanoma cohort, looking at those patients specifically for good reason, who are PD-L1-positive. We've also added a first-line non-small cell lung cohort in high PD-L1 expressers.

But I'm going to focus at the top at our arm 1/2a. And this was a small cohort treated with 4359 in combination with pembrolizumab in the first-line melanoma setting. And this is fully enrolled. We had results and these results were presented at the oral plenary for AACR a couple of months ago.

So here, we have treatment disposition at a median follow-up of 54 weeks. 7 of the 12 patients had discontinued treatment by that point, 2 because of progressive disease and 4 because of adverse events. 5 patients continued on therapy at this point. 4 had completed pembro under 4359, but continued their pembrolizumab. 1 patient remained on the combination side of the therapy because they were pretty early in these treatment cycles.

Here, we have the baseline characteristics, nothing particularly unexpected. The majority of patients had an ECOG performance status of zero. The disease stage of the majority of patients was four. About half of the patients had BRAF-mutated disease. And this is a small, but important clinically relevant cohort for us, which we'll come back to in a few slides' time. We had four patients who had prior exposure to neoadjuvant therapies, three of whom had immunotherapy exposure in the form of nivolumab.

So again, first, the safety. Here, you'll find nothing unexpected. These are -- I think a slide has gone missing. But yeah, needless to say, the 4359-related adverse events, they were all low grade in these 12 patients. The most common were those fevers, chills, pyrexia and fatigue, as you'd expect from innate immune activation after administration of an mRNA product.

Pembrolizumab-related adverse events, as determined by the investigators, were predominantly low grade. Most common -- I think that's just going to -- I'm so sorry. It looks like that's pembrolizumab, but that's the 4359. This is now the pembrolizumab.

So the majority of the most common adverse events were fatigue, nausea, increased amylase, diarrhea and pruritus as expected for anti-PD-1 monotherapies. About a third of patients had high-grade events, and these were pretty typical for immune-related adverse events that occur with checkpoint inhibitors. So again, based on a small number of patients, we're not seeing any signals that there are unexpected safety events occurring with the combination. But again, we continue to monitor carefully.

Now to the efficacy. Here on this efficacy table, we've got all the participants on the right-hand side. And in the middle, we've also looked at the subgroups by PD-L1 expression because based on the checkpoint-refractory data. We were very interested in understanding what happened by PD-L1.

So looking at all participants first, you'll see that 10 out of those 12 patients responded, including 2 patients with CRs. Median duration of response was not yet reached. Now looking at the small subgroup of patients with PD-L1 positive and negative expression, you'll see that we were very encouraged to see that there were responses across PD-L1 expression. So we had 2 out of the 3 patients who are PD-L1 negative who responded to therapy.

On this slide, we've got the swimmer plot showing the patient journey as they came on to the study. So we've got those 12 patients on the Y-axis. And just to orient you a little bit to the plot, the blue, dark shade is the treatment duration. The lighter shade is the period of follow-up. The blue and white triangles are the complete and partial responses the patients had and the red circles are the progression events.

And what you'll see here visually is that the majority of patients remain disease-free and in follow-up on the study at the time of the data cutoff. We had three progression events, two of which contributed to the PFS results because one of them, per the prespecified statistical analysis plan, was censored because of multiple missing tumor scans. The median duration -- the median PFS was not reached.

Now going back to that important small subgroup of patients who had prior neoadjuvant therapies. And these are the patients that are denoted by the asterisks on the right-hand side of the swimmer plot. There's those four patients. So what you'll see here is that three of those four patients had a response of either CR or PR, and these patients remain progression-free through the duration of the follow-up.

Now the reason this is important despite the fact that it is a small cohort is it starts to give us a sense that it may be possible to give 4359 in combination with pembrolizumab in the first-line setting with efficacy despite prior exposure to IO.

Now on this slide, it looks, in some ways, very similar to the one we saw in the checkpoint refractory disease with that spider plot. We've got the reduction in tumor target lesions over time. On the right-hand side and on the left, we've got the waterfall plot, again, colored by PD-L1 expression with the positives being in red. But the main point of difference that is quite striking on that spider plot compared to the one we saw earlier is just that the majority of patients here are responding. And again, that you do see those responses in the patients with PD-L1 negative disease.

What looks similar is the translational data. So here, we have the translational data from the first-line cohort. And again, we see biological activity demonstrated both by the development of IDO1 and PD-L1 specific T cell responses as well as de novo clonal expansion of those T cells. So again, very nice to see this based on the mechanism of action of the drug.

So in conclusion, we were very heartened by these data. We now have data that the combination of 4359 plus pembrolizumab. We have a manageable safety profile and also may have evidence of biological activity in these patients with both refractory melanoma as well as treatment-naïve advanced melanoma. In terms of efficacy, we saw durable responses in both. Of course, it was higher in the first-line setting, where we actually saw that it was regardless of PD-L1 expression, while the responses were enriched in the PD-L1 positive patients in our checkpoint-refractory disease.

So based on these data, as we mentioned, our Phase 2 expansion cohorts are ongoing, and they should help us to elucidate our strategy in terms of ideal treatment setting, in terms of our preferred combination partner and also in terms of our biomarker strategy. And we also are eagerly anticipating the results in the non-small cell lung cohort.

So with that, you've bear with me through a lot of data, but thank you so much for your attention, and we now break. Thank you.

Lin Guey - Moderna Inc - Chief Scientific Officer, Therapeutics Research

Hi, everyone. Welcome back. I have the distinct pleasure of telling you about a new modality we are creating within Horizon 2, specifically mRNA-encoded T-cell engagers against surface antigens.

And so T-cell engagers, as you know, are a well-established class of medicines with 10 FDA-approved products. T-cell engagers are a great demonstration of how we use mRED principles to build modalities. And so I'm going to walk you through our platform differentiation within those modalities, walk you through also about how we think about our sentinel, our first application and how that de-risks follow-on programs. And then also about how we think about the depth of the well, follow-on programs and diversification of the follow-on programs thereof.

Now unlike cancer vaccines, cancer antigen therapies, therapeutic vaccines, where we use our platform technology to train the immune system, specifically T cells to go and hunt their target, T-cell engagers, as you know, are bispecific antibodies that physically direct T cells to tumor cells to unleash killing activity of those T cells on tumor cells.

Now you probably know that T-cell engagers are conventionally recombinant antibodies. And you're probably wondering, well, what's our differentiation there. And so I'm going to come back to a point Rose and Kristine made, which is on multiplexing.

And so here for T-cell engagers, we really lean into our ability to multiplex. So in a single drug product, we have multiple messenger RNAs encapsulated in lipid nanoparticles. Again, that is considered a single-drug product. And we can encode, we can produce multiple T-cell engagers all at the same time.

Why that becomes advantageous is because we can go after multiple tumor targets and thereby overcome some known resistance mechanisms for given histotypes. So inter- and intratumor heterogeneity specifically and also antigen escape, which is a well-described phenomenon for certain histotypes.

On top of that, for T-cell engagers, we can think about tumor biology and really, again, resistance mechanisms and also include T-cell engagers that encode co-stimulatory molecules. So not only directing T cells to kill tumors, but also providing molecules to improve the fitness of T cells.

Now we're going to talk about the modality with respect to surface antigens, but we also are working on this modality beyond surface antigens against intracellular antigens as well. So for our sentinel application, we always try to minimize biology risk because this is the first time we're taking our platform technology into a new area. And so when we looked at T-cell engagers, the optimal sentinel application from our perspective was going after multiple myeloma, where you already have a bunch of clinically approved T-cell engagers and other T-cell engagers showing great antitumor activity in clinical development.

And so there, the thesis was we could encode multiple T-cell engagers all at the same time against clinically validated tumor-associated antigens, we use our technology. So we use our systemic lipid nanoparticle where we had a ton of repeat dosing clinical experience in patients with devastating rare diseases, over 80-plus patient years. And we leverage that technology for oncology. And I'm going to walk you through that sentinel application momentarily.

Beyond that, once we get an encouraging clinical signal from our sentinel application, we can learn and we've ungated and de-risked follow-on programs. And so here, our follow-on program, we wanted to move from multiple myeloma, a hematologic malignancy and really go towards solid tumors.

You probably know that the 10 FDA-approved T-cell engagers, eight of them are for heme malignancies and two are for solids. Solids have certainly been far more challenging. And we're up to that challenge. And we're excited about using our technology to encode not only the kill T-cell engager, but also provide that co-stimulatory signal to enhance T-cell function to have greater antitumor activity against solid tumors.

Now coming back to diversification within a modality and then broadly across the portfolio. I already touched upon our first application. We go after kind of what we know the signal should look like in myeloma in a liquid tumor and then venturing into ovarian cancer, where there are clinically validated tumor-associated antigens. And we understand some of the tumor biology resistance mechanisms, particularly around the tumor microenvironment and its hostile immunosuppressive environment.

Okay. So the sentinel application is mRNA-2808. And this sentinel application is a multiplex product. It encapsulates four different messenger RNAs that encodes three distinct T-cell engagers against clinically validated tumor-associated antigens. You recognize those antigens, I'm sure, BCMA, GPRC5D, and FcRH5.

Now our differentiation with respect to multiplexing also is because it's a single drug product, we don't have to show contribution of components for each of the T-cell engagers. And so if we were working on this with recombinant antibodies, we would have to follow a more traditional drug development path, where for each specific recombinant bispecific antibody, we would have to conduct a nonclinical program, manufacturability assessment, clinical development program for each T-cell engager and then combine them.

Because mRNA-2808 is a single drug product, we can advance this as a multiplex product, as Rose was saying, it's not a combination. It's a multiplex product, and we can advance it through preclinical, nonclinical, and currently, we're dosing in Phase 1/2. By the way, we haven't been asked a single question about contribution of components from the FDA. And I think that's incredibly exciting as you think about the multiplexing potential for T-cell engagers as a class of medicines for messenger RNA.

Now as I said, by multiplexing, we can overcome known disease biology and resistance mechanisms. And so for myeloma, we know that there is significant both inter-and intra-tumor heterogeneity. But also very importantly, we know that these antigens upon treatment can escape. They'll mutate and they will escape patients will stop responding.

And so by going after multiple targets, we should be able to overcome both the tumor heterogeneity, but also the antigen escape. And in fact, the investigators that we're working with are really excited about the potential here of going after these clinically validated tumor-associated antigens all at the same time.

Okay. So as you know, the first generation of T-cell engagers are really focused on what we call monoplex, so single target, single T-cell engagers. Of course, you have actually approved BCMA T-cell engagers and approved GPRC5D T-cell engager for multiple myeloma, and they are effective.

The second generation companies are starting to combine those T-cell engagers together. Sometimes they are separate T-cell engagers. Sometimes they are novel multi-specific antibody formats that can be difficult to manufacture. And you have a variety in clinical development and also preclinical development

2808, to our knowledge, represents the first time any drug product encodes three T-cell engagers all at the same time. And so the multispecifics that others are working on typically are focused on two tumor-associated antigens.

Here, we don't have to resort to a fancy multi-specific antibody format. We can use actually an antibody format that we designed specifically for ourselves, for our technology, and we multiplex. We can include multiple messenger RNAs so that we can encode very functional, very well-behaved molecules, all at the same time.

And so I'm going to walk you through some of the preclinical data that we showed at ASH about 1.5 years ago. First showing you that the 2808 encoded T-cell engager proteins are all incredibly potent. And so what I'm showing you here is in vitro data when we look at binding of the T-cell engagers to their respective targets. They are in nanomolar binding affinity. So these are very potent binders.

When we look at killing activity, cytotoxicity against the respective tumor cells that express their respective targets, we are in the picomolar range, so very, very potent. And then when we do a mix and match of the various tumor cells that have their respective tumor targets, as you can imagine, by multiplexing, by including multiple of these T-cell engagers, we achieved greater killing than simply going after one of these targets by itself.

Now importantly, for us, monkeys represent a highly translationally relevant species. And that's based on all of our platform experience in advancing different medicines from preclinical from monkeys to patients. And what we showed in monkeys was definitively preclinical proof of concept. where we took 2808 and we evaluated both single and repeat-dose administration studies in monkeys, both to assess pharmacology, but also we conducted repeat-dose GLP toxicology studies as well.

And what we're showing you on the left-hand side is that after a single dose administration, both intravenous administration and subcutaneous administration, that we see really nice dose-dependent expression of the T-cell engager protein. Now I'm just showing you one of the exemplary T-cell engagers. This is against GPRC5D. By the way, you can note the EC50 dashed line, that's from the cytotoxicity. That's how potent the molecule is. So we are well above what is therapeutically relevant even at these very, very low doses.

But what you'll notice from the protein expression kinetics is we actually don't hit the Cmax until about one to two days later. And that's exciting for us because if you think about how the T-cell engager field has evolved, as you probably know, they have shifted from IV administration to subcu. And that really was to flatten out the protein exposure curve because you were having CRS cytokine release syndrome that was a Cmax-driven event. So they flatten out the curve.

Well, we're excited because actually, our IV administration looks much more like a subcu curve from a recombinant protein. We're also excited because you can see from this plot, we can subcu administer 2808 as well. And in fact, we actually included subcu administration as part of our nonclinical program, and we intend to evaluate subcu administration in the ongoing Phase 1/2 study.

Okay. So on the left is we can make TCE protein at very therapeutically relevant levels. Now we know it's functional also because when we look at on-target pharmacology, specifically depletion of target expressing cells, specifically we're showing you here memory B cells. Again, these T-cell engagers are very, very potent. And so what you'll see is after a single dose administration, we have very significant depletion of target cells. This is only a single dose and the rebound is approximately two weeks later.

And so in monkeys, we've shown that we achieved good tolerability to enable the first-in-human study. We actually had a massive safety margin heading into the first-in-human study, that we can encode functional and therapeutically relevant levels of T-cell engager proteins of all three of them. And we've demonstrated on-target pharmacology. And so with that, we have an ongoing Phase 1/2 study in advanced multiple myeloma.

And so the patient population is relapsed and refractory multiple myeloma. They're triple-class-refractory, and so they've been exposed to proteasome inhibitors, immunomodulators and anti-CD38. We are currently in dose escalation where the primary endpoint, of course, is safety and tolerability. And our secondary endpoints include PK, pharmacodynamics and also antitumor activity, specifically response, duration of response, and progression-free survival. And so we are really encouraged with the ongoing Phase 1/2 study, and we look forward to presenting findings and results at an upcoming medical conference.

So with that, based on the encouraging signal that we've seen to date in 2808, we've actually un gated advancing our follow-on program, which is 2151 for ovarian cancer. And here, again, we diversify. We take more biology risk as we advance the follow-on program. And actually, the follow-on program, 2151, uses the same T-cell engager antibody format as 2808. And so with 2808 having that encouraging signal and being able to show repeat visibility, et cetera, safety, we can apply those learnings to 2151.

For 2151, is a similar idea to 2808. So it's a multiplex T-cell engager product, single drug product. It encodes in this case, two T-cell engagers that kill the so-called Signal 1. And these are against two clinically validated tumor-associated antigens for ovarian cancer.

Now when we looked at ovarian and solids in general, we thought it would be a good idea to include a co-stimulatory molecule as well, again, because of the hostile, immunosuppressive tumor microenvironment and also that many of these patients, unfortunately, as a consequence of that tumor microenvironment can have poor T-cell fitness and function.

And so in the drug product, we also included for the first time ever, a T-cell engager, a co-stimulatory signal, a Signal 2. And so 2151 combines the Signal 1, the kill, but also includes the Signal 2, the co-stimulatory. And I'm going to show you some preclinical proof-of-concept data that gets us really excited about the addition of the co-stimulatory molecule to enhance antitumor activity.

Now finally, I'll just note that by design, the antibody format, the molecules we're encoding, of course, messenger RNA being an information molecule, it's a very plug-and-play format. And so we're excited because we actually have a whole host of binders against other high unmet medical need tumor types where we can envision different Signal 1 and Signal 2 combinations going into higher unmet medical need tumor types and overcoming known resistance mechanisms and tumor biology.

Okay. So I'm going to show you some of the in vitro data first. So similar to 2808, these T-cell engagers for Signal 1, the kill T-cell engager, are very, very potent. So we're talking about picomolar, killing activity, cytotoxicity, and this has been shown in a variety of tumor cells that express high antigen levels, mid and low.

Importantly, the green is the Signal 2. And the Signal 2 molecule similarly is incredibly potent. So here, I'm showing you sub-nanomolar affinity for T-cell activation.

Now in vitro, when we look at both the Signal 1 cell and the Signal 2 co-stimulatory T-cell engager, we see enhancement of killing activity. And so the EC50 for the Signal 1 alone is shown on that dashed line on the upper right-hand side. And as we add concentrations of the Signal 2 co-stimulatory molecule, we can improve the potency, we can improve the killing activity for the drug product.

Now importantly, when we look in vitro, and we do repeat stimulation studies of the T cells with tumor cells. So we stimulate the tumor cells day after day. If you focus on the blue line there, that's just a Signal 1 T-cell engager. And day after day, stimulating those T cells, those T cells get more tired, more exhausted, more terminally differentiated, and they lose their ability to kill, which is what you see in the blue.

When we add the co-stimulatory Signal 2 molecule, you can see that we retain its ability to kill over time upon repeat stimulation. And that's because what we're showing on the other 2 plots is that those T cells have enhanced function. And so they proliferate better. They have better survival markers. They're just overall more happy.

And so we're excited with that in vitro data, but of course, we've taken this in vivo to various humanized xenograft tumor-bearing mice. Here, I'm showing you the OVCAR3 model, which is one of the kind of workhorses in the field.

The black line shows you just vehicle control. You can appreciate that these tumors grow out of control if these mice are not treated. The blue lines show you Signal 1 T-cell engager that kill T-cell engager alone. And so you have significant control of the tumor with the Signal 1 T-cell engager alone. But when we add Signal 2 in addition to Signal 1, that's exemplified in the pink and red there, that's when we start to see complete responses and really significant and durable control of tumor.

And so similar to 2808, we are administering this product intravenously, but we're excited about enabling subcutaneous administration as well. And so for 2151, the next steps are to complete the IND-enabling studies and also to initiate a Phase 1 study in 2027. We've had excellent pre-IND meetings to date, and we're excited to advance this to patients.

And so as I said, this is our T-cell engager modality against surface antigens. As part of Horizon 3, we're actually working on T-cell engagers against intracellular antigens. So these are antigens I get to that process and displayed on the surface of tumor cells with little parts, and they are HLA restricted. But there, again, we lean into our platform differentiation to multiplex. And we're excited because we should achieve broader patient coverage and also enhanced antitumor activity for that class of targets as well.

Okay. So with that, Sumana is going to walk you through our EBV therapeutic vaccine for MS.

Sumana Chandramouli - Moderna Inc - Executive Director, Program Leader, Infectious Disease

Thank you. Good morning, everyone. It's a pleasure to be here. My name is Sumana Chandramouli, and I'll be walking you through our mRNA-1195 EBV therapeutic for multiple sclerosis.

Epstein-Barr virus or EBV is a very prevalent human herpes virus. It is associated with many serious diseases. And this starts with infectious mononucleosis when EBV is contracted in early adolescents or young adulthood. And then it can -- it is -- EBV is one of the first human oncogenic viruses that was identified. So it is positively linked to several cancers such as lymphomas, Hodgkin's, Burkitt lymphoma, nasopharyngeal carcinoma, and also certain forms of gastric cancer.

On top of that, there is emerging evidence and strong evidence that links EBV to several autoimmune conditions, including multiple sclerosis or MS. That will be the focus of the talk today. And in immunocompromised patients and persons, it can also cause several diseases such as post-transplant lymphoproliferative disorder, or PTLN, in transplant patients and chronic active EBV.

The underlying complexity of the virus and these diseases and the diversity of the biological mechanisms require not only prophylactic intervention, but also therapeutic intervention to address all of these. And we believe that the unique advantages and attributes of the mRNA platform allow us to address these from all angles.

So taking a deeper look at EBV and multiple sclerosis. Multiple sclerosis or MS is a devastating neurodegenerative disease that affects predominantly women in the prime of their life. It can then lead to decades of progressive physical and cognitive disability that can be crippling in every sense of the world.

For many, many decades, people have been looking at the causative agents behind MS. There's nearly 1 million people with MS living in the US today and many millions more worldwide. And the emerging evidence from looking at the data over many decades is that EBV seropositivity and a prior infection with EBV seem to be very strongly linked to a risk of developing MS later in life. This translates to an almost negligible risk of developing MS if someone is not ever exposed to EBV.

All of this was recently summarized in a landmark study that was published a few years ago now in science that showed that quantified this risk to be a staggering 26- to 32-fold increase in risk of developing MS following EBV exposure. That is shown in the graph on the left.

The graph on the right shows something additionally interesting, which is that on top of the risk that comes from just having EBV infection, there is an additional two to threefold increase in risk of developing MS if there is a history of infectious model. So this indicates that the virus starts manipulating the immune system quite early on as soon as it encounters the body.

So EBV is a tricky virus. It's a herpes virus. So as soon as it enters the body, it stays there for the rest of the life of the host. It bounces between forming active viral particles, which is known as lytic replication and going into a very quiet immune evasive state known as latency. And it goes into a latent state in the B cells of the immune system.

So what we understand from seeing healthy people, because EBV is so seroprevalent around the world and most of the exposed people are still healthy, is that the immune system uses both arms and antibody response that actively prevents EBV replication and infection of new cells and a very strong T cell control to maintain control over the latently infected EBV cells. So from that was born the concept of mRNA-1195.

The composition of mRNA-1195 consists of six mRNAs, four of them, gHgL, gp42, and gp220 are glycoproteins that are known to be the primary targets of neutralizing antibodies on the surface of the virus. These will prevent the virus from infecting naive B cells and epithelial cells.

Then we've also added in engineered forms of two latent antigens. These are a group of proteins that the virus uses to maintain its latency and to remain latent in the B cell compartment of the body. So we've included engineered forms of EBNA3A and LMP2B,

which are key latent proteins that the virus uses to propagate latency. We are starting out with testing this in multiple sclerosis because we believe that immune dysregulation, often by EBV, may be one of the underlying mechanisms that EBV uses to not only trigger the disease, but also to drive it forward.

We also envision that other conditions like PTLD that might require a combination of antibody and T cell responses in order to prevent the condition from occurring might also benefit from this composition.

So we started out by testing mRNA-1195 in healthy seropositive adults, and we wanted to de-risk the immunogenicity of the product before going into the vulnerable patient population. So the Phase 1 Part A was designed as a randomized observer-blind, placebo-controlled study. We tested different ratios of the antigens in order to get the ratio right.

So we have two different compositions of mRNA-1195 in this trial. We also included our mRNA-1189, which is a prophylactic vaccine for EBV against infectious mono that we are developing. We use that as a comparator to understand the interplay between the different antigens between the latent and the lytic antigens we've added in, and there was a placebo group as well.

We -- of course, the primary objective of the study was to look at the safety and the reactogenicity of this candidate. And then we were also going -- we also looked at the humoral and cell-mediated immunity and the impact on EBV shedding.

So to share some of the early data we have here, this is the reactogenicity profile of mRNA-1195. As we can see from -- as we can see, the top panels show the local reactogenicity and the bottom panels show systemic reactogenicity. The shades of blue are grade 1 and grade 2, very fast resolving reactive symptoms and very, very low levels of grade 3 were detected.

So overall, mRNA-1195 was well tolerated with an acceptable safety profile. We then looked at the immunogenicity of this candidate. So here, we are looking at the binding antibodies to the glycoprotein components in the -- in this composition. So that's gHgL, gp42, and gp220.

Just to orient ourselves, the gray bars that go through the middle of these graphs are the baseline responses to natural infections seen in these seropositive individuals as they come into the trial. The line in black is the comparator mRNA-1189 that contains these glycoprotein antigens as well. And then in the shades of yellow and red are the different dose levels of mRNA-1195.

So a few things are immediately obvious when you look at the curves here. The first is that compared to the placebo, there is a significant boost in the binding antibodies following just a single or two doses of mRNA-1195 in this population. This is then sustained by the third dose, and we can see these responses maintained well above baseline out to six months after the last dose, which is the last time point in the study.

There was no pronounced dose response as we can see all of the yellow curve -- yellow and red curves are overlapping with each other as well.

Then looking at the functional antibodies. So the B cell neutralizing antibodies would be preventing the infection of EBV into B cells and the epithelial neutralizing antibodies are doing the same, protecting epithelial cells from incoming EBV. So here, what we see is that both -- all of the tested dose levels of mRNA-1195 and mRNA-1189 are able to boost significantly the neutralizing antibody response to both B cells and to epithelial cells.

The B cell nABs are considered the more relevant ones here because we are primarily studying B-cell biology-related diseases. And we did measure that all the way out to day 337, which is six months after the last dose, and we can see that the neutralizing response is well sustained above baseline.

This is an exciting piece of data we would -- we are also excited to share here, which is looking at EBV shedding and saliva of these seropositive individuals. So as EBV bounces between lytic and latent replication over a lifetime, any given moment, multiple --

majority of the EBV-infected people will be shedding EBV in their saliva. And this is shown in the gray bars in the top panel that is the average -- the genome copies of EBV DNA in saliva in placebo recipients.

And what becomes apparent is that as soon as a single dose of mRNA-1195 is given, we can see that this drops in that group and is sustained all the way through the end of the study. This is similar to what we had presented previously with mRNA-1189 as well, where we see this rapid and sustained suppression of EBV shedding in saliva.

The bottom graph is a different way to look at the data, which is to look at, at any given time, what is the percentage of individuals with detectable DNA in their saliva. This gray bar is, again, represents the placebo group and the black and the orange are mRNA-1189 and mRNA-1195. And again, we can see that as soon as either of the mRNA compositions is given, there is a rapid and sustained reduction in the frequency of individuals that are shedding over time.

As we mentioned earlier, the T cell responses are just as important in this case because the surveilling T cells are what keeps the latently infected B cells in check. So we looked at two different types of T cell responses induced by mRNA-1195. These are the CD8 T cell responses.

And what we observed is that unlike the placebo group, we can see a nice boost and sustained increase in CD8 T cell responses to the two latent antigens, which are shown in the top panels, EBNA3A and LMP2B. And in the bottom, we also observed that there were very strong CD8 T cell responses to the glycoprotein antigens -- antigen gH.

Again, we didn't see much of a dose-specific response, and we also see that these responses were sustained through the end of the study.

This panel here now shows the other type of helper T cells, CD8 T cells -- sorry, CD4 positive T cells. And again, we observed a nice boost in sustained response to both EBNA3A and gH following mRNA-1195. And this is sustained through the last time point in the study.

We are now continuing our Phase 1, knowing what we know about mRNA-1195. We are now continuing with a second part to the Phase 1. Now we are testing it both in seropositives with additional dose levels and also in seronegatives, trying to plan for the future for indication expansion as we go forward.

And we also have mRNA-1195 now actively dosing in our proof-of-concept multiple sclerosis study, P201. This is a randomized, observer-blind, placebo-controlled study, where we are again looking at the potential impact that mRNA-1195 might have in people that are living with MS, and we are looking at various time points.

In addition to safety and reactogenicity, we are also looking at the impact of mRNA-1195 on MRI markers of MS disease activity and other clinical markers as well and also looking at the humoral and cell-mediated immunogenicity in this population.

I'm very happy to share an update on this study, which is that we fully enrolled our sentinel cohort of 12 patients. And the DSMB has reviewed the safety data and has given the recommendation to proceed with the dose escalation Phase 1 in this study.

So in conclusion, we have learned through our Phase 1 data so far that mRNA-1195 is generally well tolerated and we are continuing with our Phase 1 and Phase 2 studies.

In the immunogenicity realm, we see that mRNA-1195 is able to strongly boost both B-cell and epithelial cell neutralizing antibodies, binding antibodies, CD8 positive and CD4 positive T cells. We find this very encouraging and the immune responses are sustained for well over six months after the last dose.

And we also, again, were able to demonstrate that mRNA-1195 is able to reduce measurable viral shedding in saliva, similar to our mRNA-1189 composition. We are continuing with our Phase 1 data. We expect data -- sorry, we are continuing with our Phase 1 trial. We expect data coming up soon, and we'll also have data from our proof-of-concept MS study in the future.

With that, I'll hand back to Lin to talk through our in vivo CAR-T program.

Lin Guey - Moderna Inc - Chief Scientific Officer, Therapeutics Research

Thanks so much, Sumana. So I have the pleasure of walking us through an emerging modality we are advancing as part of Horizon 3, which is in vivo CAR-T more broadly in vivo T cell therapy.

And so in contrast to the modalities that you've heard about today with our therapeutic vaccines, again, intravascular administration, we encode in antigen-presenting cells, and we train the immune system to go and hunt and find their target in contrast to T-cell engagers, where we encode multiple T-cell engagers to physically direct T cells to their tumor targets and also provide co-stimulatory signals.

Here, we are directly engineering T cells in a person's body in vivo. And so the technology here, our messenger RNA encapsulated in targeted LNPs targeted to direct preferential uptake into those T cells. And the sentinel application here is focused on deep B-cell immunity reset for autoimmune diseases.

And so you probably know that many autoimmune diseases have B cells playing a central and pathophysiologic role with respect to pathogenesis. And the unmet medical need remains high. And so you often have patients cycling through various standard of care, broad immunosuppressants, sometimes targeted biologics, specifically anti-CD20 monoclonal antibodies as an example. Those targeted biologics, as you probably know, do not deplete B cells in tissues as well as they do certainly in the blood.

And the emerging ex vivo CAR-T, autologous CAR-T experience for various late autoimmune conditions has been incredibly exciting, showing that those patients can achieve durable remission and deep B-cell depletion along with an immune reset. And so the ex vivo autologous CAR-T field for autoimmune is emerging with over 400 patients dosed to date and about 270 total years of clinical experience.

What we're really excited about for ex vivo CAR-T as well is by going after deep B-cell depletion in blood and tissues to achieve that immune reset, what we deem are encouraging signals across a variety of autoimmune conditions.

So you can see here for lupus, for myasthenia gravis, for scleroderma, myositis and so on and really encouraging rates of durable remission. Now the durability in particular, remains to be seen. The data is still emerging. But so far, it appears that the results are quite durable, about half year to a year plus. And importantly, the dose, as you probably know, is lower than what is typically required for oncology ex vivo CAR-T.

The persistence of those T cells, in particular, seem drastically shorter for autoimmune patients than what's observed for oncology. And so in autoimmune patients, they typically persist for several weeks versus in oncology, you will typically see them last for months up to several years and correlated with clinical outcomes.

Now what's been incredibly exciting as well as the tolerability with low-grade CRS and neurotoxicity observed across patients and really manageable tolerability, particularly with respect to infection risk, which is an on-target pharmacology consequence.

Now for ex vivo CAR-T, as you know, that whole process is complicated and costly. And so the manufacturing is incredibly complex. You have to take blood out of a person's body, engineer them ex vivo with a virus. And then to get them back in, you have to make space with harsh preconditioning. There are only specialized academic centers that can really realize this entire process for patients and the entire process is not scalable and quite costly.

Compare and contrast that to in vivo, which is an off-the-shelf approach to engineer T cells directly in a person's body. You do not need to lymphodeplete. You do not need to do the harsh preconditioning regimen. The field has been showing that quite definitively, which is really exciting. And because it is off-the-shelf, you're doing this in a person's body, it is scalable.

And additionally, it is transient, which confers tolerability aspects, attributes for this drug product.

And so in vivo CAR-T, in contrast to ex vivo CAR-T, where you have a single dose administration and those T cells kind of persist for several weeks, we think with in vivo CAR-T with transient expression of those CARs in T cells, we can give a limited number of repeat dose administrations. And with a concomitant deep B-cell depletion in blood and tissues, we should see a concomitant decrease in disease activity, hopefully resulting in durable remission.

Now when those B cells reconstitute or rebound, as you know, the immune system has been reset, and so they will reconstitute with a naive phenotype. And so this modality exemplifies another area in which we take mRED principles to build not only the sentinel application, which has huge value for patients across many different autoimmune conditions, as I just showed you, but also take the same technology and apply it in other aspects that we can go into such as oncology and T cell reprogramming.

So we are advancing our lead nominated candidate, 6007 that we affectionately call 007. And we selected this based on comprehensive screening of various targeted LNPs, optimization, and preclinical evaluation. It's built on the foundation of our platform, which we have extensive experience, both from a clinical perspective and manufacturing. And the LNP, the base particle that we use for the targeted LNP is actually the same LNP that we use for T-cell engagers for our rare disease programs as well.

Now we actually had screened multiple base particles to evaluate them actually in monkeys before selecting this base particle. But just to reiterate, this is an LNP where we have 80-plus patient years of repeat dose clinical experience in patients. We understand the safety profile. We understand the repeat-doseability. And importantly, we know how to manufacture and scale this particle.

Now, the LNP has to be decorated with a targeting moiety to really facilitate and preferentially drive its uptake into T cells. And here, the targeting moiety is a single domain antibody binder that was internally discovered and humanized, and it is decorated on the surface of the particle using a validated linker chemistry.

The payload itself, we lean here again into our platform differentiation to multiplex. So we have a dual CAR approach, but we use clinically validated CAR architecture. And here again, we can encapsulate multiple mRNAs without having to show contribution of components.

Now 007 is our sentinel application, as I said, I'll walk you through some of our really encouraging preclinical data, and we are advancing this rapidly into the clinic, where we will evaluate a basket of B-cell-mediated autoimmune conditions, including lupus, but other autoimmune conditions as well.

But beyond that, we're taking the same targeted LNP because it gets into T cells, and we want to explore applications for oncology as well, using both mRNA transient payload, but also working on gene insertion so that we can have integrating technology as well.

Beyond that, the team is kicking around clever ideas with respect to T cell reprogramming and what we can do broader with this targeted lipid nanoparticle.

Now our points on differentiation for in vivo CAR-T are twofold. Number one is on the platform in manufacturing; and number two is on the product. On the product -- on the platform in manufacturing, the platform is built on validated technology. So we have extensive experience, of course, with the messenger RNA.

I will note that the messenger RNA includes a chemical modification on the three prime ends of the molecule to extend the half-life of messenger RNA. So we have greater exposure, greater half-life of the encoded CAR.

The base particles, as I already mentioned, has tons of clinical repeat dose experience, and we have extensive manufacturing experience of that base particle. We have a proven global health authority regulatory strategy where we know how to take platform nonclinical studies and apply them across the board for our portfolio, including this program.

And as I already highlighted, we have extensive know-how and knowledge on manufacturing. And this includes both scale-up processes, phase-appropriate control strategies, and an infrastructure that enables end-to-end manufacturing with the long game with getting this to patients in mind. Okay. So that was point number one on differentiation with respect to platform and manufacturing.

Point number two on differentiation of the product. And so 007 actually targets CD7 on T cells. Now the rest of the field really primarily focuses on getting into CD8 T cells. We think we're differentiated because CD7 gets you into CD8s. They get you into CD4 T cells, which we know are important for oncology, and they also get you into NK cells, which have cytolytic potential.

And so we think because CD8s are not necessarily a sync for us, we can get into CD8. I'm going to show you that data momentarily, but we also get into other immune effectors. We think that is advantageous for this product.

The other differentiation on the product, again, comes back to multiplexing, where we are not encoding a single CAR, we are encoding two CARs. And so it's a dual-CAR approach. And by targeting two different antigens, we can cover not only the entire B-cell lineage, but also plasma cells, which are implicated in many autoimmune conditions. Specifically, they are responsible for the generation of pathogenic autoantibodies for many of these diseases.

And so -- but we think by targeting a broader immune effector cell population, in addition to the dual-CAR strategy, we should achieve greater biological performance, greater reset and hopefully, durable remission in patients.

Okay. I'm going to walk you through some of our preclinical data, starting with humanized mice. And so this is a CD19 CAR messenger RNA encapsulated in that targeted LNP. Here, we are doing IV administration once every few days, 3 times. And I'm showing you data in spleen after the second dose, but the data are very similar after the third dose.

And what you'll see on the left-hand side is we see really nice dose-dependent expression of the CAR in both CD8 T cells, but also CD4 T cells. And we know those CAR-Ts are functional because if you look at the B cells on the right-hand side, they're completely gone. And they're completely gone at all dose levels evaluated.

Now importantly, we have taken the product into monkey studies, several monkey studies, where for us, again, monkeys are a highly translationally relevant species. Again, that's based on our experience in advancing different medicines from monkeys to patients. But also the field has shown translatability as well using monkeys.

Here, we do use a surrogate CAR CD20 and not simply because the binder is cross-reactive with monkeys. And we have demonstrated reproducibility and consistency across lots in these monkey studies.

And so what I'm showing you here is first, the safety and tolerability of the CD20 CAR messenger RNA packaged in the targeted LNP. These monkeys received three IV dose administrations every three days and importantly, received no pre-treatment. So no dexamethasone, no diphenhydramine. We wanted to understand the safety and tolerability profile of the targeted LNP by itself. And the dose levels we evaluated were 0.5 and 1 milligram per kilogram.

And so with respect to safety and tolerability, we've been really encouraged. As you can see here by the liver enzymes, the gray shows you what's normal for monkeys. So we are well within normal. By the way, we have two controls, a vehicle and another messenger RNA control, which is simply a reporter messenger RNA control.

Beyond that, the clinical pathology also looks very clean, uneventful, clinical observations great. Again, these monkeys were not pretreated. So again, happy with the safety and tolerability profile.

Let's come to delivery. So we focus on our reporter messenger RNA here, which is GreenLantern -- it's essentially GFP. And I'm showing you data from GreenLantern versus the CAR because GreenLantern is a more stable protein, and with CAR, you have trafficking and kind of the kinetics of CAR pharmacology.

And what I hope you can appreciate from all these immune effector populations is we get great delivery. This is two days after the last dose administration in blood and various lymphoid tissues.

You can see in blood, we are in the approximate 80% plus range in CD7-positive immune cells. And in the various lymphoid tissues, we see really great uptake in various immune effectors in these lymphoid tissues as well.

Now when we look at pharmacology, so first, I'm going to show you blood, but then I'll show you B-cell depletion in lymphoid tissues. When we look at blood, I hope you can appreciate, so the vertical gray lines show you the dose administrations. We see rapid depletion of B cells in blood in comparison to the control groups that you can see in gray and green.

And we wanted to show you exemplary flow cytometry plots here just to show you how comprehensive the gating is for capturing the B cells. And I hope you can appreciate the CAR-treated animals, again, in the pink and red, B cells are completely gone, not detectable in the FACS plots, and when we look at counts completely gone and remain gone after each dose administration.

Now as we talked about, okay, blood is great, but it's all about lymphoid tissues. So two days after the last dose administration, we look at lymphoid tissues.

So starting with spleen, I'm going to show you immunohistochemistry against CD20 in these various tissues. And you can see in the control arms, you see really nice staining of CD20. You see nice follicles, you see really pronounced staining. And in all of the treated animals at both dose levels of 0.5 and 1 milligram per kilogram, in spleen, we see complete B-cell depletion. So not detectable at all, no brown spots whatsoever.

In lymph nodes and here, we looked at a variety of lymph nodes. In the control again, really nice staining of CD20. And in the treated animals, we see substantial B-cell depletion across the various animals across the various lymph nodes.

In bone marrow, similarly, we see CD20 staining and upon treatment, complete B-cell depletion in bone marrow. And so with that, we've demonstrated proof of concept, pronounced B-cell depletion in blood, lymphoid tissues, excellent delivery and uptake into NK cells and T cells, and acceptable safety and tolerability to advance this asset forward.

Now I'm also going to show you some cytokine data as well. So we evaluated really the full cytokine and chemokine panel. And what you can see here is the usual suspects for CAR-mediated cytokine induction do spike up transiently after the first dose that is on-target pharmacology that attenuates upon subsequent doses.

And just to remind you, these monkeys are not pretreated. And so interferon-gamma, IL-6, TNF-alpha definitely spike as a result of on-target pharmacology. Again, we looked at the full panel of cytokines and chemokines, saw nothing concerning, very consistent with our platform, data and knowledge of repeat dosing LNPs.

And so again, we get really excited when we see data like this in monkeys because of our experience in translating these products from monkeys to patients. And we're also really excited here because that binder that I told you about that decorates the base particle, our anti-CD7 single-domain VHH binder is actually a very weak binder for monkeys. And so actually, by monovalent format, it is not detectable for binding to monkey CD7. We can only detect it weak binding when it's in a multivalent format.

It has been optimized and was selected for human performance. And so it is a very tight binder to human CD7. It binds at sub-nanomolar binding affinity. And when we look at T cell uptake in vitro, so in PBMCs from human versus (inaudible), we see an 18-fold increase in the potency and the uptake into T cells in humans versus humans.

Moreover, when we look at the expression pattern of CD7 on sino immune cells versus human immune cells, we see far greater expression of CD7 on normal healthy donors in addition to PBMCs from autoimmune patients as well.

And finally, as you probably know, monkeys tend to be more CD8 skewed than patients. And so with our targeting approach getting into CD8, CD4s and NK cells, we are excited about the potential of the pharmacology we may observe in human patients that have been likely underestimated from our monkey studies.

And so with that, we are completing our IND-enabling studies. We are conducting a series of pre-submission health authority engagements, and we plan to advance this program into the clinic in 2027. And we're super excited about this modality.

So with that, I'm going to pass it over to David Huss, Chief Technology Officer of Research, who's going to walk through platform innovation.

David Huss - Moderna Inc - Chief Technology Officer, Research

Thank you very much, Lin. As Lin mentioned, my name is David Huss. I am responsible for our platform science organization. So I hope that you can appreciate through all of the talks we heard this morning on our therapeutic programs that there's really a common thread that goes through all of them. And that is that they are each built on a unique combination of Moderna's platform technologies.

Now one of the reasons that I'm standing in front of you today is because I firmly believe that our best technological innovations are still ahead of us. And so one of the things that we think about is how can we really innovate the technologies of the future to build the medicines of the future.

And today, I'm actually really excited to be able to give you the first glimpse into Moderna's scientific intelligence engine and where we are taking the future of our platform technologies.

So I think it's safe to say that we are truly entering a completely new era of scientific exploration. If you think back to the days of scientists in the lab doing an experiment, looking at the data, reformulating their hypothesis, going back and performing another experiment, this serial way of experimentation, while incredibly important can be very slow at generating data that can be scaled.

And so we're now in an era where the advance of new AI technologies and automation are really eliminating this slow traditional limit on hypothesis generation and experimentation. And so we truly believe that now scientific advantage really belongs to those that can learn the fastest. And so how do we set ourselves up to be that company that can learn the fastest?

This really requires fundamentally changing the way that we do experimentation and also the data infrastructure that is required to take the data in and make it usable for all of our modern AI tools. And so what I'm going to share with you is how we really think about this concept of learning at scale and positioning ourselves to be able to do that better than anyone.

And so today, I'm really excited to introduce Lucy. So Lucy is at the heart of Moderna's scientific intelligence engine. Lucy connects everything that we've built in AI, automation, experimentation, and data into a continuously improving learning system. So if we think now that experimentation is no longer done one experiment at a time, we really are conducting iterative learning cycles. And these learning cycles allow us to find that next discovery in a faster, smarter, and more predictable way.

Now importantly, if we think about all of the data that exists in people's lab notebooks, it's very disconnected. (technical difficulty) So this combination of the automation that we looked at and Lucy really creates this ultimate scientific flywheel. And the way we think about this is we're transforming the data that we generate truly into intelligence.

And so I talked a little bit about this concept, but it's really allowing us to go from an AI-driven hypothesis generation. We can go through mRNA production, formulation of that mRNA into our lipid nanoparticles. We learn from about the biophysical properties of those LNPs, going through a series of in vitro based assays and that is what we do within a closed-loop platform.

And you can envision that why this matters is because if I want to test 1,000 different LNP formulations or one LNP formulation and 1,000 different mRNA designs or I can do a combinatorial approach. And so you just start to generate data at a scale that we've never been able to do before. And now that we have the AI tools available to make sense of that, it really is able to generate new hypotheses to learn in a faster way and to make better decisions about the candidates that we move forward.

Now importantly, we don't stop just at primary human cell data. We've built platforms that allow us to do in vivo multiplex screening in mice and in nonhuman primates. And what I mean by that is instead of taking one candidate into one animal, we are able to use current barcoding systems so we can take 100 or 1,000 different candidates into a single animal and then deconvolute on the back end to understand the performance of each individual candidate.

Now of course, we view human clinical data as our ultimate ground truth. And it's probably fair to say that Moderna has more human clinical data than anybody else on the planet. And so important in our scientific flywheel is the incorporation of the volumes of human clinical data that we already have and all of the data that's emerging from our ongoing clinical trials.

So when we think about the totality here, I always think about Lucy as kind of the heart of the scientific intelligence engine. But it's not just the data that we're generating today or our internal data that we've generated over the last 15 years. We also have an ability now to look at the public domain.

And with our collaboration with OpenAI, with other large language models, with emerging AI tools that are coming today, we are able to pull in publicly available data sets. And so that allows us to kind of supercharge our existing proprietary internal data that we have and that we are generating to ultimately allow us to make better, faster decisions, not just about the therapeutic candidates that we move forward, but the diseases that are applicable if we think about the biology and pulling that in.

And it allows us to continually do this cycle where we learn, make better decisions, and are able to create better drugs.

So with that, I'm going to turn it over to Stephane.

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Thank you, David. Before I close, I would like just to thank my colleagues, not only those that presented today, but the literally hundreds and hundreds of colleagues that are working within the Emirates world trying to invent the future of medicine.

So just to close, I think you've got a good sense today of how we are trying to make sure that we both deliver for the short term through Horizon 1 initiatives, but also how we prepare the future and how we have a dedicated team within the (inaudible) community within Moderna, working on Horizon 2 and Horizon 3. And you just saw for David, we think we're just getting started, and we're very excited about what we can do in the future by investing in science to invent even newer modalities.

As we shared at Analyst Day in November of '25, for the next few years, the plan is very clear. We're going to grow through diversification of geography, as you already saw in Q1 and through diversification of products. We are very excited with the launch across the world of mNexspike happening this year. It was a start last year, as you know.

We're very encouraged by the (inaudible) meeting both last week, give us good hope about the approval of flu moving forward. And of course, the other products that are on the slide that we talked about.

If you look at this year, it's going to be a very exciting year because not only we're getting back into sales growth, we continue to make progress on the cost structure of the company, a lot of products approval across geographies. We are very, very pleased and proud with mCombria to get the first approval in the world of a flu and COVID combo.

And as you know, the COVID component is actually mNexspike with much higher performance than Spikevax as we totally reengineered the product. It's a totally different product. And so with flu, you saw the data, it was published in New England Journal of Medicine recently, showing great performance, especially for people at high risk.

And those two products are in single dose. It's already approved in Europe and many more countries are going to follow. Of course, we have very important clinical data ahead of us with Intismeran. We had very good reception at ASCO of the five-year data, not only the data and how all the subgroups look really strong, but also the transactional medicine that we understand the mechanism of action. That is how we decide Intismeran and it is doing as advertise in terms of T cells, both expansion and programming of de novo T cells.

You heard today from the team about 459. We are also expecting norovirus data, of course, depending on case accruals and PA because it's a time-based pivotal study should read out this year as well. So it could be very, very exciting in 2026.

But as you saw today through a few examples of a few modalities, we don't have time to show you everything. Just looking at the cancer antigen therapy, looking at the T cell engagers, looking at 007, just getting a sense of all the exciting new medicines that are either in the clinic for which we are waiting for human proof-of-concept data and the new medicines that are entering the clinic in the next 6, 12, to 18 months to basically expand and expand the possibility of what we do with mRNA.

And as you just saw with David, what is so exciting is we have been doing mRNA for 15 years, and we feel that we're just getting started. The ability that we have to just change totally the pace of our learning is so exciting. We've always said as a motor of a company that we don't have to be the smartest, but we have to learn the fastest. We used to do it one experiment at a time, one lipid at a time, one chemistry at a time.

But as David showed you, the team is really changing the scale of what we are doing. And what is really exciting for me is we're really best positioned, I believe, in the world to do that.

If you look at the scale that we have in science, in process engineering, in early clinical, the capability we're putting together on mRNA, the AI, the automation, all those pieces coming together. I don't believe there's a company in the world that has the scale that we have in mRNA. And that is exciting for what we can do for patients.

So if you think about where we stand today, I truly believe that we have not invented our best molecule yet. I'm very proud of what the team has accomplished. During the pandemic, obviously, the mNexspike, (inaudible), the flu product, cannot wait to see the NRO data. Intismeran is looking very exciting, what we can do in rare disease.

But what we're doing also now with mRNA-1195, EBV and MS, 007 with autoimmune disease. If you think about it, we're really expanding the domain of what we can do for patients in infectious disease, in oncology, in autoimmune disease and in rare disease, which is why I'm really excited about the future.

I'm so thankful for our team and all of our partners around the world, including the clinical trial sites, the participants in the studies. And I really look forward for the next few years, it's going to be really exciting.

So with this, I would love to ask Rose and David to join me, and we'll be happy to take your questions. And Lavina, you'll be moderating online and in the room. Thank you.

QUESTIONS AND ANSWERS

Lavina Talukdar - Moderna Inc - Senior Vice President, Head Investor Relations

Please introduce yourself before your question.

Edward Tenthoff - Piper Jaffray Inc - Analyst

This is Ted Tenthoff from Piper Sandler. So firstly, just recent things. Congrats on the flu AdCom, excited for Intismeran data, really cool new in vivo CAR-T program. I have two quick ones.

First one is kind of high level. So when it comes to really evaluating all these different new oncology products, how do you sort of prioritize and/or sequence, obviously, data-driven, but there's some overlap between Intismeran and some of the shared or tumor-associated antigen products.

So how are you going to really kind of select when one is appropriate or maybe better than another one?

David Berman - Moderna Inc - Chief Development Officer

Yes, happy to take that. So I think it's a scientific question and a strategic question. I think the Intismeran represents probably the defining clinical trial on whether cancer vaccines can work or not. It's been tested in the ideal population in the adjuvant setting. And so we are planning for that to be a success, obviously.

And that's why we are moving forward the off-the-shelf cancer antigen therapies that you heard about before. So those are moving in parallel behind Intismeran, but Intismeran will be the gatekeeper for those trials because the cancer antigen therapies, the cancer vaccines will probably require randomized trials, large investments and we don't want to do that until we know that Intismeran is positive, which I expect it to be, but I think that's the defining moment.

I think just to your other question about how do we prioritize, part of what I've seen successful over my career is a rigorous application of does the science work? Does the drug do what pharmacodynamically intended to do? And then does it clinically have a strong enough impact to be developed?

And I think both of those questions need to be answered separately for us to move something forward.

Andrew Tsai - Jefferies LLC - Analyst

Andrew Tsai, Jefferies. Thank you for sharing your vision today. Bigger picture question as well is that as you're developing these Horizon 2, Horizon 3 products and should they succeed in the clinic and so forth, can you maybe remind us the latest and greatest about your cash breakeven guidance for 2028? Does that incorporate an increased R&D spending over the next couple of years?

And then maybe a second follow-up question is there's a lot of things going on. Would it be possible to give us a brief summary of the timelines of the data readouts actually for your Horizon 2 and 3 products that you've guided to today?

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Sure. Thanks for the question. So in terms of cash guidance, there is no change. Those budgets have been all along through our long-range planning and annual budgeting process. We have not just set them apart in terms of disclosure, but those investments are in the budget.

What we'll have to do as we see in human proof of concept is to figure out what's the best strategy for the product. And we'll be looking at this on an asset-by-asset basis based on the asset performance, but also where the portfolio is, what makes sense for the company.

Some assets we're going to develop ourselves, some assets might be better in the hands of partners. So we'll just do what is practical and for the portfolio of the company, both upside and risk.

David Berman - Moderna Inc - Chief Development Officer

And for your second question in terms of the Horizon for data readout. So 4359 was data we just shared at ASCO and at AACR. So we're now in the confirmation stage of that signal. We have a larger expansion. And so that should be data, I imagine, next year to be shared.

2808, which is the myeloma program that you heard about, we hope to share initial data later this year on that. And then I think the other two -- the other programs, the cancer antigen therapy and the multiple sclerosis 1195, 1195 will probably have data not until '28 just because it's a randomized trial. The cancer antigen therapy could be data next year.

Mark Allen - Goldman Sachs - Analyst

Mark Allen of Goldman Sachs. A couple of mechanistic questions for the in vivo CAR-T. I was just wondering, because you're targeting T and NK cells and you're combining, I guess, both B cell and plasma cell targeting, is there any risk for a greater toxicity profile? Maybe these patients be at greater risk for infection?

And also, would you -- do you plan to reimmunize patients afterwards?

Rose Loughlin - Moderna Inc - Executive Vice President - Research

I can take that one. Sure. So I think a lot of these things have to be done empirically. Obviously, we're pretty comfortable with the results that we have in NHP, but you have to use surrogate programs for some of those studies. And so we're also building off our understanding of those potential targets from oncology where they've been used extensively.

So we're pretty comfortable proceeding with the plan that we have today. If the depth of depletion is such that patients do need to be revaccinated for your like standard vaccination routines, that's certainly an option, and we would look to provide that for them certainly.

David Berman - Moderna Inc - Chief Development Officer

I think -- I'd just add, I think part of the advantages of our RNA platform is we can hit the B cells extremely hard with CD19 and BCMA, but do it in a pulsatile short-term fashion without the need for gene integration and potential risk down the line there.

Unidentified Participant 1

This is [Greg] representing Tyler Van Buren from TD Cowen. So on 4106 and 4200, how should we think about the undisclosed antigen targets? Are these well characterized from existing literature? Or does their novelty represent a key differentiator?

And following on that, in the absence of robust in vivo data, what underpins your confidence that these will translate into meaningful efficacy, particularly in advanced solid tumors where the biology is more challenging than the adjuvant setting?

David Berman - Moderna Inc - Chief Development Officer

Yes. I'm happy to take both of those. So these are antigens that are known. So that's, I think, question number one.

Question number two is a great question. I mean, it's probably one of the -- it's the biggest cancer vaccine scientific question, which is cancer vaccines actually work. It's been decades, as you know, where they haven't worked. And we think mostly that's because they've been tried in late-stage patients. And I think also the vaccine technology was not the ideal one.

I think the RNP -- the RNA LNP is probably the best vaccine technology. So we don't know whether it will work. We will need to do randomized trials, but we are set up. I mean, this is the company that's set up to answer that question. So if Intismeran is positive, if neoantigen cancer vaccines do work, we are poised to have an off-the-shelf version.

And it could be complementary. It could be in adjuvant setting, and it could also be in -- we'll try it in the metastatic setting. I think that's a question which we don't yet know.

Rose Loughlin - Moderna Inc - Executive Vice President - Research

And I might just add on the validation of antigens. This has actually been an important part of our collaboration with Immutics, where, as you mentioned, in vivo models are not particularly relevant for many cancer vaccines, but we can actually access patient samples and look at what antigens were both present in those tumor types and presented on those cancer cells.

Unidentified Participant 2

This is [Matt] for Mike Yee from UBS. Maybe on the ovarian cancer program, could you talk a little bit about the target you chose, how it maybe fits into the standard of care already in ovarian cancer into the competitive landscape, the TCE modality, especially?

And would this be a novel target relative to the other ADCs out there? I'm just going to speak to how you see this fitting in the landscape here.

David Berman - Moderna Inc - Chief Development Officer

I'll handle the landscape and you can address the target. So obviously, ovarian cancer is becoming incredibly complex and crowded and it's generally divided into the platinum-resistant setting where response rate is very important and where, of course, the ADC landscape -- the ADCs are really radically transforming the landscape.

The other setting is the platinum-sensitive setting. And here, probably the maintenance setting is the right place. And this is where probably you don't want -- this is after patients have a response to platinum-based therapy. They're in the intervening period. They probably don't want to have chronic toxicity with chemotherapies or ADCs. And this is the ideal setting for where a T cell engager can work. It's also an earlier setting where the T cell fitness is better.

So the general approach would need to be study this initially in platinum-resistant setting because those -- that's where the biggest unmet need is, and we can demonstrate, hopefully, as a monotherapy signal and then decide whether it can be developed as a monotherapy approach and then study it in a platinum-sensitive maintenance, which would be a longer trial and which you would do once you validate it in the PROC setting.

Rose Loughlin - Moderna Inc - Executive Vice President - Research

I would just add that mRNA-2151, much like 2808 is actually multiplex. So it's pursuing multiple targets for Signal 1 and also includes a targeting moiety for Signal 2 co-stimulation. So that is part of our strategy for, yes, using clinically validated targets, but being able to add on to anyone who might have been exposed to a treatment targeted at one of those same proteins.

Unidentified Participant 3

This is [Tejas] from Ellie Merle's team at Barclays. Maybe I'll ask on your program in multiple myeloma. Can you expand on your target product profile in terms of safety and ease of administration as T cell engagers start to move out of the academic and community settings?

David Berman - Moderna Inc - Chief Development Officer

Yes. So the current formulation is administered intravenously, but we have the ability and plans to also test it subcutaneously. In terms of the safety profile, it's actually potentially better. And for the reasons that you heard, that when you administer a biologic T cell engager immediately, there's very rapid high Cmax that occurs very rapidly, and that results in very -- in high cytokine release syndrome.

When you use an RNA approach, the RNA has to be first translated into protein and then secreted. And so you get a gentle ramp-up in the T cell engager release. And what we know from the field is that there is a tachyphylaxis that occurs with repeated dosing or repeated exposure. And so we hypothesized actually that the safety might be better because you get a delayed and a blunted Cmax. Of course, that needs to be validated.

I believe, especially in myeloma, that T cell engagers are going to be able to be moved into the community setting. And I think our three targets we have will be acceptable for a community setting. So right now, we're focused on demonstrating, of course, activity in heavily pretreated patients, and we'll be sharing that with safety later this year.

Alexandria Hammond - Bank of America - Analyst

Alexandria Hammond from Bank of America. Thanks for hosting us here in your headquarters. A couple of pricing questions. ICER is holding a meeting today to talk about cost effectiveness of COVID-19 vaccines.

I guess, do you anticipate any price changes for your COVID products this fall? When might we hear about the price that gets set? And how do you expect price will feed into coverage and availability this season?

I guess a related follow-up, when you think about pricing for the flu/COVID combo opportunity, how do you expect this could shake out maybe using your early discussions in the EU as an indicator?

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Yes. So we're having discussions with payers like we always do. We are following what's going on, but we are not commenting on pricing at this stage.

Myles Minter - William Blair Capital Partners - Analyst

Myles Minter from William Blair. Two for me, one on the science. Just for 1195, the EBV vaccine, great healthy volunteer seropositive data that you showed there. My question is, as you move into an MS patient population that's going to be treated, I would think with CD20 therapy prior.

How does the latent portion of that vaccine work in patients that theoretically have B-cell depletion? That's the first one.

Second one, just to confirm on capital allocation. Is the potential trial that you have to run if you do get approval for your flu vaccine, that, I think, was 800,000 patients over two seasons, is that in the budget? And if you do have to run that trial, that won't impact anything that we're seeing from Horizon 2 and 3 today?

David Berman - Moderna Inc - Chief Development Officer

I'm happy to take the 1195. So the initial proof-of-concept trial that you heard about today is going to be run in recently diagnosed patients who are not on any biologics. So that's the proof-of-concept trial. After that, we'll determine based on the strength of the data, do we need to add on to an anti-CD20 or can we try and replace it, of course.

And then finally, anti-CD20s, of course, work well, but they don't completely reset the B-cell immunity because they probably don't eliminate all those residual B cells. And so I think that's where our approach can help.

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

And on your second question, yes, the discussion that we had with the FDA that was discussed are in the budget.

Unidentified Participant 4

This is [Shelby] here for Luca Issi from RBC. Maybe on the 1L metastatic melanoma data that you shared earlier, do you think that 33% Grade 3/4 AEs are attributed to just pembro? Or do you see some kind of additive toxicity since that rate does seem higher than pembro alone?

And then maybe on Lynch syndrome, how should we think about the TAM? I think you said 1 million patients in the US, but I guess, what proportion of those patients do you plan on targeting initially? And then do you expect that number to kind of increase going forward?

David Berman - Moderna Inc - Chief Development Officer

It's a really great observation. It's something that's occurred to us as well. And when we -- it's a small number to begin with. But when we spoke with investigators on the trial, they said potentially, it might be slightly higher than what we would expect, that they are traditional immune-mediated adverse events. Some pointed out that this is using the 600 milligram, so -- which they sometimes feel does have a slightly higher toxicity profile than the every three-week version.

But on the other hand, I wouldn't be surprised or necessarily upset if there is a higher rate of severe immune-mediated because it means that we are activating T cells.

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Yes. And on the Lynch syndrome, I mean, as we said, it's around 1 in 300 people. As you know, genetic tests are available for blood work today. A lot of people are not aware of Lynch syndrome. There are some geographies where there's a bit more awareness and a bit more advocacy.

So definitely, this is not the right time to do anything about it for us. But as we get more data, if we think we have a product and we have in situ approval, you will see us engaging with payers, with patient associations, with governments and so on because that will be a beautiful thing to do in terms of preventing cancer and also, of course, reducing health care costs. So we will do all that if we have a product.

Unidentified Participant 5

This is [Adam] on for Jess, JPMorgan. I apologize if I missed this. But for the in vivo CAR-T, how did you decide to pursue autoimmune? And should we expect Moderna to advance in vivo CAR-T for oncology?

Rose Loughlin - Moderna Inc - Executive Vice President - Research

Okay. So the ex vivo CAR-T results that have emerged over the last few years in the autoimmune space have been really eye-opening and started to tease out some of the important biology that some of these very rare B-cell populations are bringing to autoimmune diseases, including autoimmune diseases that we would have previously characterized as more T cell driven. These are showing responses to those ex vivo cell therapies.

Now, we think as you're going forward and thinking about patients and accessibility of that therapy, that in vivo CAR-T is the way to go. So from that perspective, with the ability with a few doses to truly put an autoimmune patient into remission, we think the platform is actually the ideal approach there.

We are pretty excited about continuing down the road into oncology, either thinking about CAR-T or TCR-T, which is similar to CAR-T, but lets you also pursue intracellular antigens.

David Berman - Moderna Inc - Chief Development Officer

Yes. And I just add one other reason I think, is important in that if you think about autoimmune diseases, the confirmatory trials and Phase 3 trials are, of course, going to be very large. The commercial opportunity is very large.

And there's no other company in the world who can really manufacture on that scale than Moderna for mRNA-LNP. So it makes sense scientifically and it makes sense also commercially for us.

Chun Yu - Morgan Stanley - Analyst

Chris Yu from Morgan Stanley on behalf of Terence Flynn. We have two questions. One is, do you have any update on the pace of event accrual for the Phase 3 INT adjuvant melanoma study?

And the second question is, the treatment landscape for multiple myeloma is rapidly shifting due to bispecifics and CAR-Ts, and you have presented multiple programs here on multiple myeloma. Just how do you think about your approaches and how that fit into the treatment landscape?

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Yes. So for Intismeran, we have not disclosed events, and so we're not going to start today, but we are confirming again that 2026 is the right time frame.

David Berman - Moderna Inc - Chief Development Officer

Yes. In terms of multiple myeloma, it's great for patients. I started working in myeloma 15 years ago, before all of the recent changes were available. It really is phenomenal. From a drug developer standpoint, it makes it extremely hard, as you point out, because the bar keeps on getting raised.

For us, it made sense for this to be our initial pilot of a modality because it is derisked biologically, and we can do it. And so the question is, can we generate sufficient response rates and a differentiated product, right? This is the first time ever three T cell engager targets have ever been administered to a patient. So we'll generate the data to see if this platform works.

And number two, is it clinically differentiated enough to develop into earlier lines? I think for us, it provides also important positive control for our modality system. You heard about the ovarian cancer T cell engagers that we're going to be moving into clinic.

But behind there as well, this is a company, I think, that could be on the forefront of not only multiplexing different targets for T cell engagers, but also figuring out how to manipulate the tumor microenvironment because, as you know, T cell engagers have had a difficult time or more difficult time in solid tumors and hematologic cancers.

And I think the science is beginning to catch up to where we have the technical ability to multiplex. And so that's sort of the background here.

Lili Nsongo - Leerink Partners LLC - Equity Analyst

Lili Nsongo from Leerink Partners. Thanks for the great overview of the pipeline. I just wanted to backtrack a little bit. So we talked about how Horizon 2 and 3 fit into the R&D guidance. And then on the other side of that, could you maybe give us a little more color in terms of the commercial performance assumptions that kind of support the development of the second and third wave of assets?

So obviously, a lot of the Horizon 2 assets are currently in early clinical stage and then a couple of INDs are expected in 2027. So how should we think about the revenue mix that supports it in terms of the contribution from the COVID vaccine, the flu vaccine, the combo, as well as the rare disease and the oncology pipeline?

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Sure. So what we're doing at this stage is developing those assets to get to human proof of concept to validate both the assets and the modality, because that's really how we've scaled the company historically. And then we will look at where the company is at that stage in terms of what do we do for the assets moving forward of the modality in terms of does it become something that we commercialize ourselves worldwide, in the US, and we have a partner? Does it go through a partner for global rights?

So we just look at the portfolio. So what we've always done with the company is to look at how do we maximize the value of a portfolio of products and manage risk at the same time.

So it will depend on when some of those products get launched, what is their ramp. So we don't have to make those decisions now. The Horizon 2, Horizon 3 right now generate the human data to know do we have a new modality or not? If we have a new modality, then we'll assess at that time the entire portfolio. And it doesn't necessarily have to be Moderna alone.

Look at Intismeran, it was a great example. Years ago, when Intismeran was a great scientific idea, it was clear to us at the time that doing it alone was going to be very expensive and much harder than partnering with best-in-class company in oncology, which is why we partnered with Merck.

We're very happy about that partnership. I think being with Merck, we're able to execute things we could not have done alone. So you always see us being very pragmatic. But where is the company at the time we have to make a decision? We will always look at how to maximize the value of the asset.

And sometimes it might not be in our hands, sometimes it will be in our hands.

Lavina Talukdar - Moderna Inc - Senior Vice President, Head Investor Relations

Great. I'll take some questions from the webcast.

The first question is: you've previously spoken about the intention to out-license or find a partner for EBV. Is this, first, still in play? And what demonstration of data do you think a partnership becomes more relevant for that asset?

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

I'm happy to take it. So 1195, as David said and the team presented, we are running the clinical studies to figure out the signal we have. And again, as I just answered right now, when we have the data, we look at the totality of the Moderna portfolio, the investment opportunities, the portfolio upside, the risk, and then we'll make a decision at that time.

Lavina Talukdar - Moderna Inc - Senior Vice President, Head Investor Relations

Great. Similar question on the CAR-T assets in oncology potentially also likely to be partnered? Or what is the strategy with Horizon 2 and Horizon 3 assets?

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

So those assets, initially, is really to get a confirmation in the clinic, do we have a modality or not? And you're going to see us being very consistent like we've done historically with infectious disease vaccine and we're doing (inaudible) and then we're doing with rare disease. You're going to see us doing the same thing, which is we think we have a very interesting way to address medical need using mRNA as a platform.

Let's take it to the clinic. Let's look out through one or two or three programs, do we have a modality or not? And at that time, it will graduate out of mRED, and we have to figure out, as I just described, what's the best home for that modality, either internally or externally.

Lavina Talukdar - Moderna Inc - Senior Vice President, Head Investor Relations

Okay. With that, it looks like we have exhausted questions. Thank you very much to everyone who came in person and to all our presenters.

Stephane Bancel - Moderna Inc - Chief Executive Officer, Director

Thank you. Have a great day.

David Berman - Moderna Inc - Chief Development Officer

Thank you.

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