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# EDITED TRANSCRIPT

MRK.N - Merck & Co Inc at Guggenheim Biopharma's Next Decade Virtual Conference

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## PRESENTATION

**Seamus Christopher Fernandez** - Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals

Okay. Good morning, everybody. Hopefully, you can -- you hear me okay. Thanks very much for joining us for this 60-minute discussion with Merck's Executive Vice President and President of Merck Research Laboratories, Dr. Dean Li.

I'm Seamus Fernandez, one of the biopharma teams' senior therapeutic analyst here at Guggenheim. I'm really pleased that we've got Dr. Li here to join us as part of our new Guggenheim strategy series, which focuses exclusively on the innovation and strategies that biopharma companies are employing to benefit patients and drive growth for many years to come.

Dr. Li, frankly, I can't wait to discuss Merck's efforts and strategy to continue driving growth in the next decade and beyond. But before we do that, I just want to provide a little background and context for the discussion. As many of you know, Dr. Li serves as Executive Vice President, President of Merck Research Laboratories. He leads companies -- the company's worldwide human vaccines and therapeutics research and development organization. Since joining Merck, Dr. Li has held leadership roles in translational medicine and discovery function, was appointed the President of Merck Research Laboratories in January 2021. Prior to this, he held a number of positions, including heading up translational medical research at University of Utah. He started multiple companies on the biotech side prior to this. And I think that positions him uniquely well for today's discussion, really talking about what we believe is going to be 2025 to 2035 time frame for Merck Research and Merck overall.

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## QUESTIONS AND ANSWERS

**Seamus Christopher Fernandez** - Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals

One of the things that we have heard from investors is some of the concerns around companies that reach a market cap of \$200 billion. Obviously, one of the areas of discussion for Merck has been the concentration that KEYTRUDA is increasingly representing with another positive clinical trial having been announced this morning in cervical cancer.

So Dr. Li, maybe without going through a history of how we got here, maybe you could just share some of your opening remarks on how Merck Research is approaching this innovation challenge as we discuss it and what Merck is doing right now to really differentiate itself and extend the company's recent successes.

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**Dean Y. Li** - Merck & Co., Inc. - EVP

Right. Well, thank you very much for having me here. It's a pleasure to be here.

There are many different approaches. There are many different strategies. I think that one can articulate lots of different strategies, but I love what you said. At the basis of it, data in human beings is a make or break point for any program and any strategy. And there are some times it's hard to make a drug, but it's also even harder to identify what I would call foundational drugs, drugs where you could go and lay out a beachhead quickly, define a patient population where you can have a beachhead, but also recognize that given that beachhead, there are many other applications. And the reason I sort of lay that out is some people talk about rare disease or precision targeted, I like molecules where I can quickly find out whether I'm right or wrong in a limited patient population and expand quickly.

And not to belabor history, but in some sense, that's what happened, for example, in pembrolizumab in relationship with the lung, it was to put it in a PD-L1, demonstrate that and then use that as an expansion. And I would just comment that programs such as belzutifan is a very similar sort of way, which is, if I put it in a von Hippel-Lindau syndrome renal cell carcinoma, and it doesn't work, I know to get out of town. But if it does work, I know to stay in town, and I know how to advance it and where I can advance it.

And the reason I sort of lay those examples out is I was asked about islatravir. Islatravir is that type of drug. We focused a lot on prevention. But the minute you start seeing how well it works as monotherapy and prevention and you think it's a really important drug in that space, you get more confidence of it in treatment.

And so yes, we had that initial q day with islatravir and doravirine. But now, it's can we move other compounds with that foundational element? And if we believe we have a foundational drug, we should be open to the possibility that we should develop other drugs that complement that, but we should not be afraid of bringing other drugs in from the outside that may complement as well because it's important for patients, but also it's important for our business to advance that type of strategy.

So I look for those opportunities as a sort of litmus test. How do I take this molecule, this pathway, this technology? How to figure out whether it will work in a relatively smaller patient population? And if it doesn't work, how do I know how to get out of town? But if it does work, the ability for me to advance it in other indications. Those are places that I think very carefully about.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Great. And then just before we get into kind of categories or products specifically, just maybe can you share an example of where just portfolio strategy positioned Merck for category leadership during your tenure there or at least how you're positioning Merck for category leadership. I think as a great example, you mentioned islatravir in HIV. PrEP itself, I think, is not particularly well understood.

So maybe you could talk a little bit of how you see Merck reemerging with category leadership because, obviously, Merck was first with ISENTRESS with a -- in the integrase inhibitor category.

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Yes. So I might give 2 examples that are obvious, one is HIV and then one in oncology. But in HIV, Merck has a proud history of inventing many of the different classes of HIV medicines and advancing them. But the ability to knit that all together was a really important thing to do in one pill, and that was transformative for the field, but also transformative for patients. And the question is whether or not we are in a position now to sort of revisit that.

You're right. The issue with PrEP is, as a monotherapy, the field has decided that as a monotherapy, one can begin to increasingly think of PrEP by itself. I would just caution that one of the things that we are very sensitive to is if you're going to do PrEP and monotherapy with islatravir or any other drug, what it's very important to do is to make sure that, that PrEP is safe.

And what do I mean by that it's safe? What you don't want to do is, in the PrEP setting, have a monotherapy that allows viral resistance to come back. Because if that viral resistance comes back, then that class of medicine, not just for PrEP, but for later on treatment will get -- will have dings in its armor.

And so our experience with PrEP and islatravir is what has given us enormous confidence in islatravir as a monotherapy and PrEP and our ability to ensure that our PrEP will be that strong. But that immediately gives us that concept of, okay, let's just separate. PrEP is really important. It's really important for many societies. It can have enormous public health impact, and it can have a market impact. But if you look at the HIV market, the PrEP market can grow, but the largest part of that market is treatment.

So now that we have that clearly in our brains that we have a beachhead and we have this special molecule, us advancing MK-8507 becomes very important. And once we advance that into later stage, then the question is, what else can we advance it? We have our own integrase programs; Gilead, their integrase program. So that's a place that we could collaborate and combine, but the other place is lenacapavir as well. So that's a -- that's -- that gives a framework of how that thinking gets advanced and what is that human data that allows you to trigger the next step. That -- was that reasonable context?

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Yes. No. Absolutely. And just in terms of the ability or some of the challenges of actually executing a collaboration like you did with Gilead in lenacapavir, maybe you could just give us some context of how long it took and how important you felt that this collaboration was to that franchise for Merck?

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

I mean it's always been at our back of our mind. But I took leadership of MRL in January. I've been lucky enough. Those islatravir programs, these programs were under my agreement in translational medicine discovery. That's where we do first in human. So my appreciation of that compound and what that clinical data was showing for us is what gave me that confidence, not just me, the whole company, the company. It's just not me. It's the whole company having confidence in it.

But I would also lay out that the way that I think about islatravir, in some way, is very informed of the way that I think about KEYTRUDA, for example. And the issue for KEYTRUDA is it's a powerful IO agent. And there are 2 ways that we can advance the field. We can go into earlier stages. We can go into diseases states where we haven't made as big of an impact, and we have the opportunity to do so. But the other one is through combinations to deepen the response.

And there's 2 angles for it. One is to take IO and make that IO better. And so we have a slew of candidates in relationship to that. We have CTLA-4, LAG-3, TIGIT, ILT4 and a bunch of other ones that are sitting in the wings, that is one approach. And the other sort of approach is the data that we have is that when you take pembro and you mix it with a non-IO agent, what I would call an intrinsic cancer killer like chemotherapy or those type of drugs, it works extremely well.

And so one of the things that we're doing is that we are expanding not just where we are in IO, IO, but we're increasingly expanding IO to what I'd call intrinsic cancer. And a company that saw the data in 2017 and '18 of KEYNOTE-189 when the minute you see pembro plus chemo, there are 2 things you think: how do I make pembro better or how does -- what's the advance in chemo that's going to happen. And so that's why our interest in antibody drug conjugates come because in some sense, you could view that as chemo with a slightly different therapeutic index. So that's how we think.

And then the final thing I would just say is, those programs have laid out an enormous amount of assay reagents know-how in relationship to immunology that is focused on cancer. But you look at every one of those signaling cascades and you flip it the other way around, instead of inhibiting the pathway for cancer, could you activate it for autoimmune? And I think that degree of that arsenal of know-how needs to be a position that Merck takes and to flip it around, and that's why some of the programs that you'll see coming out increasingly and some of the business deals most recently within the first quarter was to do Pandion, to really leverage that ability. So that's -- essentially, the strategy is use our strength, but let's not be confined by our strength.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Got it. And maybe you could just give us some big picture thoughts on some of the smaller targeted disease areas that might be considered orphan categories that hasn't necessarily been core for Merck to go after maybe not ultra-orphan categories, but even a smaller sort of categorized as orphan diseases. We've seen some business development and some of those potential indications, ArQule, Peloton, into that. We've also seen pursuit of KRAS.

So I was just hoping you might give us a little bit of your philosophy on orphan diseases or targeted indications outside of oncology that you think might be uniquely important or value added. You've got cardiovascular disease, other large orphan categories in hematology, for example, as well.

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**Dean Y. Li** - Merck & Co., Inc. - EVP

Right. And so clearly, we're not walking right from cancer, if that's not obvious. I think the other places that you've sort of laid out, the KRAS with belzutifan, that's trying to hit what I call the intrinsic cancer sort of killing mechanisms. And so we're increasingly -- our leveraging position in relationship with pembrolizumab allows us to understand what -- which of those mechanisms through or multiple partnerships and collaborations where we want to place a bet.

But as you step back, as you rightly point out, if you look outside of that and you ask yourself, where else outside would you play in that field, I would say that the places that are intriguing to me are those places that are in the cardiovascular metabolic space, but where inflammation is an important component part. And if you look at the diseases that are in that spaces, cardiovascular disease continues to be a really important disease.

I'm a cardiologist. And if you look at this, for example, I wonder whether there is more that can be done there, we have a program with vericiguat in terms of left heart failure. The way that I think about inhaled sGC program is it's initially focused on PAH. But another way to think about it is it's really the same mechanism of vericiguat, but it's giving inhaled and it can lower the pulmonary arterial pressures.

So I look at vericiguat as left heart failure. And in some sense, you could think of our inhaled sGC as a pulmonary artery hypertension play. But we're very interested in understanding what that role might be more broadly in reducing the pulmonary artery pressure. And therefore, I view it as a right heart failure play. Does that make sense? So one is a left heart failure play, the other one is a right heart failure play in some sense, and we're driving it through pulmonary artery hypertension.

But as we see positive data from that, there are natural sort of places where one could sit there and expound in your brain and say, okay, if that works for pulmonary artery hypertension, tell me other conditions where there is a high pulmonary pressure that causes right heart failure and maybe you should target there.

So that's the way -- that's emblematic of the way that we think about things where if it doesn't work for pulmonary artery hypertension, I get a little bit, hmm, maybe I should walk away. But if it does work, the concept of the basic physiology is one that is worth exploring once you lay out that beachhead.

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**Seamus Christopher Fernandez** - Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals

Got it. And maybe you could just point to a couple of areas where we've seen Merck or where you really are challenging the organization to change. I think one of the areas that many investors were, I guess, surprised to not see Merck has been a participant in the COVID vaccine area while others were successfully advanced in that space.

I guess one of the questions really is, what have you, as Merck, kind of learned from, frankly, the disappointments in that space? And then what are the ways in which you're kind of challenging the organization, not around COVID, but what you really learned from Merck's experiences throughout the pandemic?

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**Dean Y. Li** - Merck & Co., Inc. - EVP

I think that's a great question. I think there's a lot for us to learn. And we also need to be careful about what we learned and also lessons we shouldn't learn. I think it's fair to say that our efforts in the COVID vaccines probably was a little bit later than other people in terms of the start time.

Our aspirations I thought was -- were great, which was, can you create a single dose vaccines that you could widely expand? We went to the viral vectors. That was our -- some people look at mRNA as nucleic acid delivery, I view viral vectors as nucleic acid delivery. And the platforms that we

grabbed, which was those are the measles and the ones that we used in relationship to Ebola, did not give, surprisingly to us, the immunogenicity that we had hoped to have.

I think one of the lessons for me is maybe 2. One is to pressure test our decisions of starting at the time that we did start versus other people. And the second sort of issues for me is these nucleic acid delivery systems having them at your fingertips. For us to advance in April and May required us to do business development, and that accelerated our programs, but it was required. But every time you require a business development, especially in a vast turnaround time, merging 2 companies and all of that, it does have its challenges.

And so I'm very happy that we did those deals because those vectors and those know-how are now embedded in the company. And we intend to use those vector in those platforms. Though they failed for COVID, we intend to continue to invest in them in other disease states and other viruses.

So getting back to summarize, it's asking ourselves when did we start compared to other people? And then the second one is what are the platforms that we have to have internally at the company, so we could be more powerful and faster than a punch. When you look at the whole field, the lesson that I've learned is lots of things work, mRNA worked, subunit vaccines work, viral vectors work. And when you see those people who are successful, what they did is they went to what was in their wheelhouse directly. They directly went into the wheelhouse. And that was something that a lesson for me and that we need to build that wheelhouse and build that stronger.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Got it. And just in terms of -- you mentioned nucleic acid technology. There's a number of different platforms that are obviously developing and expanding as we speak. Maybe you could just give us your thoughts on business development, Merck's approach to business development and where you would say that maybe not necessarily the BD focus is, but where you think early technology really is starting to expand and could potentially disrupt treatment paradigms. We're getting a lot of incoming questions on nucleic acid technology. There's enthusiasm for ADCs. We're hearing about protein degradation and approaches there. So just love to get your broad thoughts on areas that you think that could be potentially disruptive.

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Right. So I would separate technology into maybe 2 buckets, and they're sort of 2 artificial buckets. Fundamentally, if you don't have the right target, it doesn't matter what technology you put on it, you're going to go nowhere. So there's this whole focus of what's the right target and how to get that target. When people often talk about the technology, they focus on what I would call the technology around modality or the composition of matter. And the critical question for that is often, what can you touch with that, that you couldn't touch already previously, assuming that it's a really good target?

So let me just limit my questions to that second group, which is technologies related to composition of matter. I view it as bookends of small molecule, and I have bookends of biologics, you can talk about antibodies. And you increasingly see that field beginning to blend not just in terms of the technology, but you actually look at people and how they're trained. They're also -- the way that they're training is different.

So what I mean by that is your small molecules and you have, for example, let's take antibodies, which is really a basis of molecular biology. What weaponize that is the advances in molecular biology. And you see them being merged in antibody-drug conjugates that we've discussed. But you also see it in relationship to protein engineering; cytokine engineering, cytokine engineering not with an antibody drug conjugate, but with a tissue targeting where they're now taking those protein engineering and then tissue targeting them.

Those fields I think are moving. That's why it was very important that over the last 3 to 4 years that we be bring in that talent. So the person who leads our biologics enterprise actually came from NIBR. And we've brought in talent throughout an antibody-drug conjugate and protein engineering. But to jump-start it, everyone focuses on the Pandion deal because of the IL-2 asset, but it's not just the IL-2 asset. It's their tissue tethering sort of approach to protein engineering. So you're seeing that merging of that space.

The other point I would make is oftentimes in chemistry, it's about doing a quick screen and then using structure-based design to change that. Increasingly, with mRNA display in this, the approach of chemistry looks surprisingly molecular biology and looks surprisingly look like a biologics the way that they would do things. And increasingly, people are being able to make unnatural amino acids. They're being able to make small molecules that are 200, 400, 500 but in the 1,000 and 1,200 range. If you go to the biologics sort of field, you see them increasingly using structure-based design.

And so the 2 fields are merging. So there's a lot of movement in this. I do think in the nucleic acid field, the mRNA, the sRNA and the viral vectors are all places where I think the inflection from being neat and cool to potentially being ripe and robust has been shown over the last 2 to 3 years. And that's a place that one could argue that, in some sense, Merck invested an enormous amount in 2000 and 2010. And you might say they were ahead of the curve. But now that curve has come up, and I do think we have to think in that space as well. So that gives you a sense of technology from a composition of matter standpoint.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Great. And then maybe we can just shift gears a little bit. We'll drill into some of the key products. And obviously, the -- I think probably the main controversy that isn't really all that controversial, we know when KEYTRUDA will go off-patent in the end of 2028. So I think it really is more just the overhang of having such a large asset that continues to grow and succeed as a main driver of the story.

So I was hoping maybe you could -- we'll start with just maybe the 2 or 3 early-stage assets that you feel are honestly underappreciated at the company that you would first call out in this discussion where you think not just analysts underappreciate it, but broadly speaking, these are areas where you're particularly keen to express excitement in terms of the breadth of their application.

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Right. I think that's a great question. And what I'll do is I'll take a smattering from different therapeutic areas because we often focus just on oncology given the wealth of compounds and activity in there. We've already briefly spoken in terms of antibody-drug conjugates. And we have done a number of deals. We have internal programs. And some of those deals and internal programs, whether it be the ROR1 or the LIV-1, we will see the data, and we'll have to advance them.

I think we recently showed the ROR1 data in relationship to ADCs in terms of hematologic malignancy. I think that could be an important ADC for hematologic malignancy and could be mixed and matched with other assets in relationship to hematologic malignancy. But I think it's to be seen and the card has to turn over as to whether or not it has relevance in solid tumors. And if it has relevance in solid tumors, I think when that card turns over, we're going to have to rapidly expand in almost a KEYTRUDA as sort of approach.

We've already talked about islatravir, so I won't speak about that.

In relationship to recent deals or recent things that have been shown, we'll see where the Pandion deal goes. That Pandion deal was based on internal efforts we've already had in immunology in relationship to cytokine engineering and more broadly, those sort of pathways that I think are critically important. We're focused initially as a lead program with the IL-2 alpha, and we'll have to see how that card flips over in the '24, '25 range.

But instead of going from immunosuppression to immunomodulation, if that card should turn over, I would just recount that the number of disease states will also be -- almost -- we're going to have to be very selective. If that turns over, if the card turns over in '24, '25, in that sort of range, after the Phase II -- as we get clarity in the Phase II, those are programs that we have to be in a position that if they turn over, we have to be committed to them and advance them quite fast.

We have some assets in neurosciences that we are advancing. Some of them are clearly in ClinicalTrials.gov. We're interested in both symptomatic as well as disease-modifying aspects in relationship to diseases like schizophrenia, Alzheimer's. The assets that we have in symptomatics are the ones that are beginning to show their face in our portfolio in ClinicalTrial.gov, and they will be followed out by disease-modifying.

So those are places that I think, as a company, we should be very attuned. We have to build on our strength in IO. We have to continue to build oncology. We have to build our expertise in immunology, but it is also very important that we can't predict when the next sort of transformation happens in science and medicine. So where I'm not interested in doing is becoming a cancer and a rare disease or specialty company because I don't know that, that -- that strategy does not sit at least in my experience with how science moves. All of a sudden, something is there. And so we need to play in a broad way, but in a focused way.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

And I guess what you're saying is there's a lot of different applications for new technologies, for new opportunities to emerge and be focusing exclusively on isolated areas, very small orphan categories only or solely and uniquely focused on specialty disease is not necessarily the direction for Merck.

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Yes. I don't know that we're uniquely positioned to have a compilation of rare disease as a strategy for us. And it's not just a business strategy. It's not where Merck can have the biggest impact on science.

I'll just give a general example. RSV is in the news a lot. We approached it by having a passive immunization program, which is our antibody, and there are other -- this is a competitive space. We had an active immunization program that we did with Moderna. We have since allowed them to take over that program.

And we have an antiviral approach, but that antiviral approach is not focused on RSV or influenza right now. It's actually focused on coronavirus. And the concept is if we can prove it for coronavirus that our -- the published data would suggest and our data would confirm that if we are able to show importance in clinical events in relationship, for example, to coronavirus, then you look at the mechanism and you ask yourself, hmm, why should this not also work for RSV for influenza?

So we look at the RSV space, and we're like, we have a passive. We did work on an active, and we have an antiviral approach, but some of that sort of is sometimes hidden from the broader view both within the company and outside the company.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Great. And as we look at the -- you've obviously had some great data at ASCO in kidney cancer, a number of products that the company called out at ASCO. I was hoping you could talk a little bit more about LAG-3 and TIGIT development opportunities. Obviously, you're advancing these co-formulations. But how do the decisions outside of Merck or the data outside of Merck influence your decisions to move forward versus the data that you've actually generated internally on your own programs?

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

It influences us greatly. We have 3 sources of information. We have our internal program. And then it is often stated because we have KEYTRUDA and because we have incredible network of external collaboration, we have data that comes from those collaborations and then we have what I would call totally external. What I would recount is just look at the IO, IO space. PD-1 and CTLA-4 were given a Nobel Prize for 20, 25 years of incredible work.

And it's very clear what PD-1 does. Even in this space, there can be questions of how much the CTLA-4 add to PD-1 and in what situations do they do that. That immediately tells you that it is unlikely that any of these 1 agents, whether it be TIGIT, LAG-3, whatever, is going to lift PD-1 with just that addition to a different stage in all of the breadth and the depth of where PD-1 is.

So that just tells you that we track other people's data because that influences us. And because of that, what we think was important was to have every one of these compounds, that we have a CTLA-4, that we have a TIGIT, that we have a LAG-3.

And what I would contrast maybe some of our approach is that in each one of those asset, you could argue that other companies might focus on LAG-3 and blow that program out much bigger than we do. Other people who may have a TIGIT and they may blow up that program much bigger than we do. Our -- the history of the field and what we track is that we think that it needs to be done selectively and that we don't necessarily want to carry out all -- not only do we not want to, it's just not possible to blow out each one of those assets. And so we take the data from the broader field very seriously. And we have internal inputs, we have external collaborations' inputs, and then we have total external where we look very carefully at the data, the dosing, the compound, and we fit that in to sort of shape our strategy.

And this gets played out. There was recent data in relationship to PD-1 and LAG-3 in relationship to melanoma that was shown by another company. It's very clear what our strategy is. Our strategy is to ask ourselves, where should we drive PD-1 LAG-3, where is there an unmet need and where is the comparator very -- it's that comparator, it's that unambiguous promotable differentiation is defined by what you choose as a comparator. And an IO agent in CRC, you struggle to ask yourself, what is the comparator? There isn't really a comparator. So that's a place where you have a chance to potentially lay a beachhead in MSS CRC.

And so that's how our strategy might be different from other companies. And it's great that each company is taking different strategies even with these agents because in some sense, we'll see which ones work. And the fact that we're not all taking the same strategy, ultimately be -- may be best for patients because maybe our strategy will work and the other ones won't, and that will be great for patients; and maybe that their strategy will work and ours won't, and that will be great for patients.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

So maybe we could just talk a little bit about ILT4. I think we're going to maybe get some data in the first half of 2022. I think that was discussed on the ASCO Conference call. Just what -- from our perspective, as we think about ILT4, what would be particularly relevant that Merck is kind of looking for in those data? And then what would kind of prompt advancement of this program into a full Phase III?

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Right. And so your question of how we look at the field and how we use external. So that's a field where, from an ILT4, that data came from our interest in that early on and potentially distinguished from other groups was based on the data that we had in relationship to interrogating our data and asking ourselves what are the pathways that might be important for PD-1 resistance or refractoriness or less of efficacy.

And so that's how we came to ILT4 because that came from our own internal data. And so as we advance that, there are other companies who have moved ILT compounds as well. In fact, one of our closest collaborators, which is NGM Pharmaceutical also is advancing ILT pathways.

But it's not just that. It's -- when we look at it, it's fundamentally -- the way that I think of ILT is it's essentially a myeloid checkpoint. And the fundamental question to the field is we know that T cell biology is really important in relationship to tumors.

You could argue that cytokine is proven by -- in previous interleukin and the excitement in adding that. But there's always been a hypothesis, are there other cell types like the myeloid lineage or cancer fibroblast.

And so when we look at our ILT4 program, we're also tracking not just our ILT4 programs. We're tracking every other signaling cascade that is affecting that cell type and comparing our results with them and asking where should we position it.

So we're in signal finding. We're going to be making decisions in terms of Phase II and advancing to Phase III. But I just want to -- I don't want to get ahead of the data. But our interest in it is that -- our interest would be peaked if we saw situations where we thought, for example, PD-1 did

not work especially well in an important cancer and the addition of another agent would then give you a beachhead to say IO might work here. That would be something that would be very interesting to us and in some sense, what I'm just repeating to you is how we look at LAG-3.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Okay. Got it. And maybe we could talk a little bit about the ADCs, some of the assets that you've been licensed. The Velos acquisition I think for ROR1, obviously, very exciting. Maybe you could just help us understand where else the mechanism might be relevant and if there are particular -- it sounds like solid tumors would be an area of a potential breakthrough for this particular asset. Are there particular solid tumors that you believe are uniquely well targeted with ROR1?

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Yes. What you do is you just ask yourself, where are the tumors where it would make a huge difference, where do you know that pembro chemo works biologically and where by advancing chemo further with an ADC could help you. And then you then cross-reference that to what's the expression of ROR1 in those tumors.

And equally important, I think this is equally important, is that you have to ask not just what's the expression of ROR1 in those tumor cells. You also have to ask yourself, what is the expression of ROR1 in the non-tumor cells because that tells you that index of what you want. And this is in the public domain. ROR1 is pretty -- it's pretty -- its expression is pretty low in normal states.

It's something that's early on in embryogenesis and early in development, but it really drops down. And that in certain tumor state, the expression of ROR1 does increase. And it's that delta between the baseline expression of the normal tissue and the high -- the "elevation or magnification of the ROR1 expression that one might think as a principle, a basic science principle of where you would go."

And then clearly, you have to then go in that tumor type, is there room for -- is there evidence that pembro chemo would work? Because if there's not an evidence of pembro chemo working in that setting, then you have to ask yourself, I have a next-generation chemo. Am I -- is that a logical best or is that a wish, right? Is that a real apple or is that an apple in your eye? And so that's how we've walked through it.

I think, if I'm not mistaken, there are other people who have jumped on the ROR1 bandwagon. I believe that there may actually be some solid tumor cell therapy companies who are directing it through ROR1. We track what they do simply because it teaches us how to think about ROR1, not necessarily about the cell therapy.

So I think our interest in it, in solid tumor, maybe before other people and in relationship to ADCs, but ROR1 as a marker that other people are looking at is something that is gaining momentum, and we'll just have to see where the data takes us.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

And in terms of just sort of time lines for when some of those answers may be elucidated, are we looking at that as some of the events? I mean as you look at 2022, is that a time frame within which you're hoping to see a number of Phase II assets really advance and provide the kind of clinical data that would advance you into Phase III or perhaps could even be pivotal-type data sets, whether it be, obviously, the Peloton acquisition with HIF-2 alpha advanced that asset very, very quickly. The company already has products available.

You've got the ArQule acquisition, which could be very tumor targeted, and I think many of us expected that could be advanced a little bit more quickly. But just hoping to get a little bit of a better sense of when you feel some of these programs that are in Phase II will have data for investors to really think about the next stage of Merck's evolution.

**Dean Y. Li** - Merck & Co., Inc. - EVP

So specific in relationship with ROR1, the data that we have with hematologic malignancy looked good in the beginning and continues to look good. And that's where, in some sense, we talked about exploring in solid tumor. The focus is we need to execute on that for hematologic malignancy, and we have to do it fast, and we have a time line in our brains as to when we want that looking for approval. And that's not going to be in the '21, '22 range.

But I think going a little bit further and one can sort of calculate what our expectation is. But we think that those cards will turn over in the not-so-distant future not just as to whether we want to do a Phase III, but we're talking about really setting us up for approval for hematologic malignancy. That's the focus. No different than belzutifan, the focus with VHL syndrome, not to say that you're not going to do the other things. Because you can talk about what you're going to do after the beachhead, but if you don't land the beachhead, you don't have anything.

And so I just want to sort of separate what we were talking about the solid tumor from the heme space. We are very focused in the heme space in the ROR1 ADC that's driving that at the speed of belzutifan. That's what our point of view in terms of heme malignancy.

In terms of the other sort of things where the card will turn over, that card will turn over, and it will turn over in solid tumors over some period of time. But I need to be very clear. That card turning over, if it turns out in a cancer that there's not -- there are other advances in that cancer that may make the comparator harder and therefore, your unambiguous promotable differentiation is more difficult compared to another place, of course, we're going to go and look to where we can have a comparator that is very clearly differentiated.

And so I don't want to presuppose that I know what that answer is as we're doing those signal finding in solid tumors over the next couple of years. But for the ROR1 ADC, it's can we land that beachhead in heme malignancy? Because there, I think the data that we've presented is quite convincing, at least in our minds that this is a no-brainer that we need to move this with speed and with focus, no different than the data that we saw in relationship to belzutifan in VHL syndrome.

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**Seamus Christopher Fernandez** - Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals

Great. I wanted to drill in a little bit into -- I think we talked plenty about HIV. But in terms of the hurdles necessary to get to an every 3-month combination of islatravir and lenacapavir and move that into Phase III, maybe we could just talk about what's the biggest risk to the program potentially failing and what Merck is doing elsewhere to potentially hedge that risk.

And obviously, if it were to move forward convincingly into Phase III, what is the profile or kind of the minimum duration profile? Is it 3 months is kind of the minimum duration that would have you advanced? Is 2 months sufficient? Obviously, we're seeing some long-acting program -- longer-acting program efforts starting to emerge at the -- versus the competitor. So just love to get your thoughts there.

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**Dean Y. Li** - Merck & Co., Inc. - EVP

Right. So first of all, I do -- I need to separate, though, when we talk about Q 2 months, Q 3 months, Q 6 months, those sort of things, we're not talking about an oral pill, right? We're talking about some sort of injectable. So one of the issues that I just want to sort of emphasize is the ability to get an extended HIV oral pill. Maybe not 2, 3 months, but if we could get Q week or better, that would be fantastic.

So in some sense, I don't know if I'd call it a hedge, but our ability to do a Q week oral combination is very important to us. And we think that there is an opportunity to do with MK-8507. We think that there's an opportunity to do with lenacapavir. And we think that there's a chance to do it potentially with integrase inhibitors as well. So I -- at least in my mind, I ground myself there.

The question of Q 3 months then sits and you ask yourself from an injectable standpoint, does -- how good is the other compound? Because I know how good islatravir is. How well -- how good do I think islatravir is? We've shown data where it suggested that you could make an implant that's at least a year. I mean that tells you how good islatravir is.

So the fundamental risk to the program, at least in my mind, for getting Q 3 months or Q 6 months or something like this, is what's the other compound and how well can you co-formulate the 2? And then how -- what's that volume, what is all of this, what's the local -- all the things that go on, you now mix 2 compounds together, what's the local reaction in this.

And so it's what I would call the blocking and tackling. The non-sexy part of drug development and drug discovery, that will be important. Do you have a compound that can match? We already know what islatravir can do. We've shown it when we've shown the implant. Oh, my heck, when you look at some of those curves, you sit there and you go, there is a possibility of an implant that, that could be a year. Then you sit there and you go, well, tell me the other compound that I could mix with islatravir, I can co-formulate it, put in an injection and give someone.

In terms of the minimum, I would say that in my estimation and from both family members who are infectious disease and colleagues who are in infectious disease and both people who are in the developed countries and the people that I've learned from, from the Gates Foundation who are in Africa, the number that comes out to me that's surprisingly similar for both markets is you probably need a Q 3 months.

So that answers your question. You probably need a Q 3 months. That's where people would be comfortable to have that sort of reach. But first, we have to achieve the profile of doing all the really important sort of work that we have to do in relationship by making a co-formulated with a compound that has a resistant profile that allows us to match islatravir.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Got it. And maybe we can just move to sort of wrap up in some of the other areas of interest. Obviously, you're a cardiologist. Merck has a number of efforts across cardiovascular disease. You mentioned the inhaled sGC for PAH. In terms of some of the other areas of development, where do you hope to see the company in 2 to 3 years?

Obviously, you've got efforts in NASH. Is there interest in developing assets for obesity? And then separately, obviously, resistant hypertension is an area that is of growing interest and high complexity. Just love to get your thoughts on some of those areas and the importance of approaching those 2, frankly, very large markets.

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Right. So we've talked about our interest in left heart failure, right heart failure. We all have to recognize that thrombosis still is an important program -- problem in relationship to high-risk cardiovascular events. And in certain patient populations, that will become increasingly important, especially with the ravages of diabetes. So I'm still interested in that field.

Again, the concept of there's always been discussions of inflammation in cardiovascular.

I've always been very intrigued by the work of the CANTOS trial and how to make that real. It is unclear to me that you could use an antibody to make that real and to understand what are the pathways that could make that real. There's been a long legacy of trying to affect vascular inflammation that have not really lended themselves to true success. And I wonder whether there are advances in technology that will allow us to do it. So that's a place.

But you also laid out NASH, which is essentially what we're talking about is metabolic conditions. You can think about cardiovascular disease as a metabolic condition, high LDL with inflammation gives you cardiovascular disease. Well, in some sense, you could view NASH as the same thing. You have this milieu of metabolic dysfunction. It leads to inflammation and you get fibrosis.

So those are places. That intersection of metabolic diseases more broadly or metabolic conditions that then trigger inflammation is a place that is of interest to me. And to be frank, that's why I hired the person to be in San Francisco because when you look at their CV, that is exactly what their CV is. The interface between inflammation and metabolism.

So those places are places that I think that we need to grow, and we will be growing. And having run the discovery organization, I am hoping that those cards flip over so that increasingly, we begin to make choices about advancing in Phase II some of those assets. And then that will become more visible in the near term because that's a place that if the data sorts out, those are places that we'll be very interested, that inflammation, that metabolic dysfunction and inflammation.

The issue about obesity directly is I think obesity is really important. But every time I think about what field we go into, I have a very strong basic background, but I also have a translational medicine, I immediately think about what does that clinical trial look like and what is the end point?

So obesity straight up, I'm not so sure that's a place that we will play simply because I think about the end point. These other places, it's very clear to me what that end point is. And it becomes a more linear process of me designing and understanding what my profile has to be based on new biology, new technology that I want to advance.

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**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Got it. Great. So I think maybe we have just time to wrap up. Dean, maybe just from your big picture perspective, if there's something that you feel needs to improve at Merck, and I think it's been a little bit of a critique of Merck Research has been the pace of development at times.

If there's something that you'd like to see changed at Merck, is pace something that you think can be brought to bear on Merck Research? Or are you pretty happy with where it is? What would you just say are kind of the 2 or 3 things that you'd love to really see evolve at Merck alongside with Rob in the next couple of years?

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

I would just lay it out. And maybe I wouldn't use the word pace per se. But it's -- in some sense, all pharmaceutical companies are data and technology companies, and they always have been. And so some of the pace relates to how you talked about -- we talked about taking different inputs of data, your internal, your collaboration, the external. The pace and the speed with which we digest that information I think could be improved because that's the -- that -- those are the levers that make people hesitant to move.

So the pace by which we are very aggressive within our own data, leading to what I talked about why we did ILT4, that came from our own data. But the speed with which we take these inputs and digest them and not just digest them because that digestion often leads to an association. It's not through causation, but moves to action. It's like, okay, if that is true, this is the action. But half of it is in the data sort of clear in my mind the speed with which we do that. And I think that's something that we can improve and we are improving.

In terms of technology, I think we say that we're modality-agnostic, but we can't do everything. And so to me, really defining, I'm going to do small molecules. I'm going to be in biologics. I am going to do protein engineering. I am going to be in ADCs. I'm going to play in that space where small molecules are getting larger. Those are places that you have to make a commitment, but it's very important that you don't make the commitment made on the platform because platforms don't make products. Products make platforms.

Platforms -- and so the fundamental thing is, can you find the right applications of those technologies, can you focus the company on it and can you execute it and then use that product and that platform in advancing that in a different sort of beachhead, which is a beachhead for your technology.

I think sometimes when we talk about being modality-agnostic, it's almost like -- it's almost too fluid because what you have to do is you have to make it internal. You have to make it internal and you have to bring it in for you to be truly effective.

So when I look at the -- what I think we can build on, it is how we use our data and how we think clearly about what technologies we're going to embrace and equally important, what technologies are we going to not embrace internally but keep our pulse on. And that clarity of purpose of doing that creates the ability to move faster with pace, in my view.

**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Great. Well, Dean, thank you so much for a great discussion. Really looking forward to all the advancements that hopefully are coming from Merck's Research Labs and appreciate all the time that you've given us today. Thanks again and look forward to, I guess, the second quarter results and more data to come and congratulations on today's success in cervical cancer.

**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Right. And just hopefully, next time we do this, we'll actually not be looking at your of background, we'll be in your background.

**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Yes. That's helpful. Sounds good. Take care.

**Dean Y. Li** - *Merck & Co., Inc. - EVP*

Take care. Bye-bye.

**Seamus Christopher Fernandez** - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

Bye-bye.

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