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PRESENTATION

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Hello, everyone. Thank you for joining us. Pleasure to have Merck management join us. There's tons to talk about. So I'll be talking at 1.5x speed, but let me turn it over to you guys to kick things off.

Peter Dannenbaum - Merck & Co., Inc. - VP of IR

Umer, thank you very much for having us. Always a pleasure. With me is Dr. Eliav Barr, who is -- this year he has begun to lead our Global Clinical Development at Merck. He's got a long and distinguished career here, most recently Head of Medical Affairs, but also leadership roles in oncology and infectious diseases. And with a cardiologist by training, and I just learned that's why he came to Merck back in the mid-'90s was because of the amazing cardiovascular work we were doing then.

But happy to turn it over to you, right, to get to your questions.

QUESTIONS AND ANSWERS

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Outstanding. So let me kick things off today with a topic on Merck I never get questions on, but I think it's highly relevant. And it's highly relevant less because of what this new modality is, but more so because of what it could mean to KEYTRUDA. So I'm referring specifically to TIGIT. And my question is this. There's a trial you're running -- so there are several trials you're running. They mostly report out in '24-'25 time frame, but there's also this Phase IIb, which could come out sort of summer next year. Could that be a registrational trial to form the basis of a fixed-dose combo for KEYTRUDA?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Thanks for the question. So the trials which you're referring is KEYNOTE-002, which is a Phase II study that looks at the combination of vibo/pembro with docetaxel on its own and against the standard of care, which is docetaxel in second-line patients who failed on a PD-1.

It's a Phase II study with Phase II statistics. And my strong suspicion is that it's going to be nonregistrational. So that's what our base case is. We don't think it's going to be registrational, but it will be very informative and give us a very broad ability to understand the value of that drug in that setting.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. Is there a biomarker in lung by any chance or no? I know you guys hinted at it. It may not necessarily be the case.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Not in this study and not currently as a patient selection factor. We always look at a variety of different biomarkers in the context of our Phase III programs.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. Makes sense, makes sense. And also, I know for your larger study, the KEYVIBE-003, it has sort of PFS and OS across various PD-L1 cutoffs. How are you thinking about structuring our hierarchy? I feel like that trial is going to be much more important, perhaps more so as a registrational intent on that one.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Oh, yes. So that is a registrational intent study. And it's a trial that compares pembrolizumab and vibostol members in (inaudible) against pembrolizumab. Now what's unique about the study and I think is unique to our ability to conduct such a study is that we're evaluating patients down to the CPS 1%.

If you look at the other studies that examine a PD-L1 or PD-1 with a TIGIT, they're looking at the greater than 50% population. We're looking at the broader population starting at 1% but power -- but the study is large and powered to look at various cuts of data. And that's really important because only pembrolizumab has got the ability to be evaluated in the 1%-plus population.

And I think that will give us a lot of really exciting information about where is the best place to add vibostolimab and a much more richer data set from which to demonstrate the value of the combination. So in that study, we're looking at both the greater than 50%, the all-comer population as well as the 1% to 49%.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. But the first analysis is in the PD-L1 highs. I'm sorry, I didn't -- if I didn't hear you right?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

We have -- it's hard to explain, but we have a very sophisticated statistical plan that enables us to look at both.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Okay. Got it. Okay. Got it. As well as -- sorry.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes. Go ahead.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

I was going to say there's also this extensive-stage small cell trial where OS is the only endpoint. And it looks like in terms of sort of order of readouts, maybe that small cell study comes out first before the other Phase IIIs come up. Would you expect the same?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

I don't know. I don't think. I don't know that I can say. I mean, it's a question of enrollment and endpoint. So all the studies will come in rapid-fire succession starting in the next couple of years, so who knows. But small cell question is hard. So we'll see how it goes.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Makes sense. Makes sense. Would you -- I mean, how are you thinking about structuring in terms in these trials to terminate them when you have to? And I know we saw SKYSCRAPER-02 from Roche, and small cell didn't quite pan out from a TIGIT perspective. So -- and I'm sure you're thinking about R&D allocation and prioritization all the time as well?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

First of all, we've got a lot of confidence in TIGIT. So we're not -- I'd be a little leery about saying, well, just because, let's say, a competitor's study was negative, that means that our study is going to be negative as well. Recall that there are many trials were eccentric didn't succeed and pembrolizumab did.

And so the read-through might not necessarily be one-to-one. We're very prudent in our investment decisions for TIGIT. The focus is on lung and cervix as well as in small cells, as you know. And so we'll see where the data lies. But again, I just would be leery to consider that just because, let's say, a competitor's study was negative, other studies positive. Just look at adjuvant kidney. Here, we're -- we've got a positive trial and the other 2 did not.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Right. I'd be curious, you singled out cervical. Is there some prior data that informs your opinion on that?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Well, just the -- it's important to remember that you've got a good -- that pembrolizumab is extraordinarily active in there. And so we think that there's a good opportunity there from -- in early-stage Phase I trials, signal generation seemed to be favorable.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

I seed. Okay. Okay, not based on any specific data. Okay. Got it. Okay. Excellent. But Eliav -- and I kind of went right into TIGIT in part because in my mind, I was thinking, what are some of the levers that could really turn KEYTRUDA into not a 2028 franchise but maybe, I don't know, 2035 franchise, something like that? And TIGIT to me, stood out as that.

What would you -- as you're thinking about across your portfolio, what do you think are the opportunities for innovation within oncology, where KEYTRUDA as a franchise could have many more years in combination or a different formulation, et cetera?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Well, so first of all, I would say that the oncology pipeline that Merck is going through a pretty major transformation. So we're looking at the world not only as how can we use pembrolizumab as a foundation, but also a broader question about where the best innovation is for the cancer patients.

Now within the pembrolizumab concept, our family, the idea here is to do the co-formulations and evaluate how further immunostimulation and different kinds of immunostimulation might improve outcomes. And in addition, we're also thinking hard about what other ways that we can improve on the delivery of pembrolizumab so that patients can have even more convenience, particularly in the case of patients in the adjuvant setting where we're spending most of our research time now and where the idea of reducing time in hospital getting infusions would be very, very attractive indeed.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

So -- okay. Got it. So subcu for adjuvant in particular, maybe not necessarily metastatic?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

I think either or. But I can see -- so you ask yourself, what do patients experience when they get cancer therapy. One of the amazing and exciting things about pembro is that it could just, first of all, extend life and feel better. And then the last thing they want to do, whether it's metastatic or adjuvant, is to spend a lot of time in the hospital.

Similarly, I think that the infusion centers, the oncologists are really not interested in keeping patients too long there because there's a lot of other stuff going on. They have throughput questions and issues, and they also don't want to expose patients who are otherwise healthy to the hospital environment. So I think there's a lot to do here.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. And Eliav, remind us, what will be the timing of subcu launch? Is it next year? I think you guys have shown Phase III data recently?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

No. We have data -- so we have data with our -- the first iteration, which is being able to proof of concept the subcu administration pembrolizumab. But we're interested in improving the distribution of the pembrolizumab subcutaneously. So we have a Hyaluronidase containing formulation that is in Phase I development now. And that will be likely the one that we're going to take forward, simply because it's going to be a more convenient and consistent absorption.

So we have a Phase I study ongoing. We'll take a look at the results and then initiate a Phase III program. It will be -- it will take a couple of years to do.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

I see. Got it. So there's that. And then among the co-formulations you're working on, which are the most promising? I know we talked about TIGIT, but there's some others. So which one would you flag?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Well, I think the big ones are TIGIT and LAG-3. With TIGIT, there I have -- we have the biggest investment for good reason because I think the signals have been pretty good. And as I mentioned, we have a differentiated program in lung cancer that will read out in due course.

But there's more work to be done. There's a lot of signal generation going on in TIGIT. And so we continue to be excited about it in cancers outside of lung. And if you look at our KEYMAKER study, you can see that there's a lot of TIGIT arms in various settings. So I would be on a lookout for TIGIT studies going forward.

LAG-3, we've got 2 Phase III programs: one in MSS CRC and one second-line Hodgkin's. There may be others that come along. We also have other studies in combination in renal cell and so on. So lots of work going on. I'm actually quite interested in the TIGIT asset. I know that people are -- looked at the results of Roche and said, "Oh, well, it could be paused a little bit." But at the same time, pembrolizumab is special.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. Do you -- got it. Eliav, can I also ask then, knowing how well Bristol is doing with their LAG-3 co-formulation launch, do you think the bar is really just -- as long as you have a 15 -- 0.85 or better hazard ratio, that's a pretty compelling enough data set for clinicians to do a lot of switch?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

I don't -- I think that each area is different. And I think that we would aspire to do better because I think it's going to be important from a payer point of view as well.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. Do you hear that from payers?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes. I mean, I hear it from patients, too. And most I would propose that you got to do something that's meaningful to patients, and you've got this pipeline and we would...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

And Eliav, how -- and Peter, I'd be curious if you have feedback on this too. Like as you guys think about it longer term, and again, this is so critical to sort of Merck's future and a lot of the actions that happened as a result of that. How do you guys think about some of these incremental innovations in IO? Is it 1 plus 1 equals 2 in terms of pricing? Or are these one -- or is it more like it's KEYTRUDA and the next agent could be half the price, but it's really just ensuring that KEYTRUDA stays durable? How do you guys think about that? Or is that something you guys haven't -- just haven't said much on yet and you want to see the data?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes. Things are so complex. It has to do with the data, the IRA, other regulations. It's going to be -- our commercial colleagues have their hands full thinking about all of that.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Yes. Peter, you guys base case is IRA. KEYTRUDA is an IRA in '28, correct?

Peter Dannenbaum - Merck & Co., Inc. - VP of IR

Correct.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Right. But -- and I guess that was a loaded question because to be in IRA, there must not be a biosimilar. So I guess as a base case, you guys are taking the conservative on both sides, either biosimilar or IR or both presumably?

Peter Dannenbaum - Merck & Co., Inc. - VP of IR

Right now, we have said that IRA will impact KEYTRUDA in 2028.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Makes sense. Makes sense. Excellent. Eliav, just before we move on from other IO, I know there's other assets. There's CD27, ILT4. Anything you would flag? Something we should look out for?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

We're -- we have a pretty extensive program. And all these drugs are myeloid suppressed are meant to affect the potentially suppressive microenvironment on myeloid cells. We'll see. I mean, this is how (inaudible) science. So...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

So which one was that again? I'm sorry, I missed it.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

ILT4.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

ILT4. Okay. Yes. Okay. Eliav, I have to admit there's a deal, I think you were probably a driver behind it that Merck did recently, which got my attention but also confused me a lot, which was the personalized vaccine from Moderna. And I was like, what would you guys have possibly seen knowing that some of the prior data has not quite been so overwhelming.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Well, it's interesting. The PCV field and the cancer vaccine field has been a long, long, long and long-standing field. And when we joined up with Moderna to think about these programs, we decided that we would do something pretty definitive.

First of all, create a -- focus on the immunoresponsive tumor that has a lot of neoantigens. And that's, of course, melanoma. Second of all, to use the very best technology to be able to generate as many neoantigens as possible. So that's the mRNA vaccine. And the third thing is to do a definitive evaluation, which is a Phase II study that has 2 arms and enough to make a difference in terms of our understanding of whether there's an effect or not; and patients, which means following the patients up for a sufficient period of time, 2 years or now plus.

And so the data that we saw recently was compelling, very compelling. And really, we change what our Phase III programs are going to look like going forward because we have -- we now have a collaboration with a partner who's shown itself to be extraordinarily innovative and very, very innovative also in the manufacturing and in the distribution. So we're going to have some really exciting clinical trials in melanoma and other indications.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. But Eliav, just to be clear, this is a trial that's still ongoing. And there's only so much data you could have possibly seen, basically with some sort of interim cut. How did you think about that in the context of a cut of a Phase II? And I'm assuming you wanted to see the versus control, not just overall blinded. Do you have that type of confidence?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

So again, we -- the data that we saw are really great. You'll hear about -- by the end of the month, they should be able to provide further information from Moderna as their study. So -- but I'm confident, let's put it this way. I'm confident that we...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

You saw mature enough data. Got it. Okay. Good to know. Good to know. Eric, anything we've missed so far in the IO before we move on beyond IO.

Eric Musonza

I just wanted to get a quick update on the (inaudible), as you've nailed down the formulation and dose there.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

You're a little...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

He's moving to BTK. He's moving to BTK.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

I'm sorry. Yes, yes. Sure. Yes. So there's a Phase III trial now on ClinicalTrials.gov, and it's 65 milligrams daily of nemtabrutinib. And we're going to have a blowout of that program in 2023. So I'll keep an eye out for a bunch of other studies going forward.

It's a really exciting opportunity for us. We want to expand our hematology presence. It's an area where KEYTRUDA has a very targeted area of influence. So this is a new area for us. And you can see that we're interested in that, not just with nemtabrutinib but also with (inaudible) and the ROR1 PVC.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Eliav, has there been -- I mean, I'm curious -- Peter, I'd be curious what do you think about this, too. Has there been -- what's been the perception within Merck around the ArQule acquisition? Clearly, a very active drug. But I think time line-wise, ArQule at that point in time when the acquisition was done was tied with Loxo. And I feel like because of some of this formulation stuff and doing things the right way and at the Merck quality level, Loxo has leapfrogged a little bit timing-wise, at least. How have you guys thought about that whole angle?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Well, let me start on the clinical side, and then Peter can add what he feels would be useful. First of all, Project Optimus from the FDA has been a very important and new challenge for all of us in the industry. And I think it's been important for us to be able to secure a dose that would be really quite useful in patients. And it took us a little bit of time to do that, and that's where the 55 came along. We looked higher, we looked lower, and we've got the right dose now.

The reality will be that -- and especially given IRA, we're very interested in having a broad set of indications upfront. And I think that that's -- at the end that we're -- while it appears that the competition may be a little bit ahead of us, it's not the first -- as I say, with our clinical trials, it's not the first patient and it's the last patient out.

So let's just see what the data shows and what the future shows for us. We're confident in nemtabrutinib. We think that it's going to be -- have a meaningful benefit for patients. And as I mentioned, we are going to invest in not just one trial but a set of trials that will start in the near term.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Eliav, the claim to fame for Loxo on this -- sorry, go ahead, Peter. Okay.

Peter Dannenbaum - Merck & Co., Inc. - VP of IR

Nothing to add to that. Okay.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Okay. The claim to fame from a Loxo perspective is that in BTK-experienced patients, it was able to put up very, very good response rates. Can you speak to any data generation you guys intend to do in a similar indication as well, especially as we head into registrational studies?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Sure. I mean the earlier studies that (inaudible) did was in heavily pretreated patients. So I mean, I think that's important. So the -- and I think we'll have similarly studies and failures.

It was interesting to see the pirto data. There were some -- there was a publication in New Journal looking at mutations that -- escape mutations have come from that. And as we look at our drug, we don't have -- we wouldn't expect that some of those mutations would be impactful to nemtabrutinib.

So I look at this, my background in virology tells me -- and after all, cancer cells are just slower viruses in terms of mutation. And it seems to me that these drugs are going to have overlapping but not identical resistance profile. So I'm very keen on those trials in experienced patients to be able to determine what nemtabrutinib will do.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

But Eliav, is it simply covalent/noncovalent? Or have we just never studied a BTK reinduction? Because that -- I haven't found a trial where BTK, you took it, you failed. You took a BTK again and maybe you do respond?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes. I think -- so I think it's -- there's specific mutations that inhibit -- that basically make the covalent binders impossible to...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Sure. C41?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes, the C41. Now the problem is, is that -- so now you have other mutations. When you cross against a particular cancer pathway, there'll be escape mutants that come out. It's natural and you see that in a whole variety of cancers.

So the question that's going to happen here is pirtobrutinib and nemtabrutinib are in the same class, but they're not the same molecules. So I think both molecules will have benefit in those situations, where patients have a mutation that disables things like ibrutinib and acalabrutinib. But what the issue will be is whether those other mutations will also create disadvantages for the relevant molecules. And that's actually where the proof will lie in the Phase III programs.

There's many, many analogies in the virology field and in cancer itself where you have these escape mutations and different drugs of different capabilities around that. So I think that this is a very early -- we're in the early phase of this field. I think that we -- whereas people sometimes look at cancer and think about time lines and how quickly you can get the first to market, I actually think it's -- in this particular area as we're looking at things where mutation is -- where escape mutation is really important, we want to look at the right doses so that we don't induce escape mutation. And we also want to make sure that we understand the pattern of resistance to ibrutinib and others where our drug might be interesting; and also, frankly, the resistance mutations to these next generation of drugs because it may very well be the case that one can cover for the other in story.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

So -- but it sounds like you're open to the idea of BTK reinduction for your development path as well?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Sure.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Makes sense. Okay. Excellent.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

The science is novel right now.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Makes sense. ROR1 ADC, any thoughts there? Should we be spending a lot of time on that?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Well, I mean, I think we made the purchase of this product with the idea that it might be very active, particularly in hematologic cancers but also in solid tumors. We're still in signal generation in solid tumors, but we're now finalizing the appropriate Phase II, again, with Project Optimus. And hopefully, we'll be able to get Phase III studies in the heme space moving forward.

So again, it's early days, but we're very bullish on ADCs. And I think the field is -- and we'll see what the benefit of the struggle will be in our -- in the studies in relapsed recurrent DLBCL.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. Got it. On ADC, I know there was a very high-profile series of press reports, et cetera, as well on this topic as well for large M&A transactions too. I know you guys have historically always been very consistent about having a very strong interest in ADCs, and you've done a bunch of deals. But I think on the one company mentioned in particular in the press reports, I felt like some of the transactions you did do with them have underwhelmed, tucatinib and a couple of the ADCs that came in from that side.

Granted, there's not everything on this works out, but I'm just curious where you guys stand on willingness to go down that path of sort of very large deployment. And then I'm not necessarily pinning it down to any one company versus just doing a bunch of series early-stage deals on ADC?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Sure. So first of all, ADCs are obviously the really hot topic of the day in terms of new agents. And so we're very interested in that. If you look -- and again, I'm going to be company-agnostic here. We look at one pipeline so that both our internal and external pipeline will look the best alternative among all of those, so internal pipeline and external opportunities.

Enfortumab vedotin has been actually quite a success. And as you know, KEYNOTE-869 cohort K has been filed, and we are looking forward to seeing what the FDA has to say about that, showing the benefit of combining enfortumab vedotin with pembrolizumab in bladder cancer.

The other drugs that you mentioned are early in development. Tucatinib is not an ADC, so I'll leave it. In terms of -- and of course, we just talked about ROR1 ADC. But then the drug that I think an exemplar of our work in the ADC space is actually our in-licensing of MK-2870 from Kelun. And this drug, which is ADC, is really, really active. And we've been able to generate quite a bit of -- quite a few signals.

And I think what you'll see in next year and subsequent years is a heavy emphasis on this particular one as well as other business development opportunities looking at ADCs that differentiate and can help with -- in a targeted way with relevant patients.

I think we have shown that pembro plus chemo is a really strong regimen. So now we're going to -- part of the work, not all of it, part of our work is going to be on strengthening the chemo arm through those ADCs. And again, 2870, I think, is going to be a really big deal for us going forward.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Interesting. From a lung perspective as well?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

From a lung perspective and others. But we've -- one of the things with 2870 that I'm really excited about is its activity on a whole host of tumors.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

And remind me the -- this is also topotecan-based payload, 2870?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Correct. It's a Topoisomerase inhibitor. (inaudible) is the drug. It's a really great molecule. And so...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Do you think it's differentiated over the Topoisomerase -- sorry, out there right now?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

I think it's going to be -- the differentiation will -- it's hard to say because we don't have head-to-head. But we -- but I can say that -- one of the things with ADC just to remind all of us, is that it's not just an antibody, it's the linker. It's not just a linker, it's not just the (inaudible) the drug and so on and so forth. So there's a lot of differentiation that may occur that way.

But what I could tell you is that from the perspective of objective response rates, pretty damn good. So looking forward to being able to leverage 2 things that's differentiating not about the molecule but about Merck, which is the fact that pembrolizumab is dominant. And our engine -- our clinical trial operation engine, which is -- you might say, what's a big deal about that?

Well, recently, there was a paper that looked at what are the predictors for enrollment speed and there's one very interesting independent determiner of enrollment speed in oncology trials, and that was the company called Merck. And that was very, very exciting for us because it showed us that our model for trial operations represents a differentiating feature. And it's for that reason that I'm very bullish on 2870.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

This is SKB-28 -- SKB-264, right?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes. SKB-264.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

And which is 2870 on Merck's...

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

That's old-school name.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

That's right. But -- okay. So 2 things: a, you said, "pretty damn good" on ORR. And I'm assuming you're comping that versus some of the other TROP-2 ADC data sets?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Okay. And the other thing is -- and I'm assuming all of that is from sort of this basket tumor study that were running that 400-patient trial. Is that right?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes. I mean, the trials currently are being run by our SKB colleagues there. And it's not just in China, there's been -- it's throughout the world. So a lot of good diversity of patients. And we're moving along quick.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

And Eliav, I'm curious where -- how -- and not even your opinion but just sort of the broader Merck opinion, as you said and have these discussions at the executive committee level. If you guys can find some of these promising therapies in early development, then why have -- why allocate very large tens of millions of dollars then because if you could find stuff like this in ADC land?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

I see -- look, I think that, as always, what we're trying to do is to create the best possible pipeline to address a very complex disease like cancer. If it comes from internal sources, yes; if it comes from smaller companies, fantastic; if it requires us to partner with larger companies, then we've done that successfully. Just look at Lynparza, look at Lenvima, and I think that those are -- have been really good partnerships. So we're agnostic. It's about the quality.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

So I'm realizing I got carried away by oncology, so I'm going to switch immediately and ask you some more rapid fire now. Factor XI, you have data coming in 2023. Has there been any interim on that in the ESRD population?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Not yet.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

No interim. Okay. And has your confidence changed in this in light of some of the emerging data from Bristol, which has been somewhat underwhelming?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Look, so we have a very different philosophy of development for this drug. They're -- in the land -- in indications for Factor Xa inhibition is pretty darn good, I mean, as Bristol would say, of course, right? The differentiation with Factor XI on safety is a little bit -- can be a little bit tricky, frankly, because you never know until a very, very, very big trial is complete.

On the other hand, there are areas of medicine where there's enormous unmet medical need, and Factor Xa inhibitors are not used there or cannot be used in that sense. That's why we've chosen end-stage renal disease.

We've had experience with that before. We've done this in the HCD space and elsewhere. So that development plan in ESRD, I think, is a really strong way of developing this drug in a manner that will improve outcomes for patients who really need a good antithrombotic but cannot benefit from Xa. That's a different strategy altogether.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Makes sense. Sotatercept, I know there's a very important trial on the Xenith side that's going to be coming to with the morbidity/mortality endpoint. In light of all the STELLAR data, how has your confidence changed, realizing that it was a slightly different outcomes endpoint and STELLAR than there is in Zenith?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Well, STELLAR is STELLAR. There's nothing to say about that. Sotatercept is really great. It's a profound benefit in that patient population. Now recall that one of the 8 of 9 secondary endpoints that we hit in our statistical hierarchy was time to clinical worsening. And if you look at the components of time to clinical worsening it includes the morbidity and mortality endpoint that is in Xenith.

Now obviously, Xenith is in a sicker population. But I think that given the profound benefits that we've seen with sotatercept in the STELLAR trial, there's a good chance of being able to show a benefit in Xenith. We'll see. Now there's an interim analysis that will be done. We're -- it's still enrolling the patients. So it's not going to be tomorrow, but we'll look very carefully.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

But there's a 2023 interim, right, on Zenith?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

It's event dependent. So I'm not going to commit to a particular time frame. But it depends on enrollment, and it depends on the event rate and making sure we've got the right event rate. So once we do -- once we hit that number, we'll do the interim and we'll see where we go.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. The CADENCE trial, which is Group II PH, or this is not the PH, we've always talked about over the years, what's your level of confidence in that?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

The Group II PH, as you mentioned, is a different kettle of fish than PAH. But what we're trying to do is to find the patients that are -- who respond to the increased pulmonary vascular resistance that pulmonary arterial pressures, I should say, that are caused by less heart failure is disproportionate. So this is a subpopulation of patients with heart failure. I think that the challenge will be to find the right patient population, but I think that the biology seems quite reasonable.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Are you guys doing that in the trial, like fine-tuning that right population?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Absolutely. Yes. And the good news is that one of the things that Acceleron did incredibly well is assemble a really world-class set of advisers who are just the top of the class in pulmonary hypertension. And I think that the leaders of the CADENCE trial have been very thoughtful in helping us to develop the studies. So I'm really -- it happens. But it's Phase II. So we'll report as...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Eliav, as a cardiologist, what's your favorite cardiology drug at Merck?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Now you're going to kill me. Oh, boy. Well, sotatercept wins the day every day, but that's not fair because you have already results.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

I thought you were going to say -- yes, next one, yes?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

My next one is -- my next favorite is 616, I have to say. And sorry guys who are listening in from the other teams, I love you all. The -- and why 616? Because 616 is a tour de force in medical chemistry that will democratize the ability for people to access PCSK9 inhibition. I mean, I really think that's important.

It's one thing -- when we're -- in the HIV world, we're really interested in long-acting therapies, okay? In this particular field, everyone is taking a bunch of pills every day anyway. So to have a more -- to just have the ability to provide PCSK9 inhibition in an oral form, I think, is a really good thing. And you can see that the barriers that have been put out with both the monoclonal and even with (inaudible) has been really limiting the ability of people to access this innovation. So we're really excited about it. The technology is really cool. The Phase II data were really hot. So...

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Why do you suppose Nova dropped theirs? Okay. Fair enough.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

I don't know. Maybe they didn't get good data. I don't know. But I'm super excited. Phase IIb is fully enrolled. We'll get data soon.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Makes sense. One more, pneumococcal vaccines, there's starting to be this buzz that even Merck is looking to go well beyond 20-valence, which is kind of where Pfizer capped. And I'm not talking sort of the 21 valent for adults. I'm talking even well beyond. Can you speak to that? What's the development strategy? Because it's looking like some of the competitors might be going up to 31-valence, and even Pfizer recently said we're going to go well beyond 24 also. And how -- but how do you manage carrier suppression when that happens?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Yes. So I have to tell you, there's -- so we have to talk about size and depth of response, okay? The breadth and depth, okay? When we talk about numbers, everyone is talking about, "Oh, I've got more numbers." But as we see with the PCV20, the data that have been alluded to by Pfizer, and I don't see the primary data, we see Japan data in some of their press releases. When you go -- when they went from 13 to 20, they lost a fair bit of immunogenicity. So that's not good, right?

And so what I'm focused in for our team is to understand what would be the best approach to preserve or enhance the current big-ticket PCV types even as we move forward on other more uncommon types. So imagine, for example, serotype 3, bacteria type still accounts for a fair bit of disease in kids. And if you had better outcomes in serotype 3, you could take 2 or 3 of these very rare serotypes, and that hasn't even touched your serotype 3 if you can improve outcomes by better immunogenicity.

The point that I'm making is it's not about the numbers, it's about the burden of disease. And if you go to a situation where you have 24, 28, 30, 40 valent and whatever you say, but you have a creep down in immunogenicity for those original types that represent the majority of the disease, I don't think you've done very much.

So our proposal, our charge to our development team -- our research and our early development team is that we don't want to lose any immunogenicity for the types that are already -- for which there's already effect seen and impact (inaudible) of those. And so the challenge is not just give me more numbers. It's give me more numbers and make sure that the immune response remains really, really robust for all of it.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. But I guess, Eliav, are you committing to something well beyond 24 valence or not necessarily?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Right now, we've released (1-7). That's what we're -- is our next vaccine. And we'll -- we haven't chosen -- we haven't -- it's so early in development that we're not yet ready to figure out what -- whether we're going to add more or less or whatever.

But what I am committing to, what we really are going to require of our team is not to be -- not to accept that the major types that still in the absence of a good vaccine will cause a lot more disease than the 31st, 32nd and 33rd most common PCV type that we don't lose immunogenicity. That's the key here. And it's not that I've got more numbers than you do. Do you have ordinary immune responses.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

But you guys are sticking to the CRM197 carrier protein for all this development, not necessarily changing the background carrier protein or some new chemistry to enable more?

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Not at present. Yes, we're looking at all alternatives. I think part of it is going to be adjuvant.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Got it. Okay. Not the new CRM197. Okay. Got it. I know we're at time. So I want to be very respectful. But did we miss anything, Peter? Otherwise, I just want to thank you guys so much for your time.

Peter Dannenbaum - Merck & Co., Inc. - VP of IR

There's always more to talk about, but we can do it another day, Umer. Thank you.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

That's right. On that dinner. Sounds good.

Peter Dannenbaum - Merck & Co., Inc. - VP of IR

That's right.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Excellent. Thank you, guys. Take care.

Eliav Barr - Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories

Bye.

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