So delighted to introduce our next speaker, Dr. Marjorie Green at Merck, who heads Oncology Development. Marjorie came 5 months ago from Seagen. We're also joined by representatives of Merck's IR team.

I'm going to give opportunities for those of you in the audience to ask questions throughout the day. So just raise your hand if you would like me to put a question to Marjorie, and we can kind of go from there.

Maybe we start with TIGIT, or TIGIT, as Roger used to like referring it. I like TIGIT because it rhymes with the title of the first report we wrote about it. TIGIT, we totally dig it. And on that note, Roche inversely disclosed their Phase II data, which is a whole another story.

But it's quite informative, and you obviously, did biostatistical analysis, trying to assess the probability of hitting, depending on what you assume for the alpha spend was for the PFS region and what you think the hazard ratio is going to be for the remaining patients. It's not complicated stuff.

One thing from Merck perspective, one might imagine is why not drop PFS as an endpoint, given that the treatment effect seems to be all driven by a — if there's a real treatment effect there. It's not like you saw in Cityscape with curves at 6 weeks going like this. It's a late response. So given that, why not either repower, but then it's going to cost you time, or just drop the PFS? And in that way, at least you're going to get something. So how is my thinking about KEYVIBE-003?

No. Thanks for the question. And we tend not to talk about the details of our statistical plans, which is frustrating and annoying to everybody in the investor community. We do think that overall survival is the key endpoint for TIGIT, and particularly for these diseases, where modest efficacy improvements in PFS may not always translate out into overall survival. But we have not publicly disclosed any changes in our studies at this point.

We do keep an eye on the emerging landscape. You can look at historical studies that Merck has done and how we have assigned alpha when we have had different kind of endpoints for both PFS and OS, and we usually protect both. So we're able to adequately test for both endpoints. And so OS, we think is needed, and I think that you bring up a great point.
Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

So in your KEYVIBE-003, because it's very different from SKY-01 (sic) [SKYSCRAPER-01], in that it’s testing across the whole range of PD-L1 expression from lows to highs. And I can’t remember, it’s 1,000-something patients. But when you do the math and say they split 1/3, 1/3, 1/3, your sample size isn't any different from what Roche did. In fact, it may even be smaller.

So in that sense, when you say that you can protect both, I’m not sure how you could protect both unless you run it. Isn’t it just -- I mean let’s put it like this. It would be -- if I said to you, it would be a reasonable suggestion to drop PFS if one works on a (inaudible) basis on the input from other trials, would you agree?

Marjorie Green

I'd say, thank you. So yes, I just can’t talk about the statistical designs for the study. For those who don’t know, the 003 study is building on the KEYTRUDA 042 and 24, which is looking at – KEYTRUDA was monotherapy versus chemotherapy. And so this is looking at our anti-TIGIT co-formulation compared to KEYTRUDA.

And we are one of the few drugs, as you mentioned, Andrew, that has efficacy across levels of PD-L1 expression. And one of the things that’s great about our development program is that -- in the study is that we did increase the sample size of the study to specifically test the higher PD-L1 population to the greater than 50s. And so we did increase the sample size previously.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

So it's not a 1/3. I shouldn’t assume 1/3, 1/3, 1/3?

Marjorie Green

We did increase the sample size to address the greater than 50s. And so -- because you did see when you look at the published data for 42 long term, there was efficacy across the entire population, but numerically, the hazard ratios improve the higher that you went with the PD-L1 expression.

And there are many open questions for -- I'm going to call it, TIGIT to be difficult, but -- with TIGIT is, is the efficacy going to be better where the immune system is more active? Is it going to be better where there is maybe a little bit less activity? We're well-positioned to answer both of those questions.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

So maybe segueing to your chemo combination trial.

Marjorie Green

Which is 07.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Which is 07. Now previously, I've been somewhat circumspect about the outcome of that trial because of the inclusion of the patients with PD-L1 low expression given the Cityscape data for what it's worth. And on that basis -- and also another observation is one of your colleagues, Emmett Schmidt will make a very good case that immunogenic cell death with chemotherapy, these from human studies, suggested it's limited or zero
utility, and there’s no evidence of synergy at all. So it’s a nice thing in mice, but it doesn’t exist in humans. And therefore, what’s the point? So if we take his observation as real and if we say that...

Marjorie Green

I would argue with that observation. (inaudible) from Seagen, I would argue, immunogenic cell death, I think, is real, but okay. So we’ll believe that Emmett’s correct on that aspect.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Okay. So just hang with me for a second. So if we -- and just to get everyone on the same page in the audience, what we're talking about is if you combine a chemotherapy in a tumor, which is necessarily hot, with a PD-1. Can you somehow, by causing the cell to die in a particular way, ignite a flame that synergizes with the PD-1, and you have tumor shrinkage?

The alternative thesis, which Marjorie's colleague aspires to or it -- what's the word -- puts forth is that it's just a question of not synergy, but addition, chemo shrinks tumors. You're getting some PD-1 activity in patients who are PD-1-high. You put suite together and you see a benefit. And the debate is whether we're seeing this immunogenic cell death, and that's very important in this particular trial that you're running, combining vibostolimab plus PD-1 plus chemo. Because unless you believe in immunogenic cell death, it's not entirely obvious why I should feel confident about the outcome of this trial given the SKYSCRAPER data. And if I believe in immunogenic cell death, then I can embrace it. So interested in your thoughts.

Marjorie Green

Yes. No, no. Thanks for the question. So I think that you can still have with chemotherapy, increased antigen presentation without immunogenic cell death, which causes specific immune-related responses that caused this preclinical synergy. And not all chemotherapies cause it, some do, some don't.

And so I think you still can get that kind of benefit. And I think if you look at KEYNOTE-189 and look at the efficacy across a broad expression of PD-L1, the hazard ratio for survival with a 5-year follow-up in KEYNOTE-189 for patients whose tumor’s PD-L1 expression is less than 1% is still in the 0.6-something range. It’s suggesting that you don’t necessarily need to have immunogenic cell death. It is antigen presentation, potentially some immunogenic cell death, that you’re getting more than what you would expect from KEYTRUDA by itself where you need to take the brakes off the immune system.

So I think that with 189’s data showing that activity across the range of expression, it is reasonable to say that you could see by taking the brakes off even further with an anti-TIGIT, you could have activity across that same spectrum. It’s an open question that the study will answer.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

And if there is that activity, then, seemingly, it’s not manifested by higher response rates. It will be manifested by more durable response rates in those patients who do experience tumor shrinkage.

Marjorie Green

Potentially. I think that in KEYNOTE-189, where KEYTRUDA was added to chemotherapy, you did see increased response rates. Whether you would get a marked increase with the anti-TIGIT, I think, is to be determined. But I do think overall survival is going to be the key endpoint for the TIGIT drugs.
Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

And on KEYVIBE-007, so the chemo trial that we're referencing, the timing, I think, is, I want to say, 2026 clinical trials, but I'm assuming there's interim before them. Can you talk to when we should anticipate data from that trial? And the extent to which I think that Dean has referenced that you've already had a look at the data where it's past the futility analysis. So if you could just comment on that as well.

Marjorie Green

No, no. Thanks for the question. We tend to guide to the primary completion date because that's -- the study is really powered and designed for that. We do interim analyses, the number vary from studies and have different assumptions to it, so I can't be more specific than that.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

And then within the KEYVIBE-003, so this is your PD-L1-high trial...

Marjorie Green

It's with all levels, but it is the...

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Yes. Yes. Yes. Sorry, without chemotherapy. I missed but...

Marjorie Green

KEYTRUDA versus KEYTRUDA.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

So within that, you obviously have a cohort of PD-L1-high. Can you share anything about the statistical plan? Because that has a primary completion in 2025 from Emory. I would imagine that within the highs where you'd imagine the magnitude of the dominant treatment side effect actually powered, as you indicated earlier, up in that. So you added patients in that segment. Is there any carve-out that would enable you to selectively unblind? And I'm assuming there's -- or not? What can you share about the -- is there a hierarchy? How's it -- what can you tell me about it?

Marjorie Green

I can't tell you anything about it.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Yes, I thought you might say that. Okay.

Marjorie Green

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

One does, one can't. Okay. So ADCs, which is very pertinent given your background from Seagen, seemed to be in the hands of Pfizer if the FTC doesn't get in the way. So there is a debate proposed about whether the lack of biomarker-dependent efficacy with ADCs is instead indicative of the true max of these drugs is just chemo hangs around for longer, just as a PK-driven effect.

And I know my friends at AZ would violently disagree with that and just say it's because we haven't got a decent biomarker. How do you think about that and the wisdom of biomarker selective enrollment? And this is a question that Dean also touched on the last analyst call, but obviously, Merck has benefited from the embrace of biomarkers at the expense of others thinking about Bristol. So how do you think about what we're really seeing here?

Marjorie Green

They're -- I agree with the colleagues at AZ, and that our biomarkers may not be truly where they need to be because of the heterogeneity of tumors. And you're looking, when you get a slice of a tumor, you're not getting the totality of what the actual tumor expression is for your antigen. And so -- so there is that difficulty in trying to understand for the totality of someone's cancer burden, what is the expression level of a specific antigen? So we don't have a precise way of measuring that.

I think that with ADCs, because of the instability or stability, depending on how it's designed over the linker and recycling, you do get bystander effect. So I do believe that, that actually happens, it can be shown preclinically and that also likely explains the efficacy that you're seeing where you have more heterogeneity or lower levels of expression. I think that there's public data, for example, with ADCETRIS, which is the treatment of Hodgkin's disease, that showed efficacy, even when you couldn't even measure the CD30.

And so there is likely a biomarker issue combined with bystander effect as opposed to just having the chemo hang around longer. Chemo hanging around longer is likely part of this as well. If you think about the half life of most chemotherapies, they're quite short and where ADCs are measured in days.

And so the ADCs are -- the activity goes through multiple different kinds of routes. It's -- the antibody does have an effector function. Do you have bystander effect? Is it something that it can generate ICE? Despite what Emmett says, I think that actually does happen. And all of these things play in together. And that's also what you likely see the difference efficacy between the different ADCs too, because each of these factors can be tweaked to some degree.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

So staying on the theme of ADCs, can we go to SKB-264, which is your TROP2 that you licensed from Kelun, one of several? I think your Dean has guided that you're going to be opening an expansive Phase III program this year, I assume in lung and other indications. I'm sure you'll have several folks at ESMO, presuming that's where AZ shared the data. But they're being quite tight-lipped on that, but I'm sure you'd be interested in that.

In terms of -- as it informs your trials because I know you will only want to talk about things that impact Merck and not competitors, where would you see the natural home in a PD-1 experienced patient group in lung? Because there's a sort of guessing game of in which cohort have they seen benefit. They reference a majority of patients, and it could be histology because TROP2 is expressed in oral squamous. I wondered about prior taxane exposure because that's common to all other TROP2 positive trials, but maybe not in second and third-line lung because they could have got GemCis. So perhaps for some reason, we don't understand taxane inhibition regulates TROP2 or internalization of TROP2.

What's Merck's working thesis about patient selection? Because it can't be TROP2 biomarkers because you've got the data showing that it's not predictive, at least in the earlier data. So how are you thinking about it? Because you must surely be thinking about this as you think about your own clinical trial program.
Marjorie Green

No. Thanks. There's a whole lot to unpack there. So the ability of a biomarker to be predictive. There are different ways to slice and dice data to support the hypothesis that you want. And so generating ROC curves that -- behind the cutoff to benefit a majority of patients, there are ways to look and see.

But the thing that I think becomes challenging with ADCs is that when you are first to market and you have activity in patients who've got low levels of expression, why would you want to limit your drug? And so if you're first to market and you see you can't select necessarily that a patient who's got IHC 1+, however you want to measure that antigen and that person has a benefit, you wouldn't want to admit them from getting a therapy. So an all-comer approach is definitely, if you're first, a smart way to go. That doesn't mean you can't actually enrich. I wouldn't say that. You probably could.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

And you're talking Richmond-based not on a phenotypic. You're talking about biomarker.

Marjorie Green

About active biomarker selected group.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Even with a suboptimal biomarker -- suboptimal IHC biomarker that we have projected.

Marjorie Green

So I think it's -- there are different people who -- there are different companies that develop biomarkers, and they're not all the same. So you can look at the PD-1 and PD-L1 and see that they're not all the same. And so depending upon how you develop your biomarker, you might have better ability to enrich. So that's one aspect of the question.

I think that the aspect about taxanes is interesting because we test our drugs often in late-line disease, and the patients have been exposed to a variety of different therapies. And so there has been a comment on the Kelun data about patients you've had prior -- who have EGFR mutations in their tumors and the efficacy looks better there. We've also had less chemotherapy.

And so is the taxane question is really that they had to be exposed to taxane to get TROP2 expression? I think when you look at archival samples of lung cancer tissue across different settings, you see TROP2 expression. So it may not be expression, but is it the resistance to -- like if you -- if there was a microtubule inhibitor on this as opposed to topotecan to a topoisomerase 1 inhibitor, would you have different kinds of responses?

So I think it's more not the taxane-specific as opposed to the taxanes are just commonly given to lung cancer, where if you have mechanisms of action that are a little bit more similar to a Topo-1 inhibitor you might actually have resistance. So I think it's the mechanism of payload. That's a guess.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Although, but there's -- Topo-1s are not used in (inaudible) management, right?
Marjorie Green
No.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD
It doesn’t -- we can’t test it. No.

Marjorie Green
And it’s hard. So you look at breast cancer, potentially where you do get some, but they’re just not used as widely. But it is -- the thought is, it’s having to do with just more chemo resistance as opposed to sensitivity.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD
Okay. That’s interesting. So one thing that struck me because obviously, AZ is prosecuting or trying to get approval for HER2-high tissue-agnostic indication, right? And then separately, obviously, they’ve got the HER2-low approval.

We know that HER2 low is found in up to 50% of solid tumors, right, outside breast. So if you had a HER2-low and you made from Kelun, we don’t know. But would you be looking at HER2-low outside breast as a potential biomarker to use and run trials given you’ve got an active drug? And if not, why not?

Marjorie Green
No, thanks for the question. It’s -- I probably -- my IR team is going to like yell at me, I think. They won’t yell at me. You’re getting into the theoretical stuff where I’m a breast oncologist by training. So I love talking about HER2. And so I think it’s really interesting.

We have not publicly disclosed any activity in the HER2 space. And so in a theoretical world, some of it to me is still -- ADCs are still chemotherapy at their core. And so the agnostic, you need the chemotherapy to work. And so not all tumors are going to be sensitive to the payload. And so that’s the -- interesting thing is like how -- when you look at data from these. Are they picking tumors where there’s some evidence? And I have not dug into competitor data to where I can comment, and I shouldn’t comment on their data anyway.

But are these tumors that you would -- that there’s some evidence that something like irinotecan or topotecan or some other tecan has had a little bit of activity? Or you -- are they showing activity irrespective of ability of that class of chemotherapeutic to work?

So I think that is one of the challenges of something like an agnostic ADC approval compared to something like we’ve got approvals on TMB-high and MSI-high because the mechanisms are different. And so the agnostic labels are easier there because the immune system apprise broadly, even there in those tumor types compared to chemotherapy, which will be more tumor dependent about where there’s response and where there is not.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD
Going back to SKB. When you look at differentiation, you’re going to be late, right? Because obviously, you’re yet to go into Phase III.
This year.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

This year, soon. But the -- you're still going to be late. But 1 year is not much, and stuff can happen and clinical trial design can dictate ultimate successes. We've seen with Bristol and Merck and KEYTRUDA and Opdivo. But one advantage you seem to have is ILD, which may take on additional importance. We'll see when combined with PD-1.

Could you talk to how strong your conviction is in the data that's emerged from the Chinese trials that this is real, mechanism-driven? And there's a paper on macrophages and the [alveoli] underpinning this. But it's pretty early paper, and I'm not sure how well-founded is this? Or do you -- is your mind still open that actually this may well see similar rates of ILD as we run Western trials 4, 5, 6 mg per kg in the Phase III. So what's your conviction that this drug is differentiated from an ILD perspective?

Marjorie Green

We are still in early days with the Kelun TROP2-ADC with 2870. And what we can say, there have been probably 200 to 300 patients treated so far at a variety of doses, and they recently have completed and reported out a Phase III trial, triple receptor-negative breast cancer, showing benefit over standard of care chemotherapy in a press report.

What we can say is that no serious rates of ILD have been reported so far. And the question would be, is there something inherently different about clinical care in these studies in China versus what you would see in Western countries? And I think when you're looking at these academic centers, the treatment is very comparable to what you would get in Western populations. In addition, Kelun has Phase I sites open in the United States, where patients are being treated. So that does add to the safety database.

So I think that what we're really going to find out is when we get to the Phase III is that when you get the large randomized data set. So I am cautiously optimistic that we will continue to see this as we go into our Phase III program. But I can't tell you that ILD won't be seen because it seems often with many chemotherapeutics.

And also KEYTRUDA has ILD, too. And so it may be that we will see it in combinations. And so it's too early to tell. I don't want to differentiate based solely on toxicity. I want to differentiate in different ways, but that is something that if you can avoid a fatal toxicity, that's always a benefit to patients.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

And has Merck confirmed whether or not you've got rights to their Claudin 18.2 or not?

Marjorie Green

So we have publicly disclosed that we have the TROP2-ADC 2870, two additional clinical ADCs, and then we have preclinical ADCs as well. So we have not -- Merck has not publicly disclosed the other two clinical ADCs.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

But you would -- okay. So would you find Claudin 18.2 as an interesting target?
Marjorie Green

Definitely. So definitely. So I think that the data with Astellas' monotherapy antibody is interesting, and it lends itself to be a good target for an ADC.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Maybe we could segue to the Moderna PCV. I'm not allowed to call it PCV, am I?

Marjorie Green

INT.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

INT.

Marjorie Green

Individualized neoantigen therapy.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Because PCV could get confused with the pneumococcal vaccine. So there's been a terminology shift. That was my understanding. So the data, I'm assuming that you're not going to be able to find it, that you're going to have to run a registration trial. I think that's been Merck's commentary until now. I just want to make sure that's still the case. And then perhaps you could -- I was very struck. I mean melanoma is great, but it's -- I do think that's surprising. It's a hot tumor, and it's an adjuvant setting. And look, until you've got the data in hand that needs to be replicated, but I wasn't sort of blown away by it, but it's obviously great and important new frontier.

I thought the BioNTech data in pancreatic cancer was eye-opening given the nature of that indication and the ptosis, albeit a tiny patient cohort, and there was a translational trial. But I thought that data set was actually much more encouraging for the potential breadth of indications that you could pursue. So I'd just be interested, where are you going to take this?

So I think you've indicated you're going to go broad. You said you're going to start seeing lung. How long -- how can you accelerate the development program as the regulator becomes familiar with the profile within the melanoma setting? So I mean is there a flywheel here from a regulatory perspective that you can move faster and quicker and go broader if the data pans out as we anticipate?

Marjorie Green

No, thanks for those. So maybe starting first with the melanoma data and what are we doing with melanoma data. So it's been presented twice. The melanoma data is a fairly small Phase II open-label study conducted by Moderna, and they did a lovely job with the trial comparing your INT or V940 plus KEYTRUDA versus KEYTRUDA for patients who had Stage III and Stage IV entity melanoma.

And it showed that patients' relapse-free survival is markedly improved. Distant metastasis-free survival hazard ratio was in the 0.3 range. And so you'd say not blown away. Like 0.3, that hazard ratio looks awesome. That's what people guide from with their distant metastasis. So I think that data is very compelling, and we have started a Phase III study in this setting.
So from the regulator standpoint, you can tell we've been talking to regulators and getting buy-in to be able to conduct these studies to be able to do -- we started -- in Australia, we've already started enrolling into the Phase III studies. And so we've got good relationships with regulators. I think that the mRNA technology is well established, well known by regulators.

And so thankfully, with the COVID vaccines recently, health authorities have in the top of their mind about mRNA. And so it gives us a good lead into being able to conduct Phase III studies. And so I think that there's a lot of data, historically, even prior to the COVID vaccine studies about mRNA and so our ability to go into studies there, I think, is well established.

The ability to register that, I think that we have breakthrough therapy designation, which means that we asked the FDA if they think this data is compelling because there are advantages you get with a breakthrough therapy designation. It doesn't mean that you could file or not file, but it does give you a different relationship. We'd be able to ask a lot of questions who are developing the drug.

And so the FDA thought it was compelling enough to get breakthrough therapy designation. We have prime designation. We have -- it's -- the reality is it is a fairly small Phase II trial. And we did want to get the Phase III up and going right away. And so I think we have been fairly cautious about saying that that's something that we know we can get approved. I think Moderna might be saying something a little bit differently. We both will say the data is compelling.

And so we think the data is compelling and we have started our Phase III programs there. How broad and how large we're going to go? We've talked about lung cancer publicly. I think Dean had said stuff about this. And so you will see a lung cancer study looking at INT, building upon KEYNOTE-091, our adjuvant study. And then we also have data now with KEYNOTE-671 with date in October. And so we will continue to move forward there.

**Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD**

And what you -- with regard to chemo and PD-1 in terms of the regimen, when do you administer the vaccine, at the beginning or at the end, I presume not during?

**Marjorie Green**

There are a lot of open questions, just like we were talking about TIGIT, all the open questions, that's hit here as well. and Moderna is conducting Phase I and Phase II studies, and we are as well to help try and answer some of these questions but the optimal timing.

**Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD**

Because you never had that, obviously, in the melanoma setting?

**Marjorie Green**

And so it is definitely an open question. I think that when you look at how KEYTRUDA has worked and other vaccines, there is the ability to develop an immune response during chemotherapy. So it does exist. It might be blunted depending upon what the vaccine type is.

So is it out of the realm that you could develop an immune response? The way that the studies are set up for melanoma, that one is it's not a chemotherapy question. We've not disclosed what we're doing in our lung study.
Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

And then the extent to which beyond lung, right, i.e., pancreatic is a significant unmet medical need, terrible prognosis, 20% of patients can get Whipple. I don't know what you thought of -- you look at 16 patients’ worth of data, the Balachandran data, but I thought it was interesting and compelling given the backdrop and the setting and the fact it seemed to be -- the hazard ratio seemed to be aligned quite nicely with neoantigen-reactive CD8 response. So how soon before you go to pancreatic or just more work to be done focusing on non-small cell?

Marjorie Green

No, thanks for that. I think it was a very interesting paper to read. We keep up with all the external data and where we're going. When you look at KEYTRUDA and what we've done there, is we've really invested heavily into earlier stages of cancer. We have 7 approvals. They have more studies reading out. And we think the immune system is most robust there. And our ability to be able to cure patients, that's sort of where our goal is. And so a lot of our INT focus is in that setting.

So for metastatic disease, you need to have a disease where you can have an indolent enough course to be able to get the T cells to be generated...

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

So metastatic, I assume...

Marjorie Green

Metastatic -- so going for metastatic disease, thank you. You do need to be able to get the T cell response to happen, which takes some time. With the INT for melanoma, it's 9 doses of INT given concurrently with KEYTRUDA after people have had a couple of doses of KEYTRUDA, while INT is being manufactured.

And so depending upon the regimen, it would -- it's less clear about the efficacy in the metastatic setting. So it's an open question, I think. What that data showed is it definitely showed the immunogenicity of the approach, but I don't know if it told us a lot about the efficacy.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

But that was in the adjuvant setting. The Balachandran was in the adjuvant setting, not the metastatic.

Marjorie Green

Apologize. I thought it was in the metastatic setting.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

No, it was adjuvant.

Marjorie Green

Okay.
Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Okay. Should we talk about CLL and the ArQule transaction? And nemtabrutinib, am I saying it correctly? So the IRA was unforeseen, I suspect, to the time of the ArQule transaction. And these are relatively long trials to run. There is an advantage in patients who fail earlier lines of BTK therapy, and that's not going away, and you'll be competing with pirtobrutinib. How much -- you've got a couple of large Phase III running with nemtabrutinib. How much is the IRA changing your commitment to that molecule compared to what it was previously? And then I've got a follow-on question.

Marjorie Green

The IRA is definitely having an impact on drug development for this from multiple pharmaceutical companies and Merck’s lawsuit, I think, brings the concerns we have about innovation. I think when you look historically, approvals have happened in the time frame where they might have been impacted by the IRA from drugs because of life cycle management.

And so for nemtabrutinib, we are strongly invested in developing this molecule and trying to bring an optimal regimen to patients. And there are different ways of developing a small molecule in a way that you can still meet within the IRA time frame. Some of them might have increased risk and how you develop that drug.

And so we haven't publicly disclosed our full development plans for nemtabrutinib at this point, but we are fully committed to ensuring that we can provide benefit to patients where we think this drug is going to have activity, and we like that it can potentially prevent the development of resistance to BTK inhibitors. That's something that we think is the hypothesis of these new molecules because it works where resistance occurs, and it also further delay the development of resistance, too.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

I had a question, and I warned you I was going to ask you a mean question at the beginning. So when I go through the Merck oncology pipeline and portfolio. So belzutifan was from Peloton, KEYTRUDA from (inaudible), ILT4 from Agenus, LYNPARZA from Astra, SKB from Kelun, your CTLA-4 from Akeso, the ODM from Orion, bomedemstat from Imago. I mean you get the idea. The point I'm making is that I could only find 2 molecules, vibostolimab and your LAG-3, which are in your oncology Phase II, Phase III or on the market that came from Merck discovery compared to, I think, 18, which were all either acquired licensed or partnered. So the question is, is it that there hasn't been really much focus within Merck discovery on oncology? Or is it just it's really not very good at it?

Marjorie Green

Okay. That part was mean, so the latter part. I think it's a great question. And there are different ways that companies can enrich their portfolio. I'm newer to Merck. I've been here for 4.5 months. And when I first joined, I know I was interviewing people I met with were a discovery. And there has been significant growth, I think, over the past 2 to 3 years of the discovery group, with some key hires from other companies as well as from academia. And with that, I've been very impressed with the science and some of the work that may not be as visible to industry, about the preclinical work and the molecule development we're doing internally.

But that being said, I think we're still opportunistic. So I think you're going to see probably a continued mix of acquisitions and licensing as well as internal drugs. Whether that shift toward a higher percentage from internal, external, I think it depends on what our groups come up with. But there's been significant investment in discovery. And so when I talk to the group at Merck, I don't feel that they are any less proficient or scientific or innovated compared to early development groups I've worked with at other companies.
Andrew Simon Baum  - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

So can we talk about afucosylated CTLA-4 and Xilio? So Agenus showed this very provocative data in MSS colorectal cancer, which is I know, 90% plus of colorectal cancer and seemingly showing, albeit with lots of talks, some sort of profound improvements in outcome, albeit in patients who didn’t have liver mets, which is not unimportant.

You have a collaboration with Xilio, you have this mast afucosylated CTLA-4. I’m just interested in whether, given this is an unmet medical need, how impressed or not you were by that data which is being shopped around. And how that impact your commitment to pursuing given you’ve got an internal CTLA-4 candidate that has the advantage of likely superior efficacy?

Marjorie Green

Yes. It’s -- I think there’s a lot of debate about fucosylation and its ability do you increase ADCC for things that are not fucosylated. And can you get the immune response to being more robust? And there have been multiple different molecules that have been touted as having more efficacy with not being fucosylated and have not necessarily panned out.

So I think it’s early in treating data and so when we look at our internal molecule with the CTLA-4 that we have, we really try to develop a drug that we think that could have a better therapeutic index and drugs that are on the market because of the toxicity profile, and focused on that aspect even more than potentially the immunogenicity and the ability to spark ADCC.

And so we do have Phase III studies ongoing with our CTLA-4 combination with KEYTRUDA looking to see in renal cell, are we able to do better than what’s already out there? And so whether or not that particular aspect of it plays a role, I’d look at it as an upside, but not the key driver of its activity.

Andrew Simon Baum  - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

And then on -- you have a KRAS compound, which is sitting in Phase I, KRAS G12C inhibitor. I think, it came from Merck Labs. Obviously...

Marjorie Green

In discovery.

Andrew Simon Baum  - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

In discovery. I know. I can credit. So my question is, this is an increasingly crowded field. I mean I have lost track of the number of G12Cs there are. Is there anything unique about this model? For example, the AstraZeneca molecule, which is pre-IND, I think, it’s about to go in the clinic, is brain-penetrant because of its size, which would be one way of differentiating. So I’m curious about your molecule. Is it brain-penetrant? Is there anything that is particularly unique about it?

Marjorie Green

We’re going to have data that is being presented at ESMO, looking at some of the Phase I data as well as in combination, as monotherapy in combination with KEYTRUDA. And so I think you’ll get a better sense of what the drug has to offer there.

Brain penetration is sort of interesting because people have metastatic disease, lung cancer patients, a significant number of people will develop metastasis in the brain. And the CNS and the blood-brain barrier get damaged in like very early, and there is data that chemotherapy can actually
have activity sometimes. And so I don’t know how much of a competitive advantage that is. I think these drugs do get into the brain. Eventually, in an intact model, they may not as well. But whether that’s going to have a therapeutic advantage is not clear.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD
And have you got a pan-KRAS or pan-RAS?

Marjorie Green
Not in my group.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD
Not in your -- it’s not in development yet. But are you aware of anything that I would imagine, given the magnitude of the commercial opportunity, it will be something that every pharma organization has to be pursuing?

Marjorie Green
Yes. I think when people talk -- another group I talk about today, they talked about disappointment in the first KRAS G12C. And I like, the oncologist is the optimist, going, hey, they work, what do you mean? I’m excited about this because it means it’s targetable. And so then if you can extrapolate that, there’s like how can we use that information to go to Dean then to pan-KRAS. And so I think Dean has publicly talked about, these are areas of interest for us and for our discovery group.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD
VelosBio, the ROR1 ADC. So it looked like the solid tumor work has been terminated. Is that right? When I look at clinical trials, it looks like all the focus really is on heme that you’re no longer looking at solid tumors.

Marjorie Green
We still have ongoing cohorts in solid tumor. So I think that that’s where we’re still waiting for data to make a data-informed decision about what to do there. Expression is definitely highest in hematologic malignancies. And so I think we have breakthrough therapy designation in mantle lymphoma. We’ve got Phase II, Phase III and diffuse large B-cell lymphoma. And a lot of work is ongoing in combinations in hematologic space, but I think it’s premature to say that we’re not interested in solid tumors.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD
Okay. But it’s more heme-focused as of now.

Marjorie Green
At the moment, most of our investment is in heme.
Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Got it. We’ve only got a couple of minutes left. So I’m going to look for one last chance for an arm in the air. And whilst I’m looking with my other eye, I was going to say, we’ve cut a lot of ground today, but I’m sure the stuff I haven’t asked. Is there anything that you wanted to highlight that I haven’t raised in my questions that you think I’ve missed or I should have highlighted?

Marjorie Green

I think that, definitely, our focus in early stages of cancer is something that I think is really important. And we’re very committed to try and improve cure rates. And so that’s -- we talked about that and touched on that a bit when we’re talking about INT and sort of our development plans there.

I really think that WELIREG doesn’t always get the focus that potentially it should. We have the LITESPARK-005 study readout showing improvement in progression-free survival in patients with renal cell carcinoma who they received prior IO therapy and TKI therapy. And so again, being able to go -- we talked a little bit about this, but be able to go in areas where angiogenesis is a driver beyond patients who have DHL or other predisposing conditions, I think, is really exciting there. And then I’m really also excited about bomedemstat. So the LSD1 inhibitor.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

This is the Imago...

Marjorie Green

This is the Imago drug. So those patients have a lot of burden. People who’ve got essential thrombocythemia, myeloproliferative disorders, these are diseases that really have a negative impact on the quality of life and can lead to horrible malignancies. And so to have something potentially disease-modifying is very exciting to.

Andrew Simon Baum - Citigroup Inc., Research Division - Global Head of Healthcare Research and MD

Very good. Well, on that note, I’m going to end the conversation here. Many thanks, Marjorie, Merck team for joining us today, and thank you for the audience for attending. Thanks again.

Marjorie Green

Thank you.