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PRESENTATION

Akash Tewari - Jefferies LLC - Analyst

Good morning, everyone. Day one or day one of public companies for our Jefferies Healthcare Conference here in beautiful Times Square. I'm not going to hear anything else. It's beautiful. For those who don't know me, my name is Akash Tewari. I cover pharma and biotech companies here at Jefferies. And I have the pleasure of hosting the pride of Tarrytown, Regeneron, and this is actually quite unique because we have leaders both in the hematology and oncology division, areas where I think investors definitely should be paying a lot more attention to at Regeneron.

I'm going to hand it off to Mark who's going to give some intro remarks and also introduce the execs who are joining us today. Thank you.

Mark Hudson - Regeneron Pharmaceuticals Inc - Investor Relations

Good morning, everyone, and good morning, Akash, and thank you very much for hosting us today at the Jefferies conference. As Akash said, I'm Mark Hudson from the Investor Relations team. Joining me today, as Akash said, we have two leaders from our solid oncology and hematology division. So to my right is Dr. Izzy Lowy who heads up the solid oncology efforts. And also to my right is Andres Sirulnik who heads up our hematology efforts at Regeneron. And I echo Akash's views that these two verticals are becoming very important to the Regeneron story, and we're glad that we're here post ASCO. So we're excited to address any questions that you may pose about these ongoing programs.

Before I turn it over, I do have to read forward-looking statement. So I'd like to remind you that remarks made today may include forward-looking statements about Regeneron, and each forward-looking statement is subject to risks and uncertainties that could cause actual results and events to differ materially from those projected in such statements. A description of material events and uncertainties can be found in Regeneron's SEC filings. Regeneron does not undertake any obligation to update any forward-looking statement whether as a result of new information, future events, or otherwise.

Akash, I turn it back to you.

QUESTIONS AND ANSWERS

Akash Tewari - Jefferies LLC - Analyst

Awesome. Thanks so much, Mark. And you mentioned everyone's coming back from ASCO. I did as well. And I think the general view is we're hitting a wall of when it comes to oncology, right? We're seeing therapeutic window issues and limitations on efficacy whether it's durability, immune exhaustion across the board, whether it's in IO, whether it's even with some of these ADC targets. Let's start off -- and I think the other interesting thing is we're seeing oftentimes it's not different targets, right? The talk with PD-1 VEGF. It's sometimes the assets themselves that actually can end up having differences in a clinical profile.

So I wanted to start off with your PD-1 LAG-3 program, and I think this is something top of mind for a lot of investors. You're going to have potentially first line data in NSCLC. That's going to be coming out soon. I'd hand it off to maybe your team. What did you see in terms of the development of agents in first-line and second-line NSCLC, and where do you think there's an opening for a high-efficacy PD-1 LAG-3 therapy to really differentiate here versus, let's say, using a Trop-2 ADC first line or some of these targeted therapies?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

Thank you, and it's a pleasure to be here this morning. So you asked a multipart question there, so I'm going to try to take it apart. So first of all, in terms of the wall, I think this is actually a paradigm that is something that happens in scientific development in general. There's a breakthrough, a consolidation period, people are looking for new things, and we go forward.

I think at Regeneron, we're very focused on actually researching and coming up with new approaches. And I think our co-stim program is an example, where we are trying to expand the combinatorial potential that is available for therapeutic regimens to engage the immune response. With regard to LAG-3 in particular, which is not a co-stim, it's another checkpoint, we've presented now very exciting melanoma data on the basis of three independent cohorts. It gives us a lot of confidence going forward in our melanoma program, and we have limited data that we saw in lung cancer.

And so we are basically going forward with exploratory studies that, depending if they pan out, we will then take them into Phase 3. So I don't have a on a specific answer to tell you that we're definitely going to win in first-line lung cancer, but we have reason to be optimistic based on the differentiation that we saw with our data in melanoma. So it's not always just the target. It's always -- it's also -- it could, as you pointed out, it's also the antibody itself or the agent itself that's targeting the antigen.

And we've seen very compelling data in our LAG-3 program to date. We will be able to have a definitive readout in our Phase 3 melanoma program in the coming year, and perhaps by the end of this year, we'll have early data suggesting that whether or not the lung cancer program is going to be differentiating and able to step forward.

Akash Tewari - Jefferies LLC - Analyst

Understood. And I definitely want to hit on melanoma, but maybe just to stay on NSCLC for a sec, Bristol has talked about they had a Phase 2 that I think they've verbally described. They found a signal in first line, and they talked about maybe 20% to 30% in first-line NSCLC where a PD-1 LAG-3 approach could possibly fit into the treatment paradigm. I don't know if necessarily your team shares that view where PD-1 LAG-3 is just a biomarker-driven subpopulation.

Can you talk to us about for your program where you're seeing higher levels of receptor occupancy, do you think that PD-1 LAG-3 for NSCLC is a biomarker-driven approach or is something where maybe the population can be bigger than what Bristol has recently outlined?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

I think the important thing to remember is that not all antibodies are created the same. And when we look at the difference between the data that we've seen, and again, I'm going to go back to melanoma because that's where we have our richest data source. When we go back to that, we've seen very differentiated activity at least in the patients that we've been able to look at so far. So in that setting, we have not seen a limitation in our efficacy based on high or low levels of PD-L1 expression nor LAG-3 expression. And so I think the jury is out for our agent what the right setting will be.

I don't know what Bristol -- where they're going to segment and look for a signal. But I'll also remind you that even in lung cancer, our cemiplimab has done much better in first line than Opdivo even though it pains me to say that because I helped develop it when I was at Medarex. So I think we are looking at two different agents. We will just have to see right. I don't know that it will be biomarker specific. We're just -- we'll have to see, but I am optimistic that we will see enhanced activity that will allow us to go forward.

Akash Tewari - Jefferies LLC - Analyst

Understood. Now let's hit on melanoma. And to your point, I think if we saw the Bristol LAG-3, PD-1 Ipi first-line data that came out of melanoma, they had, I think, the same if not slightly lower response rate than even your PD-1 LAG-3 in first line. I think the pushback some investors have is, okay, it's an early study. Then number two, maybe Regeneron's early data, maybe there is a lower disease burden, maybe with slight differences in terms of patient population.

And I think the second part is if we look at the multidisciplinary review for Opdualag, they tested higher doses of their LAG-3. We saw differences in terms of the response rate in that population, but I think one of the things the FDA noted is that didn't necessarily translate to PFS and OS. That's a data point, but you also have consistently shown higher responses across the board in melanoma. So when you think about your program and where you differentiate in melanoma, outside of ORR, where is your confidence that on PFS and OS, there's also going to be a clinically meaningful difference?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

So thank you. So we have -- so as you pointed out, our response rate with the combination of LAG-3 and PD-1 blockade is competitive, if not better than what was reported with the triple combination including ipi, rela, and Opdivo. I would say that what we're seeing in our cohort is not just ORR, but we're seeing an emerging story of durable progression-free survival. We're also seeing the evolution of patients with longer follow-up converting from PRs to CRs.

So as we continue to follow this cohort of about 100 patients, we're seeing a durability of response and translation into an enhancement of what we think will be a superior PFS as well as CR rate. We've also opened the study of a head-to-head versus Opdualag because we're confident that we will be superior.

Akash Tewari - Jefferies LLC - Analyst

Understood. And I think you mentioned something before, we were chatting ahead of this, LAG-3 and where is its ideal role in therapy in a lot of these solid tumors may be in that first line setting, not post PD-1. And I think that's really important here. Can you expand on that? And your point of, if we're really knocking down both of these targets in a way that's maybe different from these other agents, you're going to see efficacy with LAG-3 that maybe investors aren't really appreciating. So what is it about maybe in a first-line setting where LAG-3 really shines?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

Well, what we understand based on a vast amount of preclinical data as well as a variety of clinical data is that when LAG-3 is added to regimens after someone has already progressed on a PD-1 or PD-L1 blockade that the added benefit, the opportunity for added benefit seems to have been missed. So our focus has been to look at this as a potential replacement ultimately for PD-1 alone in those indications where the addition of LAG-3 creates an enhanced benefit. Why that is, if we can speculate what the exact evolution of the immune response is after prolonged exposure to PD-1. But that's where the data have taken us.

I don't if that -- I think that answers your question.

Akash Tewari - Jefferies LLC - Analyst

No, that -- I mean, it's a good bridge because I think head and neck, obviously there's a lot of excitement with some of the bispecific approaches we saw, really encouraging data, I think, from Merus at ASCO, but I think something a lot of investors may not be paying attention to. So you actually have in late-line patients right now in head and neck PD-1, LAG-3 data that you showed very early. But if your point is really LAG-3 as a first-line

indication, you don't want to use it after patients have been treated with checkpoint inhibition. Help me contextualize the signal that you showed in late-line patients in head and neck at ASCO. How do you think that translates as we move up to a first-line setting?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

So the signal we showed at ASCO was in patients who were pretreated but who were PD-1 naive. So again, we are now expanding that experience and looking into patients -- opportunities to treat patients with the combination of PD-1 and LAG-3 in those settings to prior exposure to PD-1. So we're opening a perioperative study, combination of neoadjuvant and adjuvant treatment, and exploring whether or not there, we get an early readout on enhancement and things such as pathologic responses with the combination.

Akash Tewari - Jefferies LLC - Analyst

Understood. Actually, you mentioned adjuvant, and actually, it makes me think. You guys do have -- your team has with PD-1 LAG-3, I think we've seen with that regimen very strong disease-free survival with some of your peers. I know there's cancer vaccine approaches that Moderna and Merck have as well. When you think about PD-1 LAG-3 in an adjuvant setting, whether it's neoadjuvant or post resection, both for melanoma and NSCLC, do you feel like maybe investors are not appreciating the trials and your approaches in those settings right now?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

I'm not sure I understood.

Akash Tewari - Jefferies LLC - Analyst

So right, you have data. We've seen competitor data from PD-1 LAG-3 where you can have disease-free survival in the 80%-plus range, which I think bodes well and stacks up well with some of the cancer vaccine data that we've seen from Moderna and Merck. I know you have approaches in adjuvant in both NSCLC and melanoma that you're you've talked about in the past. Is there -- can you talk to us about the potential of PD-1 LAG-3 in those indications in the adjuvant setting?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

Well, we have -- In melanoma, we have multiple studies underway including one in purely adjuvant as well as another one we're mounting in the perioperative setting. And again, I think, what we believe is that when you're providing combined blockade to these two targets, we expect to see an enhanced benefit particularly when we don't see much in the way of enhanced toxicity.

Akash Tewari - Jefferies LLC - Analyst

Okay, understood. Maybe lastly, before we get into the heme program on CD28. And I remember two years ago, I think, Len and George, your team was really excited about CD28. It felt like there was going to be a breakthrough in solid tumors. And I think there was investor skepticism. You mentioned a lot of times, there's a wave of hysteria, then there's consolidation, and then we start understanding really the therapeutic window.

I mean, your team had data, EGFR, CD28, at ASCO this year. You are taking approaches where you're dosing with IL-6. You're also taking approaches where you're dosing with other CD3s. Talk to me about where you stand with the CD28 program. Why should investors start paying attention to this given some of the early signals that we saw on the safety side last year?

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

So we took an approach of testing a variety of co-stim bispecifics, anti-CD28 bispecifics, both in solid tumors. And Andres is also running trials in the hematologic space. What we're excited about and what we think the EGFR by CD28 data clearly demonstrate is that this platform, this approach, has legs. Now exactly where the optimal place to deploy it will emerge with time.

So what we were stunned by with the PSMA by CD28 was that in the tumor setting where PD-1 has failed multiple Phase 3 trials and various conventional combinations with chemotherapy or androgen blockade agents, we were able to see some remarkable responses. We did see some enhanced immune-mediated adverse events. But even in patients who didn't have clear responses, we've been able to see benefit in terms of durable stable disease and delay until progression.

So we're working very hard now in in the prostate setting to try to decouple the safety issues from the efficacy issues. And we have a variety of approaches underway. And we know now with the EGFR by CD28 that it is possible to demonstrate this efficacy platform in different settings. And so far, in the EGFR by CD28, we're not seeing the same kind of toxicity that we ran into.

So I think each one is individual. But to me, the big message is that this concept works. We can actually, in various settings, turn tumors into antigen-presenting cells and enable the immune response to have a more profound antitumor response.

Akash Tewari - Jefferies LLC - Analyst

So you mentioned prostate, and actually, I'm going to ask a follow-up because I agree. I think in ASCO, it's now sequencing therapies together especially when it comes to IO. That might be more thoughtful and more may not always be better as well. We're seeing some signs of that.
It's interesting because there are some SMID companies which are showing interesting data with the PSMA CD3 approach. We don't have the durability question.

Regeneron, I mean, you have -- Probably, you know more about that target than a lot of companies. Why are you going with the PSMA CD3 with a PSMA CD28? What's special when you're hitting -- its same target, but you're hitting CD28 and CD3 separately. How can that maybe differentiate versus other therapies when it comes to not only response rate but, as you mentioned, the durability of response which is really critical in prostate.

Israel Lowy - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Oncology

Well, I'd need probably a lot more time to go through the preclinical scientific rationale. But suffice it to say, we think that the opportunity to combine a CD3 PSMA with the CD28 PSMA offers us an opportunity to get good responses in a way in which we can hopefully mitigate both the toxicity that people have seen with the PSMA by CD3 class in terms of cytokine release syndrome as well as potentially focus the immune response more to tumor-specific effect and avoid some of the immune-mediated adverse events we've seen by combining PD-1 with the co-stim.

So we are about to start in that. We have -- and we're looking forward to sharing those results in the -- I don't even know if I should say a date, but probably the coming year or so, we should have something.

Akash Tewari - Jefferies LLC - Analyst

Interesting. Very helpful. Okay. On heme, I wanted to start off with GA. And I could tell you, I cover Apellis. I've kind of in the back of my mind said, okay, this is more of a problem for me in two years. I'm going to willingly ignore this question. So I'm facing my fears here as well.

obviously, back of the eye therapies, there's issues in terms of getting chairs available, but obviously, retinal vasculitis and safety is really critical here. The question that I think we're all wondering is, with these kind of systemic approaches, how do you ensure you're not having so much immune suppression that there's some type of infection issue? But then number two, where is your confidence that you are going to be able to

get adequate exposure in the back of the eye? What work has your team done internally? You guys are famous on the translational side that maybe investors should be paying attention to here.

Andres Sirulnik - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Hematology

So first, thank you for having us here today. I think that, first of all, most of C5 which is the target of our approach in GA, our systemic approach approach in GA, most of C5 is made in the liver. And we believe that a systemic approach will pan out by understanding that the C5 is really activated in the vascular bed on the back of the eye. So the approach that we are taking is inhibiting or reducing the production of C5 in the liver using an siRNA and combining this with an antibody that will essentially capture whatever target there is left for activation with an antibody, therefore reducing the burden.

So the siRNA reduces the target burden by inhibiting C5 production in the liver and whatever is left will be inhibited by the antibody. We think that this is a systemic issue and activation occurs in the vascular bed, rather than a purely local issue of production of C5 in the eye. So we think that this is a reasonable approach.

The other issue is that GA is a bilateral disease. Injecting in the eye, you're treating one eye. Here, you're treating -- you have the opportunity to treat a bilateral disease with a systemic approach. So we think that that is an advantage. I think that the issue of the potential for infections, it begs to be answered in the context of a clinical trial. We are being very thoughtful and careful on the way we will be selecting patients for the trial and putting in place mitigation strategies that we think are reasonable in this setting.

Mind you, there are major risks also with intravitreal injection. Remember, this is a slow progressing disease where complications of intravitreal injection could actually lead to blindness or losing an eye. So it's all about the risk benefit.

Akash Tewari - Jefferies LLC - Analyst

Understood. Quickly on your Factor XI program, again, no one seems to be working on that right now, especially after the OCEANIC study. I don't really buy Bristol's argument. There's very marginal differences in terms of how hard they're hitting. In fact, I think, J&J might actually be hitting Factor XI harder with some of the oral approaches, so I'm skeptical there.

But with an antibody approach, you might be able to get levels of inhibition with Factor XI that we're not seeing with these oral compounds. Why should we not be running our Factor XI, and why would it maybe make a difference when you're completely suppressing that knockdown when it comes to clinical efficacy?

Andres Sirulnik - Regeneron Pharmaceuticals Inc - Senior Vice President, Translational and Clinical Sciences, Hematology

So I think that when it comes to an oral inhibitor versus an antibody inhibitor, you very much highlighted the advantage of an antibody. You can reach target inhibition to a level that you cannot with an oral inhibitor, which will, at that level, have off-target undesirable effects. So I think that that's a key aspect.

When we look at our preclinical data with our Factor XI, we have two antibodies, the differentiated mechanism of action in terms of the way they target Factor 11, we see potential best efficacy in terms of prolongation of the PTT which is the biomarker that we're using as it compares to other antibodies or small molecules. So we feel confident that we have two very good antibodies that we are bringing to the clinic.

Today, we are conducting two proof-of-concept studies. We will have our readouts towards the end of the year. And we think the risk-benefit profile that these antibodies can afford will potentially pan out to be of use in particular settings and be very competitive vis-a-vis DOACs.

Akash Tewari - Jefferies LLC - Analyst

Understood. We are out of time, but I would love to know what those settings are after. But, hey, thank you so much for everyone for joining us. Thanks so much for the Regeneron team.