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REGN.OQ - Regeneron Pharmaceuticals Inc at SVB Securities Global Biopharma Conference (Virtual)

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CORPORATE PARTICIPANTS

Israel Lowy *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

L. Andres Sirulnik *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology*

Ryan Crowe *Regeneron Pharmaceuticals, Inc. - VP of IR*

CONFERENCE CALL PARTICIPANTS

David Reed Risinger *SVB Securities LLC, Research Division - Senior MD*

PRESENTATION

David Reed Risinger *- SVB Securities LLC, Research Division - Senior MD*

So good morning, everybody, and thank you for joining our session with Regeneron. My name is Dave Risinger. I'm responsible for diversified biopharmaceuticals coverage at SVB Securities. And on behalf of the firm, it's very much my pleasure to welcome senior executives from Regeneron.

So with us today, we have Izzy Lowy, who is Senior Vice President of Clinical Development for Oncology; Andres Sirulnik, Senior Vice President of Clinical Development for Hematology; and Ryan Crowe, Vice President of Investor Relations.

And so with that, let me turn it over to Ryan to read some disclaimers and then we'll take it from there.

Ryan Crowe *- Regeneron Pharmaceuticals, Inc. - VP of IR*

Thanks, Dave. It's great to be here, and I appreciate the invitation to present at the SVB Securities Global Biopharma Conference.

Before we start, I'd like to remind you that remarks made today may include forward-looking statements about Regeneron. 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 risks and uncertainties can be found in Regeneron's SEC filings. Regeneron does not undertake any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise.

Back to you, Dave. Thank you.

QUESTIONS AND ANSWERS

David Reed Risinger *- SVB Securities LLC, Research Division - Senior MD*

Great. Thanks, Ryan.

So Izzy, I thought it would be great if you could frame, just to start off, Regeneron's vision for oncology looking out over the next 3 to 5 years and what you're hoping to deliver.

Israel Lowy *- Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

Thank you, David, and it's a pleasure to be here with all of you this morning. We started on a journey to developing a transformational oncology portfolio quite a few years ago, when we recognized that ultimately being able to make a really profound impact on the future of oncology is going

to depend on the ability to deliver combinations of agents. And we also recognized that fundamental to this immuno-oncology revolution is having a high-quality anti-PD-1.

So we set out to do that first, which we succeeded with Libtayo, which we believe stands as good as any other anti-PD-1 in the class. And we also developed a several bispecific platforms, the first being fully human antibodies that are CD3 bispecifics. We established some initial proof of concept of that in hematologic malignancies that my colleague, Andres, is going to expand on. And most recently, we brought into the clinic a series of co-stimulatory bispecifics that target CD28, which puts us actually at the forefront of that field, having now 4 such agents in the clinic.

The -- in addition to that, we also recognize that there would be opportunities to develop additional checkpoint inhibitors in the class along like PD-1, and we have so a LAG-3 that is in the clinic now looking very promising. So we believe that having under this single roof the ability to mix and match these various immunoregulatory, regular antibodies, CD3 bispecifics, CD28 costim bispecifics, enables us to in a, I think unprecedented way, find various combinations to unlock and open up leverage of the immune system to control infectious -- control tumors. I'm an infectious disease physician by training, so that almost slipped out.

So that's our vision. And I think what you see now with our growing portfolio is we've achieved now with these long years of sowing the fields of these various approaches that we're now beginning to reap the harvest from it. And I think we're approaching an inflection point over the coming couple of years where you will see dramatic activity being unleashed from a variety of these approaches. And we are -- we believe, that not only will these possibilities of combination within our portfolio be useful, but they will also allow us to combine with agents that other companies develop that have complementary mechanisms of action.

So we're very excited about where we stand today. We feel like we have been marching steadily forward, and the drumbeat of progress just keeps on going. And we're looking towards making some significant, hitting some significant milestones over the next couple of years.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Great. And thank you for that framework. Maybe we could just turn to 2023. And obviously, in a moment, I'm going to want to talk about the abstract from yesterday on your PMSA by -- or PSMA by CD28. But could you talk about the event path for 2023 that we should be focused on?

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

Well, in this year, we hope to -- with PD-1, we hope to achieve approval in the EMA for our chemo combination, which we got approval for from the FDA last year. We are moving forward in our non-melanoma skin cancer. We have an adjuvant study, which is more than halfway enrolled. And I don't know that we'll have a readout this year, but we're making a lot of progress towards fully enrolling that study.

We, at ESMO, presented data on our neoadjuvant success with anti-PD-1 with Libtayo in CSCC. And that has been a, I think, a transformational observation that is already even before any listings by NCCN or formal approval. I think lots of clinicians have seen the data and are adopting it in practice.

We have in our bispecific program at ESMO, we also presented data on our MUC16xCD3 program in ovarian cancer. We expect to hopefully be able to present some data on our combination with cemiplimab with Libtayo and MUC16xCD3 during this coming year, with -- and I'll wait for your PSMA question separately so I won't say to talk about those.

We are moving forward with combinations of our MUC16xCD28, a costim MUC16, both with cemiplimab as well as with the MUC16xCD3 bispecific, so those combinations are moving forward. We have our EGFRxCD28 that is in dose escalation, where we may be able to hopefully present some initial proof-of-concept data by the end of the year. And then the remainder, actually, if I can move into the PSMAxCD28, we announced some data over the summer. We are fleshing out that data at ASCO GU and providing more details on the findings that we've had, where we believe we have achieved proof of concept that this co-stimulatory pathway has the possibility of actually turning cold tumors into tumors that can respond to immunotherapy. So hopefully, we'll be able to present additional data on that program as the year goes on.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Right. And so given the disclosure of the abstract yesterday, could you talk about that and provide a little more detail?

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

Well, what we talked about there is that as we were asked -- because of the prior experience of CD28 agents with TeGenero and the toxicity that was experienced in healthy volunteers who were exposed to that antibody, we were asked to begin these studies at very low doses. And what we found was in our first 5 cohorts in combination with Libtayo, in patients with advanced prostate cancer, many of whom -- almost all of whom had actually even exposure and progression after chemotherapy, was we saw very little to no activity.

But when we finally got to the last 3 doses that we've been testing, we started to see some promising activity. Dose level 6, 30 milligrams, we actually have a patient who promptly after the addition of Libtayo to the -- after the safety run-in of the costim, developed a dramatic drop in their PSA. Over the next month or 2, he develops immune-mediated adverse events of a rash and some stomatitis. And so we had to stop the treatment and treat those toxicities and which resolved, but he continued to respond. And now 1.5 years later, he has basically maintained undetectable PSA. He had visceral lesions, non-bone lesions that disappeared. He has a bone scan that is normalizing and a PSMA PET scan that is negative. So this patient basically has had as close to a cure as one can describe.

And then beyond that, we've had several additional patients at the next doses that also had dramatic drops in their PSA. And interestingly, the patients who had the drops in the PSA are the only patients who have experienced any immune-mediated adverse events, as if we are unleashing PD-1 in these patients with the addition of the costim bispecific.

We've had some, in general, the toxicities have all been reversible, and we've seen some good outcomes for these patients. And our focus now is to really work hard at being able to succeed in giving the treatments for a prolonged period of time to get the most durable response possible and mitigate against the immune-mediated adverse events. And we're trying a number of interventions to do that.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Okay. That's extremely helpful. So actually to follow on, could you discuss how you're using Kevzara to do that?

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

Sure. So as you know, IL-6 blockade has been adopted in the CAR-T environment for mitigation against cytokine release syndrome. We're not using it for cytokine release syndrome because we're not experiencing cytokine release syndrome, we're experiencing immune-mediated adverse events of the type that you would get from PD-1 or PD-L1 treatments. And there is increasing evidence that IL-6 blockade can also mitigate against those, particularly there have been studies combining anti-CTLA-4 and anti-PD-1, where we know the frequency and severity of immune-mediated adverse events is higher than with anti-PD-1 alone. And several reports have been out there that IL-6 blockade can mitigate against that.

So we're testing using Kevzara, sarilumab, in this setting to see, to explore whether we can decouple the immune-mediated adverse events from the promising antitumor activity that we're seeing with the combination.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Great. And then just to follow up on the very compelling point that all of the grade 3 adverse events occurred in patients with PSA declines. Could you just describe what percentage of patients didn't have PSA declines in the data that was presented in the abstract?

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

Well, I think across the board, we're looking at this point, the numbers are still small. But if you combine the last 3 cohorts together and our increasing observations, I think we're looking at somewhere between 1/4 to 1/3 of patients having a PSA decline. And those are the patients that are experiencing also immune-mediated adverse events. Not all of them are grade 3, but that's the only place that those high-grade adverse events are happening.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Got it. Okay, very compelling. So let's turn to LAG-3. With respect to LAG-3, could you just remind us about your fianlimab's differentiation versus Bristol's LAG-3? And then I have a couple of follow-ups.

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

Sure. So what we presented, we also presented this at ESMO as well as the year before at ASCO. We did a broad-ranging, first-in-human study across many different indications. And we saw very compelling evidence of efficacy in patients with first-line advanced melanoma who were naive to any immunotherapy where we, in 2 separate cohorts of about 40 patients each, so like a test cohort and a retest cohort, we are seeing responses in the low 60% range. And we will be -- we have additional cohorts that we are accruing that have also shown a similar rate. So what we do know is that in the registration study of Opdualag, the response rate for the combination was 43%. So on response rate alone, we are doing significantly better.

We don't have hundreds of patients yet. But as I said, we have 2 substantial sized cohorts of test and retest. And in addition to the response rate, we've also seen a duration of response that where we have not reached the median and a progression-free survival better than a year when that has not been quite reached in the Opdualag program. So I don't know at a molecular level, what the difference is between our anti-LAG3 and their anti-LAG3. But what we do know is that the combination with Libtayo and fianlimab that we are seeing compelling activities.

So we have already launched a Phase III of our own in advanced melanoma in patients who are naive to anti-immunotherapy. We have begun enrollment into an adjuvant study in this setting, and we are also will be opening in the near future, a perioperative study for patients to get a combination of neoadjuvant and post-surgical combination of fianlumab and Libtayo.

In addition to that, we have some compelling activity that we've seen, albeit in small cohorts, but nonetheless compelling activity in lung cancer and some other indications. And so as a consequence, we expect to open this year a large Phase II program, of the combination of cemiplimab and fianlimab in patients with high PD-L1 expression, to compare the combination versus cemiplimab as well as in all comers of PD-L1 levels to explore the combination of the 2 IO agents on top of chemotherapy versus Libtayo and chemotherapy.

And as you know, we have approvals in first-line lung cancer for Libtayo monotherapy in greater than 50% PD-L1 expression, as well now in chemo combination across all levels. So that's what's cooking with LAG3 and we're actively looking for additional indications where we think this combination can be potent.

Now if it turns out that the combination activity of fianlumab and Libtayo transfers beyond melanoma and indeed provides increased responses and more durable responses and enhanced progression-free survival and survival overall in multiple other indications, I think the combination of LAG3 and PD-1 has the possibility of being the next big thing beyond PD-1 alone, because it will be working in multiple indications.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Right. So for that large Phase II program in lung, is that a registrational program?

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

So we are doing a Phase II program with an associated Phase III follow-on to it. It's not a -- it's not going to be a seamless protocol. We want to do it to first prove to ourselves that the activity is there, get some more refinement around the dose, the optimal dose for this activity. And then we will transition that into a registrational program. Assuming the data are good, of course.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Great. Okay, perfect. So let's transition to Andres. So -- maybe Andres, I'll give you a chance to talk about heme as a significant opportunity for Regeneron and what you'd like to highlight, and then we'll go into some specific programs.

L. Andres Sirulnik - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology*

Thank you, David, and good morning, everyone. So all in all, we're very excited on the progress we are making with our programs in the hematology space. As you know, we have 2 advanced molecules odronextamab in the lymphoma space and linvoseltamab in the myeloma space. Both programs are advancing very rapidly. And we have initiated a large clinical development plan for both molecules with Phase III studies in early lines of therapies that we believe will put us well underway to support filings for both molecules with accelerated approval filings potentially unlikely as we expect in the second half of this year.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Great. So could you talk a little bit more about the potential for differentiation for the -- each of those assets?

L. Andres Sirulnik - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology*

Yes, absolutely. So let me start with the odronextamab in lymphoma. We truly believe that odronextamab has the potential to be best-in-class given the efficacy profile that we have observed in follicular lymphoma. We have a very high overall response rate in the over of 82%, with 92%of these responders achieving a complete response. And this is in late-line patients and very encouraging durability of these responses really is very exciting.

Also, our optimized step-up dosing regimen has improved odronextamab's safety while retaining efficacy compared with the prior dosing regimen when we initiated the program. In diffuse large B-cell lymphoma, odronextamab also demonstrated efficacy of regardless of prior CAR-T experience. And this asset has the same safety profile that we observed in follicular lymphoma.

We also believe that our diversified approach, particularly the combination with our CD28 co-stimulatory molecules that are entering the clinic in the hematology space as well, can really improve the competitive profile of odronextamab in the long run. We also plan to enter in the clinic with co-stimulatory molecules with linvoseltamab in multiple myeloma. But let me tell you a little bit more what we believe that we can differentiate with linvoseltamab.

When we look at this molecule in terms of the data we have presented lately at ASH and that is emerging, when we look at the safety profile and -- that is emerging, we have the lowest rate of CRS in the class. 37% of CRS, mostly grades 1 and 2, we have not observe grade 3 CRS. And importantly, we have a very predictable onset of CRS and short-lived. Also, I would say that we have the least number of hospitalizations with only hospitalizations -- 2 hospitalizations in the first 2 doses. And we are very encouraged by the depth and durability of the responses.

Another point of differentiation with linvoseltamab is that when we look at the population that were in -- was included in the clinical trial, we have observed not only a heavily pre-treated group of patients based on prior therapies, but when we look at the disease burden by means of plasma cell numbers in the bone marrow, and soluable CMA, the target, we have the highest that has been described in comparing the class. So all in all, they show us really a very good profile in terms of efficacy and a very good profile in terms of safety today.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Very helpful. And then just going back to the combos with costims. At a high level, since costims toxicities have to be very carefully managed and dosing has to be fine-tuned and it may vary by patient, how should we -- or how do you envision delivering combos that are safe and able to be adopted longer term?

L. Andres Sirulnik - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology*

Yes, absolutely. I think the approach that we are taking in the development of these molecules is similar to the approach that has been taken in solid tumors. We have a very good understanding of the safety and tolerability of our CD3 engagers. And the approach that we will take in, of course, will be in the dose escalation by starting slow. But we think that given the preclinical data that we have observed to date, we have really a very good approach in terms of dosing and schedule, and that is how we are entering the clinic. We think that we have devised an approach that it is safe and, as data emerge, we will be able to present this data. But we are very encouraged about what we have seen in our preclinical models and what data is emerging from the bispecifics and co-stimulatory molecules in solid tumors.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Got it. And so -- just maybe take the next step. So the FDA is very concerned about costim safety. So could you just talk about the event path and how you're going to be developing combos with costims given that backdrop?

L. Andres Sirulnik - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology*

Yes. I don't want to go into the details of our, I will call it, the secret sauce in exactly our dosing and schedule. What I can say is that in conversation with the agency, we have found a very clear path forward.

As Izzy mentioned, we were very confident based on preclinical data on the issues related to the theoretical based on prior experiences with CD28 super-agonist. Our preclinical data suggested that giving a single agent our costimulatory molecules may not carry the risk of a super-agonist.

We think that in terms of providing Signal 1 with our CD3 bispecific, followed by in a stepwise approach providing the Signal 2 in a sequencing fashion will allow us to do this in a safe fashion, particularly by first introducing our CD3 engager, passing the time of where you see the highest CRS, which is the step-up dosing, and then introducing our costimulatory molecule. That's as far as I go, I think that we will be presenting data as it emerges.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Very helpful. That's great. And then just to wrap up, I wanted to go back to Izzy. Izzy, if you could just highlight some of the earlier-stage programs that could come to light in coming years?

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

So as you can see, we've made a big bet on our costim bispecifics, with 4 in the clinic and more to come. We have additional CD3 bispecifics that will be coming into the clinic.

We have other molecules that are along the immunoregulatory pathway that we're exploring. We are also looking at a variety of other approaches towards targeting cytokines. We've talked about Signal 1 being CD3, Signal 2 being CD28. Signal 3 is really cytokine delivery, and we're approaching various ways of thinking about delivering those.

On top of that, we also have developed a technology to identify with antibodies, the actual, what we call them PIG antibodies because they recognize peptide in groove, the peptides that are displayed on the surface of HLA molecules that is what cellular immunity sees and enables us to target not only surface molecules, but intracellular molecules that happen to have fragments of them displayed on the cell surface.

And we're developing novel types of bispecific antibodies with different formats to try to address these as additional targets and expand the vista of what we can target from just molecules that are expressed only on the cell surface to those that are expressed intracellularly, but display parts of their sequences on the cell surface.

In addition, we have established many collaborations. We have collaborations with cellular therapy companies, with companies developing oncolytic viruses, companies developing various formats of vaccines, DNA vaccines, RNA vaccines, peptide, protein vaccines, all of these modalities that can complement our approaches.

And separately from this, I would add that we also have a big effort in targeting gene therapy deliveries, and these too could potentially be brought to bear in the cancer setting. So we have a pipeline that I think is bursting at the seams, that we have a lot in the clinic now that is very promising and that we're very excited about, and it's only going to get better. And we hope to deliver real important new therapies to help patients.

David Reed Risinger - *SVB Securities LLC, Research Division - Senior MD*

Phenomenal. Well, that's a great way to wrap up. We really appreciate you taking the time with us today and hope you all have a great rest of the week.

Israel Lowy - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences - Oncology*

Thank you very much.

L. Andres Sirulnik - *Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology*

Thank you.

Ryan Crowe - *Regeneron Pharmaceuticals, Inc. - VP of IR*

Thanks, Dave.
