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CORPORATE PARTICIPANTS

Franklin K. Clyburn Merck & Co., Inc. - Chief Commercial Officer & Executive VP

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

Roger M. Perlmutter Merck Research Laboratories - President

Roy D. Baynes Merck & Co., Inc. - Chief Medical Officer

CONFERENCE CALL PARTICIPANTS

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

Christopher Thomas Schott JP Morgan Chase & Co, Research Division - Senior Analyst

Daina Michelle Graybosch SVB Leerink LLC, Research Division - MD & Senior Research Analyst

Mara Goldstein Mizuho Securities USA LLC, Research Division - MD of Equity Research Department

Navin Cyriac Jacob UBS Investment Bank, Research Division - Equity Research Analyst of Specialty Pharmaceuticals and Large Cap Pharmaceutic

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

Stephen Michael Scala Cowen and Company, LLC, Research Division - MD & Senior Research Analyst

Timothy Minton Anderson Wolfe Research, LLC - MD of Equity Research

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

PRESENTATION

Operator

Good afternoon. My name is Jerome, and I will be your conference operator today. At this time, I would like to welcome everyone to the Merck Oncology ASCO Event Conference Call. (Operator Instructions) Thank you. I would now like to turn the call over to Peter Dannenbaum, Vice President, Investor Relations. Please go ahead.

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

Thank you, Jerome, and good afternoon, everybody. Welcome to Merck's 2020 Virtual ASCO Investor Call. I'm joined by Dr. Roger Perlmutter, President of Merck Research Labs; Dr. Roy Baynes, Head of Global Clinical Development and Chief Medical Officer of Merck Research Labs; and Frank Clyburn, Chief Commercial Officer.

Before we begin, I would like to remind you that some of the statements that we make during today's call may be considered forward-looking statements within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. Such statements are made based on the current beliefs of Merck's management and are subject to significant risks and uncertainties. If our underlying assumptions prove inaccurate or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Our SEC filings, including Item 1A in the 2019 10-K, identify certain risk factors and cautionary statements that could cause the company's actual results to differ materially from those projected in any of our forward-looking statements made this morning. Merck undertakes no obligation to publicly update any forward-looking statements.

Roger will begin today's session with a slide presentation, which has been posted to our website, and we'll follow that with Q&A. With that, I'd like to turn the call over to Roger.



Roger M. Perlmutter - Merck Research Laboratories - President

Thank you very much, Peter. And thank you, everyone, for joining us on this virtual call. We're sorry that we can't be there together, but this is an opportunity for us to review exciting new information that we presented at ASCO 2020 and to try and place that information in the context of our broader oncology program.

So if I could advance the slide, we have, first, our safe harbor statement, which you've already heard from Peter. And if we go to the next slide, the slide is one that you're familiar with, in some ways. That is that we've talked a lot about our broad oncology strategy designed to improve outcomes for patients around the world.

The first, of course, is that we have made KEYTRUDA a foundational treatment in cancer therapy. And we've explored combinations with KEYTRUDA, including chemotherapy and also targeted therapies that have clearly demonstrated that additional value can be brought to patients in terms of improving and extending life. We're also advancing the pipeline by bringing new strategic collaborations into the pipeline. And we've used our biomarker capabilities to identify patients, who are most likely to benefit. And that includes, of course, patients who have microsatellite instability and also high tumor mutational burdens. Next slide.

So when you look at KEYTRUDA, what you can say is that it is an extraordinary drug. This is a slide that we update frequently. It simply shows waterfall plots for a whole variety of different tumor types defined by site of origin, by histology or by genetic markers. And what you can see on this slide is that more than 30 different types of cancer have demonstrated meaningful responses to KEYTRUDA. Sometimes those responses are really quite extraordinary. You can see some of those in the circles. As an example, if you look at primary mediastinal B-cell lymphoma, top line, second in from right, pretty extraordinary. And right next to it, classical Hodgkin lymphoma, really, really quite dramatic. But it's also quite dramatic in the response to melanoma or non-small cell lung cancer. As you see in those tumors, all the way over on the left-hand side on the top line, again, the waterfall plots where the green line's going down each line representing an individual patient that showed improvement as opposed to going up and the tumor is advancing. It's really special. And these responses, these overall responses that we see demonstrated in these kinds of waterfall plots are mirrored in outcome measures.

So in the next slide, what you can see is a set of different overall survival studies, each one of which demonstrates that KEYTRUDA, either as monotherapy in the top group or in combinations in the bottom group, improves overall survival in a variety of different tumor types, many of which were shown -- all of which were shown in the overall response diagrams on the previous slide. So that includes, of course, in melanoma, a relatively responsive tumor. But also in non-small cell lung cancer based on our KEYNOTE-024 study in the -- those patients whose tumors express PD-L1 at a high level; or in the KEYNOTE-042 study in patients whose tumors expressed less PD-L1 greater than 1%. In lung cancer, of course, the combination data, KEYNOTE-189, shown in the bottom left, has really become the standard of care in most jurisdictions for the way in which one treats advanced lung cancer in this population and the non-squamous population, and similarly for KEYNOTE-407 in this first-line squamous cell population, as most of you are aware.

So it's really quite an extraordinary track record that's been driven by a large set of clinical studies now since we first registered KEYTRUDA about 6 years ago. Next slide.

The development program for KEYTRUDA, though, continues, and in many ways, is simply expanding. We have in excess of 1,200 ongoing clinical trials, of which about 90 are registrational. And about something over 100 are trials in earlier settings, adjuvant and neoadjuvant. We'll have a little bit more to say about that in a few minutes. And the vast majority at this point are combination trials. I've said in many of our earnings calls that we're pretty much done with our monotherapy studies, but we're gaining more and more traction in combination studies. And that, of course, will lead to more and more registration programs with combinations. Next slide.

So at ASCO 2020, we had the opportunity to update the broader oncology community, including more than 40,000 people who attended "the meeting" via virtual mechanisms. It included a lot of new Phase III data, which we'll look at for KEYTRUDA in triple-negative breast cancer, in the MSI-high colorectal cancer setting and in classical Hodgkin lymphoma as well as some Phase II data for KEYTRUDA in stage 3 non-small cell lung cancer, which we believe will expand the field substantially. We won't discuss it in detail here, but happy to respond to questions about the KEYNOTE-799 program. We also had the opportunity to update long-term survival data. And the good news there is that the treatment effects of

KEYTRUDA are very durable, both in monotherapy and combination therapy settings. And we also had the opportunity to talk about some novel mechanisms, some of which we'll mention here as well. Next slide.

So to begin, KEYNOTE-355 was -- or is a study in patients with triple-negative breast cancer. We had the opportunity, which we top-lined a little while ago, to talk about the progression-free survival data. One endpoint of the study, the overall survival endpoint was not examined at this interim analysis. But what you can see here is that if you compare KEYTRUDA plus chemo versus chemo alone, for certain patients with triple-negative breast cancer, the outcome in terms of progression-free survival is really quite impressive. And we have a strong view that, that will ultimately translate into overall survival benefit. But of course, we have to demonstrate that. I should say that this trial complements very much the KEYNOTE-522 study, which we had the opportunity to present at ESMO last year. And which demonstrated in that particular case in the neoadjuvant setting that administration of KEYTRUDA in combination with traditional chemotherapy in triple-negative breast cancer improve the pathologic complete response rate. And that study continues for -- to obtain event-free survival data. So those 2 studies, in a way, are mutually reinforcing with respect to triple-negative breast cancer, along with prior studies that we have in that setting. Next slide.

So we also had the opportunity to show the data from KEYNOTE-177. And as was pointed out by the discussant, who reviewed the presentation after it was given at ASCO, this really does represent a new standard of care in first-line MSI-high colorectal cancer patients. As you can see, of 307 patients who were randomized either to receive KEYTRUDA monotherapy or to receive traditional therapy investigator's choice in the setting of individuals, who present with MSI-high colorectal cancer in the first line. And the results are quite dramatic. KEYTRUDA monotherapy in terms of progression-free survival is far superior, and that trial as well as continuing for overall survival. So we hope to have the opportunity to see that soon. But it really is important to look at the 24-month PFS rate with 48%, nearly half, who have not progressed receiving KEYTRUDA as compared to around 20% with traditional therapy. So really quite an impressive result.

And the next slide shows you the results from the KEYNOTE-204 study. This is a head-to-head study comparing an antibody drug conjugate, shown here as BD, which is commonly used, Seattle genetics product commonly used in the late-line treatment relapsed/refractory classic Hodgkin's lymphoma as compared with KEYTRUDA monotherapy. And here, you can see that in this second line plus setting that KEYTRUDA monotherapy is clearly superior because, as I mentioned, classic Hodgkin lymphoma is really a very responsive tumor. And it's very responsive even after having nonresponse to multiple product therapy. So quite a good result in terms of progression-free survival on the trial here and also continues for overall survival. Next slide.

So in addition to these new Phase III data that we had a chance to present, we also had a chance to present relevant to the durability of the treatment effect of KEYTRUDA and administered in non-small cell lung cancer, renal cell carcinoma or melanoma. And you can see on the left-hand side a final analysis, prespecified final analysis for KEYNOTE-189, demonstrating the extraordinary window that sort of adapt between individuals receiving KEYTRUDA in combination with chemotherapy as opposed to chemotherapy alone. It really is quite remarkable and something that we hear about frequently from our colleagues, who are practicing thoracic oncology, that they are just seeing more and more patients surviving for a longer period of time. You can see it at 24 months. The overall survival is around nearly 46% for the KEYTRUDA plus chemotherapy combination. And hazard ratio for this comparison at that point is 0.56. So it's really quite an impressive result for what would otherwise be continue -- considered to be a completely refractory disease. KEYTRUDA in combination with chemotherapy has really changed even dramatically.

Similarly, if you look at cell carcinoma, the updated analysis from KEYNOTE-426, which is a combination of KEYTRUDA plus axitinib, continue to demonstrate really impressive activity versus sunitinib in this case. And you can see overall survival numbers at 24 months, 74% in renal cell carcinoma, which is certainly a very impressive number.

The last one I'd like to point out, though, is KEYNOTE-054, which, in this case, we had the opportunity to look at a 3-year follow-up data from EORTC for adjuvant treatment of melanoma with KEYTRUDA. And you can see, as we look at those curves, the KEYTRUDA curve at the top, the green curve, separates early from the placebo in this adjuvant study. These are individuals, who have undergone a definitive stable resection of malignant melanoma but are at high risk of recurrence. So this is resected high-risk stage 3 melanoma. And when you look at those individuals, what you can see is that at 3 years, the recurrence -- percent live and recurrence-free is nearly 64%, which is quite remarkable compared to the 44% from those who just underwent surgical resection, the hazard ratio for that comparison, again, 0.56. So there is no doubt that these 3-year follow-up KEYTRUDA as monotherapy in an adjuvant setting is providing substantial value to patients with malignant melanoma. These adjuvant and neoadjuvant studies are continuing next slide.



And we are interested in a variety of them. But we're also interested in the new mechanism. And one of those is MK-6482. We had the opportunity to show data from 6482 in the von Hippel-Lindau setting. And von Hippel-Lindau disease is a disease that results from typically an inherited mutation in the VHL protein, which results in the relative persistence of a transcription factor called HIF-2 alpha. MK-6482 is a HIF-2 alpha inhibitor. And if you look in von-Hippel Lindau disease and look at patients who have clear cell renal cell carcinoma, which is an extremely frequent complication of von-Hippel Lindau, one of the most prominent complications, although there are many other tumors, so the one that was dealt with most frequently, the overall response rate in the setting of 6482, which is the first time this has been examined in a small study on VHL disease, overall response rate is nearly 28%. And maybe more profoundly, 87% of the patients decreased in target lesion size because these target lesions, these tumors really are driven by the stabilization of HIF-2 alpha as a result of the lack of the VHL protein. And so 6482 can be very effective, we believe, in that setting. And the Phase III trial is underway studying 6482 versus everolimus in patients with advanced second line renal cell carcinoma, who progressed following currently accepted standard of therapy. Next slide.

So looking at across all of those things, I think it's important to emphasize, as I was just saying, that we're doing a lot of work in the adjuvant and neoadjuvant setting. We've already talked about KEYNOTE-054, which was approved a couple of years ago. And I've already mentioned our triple negative breast cancer neoadjuvant and adjuvant study KEYNOTE-522. But there are a variety of other important studies in squamous cell carcinoma, in head and neck cancer, non-small cell lung cancer and melanoma that will be rolling out over the next several years. And we're optimistic, given the strong performance of KEYTRUDA in all of these different types, and the fact that, in general, KEYTRUDA performs better in earlier stage disease, that we will see meaningful improvements in patients' responses, and, in fact, in recurrence-free survival, perhaps even in an overall survival in some settings. So we're quite enthusiastic about that. Next slide.

But KEYTRUDA, of course, in addition to being used with chemotherapy, can also be used in combination with 2 other molecules that we are pursuing, LYNPARZA and LENVIMA. For LYNPARZA, of course, LYNPARZA as a monotherapy is already an extremely important drug. It's been demonstrated to have activity and maintenance of treatment response ovarian cancer, in breast cancer, in pancreatic cancer. And I think you all saw that, in addition to the U.S. approval, we had a recommendation of a positive review from the CHMP. They adopted a positive opinion of the -- based on the POLO 1 data for the use of LYNPARZA in that extremely refractory study, where patients with BRCA 1 or 2 mutations in pancreatic cancer, but it's still an important proof of concept. And of course, the profound data in prostate cancer, which is extremely important. But going forward, a lot of combination studies will be pursued in each one of these things. So it gave us the opportunity to see whether, as we believe, based on our early studies, KEYTRUDA in combination with LYNPARZA can be used effectively to further improve patient outcomes. Next slide.

For the LENVIMA program, and LENVIMA also was approved as a monotherapy, for example, in thyroid cancer and hepatocellular carcinoma, but here we have a large number of combinations, including some improved combinations. So for example, in the second line endometrial cancer setting, where a combination of KEYTRUDA and LENVIMA shown in KEYNOTE-136 study is extremely effective. And we also have data that's emerged in renal cell carcinoma and in non-small cellular carcinoma and in a variety of other tumor types. And so we expect that we'll have a chance to see those going forward.

So if I could now go to the next slide, and I understand that maybe the audio feed is -- I'll try -- I'll speak a little bit more clearly. But this slide simply shows that in our oncology pipeline, we have a set of investigational immunotherapeutic candidates, more than 20, in fact, which includes many that you've heard of, a large number of which are now in Phase II studies designed to demonstrate that they have activity, particularly that they have activity when used in combination with KEYTRUDA. And I should emphasize here, as I have on earnings calls, that, to date, despite the fact that we have studied many, many different mechanisms, including immune agonists, including those things that inhibit negative regulators as KEYTRUDA itself does, but also LAG-3 antibodies, CTLA-4 ticket and the ILT4 agonist, personalized cancer vaccines, which we have a number, and things that act on the tumor microenvironment, there is nothing that has the broad spectrum and dramatic efficacy of KEYTRUDA by itself. We've not seen anything that has that sort of activity. We are, however, seeing signals in the combinations that make us actually feel quite optimistic that some of these combinations are going to prove to be important and will become future standards of care in many tumor types. And we continue to pursue those for these different molecules that are mentioned here. And we'll have a chance to update you on those at future meetings, including, of course, future ASCO and AACR meetings.

The next slide mentions that while we have generated a lot of these different molecules ourselves, we also have had the opportunity to acquire important molecules. And I talked about one of those, which is the HIF-2 alpha inhibitor that we acquired from Peloton, which is currently in Phase III in renal cell carcinoma, and for which data were obtained in the setting of von Hippel-Lindau syndrome, which are really very impressive. We



are quite optimistic that this HIF-2 alpha inhibitor, the first molecule of its kind, will prove to be effective in this setting. And it's potentially useful in other settings as well. We also had the opportunity to obtain, through the acquisition of ArQule, a noncovalent BTK inhibitor that has impressive properties, and that is currently in Phase II in chronic lymphocytic leukemia, but in principle, can be used to address the whole spectrum of B-cell malignancies that a BTK inhibitor can generally be used for. And should be quite active, in fact, has been shown to be active in individuals whose tumors have sustained the mutation of BTK, such that they are no longer susceptible to the system acting covalent inhibitors. But we've also had opportunity to gain new oncolytic viruses, for example, from our acquisition of Viralytics. And to have collaborations, for example, with Taiho Astex for the development of KRAS -- various different KRAS inhibitors, which, in fact, target the entire RAS pathway, including both GDP and GTP bound and other isoforms besides KRAS. So those are things at the preclinical stage. But it gives you a sense that we have a broad commitment to oncology mechanisms and a quite broad opportunity to further develop KEYTRUDA in combination with many new molecules. Next slide.

So over the next 5 years, you have a sense of what we will be delivering because you can see the new studies that are going to appear. And more importantly, you see already the data that we have published and the data that we have registered, which provides a substrate for really meaningful revenue growth, margin expansion and, hence, accelerated bottom line growth, which we can talk about -- Frank can talk about a little bit later.

Beyond 5 years, the pipeline is extremely rich. And as I've said, we're optimistic that many new molecules used with KEYTRUDA in combination and some as single agents that will be important. And then over 10 years, of course, well, that's out at the horizon of what can be predicted. But I have to say that the expertise that we've developed in fundamental biology, in understanding malignant cells and an understanding of the tumor micro environment bodes very well for improved therapies for many years to come.

And with that, I will close the slide presentation. I thank you for your attention, and we look forward to your questions.

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

Great. Thank you so much, Roger. Jerome, we're ready to put together the queue for Q&A. (Operator Instructions)

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from the line of Umer Raffat with Evercore ISI.

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

Umer, are you muted? Okay. Let's go to the next question, please, Jerome.

Operator

Your next question comes from the line of Steve Scala with Cowen.

Stephen Michael Scala - Cowen and Company, LLC, Research Division - MD & Senior Research Analyst

Roger, many novel I-O targets have disappointed, but TIGIT appears more promising. TIGIT antibody effector function has been cited by at least Roche as an important factor for efficacy. So Merck's molecule has an intact IgG1 effector function, but it still appears to underperform the Roche molecule. What other factors could explain the efficacy difference? So that's the first question.

And second, Frank, if Roche anti-TIGIT Phase III data replicates Phase II, then how do you see Merck's competitive position changing in lung cancer?



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

Roger?

Roger M. Perlmutter - Merck Research Laboratories - President

Steve, thanks for that. So first of all, we have seen the data from Roche for their molecule. And what you can see is that the combination with atezolizumab in their study seemed to generate some improvement. It's a little hard to -- of course, you can't -- these cross-study comparisons are extremely difficult to do. The data, which were obtained using our 22C3 antibody to define a TPS population, don't look that remarkable. And that may be because atezolizumab as monotherapy doesn't really provide that much benefit as compared to what we see with KEYTRUDA. I mean, if you compare the KEYTRUDA-024 results, for example, which are pretty impressive, we don't know how much headroom there is beyond what KEYTRUDA-024 does. Our -- we are looking at our molecule, our ticket molecule, and we think that there is some evidence for meaningful headroom there. We -- what we've shown is that -- though we haven't had the opportunity to present our data in detail, what we've shown is that the combination of the 2 looks pretty intriguing. But what we really need to see are data that compare KEYTRUDA alone with KEYTRUDA plus TIGIT in a very rigorous fashion. And those data are coming along. So when we have a chance to look at those, we'll be able to say. I don't see any reason to believe that our molecule would be any different from the Roche molecule ab initio. It all comes down to the data. I'm struck by the fact that I would say that, at this point, KEYTRUDA has demonstrated over and over and over again a remarkable spectrum of activity. And that could be because KEYTRUDA, for example, is superior to other anti-PD-1s for reasons that we can't establish exactly preclinically. Or it could be because of aspects of clinical trial design. And so without really seeing that kind of information and having it come out broadly in a lot of studies, pretty difficult to make a comparison. Frank?

Franklin K. Clyburn - Merck & Co., Inc. - Chief Commercial Officer & Executive VP

Yes, Roger. Thank you. And to just follow up on Roger's point, I think the data we are saying from Roche from CITYSCAPE in non-small cell lung cancer was scientifically interesting, but I think we'll have to wait and see how the data continues to materialize. But I would want to make sure that we reinforce how confident we are in our leadership position in non-small cell lung cancer with our overall survival data. And as Roger highlighted, from our Phase III trials across monotherapy and combination, regardless of PD-L1 expression, we believe the bar is extremely high. Right now, we're seeing in the marketplace over 8 out of every 10 eligible patient that does not have a genomic marker of ALK or EGFRs being treated with KEYTRUDA. And in the high patient population, PD-L1 50% and above, KEYNOTE on 20 -- 024 is a very strong monotherapy regimen. Probably about 60% of the patients in the U.S. are being treated monotherapy. The rest are in a combination with chemotherapy. So we feel extremely confident in our current position, as we've mentioned previously, in non-small cell lung cancer.

Operator

Your next question comes from the line of Umer Raffat with Evercore ISI.

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

Sorry. I'm learning how to use the mute button here. I guess, 2 questions, if I may. The first one really has to do with the -- your thoughts perhaps on effector function, and if you think, in the context of TIGIT, that will be a big deal or not. And I think the -- and especially as we saw, obviously, some of the preclinical data from Roche suggesting it could be very relevant, and I know there have been question marks whether or not it is relevant based on human experience.

And the second one is, would it or would it not make sense for Merck to have a randomized trial in lung initiated and caught up on time lines right away? Because I think there's been question marks over whether it makes sense to be -- whether it would make sense to be doing that down the road when competitors have made further progress. And finally, if you could just catch us up on Peloton. It looked like the early responses were quite interesting between confirmed and unconfirmed and what the development track would look like.



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

Roger?

Roger M. Perlmutter - Merck Research Laboratories - President

Right. So first of all, with respect to effector function, what I would say is that we don't have any information that's germane here. The -- we -- as has been mentioned, of course, we have an intact IgG1 in terms of the TIGIT molecule. And we were seeing results. There's no doubt that our TIGIT molecule has activity. I can't tell you what others would look like, and we just have to continue to pursue the studies. And we do intend to move that thing forward as the data emerge. I think one of the things that we've demonstrated is that patient selection's really extremely important, and understanding what you're doing is very important. And so we're -- I wouldn't say that we are, in any way, lagging behind on this. I think when our data comes forward, I think you'll be pleased with the way we prosecuted that program.

And then with respect to the Peloton molecule, yes, the results look terrific. And we are engaged, in fact, in registration-enabling studies in the renal cell carcinoma setting, as I mentioned. So the question, of course, beyond -- I really believe, based on what we've seen thus far in early studies in VHL that we'll see activity there. I think the question is, will we see an activity in other tumor types? And Roy, maybe you'd like to say a few words about this.

Roy D. Baynes - Merck & Co., Inc. - Chief Medical Officer

Thanks, Roger. Yes. So firstly, on the VHL side of the discussion, remember, this is a multisystem disease. And the most problematic is the development of malignancies, including kidney, pancreas, pheochromocytoma. And interestingly, the natural history of this disease is one of recurrence. So typically, patients will undergo surgical resection of a tumor only to have another one pop up. And these patients are destined to have lifelong surgeries. Now importantly, what this drug has shown early on is that disease control is extremely high. So while the response rate now is approximating 30%, we're quite early in the course of this. And what we've seen, our responses continue to accrue over time. And I don't believe there's -- I think there might be one patient that has actually progressed during this time. The vast majority have had disease control.

It's also important to recognize that many other manifestations of the disease are also controlled, such as, for example, pancreatic neoplasms, various cystic lesions, hemangioblastomas of the -- involving the brain and the eye. So this does look as though it's going to be a fundamentally important treatment for this disease. Now this is a good area to focus on because clearly deranged VHL bio -- VHL and HIF-2 alpha biology is a hallmark of renal cell cancer and particularly in the advanced setting. And so we have, as you've already seen, had some salvage data to establish proof of concept. And we have, as Roger mentions, Phase III studies in the relapsed setting comparing the HIF-2 alpha molecule to everolimus. We are also moving into additional lines of treatment. These are under design at the moment. And then as Roger mentions, we are also looking at other solid tumors where indeed VHL biology and HIF-2 alpha biology seems to be an important axis. So more to come.

Operator

Your next question comes from the line of Andrew Baum with Citi.

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

A couple of questions for Roger. First, on TIGIT. Biologically -- and I appreciate that you're running the trials. But biologically, would you expect TIGIT to be additive to efficacy with a chemo PD-1 combination in non-small cell to PD-L1 low tumors? Number one.

And then the second question is in reference to your KEYNOTE-006 and 008 Phase III non-small cell lung cancer trials. As you seek to use PARP inhibitor maintenance therapy and first-line lung to extend your franchise, there's been some papers suggesting that biallelic loss is relatively rare



in the non-small cell lung indication. Does that diminish your confidence in a positive outcome for this trial compared to some other tumor types where there seems to be more common?

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

Thank you, Andrew. Roger?

Roger M. Perlmutter - Merck Research Laboratories - President

Yes. Thanks, Andrew. So the first question is, okay, so an anti-TIGIT antibody, where would it work? And it appears to be a separate inhibitory input to T-cells and NK cells. The question is, how important is that inhibitory input? And what is the population in which that inhibitory input is important? So poliovirus receptor interacting with TIGIT does what exactly? And that's an important thing to understand. But ultimately, I don't think we can -- we get much without going into the clinical setting. And that's, of course, the setting we're exploring, and we're doing a lot of studies in which we measure the activity of the molecules. But I mean, ultimately, it depends on accruing data in those places. So not much I can add to that.

And then with respect to the KEYLYNK program and PARP inhibitor, what we've learned is that there are many potential contributors to the activity of PARP inhibitors that include, of course, BRCA1, BRCA2, but also a whole variety of other mutations. So the question is, what sort of the burden of those mutations on mismatch repair in tumor populations? And keep in mind, of course, that the tumor itself may be heterogeneous. To the extent that tumor cells are -- actually die as a result of this treatment, tumor cell death is pro inflammatory, and that could turn out to be quite positive in the setting of KEYTRUDA administration, where, of course, KEYTRUDA works better in tumors that are more inflamed. So all of this is a bit of hand-waving. We just have to do the studies and see. But I'm optimistic actually that we'll see responses in that combination. And indeed, we have had both preclinical and clinical data that suggest that that's true. Roy, am I missing something?

Roy D. Baynes - Merck & Co., Inc. - Chief Medical Officer

No, Roger. I think you've got it right. And just to remember that we have multiple other signal detection projects ongoing looking at other doublets and other triplets. So this is a very active field, and we are quite compelled by the PARP data, and we're confident enough to move that forward into Phase III.

Operator

Your next question comes from the line of Navin Jacob with UBS.

Navin Cyriac Jacob - UBS Investment Bank, Research Division - Equity Research Analyst of Specialty Pharmaceuticals and Large Cap Pharmaceutic

Great. 2 questions for Roger and Roy, one on TIGIT and one on HIF alpha. On the TIGIT, if Roche's TIGIT was to show low monotherapy efficacy at AACR 2, say, low single digits, for example, but yet we're seeing good data in combination with PD-L1 and over the 50% PD-L1 expressers, that would suggest synergy in a way that was expected by other mechanisms, but never realized such as IDO or IL -- pegylated IL-2. And because of the weakness of those latter 2 products that I mentioned or mechanisms that I mentioned, I think there was a shift in strategy to perhaps not go forward with assets that were -- that looked weak on a monotherapy basis. And so would that -- with the Roche TIGIT data showing low monotherapy efficacy, would that change the way you approach your development programs for I-O products even if they show low monotherapy efficacy? And then a follow-up question on HIF alpha.

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

Roger?



Roger M. Perlmutter - Merck Research Laboratories - President

Okay. So you want to do that seriatim? Okay. So first of all, what I would say about the general question of, what does it take before you want to advance a molecule? What we have tried to do with a very large set now is signal trends -- signal detection studies in which we introduce new molecules into clinical trials both as a monotherapy with a monotherapy arm and a combination arm. If a monotherapy arm is flat negative, we just don't see any responses, that makes it a much higher bar to think about advancing combination studies. And again, these are small numbers of patients. But if you do 20 or 30 in monotherapy in a particular tumor type and see nothing, it makes you feel like, well, that's probably not a large treatment effect. But I would say the molecules that we are advancing at this point have really pretty weak monotherapy activity. And nevertheless, we're optimistic based on what we're seeing in chemotherapy -- or, I'm sorry, in combination therapy that, that could prove to be important. So I think we've already adapted basically because of what the data tell us. We've adapted to the idea that we're unlikely to see a molecule that has the sort of activity that a PD-1 antagonist certainly KEYTRUDA has. But on the other hand, we can still potentially gain some benefit. There's still some headroom in terms of certainly response rate and we hope overall survival with some of these other molecules. And we have a few, actually, that are demonstrating that kind of activity in the combination studies. We just now have to actually rigorously show the contribution of each component. So now on to HIF-1 alpha, I guess.

Navin Cyriac Jacob - UBS Investment Bank, Research Division - Equity Research Analyst of Specialty Pharmaceuticals and Large Cap Pharmaceutical

How do you think about potential synergistic effect with a VEGF TKI? And then also, are you concerned at all about potential down-regulation that HIF alpha could cause tumor microenvironment offsetting any efficacy with KEYTRUDA? And where are you looking for potential combinations in the broader RCC earlier lines of therapy as part of your development plan?

Roger M. Perlmutter - Merck Research Laboratories - President

Maybe, Roy, you want to respond to that question specifically about HIF-2 alpha. I would say that it's early days here. We have a relatively small amount of data from monotherapy with 6482. So we don't really know. But maybe, Roy, you have a few comments.

Roy D. Baynes - Merck & Co., Inc. - Chief Medical Officer

Sure. So I think in the front-line treatment of renal cell cancer, I think we would all agree that the results of I-O VEGF combinations, particularly the KEYTRUDA plus axitinib combination, is pretty impressive. And again, how much headroom you will have there is not terribly clear, but it still merits pursuit. And so, yes, absolutely. We're thinking quite diligently about what -- where we might sit HIF-2 alpha into that mix. Probably more important will be in the -- at least initially, in the salvage situation, where patients have failed an I-O and a VEGF modulator. And that's sort of where we're pursuing things fairly actively right now. And again, this could be in combination with other agents that the patient might not have seen or, frankly, in combination with agents they might have seen. And so there is an emerging program there, which is, again, going to be fairly broad. And certainly, frontline is in the mix, but the headroom may be quite limited just given the efficacy that we see with VEGF I-O combinations.

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

Great. If you could state your second question upfront, that would be helpful, please.

Operator

Your next question comes from the line of Dana Graybosch with SVB Leerink.



Daina Michelle Graybosch - *SVB Leerink LLC, Research Division - MD & Senior Research Analyst*

Great. Two from me. One, we've noticed you recently posted many new umbrella studies, and you've added 1 or 2 cohorts. I think some of these have TIGIT or you're staying. And I wonder if you can speak to your approach of those trials, if you're going to include single-agent KEYTRUDA randomization arms in that.

And the second question is, I know ahead of some more data coming in frontline RCC, I wonder if you can speak to differences you see in the TKIs between axitinib, lenvatinib and cabozantinib, in particular in relation to cancer immunity. And also, if you can give an update on when we could expect data from the CLEAR trial.

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

Great. Thank you. Roger?

Roger M. Perlmutter - *Merck Research Laboratories - President*

Yes. I'll just provide a brief introduction, but this, again, is something that I think Roy can comment on and provide more detail. Part of what we try and do through these umbrella studies is really help to define the patient populations with some precision in terms of where to pursue registration-enabling studies. The goal of the umbrella studies sometimes is the definitive identification of contribution of components. But more often, we're looking at signals. And so I'll let Roy speak about that more.

And of course, with respect to the first-line RCC, all we can do is look at the numbers, absent head-to-head comparisons, it's pretty hard to tell. But clearly, we've shown already the combination of KEYTRUDA plus axitinib. And as Roy has mentioned, the data are really very impressive, and we saw some of those data also in the presentation. But of course, this -- a very similar data set, we believe, will accrue, who knows, maybe stronger with lenvatinib based on our Phase II data, extremely strong data for the combination of renal cell carcinoma. So we believe that each one of the small molecule inhibitors of protein tyrosine kinases has its own set of strengths and weaknesses. And it will be important to look at each data set as a stand-alone, but, Roy, maybe you can add something about umbrella strategy or renal cell.

Roy D. Baynes - *Merck & Co., Inc. - Chief Medical Officer*

Sure. Yes. As you can imagine, with our very strong pipeline as well as a number of the assets that Roger's referred to that we have brought in, we do need to have an efficient signal detection mechanism. And as Roger's mentioned, some of these can actually pave the way to accelerated approvals, if indeed, big effect sizes are seen. So you referenced a number of umbrellas. And essentially, the idea here is to have for the major tumor types umbrellas that we can explore signal detection fairly readily and in a flexible way where we can actually add arms as needed. You had a question about controls. Yes, we do gather parallel controls in a somewhat analogous way to I-SPY, not quite Bayesian, but that type of idea.

In terms of the different TKIs, I think Roger has answered that perfectly. It's sort of impressive when you look at KEYTRUDA monotherapy in RCC how active the drug is. Certainly, when you add TKI to it and -- as in the case of axitinib, clearly, we've demonstrated remarkable efficacy. We've already shown Phase II data in combination with lenvatinib, which is quite dramatic. And we had data at ASCO, as you know, in the PD-1 experience population. Also that was really quite impressive. So we do think that both as our front-line treatment and potentially as salvage treatments, TKIs plus KEYTRUDA will have a role to play.

Operator

Your next question comes from the line of Tim Anderson with Wolfe Research.



Timothy Minton Anderson - Wolfe Research, LLC - MD of Equity Research

Roger, suppressed you on the potential risk that the PD-1s don't -- in the adjuvant study in contrast to their consistent activity in an aesthetic disease based on the idea that the underlying may be different in tumor disease versus metastatic. And you have a bit of a mixed track record for positive result, melanoma trial. You've been adamant that this is a midterm. You said ones will work even better than the earlier. So I'd like to get a perspective on this in light of adjuvant. I know that's a different tumor type. It's a different cost of drug, but it does lend support to the idea that restated advanced stage that might act differently. This question that Sanofi Regeneron keep talking about their PD-1s and have collectivity to KEYTRUDA in lung. An important difference in their trial, they excluded no smokers. And I'd like to get your thoughts on what sort of steps might make it in interpreting the results.

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

Tim, you were breaking up quite a bit when you asked the question. So I'm not sure if Roger was able to understand the question or not. I know the first one related to the difference in PD-1 versus adjuvant versus metastatic. Roger, could you understand the question?

Roger M. Perlmutter - Merck Research Laboratories - President

Well, I think the question, Tim, if I'm not mistaken, had to do with the -- isn't the tumor environment different in metastatic versus the early stage? And what gives me confidence that the statement I've made repeatedly that KEYTRUDA appears to work better earlier on when, from your perspective, I think that you felt the data were a little mixed. Is that right?

Timothy Minton Anderson - Wolfe Research, LLC - MD of Equity Research

Yes. I'm just wondering if there was risk in essentially in light of IBRANCE filing. You've been different at mech -- it lends support to the idea that maybe the early-stage single tumor disease is going to look and -- you that is static to these.

Roger M. Perlmutter - Merck Research Laboratories - President

Yes. So I don't think -- of course, and as you said, I mean, you can't really reason from IBRANCE. And their observation to KEYTRUDA, the mechanisms are so different signal transduction inhibitor that to a first approximation is cell autonomous as opposed to KEYTRUDA, which is acting in the entire tumor system. The response to KEYTRUDA is so dependent upon the characteristics of the tumor itself. And of course, we're learning an awful lot about tumor biology in the course of studying this because all of us grew up with the idea that cancer is a somatic genetic disease. And it's a cell autonomous disease, and the malignant clones evolve by stepwise accrual of mutations. And they eventually lose growth factor dependence and substrate adherence and no longer respect basement membranes. And then individual clones seed out, and there's this environment that selects for them. And in fact, it appears that the situation is much more complicated than that in that the cancers are very dependent upon the sustaining cells, what we refer to broadly as the tumor microenvironment. And those sustaining cells participate in tumor growth. And that interaction between immune cells, sustaining cells, myeloid-derived cells, some of which are described as suppressor cells as well as the cancer itself, the malignant cell itself is very important.

As we know in most tumors, the majority of cells are not the transformed cell population. There are other cells. And KEYTRUDA is very much interacting with those. I would say that all of the evidence that we have, from everything that we've done preclinically and clinically, indicates that KEYTRUDA reveals the preexisting immunity directed against tumors. And as a result, those tumors either shrink or just disappear. In many cases, it will hold the tumor in check, even though there are a few malignant cells left. Some people call that sort of reestablishing a balance between immune function and the tumor. But there's -- everything that suggests that those mechanisms remain intact both in the metastatic setting, where, obviously, we have a huge amount of data, but as well in the earlier settings. And I think our adjuvant data are very clear in that point. And that's true when you look in the breast cancer population. That's true when you look in the melanoma population. That's true in a whole variety of settings. So I feel quite confident about that. And I think, mechanistically, these are really quite distinct. And then you had another question, but that one broke up a bit more. So Tim, what was that?



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

It's -- I think we're going to go to the next question. Tim, if you want to e-mail me your second question, perhaps we can get that toward the end.

Operator

Your next question comes from the line of Seamus Fernandez with Guggenheim securities.

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

Great. Hopefully, you guys can hear me okay.

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

Yes, we've got you.

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

All right. Great. So just a couple of questions. Roger, just hoping you could comment on what feels like a couple of gaps in your internal development pool, and you've been accessing that by buying companies like ArQule. We're seeing a lot of encouraging early data with point mutation kinase inhibitors. Just hoping you could give us a general sense of the Merck philosophy around kinase inhibitors development there and the ability or Merck's interest in potentially building out that space. Incremental to that, I think we're starting to see more ADCs actually showing some really interesting data in the CPI refractory patient population or the PD-1 refractory area and also more ADCs kind of building out into that space. Wondering what Merck's efforts are there currently outside of direct collaboration.

Roger M. Perlmutter - Merck Research Laboratories - President

Right. Thanks, Seamus. I think, first of all, the idea of looking at kinase inhibitors, of course, we are interested in them potentially in our using LENVIMA as a way to probe the protein tyrosine kinase inhibitor field. So field, of course, that I know extremely well and been involved in it for the better part of 40 years. So I have a lot of experience in looking at these molecules. I have to say that the -- a lot of our attention has been drawn, of course, to immuno-oncology mechanisms because of what we found with KEYTRUDA. And we've naturally gone and asked, well, okay. What can you do to improve KEYTRUDA responses to get beyond where we are? Because we want to do better. And what we've learned some things about that, we've certainly shown that combinations in a variety of different settings can be helpful. And that includes a lot of things that just kill tumor cells. So chemotherapy, working cytotoxic agents, traditional chemotherapy, radiotherapy, and, of course, signal transduction targeting agents. And all of them, I think, have similar kinds of effects. We're interested in them. And what we're trying to do is improve the benefit risk profile. So where we can find more selective compounds at a fewer adverse effects, in general, my guess is that those things will pair pretty well with KEYTRUDA, and we are interested in those. And we have tried to address them principally by taking advantage of the very large number of companies out there, small and large, that have pursued such things. So that's that.

I don't think the answer's very different for the antibody drug conjugates. Of course, we've been doing experiments with these, particularly the EV data that you've seen in urothelial cancer is working with Seattle Genetics. And we're looking at a number of other programs. We set up at the beginning, as you know, a mechanism, and Roy set this up, whereby we can provide KEYTRUDA to lots of people who are doing studies to get an early look at which sorts of things work in combination with KEYTRUDA. And that's been very helpful to us in terms of targeting licensing opportunities and acquisitions. That's the general approach we're taking. And at the high level, I would say, it appears that things that kill malignant cells, maybe because they have a pro-inflammatory effect, perhaps for other reasons, tend to work pretty well in combination with KEYTRUDA.



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

Great. Thank you, Roger. We're at the top of the hour, but perhaps we could take questions from 2 more analysts.

Operator

Your next question comes from the line of Mara Goldstein with Mizuho.

Mara Goldstein - Mizuho Securities USA LLC, Research Division - MD of Equity Research Department

Great. I'm wondering if you could maybe put KEYNOTE-524, the LENVIMA plus KEYTRUDA combination, sort of in context with what we just saw as approval in first-line liver cancer for the atezolizumab plus Avastin program?

Roger M. Perlmutter - Merck Research Laboratories - President

Yes. I mean, just to say that the 524 data are really quite strong, as you saw, and relate to the broader LENVIMA combination studies that we have. Roy, maybe you could comment on specifically on those data and also on the larger control data with respect to hepatocellular carcinoma.

Roy D. Baynes - Merck & Co., Inc. - Chief Medical Officer

Sure. So the combination that we showed was obviously a single-arm Phase II experience. And the magnitude of the response was really impressive. It's certainly among the probably highest response rates seen. And the responses at this stage, a follow-up look quite durable. So we think that portends a very favorable outcome for this combination in HCC. And then we do have a large Phase III study, which is exploring this combination versus standard care.

Operator

Our last question comes from the line of Chris M. Schott with JPMorgan.

Christopher Thomas Schott - JP Morgan Chase & Co, Research Division - Senior Analyst

Great. Just 2 here. Maybe just update next steps with the BTK program. And maybe more broadly, just do you see an ability for the reversible BTKs to move earlier in the treatment paradigm? Or should we think of these as most likely kind of post Imbruvica-type agents?

And then my second question was maybe less ASCO-related, but just an update on some of the near-term KEYTRUDA dynamics as we're starting to move beyond some of the peak COVID-containment efforts there. Are you seeing any signs at this point that either treatment rates or new starts are beginning to normalize? Or is it still too early to get a look at how those dynamics are playing out?

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

Thanks, Chris. Perhaps the first question, Roger or Roy, and the second question, maybe Frank.



Roger M. Perlmutter - Merck Research Laboratories - President

Well, just quickly, Chris, on BTK. I think the fundamental question, which is we still don't know the answer to because it has to do with the way in which you explore it, is when do the cystine mutations occur in individuals who receive a covalent cystine acting BTK inhibitor? And what is the right approach to treating individuals from the time that, that mutation occurs? Is that the time in which because, of course, that resistant clone should expand? Is that the time when you should pursue aggressively a molecule like ours, which is, of course, unaffected by that mutation? Or are there other approaches that you should use? And then more generally, you can ask the question, well, gee, is the right approach to use a non-covalent? And then at some point, you could come back with a covalent one in those who have escaped, but still have the cystine intact. All of that remains to be explored. I think the first question is, in individuals who are clearly refractory, can you reintroduce response? And I think we already have data from a small number of patients that says Yes. and we're clearly going to get an answer to that. And Frank, on KEYTRUDA dynamics?

Franklin K. Clyburn - Merck & Co., Inc. - Chief Commercial Officer & Executive VP

Yes. And Chris, I think it's too early to give any additional COVID updates as we were discussing on our last quarterly call. We are seeing a dynamic where there is some new patient start declines or, I should say, with regards to just visits of new patients, depending on the different cancer type. And we'll have a chance at the end of the second quarter to give an update. I think the most important part, though, Chris, we see oncology as being very resilient. We do not think this change is the fundamental picture of the opportunity. As you can see, the momentum that we had in Q1 of 46% growth, if you would exclude foreign exchange. So we do believe there'll be some impact, as we mentioned, across the portfolio based on COVID. But clearly, for KEYTRUDA, we're very confident in the outlook. And I think the feedback that we're hearing coming out of ASCO has been very positive from both the community and KOLs about the data that Roger shared.

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

Great. Thank you all for your participation and your interest today. Really appreciate it. Please reach out to IR if you have any follow-up questions, and we look forward to seeing you soon.

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