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PFE.N - Pfizer Inc Analyst and Investor Call to Review Oncology Business

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OVERVIEW:

PFE provided updates on and discussed about its oncology business.

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PRESENTATION

Operator

Good day, everyone, and welcome to Pfizer's analyst and investor call to review Oncology business. Today's call is being recorded.

At this time, I would like to turn the call over to Mr. Chuck Triano, Senior Vice President of Investor Relations. Please go ahead, sir.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Thank you, operator. Good morning, and good afternoon, everyone. And thanks for joining us today to provide an update on our oncology pipeline progress, specifically how we are applying our capabilities to move more quickly and utilize cutting-edge science to key programs.

As a note, we plan to conduct a series of these sessions across our therapeutic areas as our pipeline progresses, and we have new data and insights to share with you all.

We'll be making forward-looking statements during this call and actual results may be different. Additional information regarding forward-looking statements is available in our SEC filings on our forms 10-K and 10-Q.

Forward-looking statements on this call speak only as of the original date of this call, and we undertake no obligation to update or revise any of the statements.

With that, I'll now turn the call over to Andy Schmeltz. Andy?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Chuck. I'm Andy Schmeltz, and on behalf of my colleagues, Chris Boshoff and Jeff Settleman, we're pleased to have this opportunity to engage with you today.

The 3 of us have joint accountability for Pfizer's end-to-end oncology presence, inclusive of strategy, investments and the full R&D and commercialization continuum.

Today, we'll spend about 20 minutes on how we're applying the mindset from Pfizer's recent COVID-19 vaccine light speed effort to key clinical programs within oncology. We believe this purposeful, more ambitious approach can make a significant positive impact, both for people with cancer and for Pfizer. Then we'll open it up to Q&A.

Before jumping into the primary focus of our discussion, let me take a minute to highlight Pfizer Oncology today. We have a broad portfolio of 24 medicines across 30 types of cancer that brought hope to more than 716,000 people living with cancer in 2020. We continue to see outstanding year-over-year growth for oncology globally, almost $11 billion of revenue.

Even through a difficult year with the pandemic, we delivered 21% operational growth in 2020. IBRANCE, representing about half the revenue of the portfolio, grew 9%. While our other medicines grew a total of 36% operationally, led by our biosimilars portfolio, BRAFTOVI and MEKTOVI in melanoma, BRAFTOVI in colorectal cancer and Xtandi in prostate cancer.

We also have an incredible amount of activity in clinical development, more than 275 clinical trials currently underway and 6 additional Phase 1 first-in-patient clinical program starts since our last discussion with you at Pfizer Investor Day this past September.

We've also initiated several new registrational trials in recent months. 2 new trials with BRAFTOVI - BREAKWATER in first-line BRAF-mutated colorectal cancer, which started in late 2020; and a new Phase 3 trial that started in February, called STARBOARD, with BRAFTOVI/MEKTOVI combined with pembrolizumab in first-line melanoma.

And in prostate cancer, we're expecting data this year from the ongoing Phase 3 TALAPRO-2 trial with Xtandi plus Talzenna (talazoparib) in men with metastatic castration-resistant prostate cancer. Bottom line, we're proud of our track record and our future prospects for Pfizer Oncology.

Let's now shift gears. I cannot understate just how incredibly proud and excited we at Pfizer are about the light speed development in collaboration with BioNTech that delivered the world's first breakthrough COVID-19 vaccine in less than a year.

Our ability to move at such extraordinary speed while always maintaining our focus on quality and safety was the first powerful display of what the new Pfizer is capable of.

Through the vaccine, we found ways to use digital technology to perform tasks in parallel rather than sequentially and to reduce white space between clinical trial cycle times. All of which we're now looking to apply to transfer the way we bring breakthrough cancer medicines to patients faster.

These light speed learnings and concepts are something that we within oncology have been focusing on to incorporate into our oncology development approach for some time. Today, we'll walk you through 3 exciting Pfizer discovered programs.

Advancing with this light-speed mindset, moving at the speed of science. First, a recent example with LORBRENA, or LORVIQUA internationally, in ALK positive non-small cell lung cancer. Then our BCMA bispecific candidate, elranatamab in multiple myeloma and how we're taking ambitious steps in what is sure to be a dynamic market.

And finally, Jeff Settleman will talk about a collection of early development programs in the breast cancer space, building on our already strong position here with IBRANCE.

These examples to be highlighted represent just a small subset of our pipeline portfolio. However, we believe they're indicative of how this new breakthrough mindset is being applied and will propel Pfizer oncology to continue our growth trajectory and to make a meaningful difference for people with cancer.

Now I'd like to turn it over to Chris Boshoff to discuss LORBRENA in more detail. Chris?

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Thank you very much, Andy. Thank you. As you all know, ALK positive lung cancer accounts for 3% to 5% of all lung cancer.

Almost a decade ago, we pioneered the field for the development of XALKORI. Lorlatinib was discovered and developed in-house by Pfizer chemists, and it has a unique macrocyclic structure as illustrated in the center of the slide.

Up to 40% of patients with ALK-positive non-small cell lung cancer present with brain metastases. LORBRENA is a next-generation ALK inhibitor, targeting most of the known resistant mutations and also covering brain metastases. On the right side is the list of the most common mutations developing to other ALK inhibitors demonstrating the coverage offered by lorlatinib to this.

We're very proud of the flawless execution and accelerated development of lorlatinib. From first patient dosed to first regulatory approval was less than 5 years. For our CROWN first-line Phase 3 study, from topline report to FDA approval was just over 6 months.

We utilized the latest regulatory tools, including real-time oncology review pilot and project Orbis, allowing simultaneous reviews in the participating countries and all submissions are now complete.

The FDA approval in first-line non-small cell lung cancer is based on the compelling results from the CROWN trial, which demonstrated the 72% reduction in the risk of progression or death. This study also showed in patients presenting with intracranial disease, a 78% complete remission, which is the highest ever demonstrated for any ALK inhibitor.

For those presenting without any intracranial metastases, the CROWN study also demonstrated a hazard ratio of 0.06 for progression in the brain versus XALKORI. We believe that the CROWN results will position LORBRENA to be highly competitive with second-generation ALK inhibitors in the first-line setting, especially in those 40% of patients presenting with brain metastases.

Furthermore, LORBRENA will continue to be a standard of care after second-generation ALK inhibitors in the second-line setting. We are also pleased to still have 27 patients on treatment more than 5 years after starting LORBRENA on our Phase 1 dose escalation and expansion study in 2014.

Moving now to our investigational BCMA bispecific, elranatamab, which we've recently announced the initiation of the first pivotal trial in relapsed/refractory multiple myeloma. Multiple myeloma remains a significant unmet need with only 50% of patients surviving past 5 years with current standard of care.

As multiple myeloma progresses, tumors become resistant to the 3 main classes of therapies: the IMiDs, including lenalidomide; the proteasome inhibitors; and the anti-CD38 antibodies.

We believe that the next major pillar of treatment for multiple myeloma will be medicines targeting BCMA, which is highly expressed on multiple myeloma cells. And among the BCMA-targeted therapies, we believe the bispecific molecules will become the next standard of care backbone across the treatment paradigm because of efficacy, their safety profile, combination opportunities and convenience.

Elranatamab is a full length, humanized, bispecific antibody optimized for binding affinity to both BCMA and to CD3, enabling more potent T cell mediated tumor cell killing. Elranatamab is being developed as a subcutaneous injection with the aim of reducing the incidence and grade of cytokine release syndrome or CRS, which is a dose-limiting toxicity, particularly for CAR-T cells.

The development program for elranatamab is called MagnetisMM. Shown are data from Phase 1 trial presented at ASH in December 2020, updates of these data will be presented at an upcoming medical conference. In patients with relapsed/refractory multiple myeloma, 83% of patients achieved a clinical response at the recommended Phase 2 dose.

Overall, 30% of patients treated, achieved complete response or stringent complete response. This is also the first study with a BCMA bispecific to show responses in patients who received prior BCMA targeted therapy, including ADC or CAR-T.

Note, 3 out of 4 responses, including a stringent complete remission were observed in patients with multiple myeloma progressing on BCMA-targeted therapy. Based on these data, we initiated the pivotal Phase 2 study MagnetisMM3 earlier this year.

This study is now recruiting patients with triple cross refractory multiple myeloma globally.

MagnetisMM-3 is enrolling 2 cohorts of participants, one with and one without prior treatment with a BCMA-directed ADC or CAR-T therapy. The primary endpoint is objective response rate, as assessed by blinded independent central review, the study's estimated primary completion date is June 2022.

Elranatamab is one of the key medicines we are prioritizing at Pfizer to apply light speed concept from the COVID-19 vaccine to accelerate the clinical development program.

We are doing this in a variety of ways, including real-time monitoring of blinded independent central review, acceleration of commercial-ready product supply by leveraging internal resources, data review and analysis powered by machine learning technologies.

As an illustration, from final approved protocol for this study to first subject dosed for MagnetisMM-3 was achieved within 30 days, condensed from the typical 20 weeks.

In addition to MagnetisMM-3, we are initiating a comprehensive development program, building on all of clinical studies. This includes other Phase 3 studies in earlier lines of therapy, MagnetisMM-5, 6 and 7, expected to initiate over the coming -- over the coming 12 months.

We also initiated MagnetisMM-4, exploring the potential role of novel combinations through an umbrella study with both internal and external molecules. In the future, the appropriate sequencing and rational combinations of elranatamab with other medicines have the potential to transform the outcome of patients with multiple myeloma.

I'll now hand it over to Jeff to talk to you about our next-generation breast cancer franchise.

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Thanks, Chris. So as you've just heard from Andy and Chris, we're now applying the learnings of the COVID vaccine development experience to our oncology programs.

And I'll briefly describe how we're applying these principles as we explore potential new therapies for estrogen receptor positive breast cancer patients.

As you know, the approval of palbociclib, IBRANCE, in 2017 established Pfizer as a leader in the treatment of ER-positive breast cancer. And we've maintained a strong commitment to these patients.

One of the most significant challenges still facing ER-positive breast cancer patients is that there is no clear standard of care in the post CDK4/6 inhibitor setting.

So to address that important unmet need, we've been focused intensively on the development of additional therapies that can overcome drug resistance and potentially provide these patients with more effective and safer treatment options.

We've been taking a multipronged approach to targeting ER-positive breast cancer, not only targeting the cell cycle, but also targeting estrogen receptor activity, disrupting signaling pathways that drive breast cancer cell survival and through immuno-oncology approaches that promote engagement of immune cells with breast cancer cells.

Here, I'll briefly highlight 4 of these programs, including 3, which all entered the clinic at nearly the same time last year: First, I'll describe our 3 most advanced next-generation CDK inhibitor programs, which each enable disruption of the critical G1 cell cycle checkpoint.

On the left is our CDK2/4/6 inhibitor, which differentiates from our CDK4/6 inhibitor, palbociclib, with the availability to additionally target CDK2. And since CDK2 activation seems to drive palbociclib resistance in some breast cancers, this molecule has the potential to overcome such resistance.

We also see opportunities to develop this inhibitor in other tumor types, including triple-negative breast cancer and ovarian cancer. This molecule is currently in Phase 1 clinical development and combination studies with endocrine therapy are now underway.

And it's worth noting that we've been very encouraged by the early responses we're seeing thus far with this inhibitor, even as monotherapy, especially considering that we're treating patients who have previously progressed on CDK4/6 inhibitors, which is consistent with our hypothesis that CDK2 contributes to resistance to current standard of care treatments and that a CDK/2/4/6 inhibitor can potentially mitigate such resistance.

Next is our CDK4 selective inhibitor, which has been shown preclinically to target CDK4 with more than 10x the potency of palbociclib and without the neutropenia, sometimes seen with CDK4/6 inhibition. And that improved TI potentially provides more opportunity for safer combination treatments in additional cancer types, including lung, colorectal and prostate cancers.

To the right of CDK4 is our CDK2 selective inhibitor, which has been shown in preclinical models to combine with palbociclib or with our CDK4-selective inhibitor to overcome resistance in the ER-positive breast cancer and has the potential to drive efficacy in a variety of tumors exhibiting CDK2 activation, especially in combination with standard of care therapies.

Following the successful acceleration of preclinical timelines for these programs, we were able to move both the CDK2 and CDK4 molecules into the clinic within 8 days of each other in October of 2020.

And it's worth noting that each of these next-generation CDK inhibitors resulted from innovative structure-guided medicinal chemistry efforts from Pfizer scientists that yielded candidates with selectivity profiles that many had predicted would not be possible to achieve.

Now in addition to our robust CDK franchise, we're very excited about the potential for our novel KAT6 small molecule inhibitor, a potential first-in-class agent that blocks the enzymatic activity of the histone acetyltransferase KAT6A, an epigenetic regulator that's amplified and overexpressed in breast cancer.

KAT6A is required for expression of the gene encoding the estrogen receptor, ESR1, and we've observed that this inhibitor can overcome endocrine therapy resistance associated with ER mutations in preclinical models of ER-positive breast cancer and show synergistic activity with CDK inhibition in combination studies. And this program also moved into the clinic in late 2020.

Now it's important to emphasize that we've applied light speed principles to the discovery and development of each of these assets that I just described.

Our work on both the cell cycle and KAT6 inhibitors has yielded both complementary and overlapping opportunities with multiple shots on goal to deliver clinical benefit for patients. And with strategic optimization of resources across programs, we took the approach of developing these assets in parallel, and we were able to deliver 3 new programs in the clinic within 1.5 months of each other in 2020.

Going forward, we also plan to efficiently drive acceleration or de-prioritization, if appropriate, of individual assets via umbrella studies and by employing specifically predefined go/no-go criteria.

This is a paradigm that will continue to guide our oncology research enterprise as we work to bring additional breakthrough therapies to cancer patients in the future.

So with that, I'll pass it back to Andy to wrap up the presentation.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Jeff. As you've just heard, we're moving at light speed to advance these programs using enhanced processes, efficiency and technology. Each of the programs highlighted by Chris and Jeff, respectively, represents a compelling opportunity for patients, and for our business.

Here, we're depicting the opportunity for the G7 markets. For LORBRENA, the first-line indication will allow us to expand our share of the ALK positive non-small cell lung cancer market, which we anticipate to peak in the range of 25% to 30% share overall.

For elranatamab, the multiple myeloma market is large and is expected to reach $34 billion by 2030 due to multidrug combinations and increased duration of therapy as well as the emergence of the BCMA modality.

Within BCMA, we believe the bispecifics will become the standard of care, being preferred over the antibody drug conjugants and CAR-Ts, offering the potential for the efficacy of a CAR-T with compelling safety and convenience advantages.

While it's still early days, we believe elranatamab truly has a right to win. Not only in the initial triple refractory indication, but also over time in the double relapse and newly diagnosed multiple myeloma settings.

We anticipate 15% to 20% peak share across multiple myeloma lines of therapy. And for our next-generation breast cancer portfolio, we have a strong scientific rationale for CDK programs as well as for our KAT6A program.

We believe there is potential for breakthrough efficacy in the post CDK4/6 setting where no clear standard of care exists and also in the first-line metastatic setting to prevent the emergence of CDK resistance.

Leveraging our leadership in HR-positive HER2-negative breast cancer, we believe this multiple shots on goal approach will lead to tremendous opportunity and leadership as a follow-on to IBRANCE.

So there you have it. Hopefully, our enthusiasm and conviction regarding our future prospects and our light speed mindset have shown through.

Thanks for your time. We would now like to take questions. Chuck, over to you.

QUESTIONS AND ANSWERS

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Thanks, Andy, and thanks to Chris and Jeff for the presentation as well. Operator, can we please poll the audience for questions. Thank you.

Operator

(Operator Instructions)

Your first question comes from the line of Louise Chen from Cantor.

Louise Alesandra Chen - *Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD*

So first question I had for you is, if it's approved, where do you see your next-gen CDK inhibitors fitting into the treatment paradigm? You have three. So what's your go-to-market strategy?

Second question I had for you is, how important is your heme malignancy franchise to you going forward? And if it's important, how do you plan to build this franchise out, what type of targets, the type of drugs are you most interested in?

And then last question is just on your early stage oncology pipeline, which you didn't talk as much about today, what gets you most excited? I know you have a lot of compounds in development.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Louise, for your 3 questions. We'll try to take them one at a time. I'll talk about the next-gen CDK go-to-market strategy and the heme build-out. Maybe, Chris, you can chime in.

And then Jeff, certainly, over to you for the early pipeline. So with our next-gen CDK franchise, we see clear opportunity here. While CDK inhibitors, led by IBRANCE, have really established themselves as the modality and standard of care for metastatic HR-positive HER2-negative breast cancer that there's clear unmet need.

70% of first-line metastatic patients are on a CDK inhibitor, and so they're going to need options eventually when the cancer wins out. And so clearly, we're designing this portfolio of early compounds to be able to be effective after prior CDK therapy.

But then also, as the next generation, we envision them having addressed, as Jeff kind of commented on some of the toxicities of the current CDKs. And so they certainly could have a strong role in first-line as well.

So we see quite broad opportunity there for the next-gen CDKs. And as Jeff also mentioned, there is the possibility with some these that breast cancer is not the only tumor area that could be applicable that by having a larger therapeutic window, a broader therapeutic window that there'll be potential in other tumor areas.

Maybe before we go on to the heme question, Chris or Jeff, do you want to add anything there?

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

And I'll just quickly add first, and Jeff, a little bit to just expand on. Remember in our Paloma studies, we show that one of the mechanisms of resistance that was demonstrated was those tumors that mainly express or overexpress CyclinE. We know CyclinE binds to CDK2, so that was -- that propelled the development of a next-generation CDK2 inhibitor.

So the CDK2/4/6 could either be to prevent or to manage and treat resistance to the current therapies. And Jeff, perhaps, you can also expand on why we're specifically interested in the CDK4?

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Sure. Yes. So the CDK4 selective inhibitor, we see the opportunities, as I mentioned, not only in ER-positive breast cancer as a potentially safer molecule than the 4/6 inhibitors, but also a molecule that more potently hit CDK4. And therefore, could be more effective in the early line setting, especially when combined with CDK2, as Chris mentioned, to prevent resistance.

That's one scenario for 2/4 combination. We also see opportunities, as I mentioned, in other indications outside of ER-positive breast cancer where preclinically that more potent coverage of CDK4 has yielded efficacy in preclinical models that we don't see with palbociclib.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks. Let me tackle to the hematology franchise. Clearly, we're very excited by the prospects of elranatamab in multiple myeloma. But we should note that we have an existing -- actually fast-growing hematology portfolio with 4 medicines.

We've got Bosulif in CML, besponsa in ALL, and then we have 2 medicines in AML. And collectively, we're approaching $1 billion in revenue with this portfolio. We've got infrastructure globally, and most importantly, we understand the dynamics in the blood cancer space. So very excited to bring on and see elranatamab progress quickly. And to tap into this infrastructure, but certainly, if there are other opportunities to further expand our hematology portfolio, we'll be prime to do so.

Maybe to touch on the early pipeline, the last question, Jeff, anything you want to add about the early pipeline?

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Sure. Yes. We're very excited about our early programs. And maybe I can comment on a couple of areas that are particularly a high priority. In the IO space, so in addition to our approved PD-L1 antibody avelumab and our PD-1 antibody, sasanlimab, which is in Phase 3 development in early bladder cancer.

We have several NMEs in Phase 1 now, including 2 different T cell redirecting bispecific antibodies. You heard about BCMA. We also have a bispecific T-cell redirecting antibody targeting GUCY2C, an antigen that's highly expressed in GI malignancies. We have 2 different programs targeting the immunosuppressive TGF-beta pathway, and we have recently introduced into the clinic, a PD-1 antibody conjugated to a modified version of an IL-15 cytokine.

We're really excited about that one. Also from our Boulder site, we have a small molecule inhibitor of the TAM kinases. So if we have a robust early pipeline in immuno-oncology, we also have several promising earlier-stage programs that are focused on the PDX refractory IO space, a few of which we're expecting to bring into the clinic in the second half of this year, including an oncolytic virus that looks very promising in preclinical studies.

Another area of scientific emphasis has been on regulators of chromatin at the genetic modulators. I've mentioned KAT6. We also have an EZH2 program that we're excited about and our PRMT5 inhibitor, which is differentiated from some of the other programs in the clinic with some very high potency and unique mechanism of target engagement.

So those are a few of the areas that we're especially excited about with respect to our early pipeline.

Operator

Our next question comes from the line of Terence Flynn with Goldman Sachs.

Terence C. Flynn - *Goldman Sachs Group, Inc., Research Division - MD*

I appreciate you walking through all this today. I guess a couple for me. The BCMA market, you mentioned differentiation versus the ADCs and the CAR Ts. But if you look at the various bispecific antibodies, what do you see as kind of the key differentiated features there for your asset?

And what's going to really drive market share shift among those various agents? And then the second one I had is, on your CDK2/4/6 inhibitor, are we going to see any data there at ASCO this year or potentially maybe another conference later this year? And what is the bar?

What are you guys looking for in terms of level of activity to really advance that into further studies? And then the second part of that question is just, can you remind us if you ever saw any activity for palbo in other tumor types beyond breast cancer.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks for your questions. I'll start, and then we'll tag team with Chris and Jeff on these others regarding CDK2/4/6 and palbo activity. So for elranatamab, role and differentiation within relative to other BCMA modalities.

So first, again, BCMA relative to CAR-T relative to antibody drug conjugants, we believe that the bispecifics are going to be the winners in the long run here.

The efficacy of the CAR-Ts, combined with safety and convenience advantages, elranatamab from day one designed to be subcutaneous administration. Many of the other bispecifics started out as infusion molecules, and they're trying to make them more convenient into subcutaneous.

Certainly, it's early days in terms of differentiation amongst the bispecifics. We're very excited about the early efficacy results and safety results that we have in our trial, and we'll have to see how this plays out. But given the -- our intent to move quickly, and to generate robust data across different patient segments, we're quite confident that we're going to be primed and have a right to win over time.

Chris, anything to add there?

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Two other points of differentiation is the molecule itself. The molecule was designed for optimal affinity to both BCMA and CD3, which resulted in a very favorable PK profile for us.

So as Andy pointed out, we're starting in the trial with weekly and then 2 weekly subcutaneous dosing, but we're also now starting to test in MagnetisMM-9 4 weekly subcutaneous dosing, which, of course, could be differentiated.

The overall risk benefit profile, as mentioned, the safety, so far only had Grade 1 or Grade 2 cytokine release syndrome and specifically, we were the first to notice observed responses including a stringent complete remission in patients previously exposed to either ADC, BCMA or BCMA Car T. So we certainly believe we will be in the first wave with elranatamab.

Jeff, with CDK?

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Yes. I think there was a question about the path for CDK2/4/6. I think while we don't have a specific plan for the presentation of the data. As I mentioned, what we're especially encouraged by is seeing responses with the monotherapy treatment in patients who have progressed on CDK4/6.

So again, this does seem to support our hypothesis around the role of CDK2 in driving resistance. As I mentioned, we're also exploring the endocrine therapy combination, which is already underway.

I think as far as where the bar is, we don't have specific metrics to point to it at this time. But I would say that we do see CDK2/4/6 monotherapy, if there is transformational efficacy as our first path to an approval with our next-generation CDK molecules. I think there was also a question about palbociclib in other tumor types. And maybe, Chris, I'll hand back to you for that one.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Thank you. So we did observe a number of some of the rarer tumors or the rarer lymphomas and sarcomas, soft tissue sarcomas, where we did observe single-agent activity with palbociclib. One of the challenges have been in combinations, apart from hormonaltherapy has been either DDIs or the therapeutic index, especially with cytotoxic therapy.

Although we've noticed in some of the Phase 1 study, significant activity with palbociclib combination with cytotoxic therapy that has always been hampered by an hematological toxicity.

And we hope that, that can be overcome with the CDK4-specific inhibitor. Having said that, we still have ongoing pediatric studies in Ewing sarcomas and other types of sarcomas with a combination of palbo plus cytotoxic therapy, which appears to be better tolerated in the pediatric population.

Operator

Our next question comes from Vamil Divan from Mizuho Securities.

Vamil Kishore Divan - *Mizuho Securities USA LLC, Research Division - MD*

So one, maybe -- I may miss it, but just on the earlier stage assets, your HER2 ADC -- we get questions on that periodically. I'm wondering if you can just give any update on when we might see some more data that product or 103?

And then maybe just -- you talked a lot about encouragingly on the learning from the COVID situation, how you're transferring over? I'm wondering if you can just talk more specially around sort of mRNA technology, and how you sort of need to see that further development you look to doing on that in terms of oncology vaccines or otherwise would be helpful.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Jeff, I think both of these are squarely in your shop.

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Sure. Yes. So for our HER2 ADC, and we've recently stopped that program, we had seen robust clinical responses, but we just felt that the therapeutic index wouldn't quite be adequate to move into earlier line indications when considering the competitive landscape.

And so we decided to prioritize other programs where we see greater potential. Also worth mentioning that from our Boulder site, we have a small molecule program that targets HER2 exon 20 mutations.

As far as the RNA technology in cancer vaccines. Absolutely, this is something we're looking at very carefully. We do have an interest in cancer vaccines. We've seen how the power of RNA as producing immunogens that seem to be quite effective in the preventive vaccine setting. We think that, that technology may very well translate into therapeutic cancer vaccines. We're excited about that possibility. So that's something that we're actively investigating.

Operator

Your next question comes from Geoffrey Porges from SVB Leerink.

Geoffrey Craig Porges - *SVB Leerink LLC, Research Division - Director of Therapeutics Research & Diversified Biopharma and Senior Research Analyst*

Chuck, I hope they let you out of the witness protection program soon. It looks a little austere where you are.

So 2 questions, both related about earlier lines of treatment. First, on the CDK4/6. Do you have any insight yet as to why IBRANCE was not successful in the adjuvant setting?

And then secondly, which of the CDKs that you outlined, you believe has the best opportunity to move into the adjuvant setting? And related to that, are there any principles from light speed that you think can accelerate the path to either first-line or to adjuvant, short of showing an overall survival benefit?

And if you could address that, for both the CDKs and for the BCMA because as you alluded to, the first-line indication and/or the adjuvant indications for both of these diseases are, by far, the majority of the revenue opportunity.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks for the questions. Chris, I think that you're probably best positioned to speak to our early breast cancer experience with IBRANCE, and how we would apply learnings to next-gen CDKs perhaps for early breast cancer as well as our light speed approach with elranatamab.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Thank you very much, Andy. We're obviously very disappointed in the data from our early breast cancer studies, especially PALLAS. Overall, it's very difficult to compare the various studies in the early breast cancer because of, obviously, demographics.

I need to point out as well that these were not Pfizer sponsored studies. So we're working with the sponsors of those trials in the [inaudible] (corrected by company after the call) groups who conducted those studies.

As you may have noticed in the presentations last year, there was high number of high percentage of patients that discontinued palbociclib during the study, that was also disappointing to us.

Having said that, we have collected both tissue samples as well as plasma samples during that study, and that is starting to reveal a lot of interesting data for us. And data that could be applied to our future studies, specifically on CDK4 and CDK2/4/6 programs, as we could potentially develop them into earlier settings. So early breast cancer, we believe will become molecularly fractionated between different risk groups.

Not everyone will benefit from adding a CDK2/4/6 or CDK4 with CDK4/6. And so using those translational data, I think is going to be enormously helpful to us. I do want to point out quickly another study we just initiated was -- that's been led by Yale University as CRC and/or collaborative research study is in the early setting called M-Zero.

So what this study does is the very novel setting breast cancer patients very early on we sequence all their samples then determine the genetic drivers of their specific disease. Those genetic drivers are then detected in plasma with circulating tumor DNA and as soon as they become detectable, patients are randomized to either continue their standard of careful hormonal therapy or to be randomized to be added at CDK4/6.

So that study, which is just open a randomized trial, we also believe will give significant insight how to develop the base combination and at what time point in the treatment paradigm. Thank you.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

And Chris, do you want to comment on applying light speed to elranatamab.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Yes. So I think, as you've seen from the slide we've shown with the 9 studies that's now in initiation and some of them have started, MagnetisMM 1 to 9. A lot of things have been done in parallel.

We're using the latest digital tools, virtual tools for virtual site initiation, getting data in from sites using artificial intelligence, machine learning, pattern recognition to see if there is any regarding AEs or any other information we're collecting from the sites, particularly also the acceleration of our CMC and commercial-ready product will be ready shipping launch.

As you've seen the current primary completion date is June 2022 for our first study. So we're very excited to do things in parallel and apply the latest digital technologies in that program.

Operator

Our next question comes from Steve Scala from Cowen.

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

Two questions. I think CDK4/6 inhibitors overall have been studied unsuccessfully in lung, pancreatic and prostate cancer. I think you mentioned interest in triple-negative breast and ovarian as targets now. Is that the totality of the other tumors that you plan to pursue? And secondly, why did Pfizer out-license the PI3K mTOR, given its promising clinical response post CDK4/6 inhibitor failure?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Steve, for those questions. Jeff, let me hand it to you first for other opportunities for our CDK franchise.

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Right. So based on preclinical data, we've been exploring each of these next-generation CDK inhibitors in a broad panel of preclinical models across many indications.

For the CDK 2 and 2/4/6 programs, there are clearly settings where CDK2 activity is driven by, for example, increased cyclin e expression or amplification, loss of RV, such as seen frequently in small cell lung cancer.

So that would be one triple-negative breast cancer, endometrial cancer, ovarian cancers. These are places where CDK2 activation seems to play an important role. In terms of CDK4 activity, as I've mentioned briefly there with the greater potency we can achieve in the absence of the CDK6 associated neutropenia, we can push the coverage of CDK4, and at least based on preclinical modelling, we can see activity in settings like lung cancer, colorectal, and prostate cancer, where with palbociclib at similar concentrations that is lower exposures of CDK4, we're not seeing that kind of efficacy.

So that gives you some sense as to how we're thinking about positioning each of these molecules in other indications beyond ER-positive breast cancer.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Jeff. I don't know, Chris, do you want to take the out-licensing of gedatolisib?

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Yes, I'll be quick. Thanks, Andy. As Jeff mentioned earlier, and by the end of 2021, we'll have 21 new molecular entities in the clinic.

In 2020 alone, we had five FIHs, first-in-humans, and already 3 achieved in 2020 and in 2021. So we really have to prioritize across our portfolio. We agree that's an active medicine. It's an intravenous PI3K inhibitor and mTOR inhibitor, and we are very pleased that there's a home now with Celcuity, and they will take it on and develop it further, but it's clearly an active molecule, you're correct.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Great. Thanks, Chris. And operator, if we could take our last question now, please.

Operator

Your final question comes from the line of Seamus Fernandez from Guggenheim.

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

So just a couple of questions here. First off, in terms of the interest in other mechanisms on the breast cancer side.

I was just wondering if you guys could update us if you're doing work on oral SERDs or if you're watching that space relatively closely.

And if not, what are the issues that you see with regard to the oral SERD class? Is it just sort of the hurdle of stepping above fulvestrant or other dynamics in that regard? The second question, just in terms of protein degrader technology.

Do you guys mind updating us on the work that Pfizer is doing in this space? Whether it be through the Arvinas collaboration or otherwise? And when might we see some more products from Pfizer on the protein degrader side of things?

And then the last question, in terms of feedback that we've gotten so far, can you just update us on when we might know the sort of ultimate dosing regimen for your BCMA?

I believe you'll start with kind of a once-a-week dosing profile, follow that with expansion to kind of every 2-week and then pursue every 3 week. But just wondering when we might have good visibility on the treatment duration?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks for your questions. We'll try to tick them off one at a time. So in breast cancer, you asked about additional mechanism of actions, specifically oral SERDs.

Clearly, this is an interesting space where it looks like if they can actually have significant improvement upon fulvestrant that have utility in the breast cancer setting. And we're actually working with many of the companies that have oral SERDs today because it's about combination studies.

And IBRANCE, palbociclib is the combination agent of choice. So we're closely monitoring the space to see how it plays out. And if there is really a true winner that can establish a new standard of care for hormone therapy.

Chris, do you want to add to that?

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

I think you said it. And importantly, those companies that you're all very well aware of, and that's now got clinical study starting or started with a SERD those in the earlier lines have been combined with IBRANCE and we're partnering with them with IBRANCE for those SERDs, at least 3.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Okay. The next question is about protein degrader technology and how that's playing out. Jeff, do you want to take that? Or maybe Chris?

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Yes. Thanks, Andy. Yes. No, as was mentioned, we have an active collaboration with Arvinas on protein degraders. It's a research collaboration. We have several programs that are part of that collaboration.

We haven't yet disclosed the targets that we're working on, but just fair to say that we've been very thoughtful about choosing targets for which we think that protac type technology is especially relevant. And we're excited about how that collaboration is going. We also have internal programs focused on similar technology.

We've developed that capability in-house, and we have a few complementary programs that we're driving internally that we're very excited about. So that's what I can say about degrader technology. It's really opening up the difficult drug space. And so we're excited about what we're doing there.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Great. And Chris, on you for dosing with elranatamab.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

You're absolutely correct. The current studies, that's the Phase 1 study, is weekly. All our PK modeling has indicated that we can move to 2 weekly. The pivotal trial that is now ongoing, MagnetisMM-3, therefore has a regimen of weekly with step up-dosing to further reduce any cytokine release syndrome, and then after a couple of months moving to 2 weekly. We've also just initiated MagnetisMM-9. And again, from PK modeling, inferring that this molecule can be moved to 4 weekly.

So later, probably more I would say in 2022, you'll see data emerging with -- moving from 2 weekly to 4 weekly. You asked about the duration of response, as I mentioned, we'll update later this year.

You'll see updated data from our Phase 1 study, just to point out that the data I've shown, of all those patients that's responding, there's only one that has progressed, and that was at the lowest dose during dose escalation. So all the other responses are currently ongoing. It's highly encouraging for us.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Terrific. So as you can all hear, a lot going on in the oncology portfolio and broadly at Pfizer. So we will look forward to periodically hosting similar sessions like this to highlight other parts of our portfolio. So I'd like to thank everyone for their attention this morning, and to Andy, Chris and Jeff for their insights. Have a great day.

Operator

Ladies and gentlemen, this concludes today's conference. Thank you for your participation. You may now all disconnect.
