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# EDITED TRANSCRIPT

MRK.N - Merck & Co Inc Oncology Event at ESMO 2021

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## PRESENTATION

**Dean Y. Li** - Merck & Co., Inc. - EVP

(technical difficulty) medical need and tremendous opportunity for improvement. Our clinical development strategy continues to build and expand fueled by insight and learnings from our pioneering work and wide-ranging clinical experience of KEYTRUDA. Today, we have a broad oncology program with a rich and deep pipeline of early- and late-stage assets.

We have established high-performing teams. Our scientific expertise, clinical know-how and unmatched data sets, uniquely position us to strategically optimize and prioritize our portfolio to make significant strides in advancing cancer treatments. We are focused on flawless and timely execution to harness the attributes of our oncology assets, and we transform treatment options delivering meaningful benefits to patients remain an unwavering priority.

Today, you will hear from Jannie on the important commercial opportunities ahead of us. Our track record of clinical and commercial execution is second to none, and we are confident in our skill to unlock value from our portfolio based on our ability to design and execute clinical trials that generate robust data and provide unambiguous evidence for clinical benefit.

Now as highlighted at ASCO in June, we continue to make tremendous progress building upon KEYTRUDA as a foundational cancer treatment across many tumor types. The latest exciting data presented at ESMO reinforces our commitment and our focus to expand, to deepen and to extend our reach to more patients. We have the industry's most expansive and diverse immuno-oncology program. We continue to study candidates with mechanisms that have the potential to transform the field and add differentiating value, whether that is in combination with current assets through evaluation of earlier stages of disease or by means of clinical development. We have over 20 candidates targeting novel mechanisms in-house, and several of which we are advancing to Phase III as co-formulations with KEYTRUDA, including TIGIT, LAG-3, CTLA-4 and potentially ILT4.

We are also excited about the prospects of our externally sourced candidate, notably our antibody drug conjugates, ROR1 and LIV-1 as well as our BTK inhibitor. We have a vast program, and the data fit that Roy will speak about momentarily are just the latest examples of readouts from the torrent of clinical data we are amassing.

I do want to highlight 3 key points. First, we are expanding to earlier stages of disease to extend the benefit of KEYTRUDA to more patients. Earlier intervention provides the opportunity for us to significantly impact and transform treatment for patients across numerous cancer types, including melanoma, triple-negative breast cancer, renal cell carcinoma, non-small cell lung cancer, head and neck and more. We are excited to lead the way here.

Secondly, our emerging leadership across women's cancers brings hope to many. With high incidents and significant unmet medical need, we have now generated meaningful clinical data across breast, cervical, ovarian and endometrial cancers. And these advancements come from multiple assets, including KEYTRUDA, LYNPARZA, LENVIMA and TUKYSA.

And finally, ongoing extensive programs evaluating our diverse pipeline and portfolio are poised to strengthen our leadership position across multiple cancer types. As we did 7 years ago in KEYNOTE-001, we continue to change the practice of oncology by generating strong clinical data and advancing novel medicines and treatment paradigms for the patients we serve.

Prior to handing over to Roy for the main feature of today's event, I want to reiterate we remain committed to advancing the treatment of cancer. We believe our success and progress positions us well to become the industry leader by 2025.

With that, I will turn the call over to Roy.

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

Thank you, Dean. As Dean noted, with our broad-based oncology development program, there are many areas to be excited about today. Today, I will focus on a subset of our key ESMO data sets and try to contextualize the importance of each. I will cover key Phase III studies presented in support of KEYTRUDA as a foundational therapy in early-stage disease treatment. These studies will include KEYNOTE-716, a landmark adjuvant study of monotherapy in stage II melanoma included in the ESMO Presidential Plenary; KEYNOTE-522, a groundbreaking neoadjuvant adjuvant KEYTRUDA chemotherapy combination treatment in high-risk primary triple-negative breast cancer recently presented as an ESMO monthly plenary meeting; and additional data from KEYNOTE-564, a potentially practice-changing study of KEYTRUDA as adjuvant monotherapy in renal cell cancer.

I will then highlight our remarkable progress in women's malignancies. A number of key studies presented include KEYNOTE-826, a landmark study of KEYTRUDA combination treatment with chemotherapy in the setting of chemo-naïve persistent, recurrent or metastatic cervical cancer, which was presented in the Presidential Plenary session and simultaneously published in the New England Journal of Medicine; KEYNOTE-355, a breakthrough study of KEYTRUDA in combination with chemotherapy for chemo-naïve, PD-L1-positive advanced triple-negative breast cancer-positive patients.

I draw your attention also to additional data regarding the KEYTRUDA-LENVIMA combination in second-line proficient MMR endometrial cancer from the KEYNOTE-775 study and monotherapy in second-line dMMR endometrial cancer from the KEYNOTE-158 study, as well as important new data from the OReO trial establishing the role of LYNPARZA-rechallenged maintenance in patients with ovarian cancer relapse after initial PARP inhibitor maintenance. I will not cover these latter 2 in additional detail.

I will also cover some exemplars of pipeline progress by presenting important combination data of WELIREG, our HIF2-alpha antagonist, in combination with a tyrosine kinase inhibitor in advanced, relapsed, metastatic sporadic renal cell cancer and highlighting data from our expansive prostate cancer program.

This slide highlights the KEYNOTE-716 study in Stage II malignant melanoma. As background, KEYTRUDA was approved for the adjuvant treatment of resected Stage III disease, that is to say a local lesion plus lymph node involvement, based upon KEYNOTE-054, which showed a highly significant improvement in recurrence-free survival, the approvable endpoint, and distant metastasis-free survival and has become a standard of care in the stage of melanoma.

Almost as many patients have Stage II disease, that is without lymph node involvement. Importantly, Stage IIb and IIc disease have outcomes pre-I-O similar to stage III disease. Stage II has had limited study and current standard of care after surgery is observation. In this study, patients

were randomized to receive either KEYTRUDA-adjuvant therapy or placebo. At the first interim analysis, the efficacy boundary was crossed, showing a statistically significant and clinically highly meaningful reduction in the risk of recurrence. There were no new safety signals.

Findings from a relapse-free survival sensitivity analysis that included new primary melanomas demonstrated consistent findings. This becomes the first and only I-O agent to have established clinical benefit in this population and will potentially be practice-changing. It is currently under priority review at the FDA.

We will now turn our attention to KEYNOTE-826, the study of patients with chemotherapy-naïve, persistent, recurrent or metastatic cervical cancer. As background, standard of care in such patients has been chemotherapy with or without bevacizumab. In this landmark study, we compared current standard of care plus KEYTRUDA to standard of care plus placebo.

In the primary all-comers analysis, the KEYTRUDA arm showed a clinically meaningful and statistically highly significant 35% reduction in the risk of progression or death, and a 33% reduction in the risk of death. Not surprisingly, there was also a marked improvement in overall response. The safety profile was as expected for the combination. This is the first and only PD-1 antibody to have established this benefit in the frontline treatment of cervical cancer. This is also under priority review at the FDA and has the potential to become a new standard of care.

We had the privilege of presenting the final analysis of KEYNOTE-355, the study of KEYTRUDA plus chemotherapy, in the treatment of chemotherapy-naïve patients with metastatic triple-negative breast cancer, a particularly aggressive form of breast cancer. The agent had previously received accelerated approval in PD-L1-positive patients based upon progression-free survival in the same study.

At the final analysis, there was a highly significant and clinically meaningful 27% reduction in the risk of death demonstrated for the combination arm. The accelerated approval has been converted to full approval based upon this, and the highly significant data from KEYNOTE-522, which we will discuss next. Importantly, this is the only I-O agent approved in this metastatic triple-negative breast cancer patient population in the U.S.

Turning attention now to KEYNOTE-522, a landmark study of neoadjuvant followed by adjuvant approach to treating high-risk primary triple-negative breast cancer disease with a high rate of recurrence, particularly if a pathologic complete response cannot be achieved with the neoadjuvant phase of therapy. In this study, we compared the combination of platinum-based chemotherapy plus KEYTRUDA before surgery and KEYTRUDA after surgery with platinum-based chemotherapy plus placebo followed by placebo.

The choice of platinum-based chemotherapy was indeed prescient, as it has now been shown to be the most effective neoadjuvant chemotherapy regimen in the setting as presented at this meeting in the so-called BRIGHTNESS study. The combination neoadjuvant therapy produced a highly significant and clinically meaningful improvement in pathologic complete response, and the complete regimen resulted in a highly significant and clinically meaningful 37% reduction in the risk of progression event or death. No new safety signals were observed.

At this readout of the early time, there is a favorable trend in overall survival. Based upon this result, FDA granted full approval, and this also contributed to the conversion of KEYNOTE-355 accelerated approval to full approval. This is a major advance in the treatment of this aggressive disease, and KEYTRUDA is the only agent to have such an approval. This has the potential to rapidly become standard of care.

KEYNOTE-564 is the first study to show a benefit for I-O monotherapy as adjuvant treatment for patient's post-surgical removal of kidney cancer, including patients rendered NED by metastectomy. In this study, KEYTRUDA monotherapy was associated with a clinically meaningful and highly significant 32% reduction in the risk of disease recurrence or death. At this time -- early time point, there was an impressive trend towards a 46% reduction in the risk of death.

Importantly, as shown in the graphic on the right panel, this was achieved without a decrement in quality of life. No new safety issues were observed. This study is currently under priority review and has the potential to become the new standard of care.

This slide provides me the opportunity to highlight some important aspects of pipeline progression. On the left-hand panel, you see a waterfall plot showing impressive responses of patients with castrate-resistant prostate cancer, who have failed other therapies to the combination of KEYTRUDA plus LYNPARZA. Data such as these has led to a substantial Phase III program in prostate cancer, which I will comment on subsequently.

On the right-hand panel, you again see a waterfall plot reflecting important combination data of WELIREG, our recently approved HIF2-alpha antagonist, in combination with the tyrosine kinase inhibitor in advanced relapsed metastatic sporadic renal cell cancer. I will say more about the substantive WELIREG program subsequently.

This slide depicts the vast array of studies we are conducting in the early-stage setting of cancer. This spans a large number of the major cancer types. Shown in teal are indications already approved, including KEYNOTE-057 for non-muscle invasive bladder cancer, KEYNOTE-054 for Stage III malignant melanoma, and KEYNOTE-522 a perioperative management of high-risk primary triple-negative breast cancer. In addition, as mentioned, we have positive data under review or soon to be under review for KEYNOTE-716 Stage II melanoma, KEYNOTE-564 adjuvant treatment of kidney cancer, and OlympiA for the adjuvant use of LYNPARZA in BRCA mutant breast cancer. We codevelop and commercialize LYNPARZA with AstraZeneca.

This large early-stage treatment program will provide rich information over the next months and years, and is likely to bring major benefit to many patients.

On the R&D side, we hope to provide the research base to enable Merck to become an overall leader in oncology. We have, in a few short years, become an oncology leader in a number of areas of advanced cancer across multiple lines of treatment, including melanoma and other skin cancers, nonsquamous non-small cell lung cancer, squamous non-small cell lung cancer, head and neck squamous cell cancer, bladder cancer, renal cancer based on our I-O TKI combinations, and belzutifan or WELIREG in VHL disease or Von Hippel-Lindau disease, hematological malignancies where KEYTRUDA has become a mainstay in Hodgkin's and primary mediastinal B-cell lymphoma and enhanced with our acquisition of the BTK molecule through ArQule and of the Rule 1 ADC through VelosBio; GI malignancies, including esophageal, HER2-positive gastric colorectal cancer of the MSI high variety; and PARP inhibition with LYNPARZA in BRCA mutant pancreas cancer; ovarian cancer through our partnership with AZ relating to LYNPARZA; and in histology-agnostic approvals in MSI-high malignancies and tumor mutational burden high malignancies.

The data summarized coming out of this meeting highlights other areas where we're advancing this aspiration. Clearly, with the groundbreaking data in breast cancer, cervical cancer, endometrial cancer and ovarian cancer, Merck can now legitimately claim leadership in many women's cancers.

I highlight the further strengthening of our efforts in breast cancer with our collaborative partnership with CGEN in relation to KAISER, an HER2-targeting tyrosine kinase inhibitor, and the LIV-1-directed antibody-drug conjugate.

It is worth noting that cervical cancer is a papillomavirus-driven disease and is a preventable disease with papillomavirus vaccination. In this regard, Merck through its development of GARDASIL 4 and GARDASIL 9 has been the leader in papillomavirus vaccination.

In the area of prostate cancer, we have deployed a very substantive Phase III program. We already have LYNPARZA in partnership with AstraZeneca approved via the PROFOUND study in second-line-plus metastatic castrate-resistant prostate cancer patients, who are homologous recombination repair mutants, also known as HRRM. We look forward to the first interim analysis of the PROPEL study of LYNPARZA in combination with abiraterone in the frontline treatment of metastatic castrate-resistant prostate cancer and are optimistic based upon our prior readouts from Study 8.

We are exploring combinations with KEYTRUDA and LYNPARZA in either abiraterone or enzalutamide-experienced metastatic castrate-resistant prostate cancer in combination with docetaxel in metastatic castrate-resistant prostate cancer, who have failed novel hormonal agents, and in combination with enzalutamide in metastatic castrate-resistant prostate cancer that are abiraterone-experienced patients, and finally, in combination with enzalutamide in metastatic hormone-sensitive prostate cancer.

We also legitimately seek to strengthen our leadership position in renal cell cancer. We have a very solid basis for this given our already approved LENVIMA in partnership with Eisai, combination in second-line renal cell cancer and first-line approvals of KEYTRUDA in combination with LENVIMA and ixatinib. The KEYNOTE-564 adjuvant indication, if approved, will further enhance this position.

Our HIF2-alpha antagonist, WELIREG, was recently approved for treatment of patients with renal cell cancer and other tumors associated with Von Hippel-Lindau disease or VHL disease. It's important to note that VHL abnormalities are almost uniform in the setting of sporadic renal cell cancer,

and it was with this in mind that we are now exploring an expansive Phase III effort as monotherapy and in various combinations across lines of treatment in sporadic renal cell cancer.

I thank you for your attention. This is an exciting meeting for Merck and a number of really important and transformational data sets were on display. I will now turn the presentation over to Jannie Oosthuizen for the commercial perspective.

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**Jannie Oosthuizen** - Merck & Co., Inc. - President of Global Oncology

Thank you, Roy. I'm indeed excited to be here today. As Dean mentioned in the opening, I will highlight how we believe the data and our ongoing efforts to address unmet need will continue to drive significant commercial opportunity and growth for Merck.

We remain committed to driving global leadership across multiple and diverse assets. This slide has been updated since ASCO. The increase you see across the number of approved indications, tumor types and the number of patients treated, exemplifies that the impact we are having on patients' lives is real and meaningful. We are in a leadership position with KEYTRUDA as a foundational cancer medicine across many cancer types.

As you heard from Roy, we continue to build our wall of data to further enhance the science and our opportunity to help even more patients with cancer. In addition, LYNPARZA and LENVIMA continue to play a pivotal role as treatment options both in monotherapy as well as in combination. We look forward to continuing to expand the reach of TUKYSA in HER2-positive breast cancer as well as future readouts from multiple Phase II and III trials that are currently underway. And with our recent approval last month, we are very excited about the potential of WELIREG as a first-in-class HIF2-alpha inhibitor, we see strong growth opportunities in renal cell cancer and beyond.

Overall, we are very well positioned for continued success as we roll out new indications and combinations, move to earlier lines of therapy and launch new assets.

As you heard from Roy and Dean, we are uniquely positioned to win in early-stage treatment, which provides patients with the best chance for long-term survival. Merck has the broadest immuno-oncology clinical development program for early-stage disease. With our recent approval in triple-negative breast cancer, we now have a total of 3 approved early-stage indications, including adjuvant melanoma and nonmuscle-invasive bladder cancer. As Roy highlighted earlier, we've demonstrated improved patient benefit across 3 key tumors already in stage II melanoma based on data from KEYNOTE-716, neoadjuvant and adjuvant triple-negative breast cancer based on KEYNOTE-522 and adjuvant renal cell cancer based on the KEYNOTE-564 data.

The early-stage setting represents a critical opportunity and will contribute to more than half of KEYTRUDA's growth over the next 5 years.

We are creating a meaningful impact and transforming the clinical landscape across women's cancers in both the metastatic and early-stage settings. The notable milestones across our total women's cancer portfolio demonstrates our commitment and ability to both pioneer and transform treatment options. We will continue to deliver on our strong commercial execution with approximately 15 launches in the next 4 years across triple-negative breast cancer, endometrial, cervical and ovarian cancers.

The women's cancers portfolio will be a strong contributor of significant growth with the potential to further enhance our leadership position. We are also very excited about our robust Phase III prostate program. KEYTRUDA has the potential to be the first I-O in metastatic disease across multiple patient settings in prostate cancer. The burden of this disease is particularly high, and despite significant advances in treating metastatic prostate cancer, the 5-year overall survival rate continues to be less than 30%.

Our immuno-oncology combinations program is uniquely broad, leveraging both disease immunologic progression and treatment-induced immunogenicity. In addition, we are encouraged by the durable responses in the KEYNOTE-365 study that Roy spoke to earlier.

As a result of improved diagnostics with PSMA and next-generation imaging, the metastatic patient population is increasing, representing a significant opportunity in this space. We look forward to offering new treatment options with our vision to ultimately improve survival for all prostate cancer patients.

Next on WELIREG, we are on an important journey here with many firsts. WELIREG is the first HIF2-alpha inhibitor to come to market, the first therapy targeting a gene transcription factor and the first systemic treatment for VHL-associated tumors. As a reminder, this asset was a result of business development where we saw an opportunity in early stages, acquired this compound and rapidly and successfully developed and launched in this first indication.

With our recent FDA approval for WELIREG beginning in VHL disease, central nervous system, hemangiomas and pancreatic neuroendocrine tumors, we are looking to expand into advanced RCC in years to come in the form of mono and combination offerings. We believe this medicine has blockbuster potential and are excited about its potential to help patients in need of new treatment options.

Our significant investments and broad clinical program in oncology are expected to result in more than 90 potential approvals between now and 2028, as you can see on the left-hand side of the slide. Overall, we expect a number of our indications to more than triple over the next 8 years.

As you have heard from both Dean and Roy, new tumor types, earlier lines of therapy, including adjuvant/neoadjuvant, new mechanisms, combinations and co-formulations, will all be important growth drivers for us, as we aspire to be the world's leading oncology company. I am very confident in our company's ability to have an enduring and meaningful impact on patients' lives through this decade and beyond.

Thank you for your attention. And now we look forward to taking your questions.

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

Thank you, Jannie. Grace, can you please start the question-and-answer session?

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## QUESTIONS AND ANSWERS

### Operator

(Operator Instructions) Your first question comes from the line of Mara Goldstein from Mizuho.

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

Maybe if you could just kind of give us a sense of from a commercial perspective, a lot of the data that's been shown today and the efforts going forward around moving KEYTRUDA into earlier lines of therapy. And what I'm most curious about is that transition from some of the later lines of indication commercially to earlier lines and what you think the delta from commercial potential is there?

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**Jannie Oosthuizen** - Merck & Co., Inc. - President of Global Oncology

Yes. Thank you. As we highlighted earlier in this presentation and also during the ASCO call, we expect the early-stage setting to drive more than 50% of KEYTRUDA's growth over the next 5 years. So this will be a significant contribution as we move into this earlier setting.

From a commercial perspective, we're very excited that in a lot of these settings, we will be talking to the same customers that had experience with KEYTRUDA in later lines in the metastatic settings. So there's already a good level of experience with KEYTRUDA, but certainly, a very exciting opportunity to take this into this early stage, which is potentially a curative setting for these patients.

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### Operator

And your next question comes from the line of Daina Graybosch from SVB Leerink.

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

I have one on early stage. You had a lot of plenaries at ESMO and a lot of plenary debates in Q&A. And I think as these doctors are considering using I-O in early stage, they are definitely thinking about how to get the most benefit at the lowest risk and cost. Should they use neoadjuvant and not adjuvant? Can they use less adjuvant duration? Can you target it to the highest-risk patients or the highest-benefit patients? And I wonder, as you move forward, what is Merck doing to lead this conversation and help these doctors and lead the benefit-risk application of KEYTRUDA?

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

Yes. Thank you for the question. So I think if you look at how we've structured the adjuvant and neoadjuvant and early-stage programs, for the most part, these focus on patients at high risk. These are patients who are at high risk for recurrence.

This is important because in the early phase of disease, this is the potentially curable stage of the illness. Now we're not making a cure claim at this point, but what we are suggesting is that if you can meaningfully reduce the risk of recurrence in these high-risk situations, there is a reasonable possibility that this will translate into cure. I think that it's well described that the quality of life when patients progress with the disease is devastating. And so it is important that patients be offered the option of avoiding that recurrence. Again, to emphasize, we have focused primarily in areas where the tumors have high risk for recurrence.

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**Operator**

And your next question comes from the line of Geoff Meacham from Bank of America.

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**Geoffrey Christopher Meacham** - *BofA Securities, Research Division - Research Analyst*

Thanks for doing the webcast, that's really helpful. Just sort of a question for Jannie and first-line triple negative. Just wanted to ask what you've seen in the marketplace since the Roche regulatory update more recently? I know it's just been a few weeks, but are you seeing any shift in the way that physicians are looking at PD-1s in the earlier-line setting in triple-negative? And how do you think KEYTRUDA could do in that scenario?

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**Jannie Oosthuizen** - *Merck & Co., Inc. - President of Global Oncology*

You're talking about the adjuvant/neoadjuvant setting?

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**Geoffrey Christopher Meacham** - *BofA Securities, Research Division - Research Analyst*

That's right. Yes.

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**Jannie Oosthuizen** - *Merck & Co., Inc. - President of Global Oncology*

Oh, the metastatic setting? The...

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

I think he is talking about the metastatic and the withdrawal.

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**Jannie Oosthuizen** - Merck & Co., Inc. - President of Global Oncology

Oh, the withdrawal. Yes. So we have really seen an accelerated uptake in terms of use of KEYTRUDA for patients in this metastatic setting -- first-line setting. And the data shows now that we are getting most of the new patient starts on KEYTRUDA. And I think it's driven by, obviously, the data itself, but also the fact that physicians have choice in terms of the chemo component that they can add in this treatment option. So we expect that to play a significant role also outside of the U.S. and Europe as well as in Japan.

In Japan, we also -- there's a publicly announced supply shortage with one of our competitors. So we really see an accelerated uptake for 355 across the markets.

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**Operator**

Next one we have Umer Raffat from Evercore ISI.

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**Jonathan Miller** - Evercore ISI Institutional Equities, Research Division - VP

This is Jon Miller on for Umer. I wanted to also ask about adjuvant setting, but I want to focus on adjuvant lung in the upcoming 091 readout that everybody is expecting. Can you tell us today if you had an interim -- have already had an interim on 091 at this point? And if not, what your updated expectations are for timing there?

And then secondly, when we think about the PEARLE study, how many of those patients had adjuvant chemo prior at baseline? What were you expecting in terms of the distribution of patients there? And same question for PD-L1 expression, since those are both relevant drivers of response.

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

Right. So for clarity, the 091 study is a trial being conducted by the EORTC. Obviously, it's a collaborative effort with the sponsor. In terms of the specifics of that trial, it's an event-driven trial and we are coming up on an interim analysis, which again will be event-driven.

The breakdown of PD-L1 is not yet fully identified. But from all prior trials, we would expect roughly 1/3-1/3-1/3 for less than 1, 1 to 49, and greater than 50. And I think the trial in terms of the number of patients, who have had neoadjuvant treatment in that -- or pardon me, adjuvant -- prior neoadjuvant is relatively small. So again, I don't have an exact number for you, but we don't expect that to be a large number.

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**Operator**

Next up, we have Carter Gould from Barclays.

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**Carter Lewis Gould** - Barclays Bank PLC, Research Division - Senior Analyst

One of the things we've heard repeatedly during the WELIREG presentation was attractiveness potentially of this agent in the adjuvant setting given its oral administration, its tolerability. Can you talk about maybe your appetite there for ultimately moving into that setting, particularly against the backdrop of the KEYNOTE-564 data we've seen? And then also when the drug was approved, there was sort of that vague reference to manufacturing and sort of improving and optimizing that. Can you just give us an update on kind of where you stand in your ability to meet demand?

**Dean Y. Li** - Merck & Co., Inc. - EVP

Let me just make sure. So WELIREG is in the VHL syndrome, and we're advancing it in this more sporadic case. But I'll let Roy -- I think your question is, when will we go from late stage in this sporadic to the adjuvant stage. Roy?

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

Right. So far, our experience with WELIREG is really quite informative. So the drug is actually well tolerated. It has a few major side effects, most of which are correctable by dose interruption, sometimes dose reduction, but well tolerated overall.

The other important aspect is the responses as gauged in the VHL syndrome take time to develop. So it's interesting, as we've taken data cuts longitudinally, the response rate keeps going up. And so that's an important attribute of this molecule, and we think this will play out in other settings as well.

As I mentioned, the VHL is a unique circumstance, but VHL dysregulation and abnormalities are extremely common. In fact, the vast majority of sporadic renal cell cancers have this abnormality. Based upon this, we have extended the program very rapidly through a series of registrational-enabling trials into different lines of therapy.

It's certainly very likely that if we were to see important outcomes in any of these trials, that would be a good catalyst to move into the adjuvant setting. We certainly are already discussing the adjuvant setting, but our first priority here is front line, second line, third line as either monotherapy in the case of the third line or combinations in the other lines of therapy.

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**Dean Y. Li** - Merck & Co., Inc. - EVP

And in terms of making the molecule, I don't -- there have been improvements of it, but we foresee no problems whatsoever supplying the demand, however, great it should be.

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**Operator**

Next up, we have Luisa Hector from Berenberg.

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**Luisa Caroline Hector** - Joh. Berenberg, Gossler & Co. KG, Research Division - Co-Head of Global Pharmaceutical Team

I wanted to go back to the triple-negative, and clearly, KEYTRUDA is emerging as the winner here. But could you talk a little bit about the neoadjuvant/adjuvant, so the 522 data. I think PD-L1 was not a marker of response. I just wondered why not and whether anything else was predicted.

And as we think about that sort of adjuvant into metastatic group, what percentage of patients are diagnosed de novo metastatic? And then could we see patients be rechallenged if they have the adjuvant KEYTRUDA? Might they yet be eligible for metastatic first line?

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

Okay. So a few questions embedded there. So the trial, basically, as I mentioned, looked at KEYTRUDA plus platinum-based chemotherapy as neoadjuvant, followed by KEYTRUDA as adjuvant. Duration of treatment sums across those 2 components to about a year of treatment with KEYTRUDA.

The question, I think, was PD-L1 status and was there any difference in terms of PD-L1 status. And the short answer is no. In the neoadjuvant/adjuvant setting, we did not see an impact of PD-L1. Obviously, in the metastatic setting, frontline, we did see a strong PD-L1 influence. And it's informative across the program to look also at the second- and third-line treatments. We saw an even stronger enrichment for PD-L1. So it does look as though you enrich as the disease progresses for PD-L1, but not in the case of the neoadjuvant and adjuvant setting.

The response rates in terms of PADCEV are obviously really the highest ever recorded by the combination. And indeed, the -- if you looked at the curves, you'll see the striking observation is for patients, who had a complete pathologic response and who got adjuvant. The outcomes really look extremely good. Remembering that this is a disease that tends to recur fairly quickly. Not getting to PCR is certainly benefited by adjuvant therapy.

The question has not yet been formally studied as to if someone were to progress either on adjuvant therapy or after adjuvant therapy, whether either continuing PD-1 with an alternate therapy. And obviously, there are an emerging number of possibilities there, particularly with, for example, ADCs coming to the fore. And so that's all work that's going to have to be done in the future. But for the moment, this becomes, at least from what we hear, a very likely standard of care in this high-risk primary setting of triple-negative breast cancer.

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#### Operator

Next up, we have Louise Chen from Cantor.

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

So first question I have for you is, could you provide some color on the size of the triple-negative breast cancer market opportunity to Merck? And then my second question is on WELIREG and opportunities outside of renal cell carcinoma and how you get to that blockbuster potential for the drugs. What does include in your assumptions there?

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**Jannie Oosthuizen** - *Merck & Co., Inc. - President of Global Oncology*

So I'll take the first one. I mean as you note, triple-negative is about 10% to 15% of the overall breast market. It's also notable that breast has, on a worldwide basis, just overtook lung as the biggest tumor area across the world in oncology. So it clearly is overall a significant tumor, and 10% to 15% within breast is triple-negative.

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**Dean Y. Li** - *Merck & Co., Inc. - EVP*

And question on WELIREG...

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

Yes. In terms of WELIREG and opportunities outside of VHL and sporadic renal cell cancer, it's important to recognize that the HIF1/HIF2 access is involved in many aspects of cancer biology, not least of which, for example, is the production of angiogenesis factors such as VEGF.

So you are absolutely correct. In terms of the near-term valuation, and I'll let Jannie talk to that, it's all basically driven off of RCC and sporadic and VHL. But we are exploring in a broad signal-finding way potential for this agent in other tumor types. And you could imagine the focus given the biology of the HIF1/HIF2 access might focus, for example, on tumors known to have a profound angiogenesis component. There are other considerations that are a little bit more speculative, which I won't enter into now. But suffice it to say, we have a broad signal detection program.

**Jannie Oosthuizen** - Merck & Co., Inc. - President of Global Oncology

Yes. So in terms of VHL-related disease, I mean this is an orphan disease. It's about -- it's estimated to be in the U.S. maybe 1 in 30,000 to 1 in 50,000 people being affected through VHL mutations. And within that, there's about 10,000 patients per year diagnosed with VHL-related disease. And of that, about 30% to 40% will develop VHL-related renal cell carcinoma. So the focus is really on that 3,000 to 4,000 patients right now per annum that would develop renal cell carcinoma.

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**Operator**

(Operator Instructions) Moving on, we also have a question from Mike Nedelcovych from Cowen.

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**Michael Thomas Nedelcovych** - Cowen and Company, LLC, Research Division - Research Associate

I'm curious about Part 2 of KEYNOTE-716. It would seem, based on the RFS data and the discontinuation rate that was reported at ESMO that a substantial portion of the patients enrolled in the trial would be eligible for Part 2. Do you have an early sense of what median duration of treatment might look like in this trial?

And then for the prostate cancer program, prostate cancer, in general, is not because of particularly immune-sensitive tumor type. It would seem the Phase III program could be characterized as high risk, high reward. Is that a fair characterization? Or would you characterize it at all?

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

So I think I heard the first part. I didn't hear the second part too well. So the first part, it sounded to me like you were wanting to know about part 2 of the KEYNOTE-716 study.

This particular trial has a design where if patients progress on the control arm, they are able to cross over and get the salvage treatment. That becomes important in a number of disease settings. You might remember, we followed the same design in KEYNOTE-054. It serves to answer a question. It also serves to make it clear to patients that they will get the treatment at some point if it's their desire to get it.

We have not yet looked at part 2, and so I really don't have any data to share with you on that. And I'm afraid I did not hear the second part of the question terribly clearly.

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

So the second part of the question was in prostate, it's a difficult-to-treat tumor, do we view our Phase III program as a high-risk, high-reward approach?

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

So it's a good question. When we started out exploring in our Phase II program signs of activity, generally, the PD-1s did not do much in prostate cancer other than in patients that were either TMB-high or had MSI-high status. And that's a relatively uncommon subset.

We then explored in a fairly effective way in a basket-type trial, a number of different combinations, and we have presented much of these data. I think the field is generally quite impressed at the combinatorial outcomes with -- in the metastatic castrate-resistant prostate cancer group patients in combination with docetaxel, those Phase II data are really quite impressive, the combination with effective new or novel hormonal agents, and in addition, the combination with LYNPARZA. So in fact, all 3 of those have had meaningful response Phase II-type data.

We now have a very extensive Phase III program across all of those. In addition, we have a program in the hormone-sensitive prostate cancer group looking at the combination with enzalutamide.

I would also say, one other signal that we found was despite there being an absence of a signal with monotherapy, an investigator study looking at the combination of enzalutamide plus pembro in patients, who had failed enzalutamide, provided actually quite a high rate of not only responses but complete PSA responses, which gave quite a lot of encouragement. So it's certainly a high-risk, high-reward setting, but we do feel it's partially derisked based upon some very robust Phase II data.

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**Dean Y. Li** - Merck & Co., Inc. - EVP

Roy, did you want to make any comments that was in relationship of KEYTRUDA in combination with a series of agents? Did you want to make any comments on the PARP inhibitor program outside of KEYTRUDA?

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

Absolutely. So as Dean is indicating, we have a co-development, co-commercialization partnership with AstraZeneca around LYNPARZA. You've seen the data for PROFOUND already, which was really quite an impressive response in the second-line setting, and that led to pretty much worldwide approval. In the U.S., it was what's called the HRRm population. That is to say, homologous recombination repair-deficient population or mutant population.

As mentioned, we are eagerly awaiting the readout from the PROPEL study. This is actually looking at the frontline use in combination with abiraterone compared with abiraterone in the metastatic castrate-resistant patient population. And that trial has been conducted by AstraZeneca. We have some confidence around this readout given the positive data that we had seen previously in the Phase II experiment, which was really the Study #8.

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**Operator**

Actually, that is all the questions that we have. I will turn the call over back to Mr. Peter Dannenbaum for any closing remarks. Sir?

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

Yes. Great. Thank you very much, Grace, and thank you all for your attention and for your questions today. Please follow up with the Investor Relations team if you have additional questions. Thank you very much, and we'll talk to you soon.

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**Operator**

Thank you, presenters. Ladies and gentlemen, this concludes today's conference call. Thank you all for joining. You may now all disconnect.

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