

# Bayer AG – Investor Relations

## Nubeqa Investor Webinar

18 February 2022

### Welcome

**Oliver Maier**

**Head of Investor Relations, Bayer AG**

Good afternoon and good morning, everybody. It's a great pleasure to be with you today, and I welcome you to our next investor webinar of our Pharma division. With this second webinar this week we continue our series of events to keep you apprised of key developments and milestones across the Group. Following our webinar on Kerendia in November last year, we today focus on our second promising launch asset, Nubeqa or darolutamide. Last night, detailed study data of ARASENS, our Phase 3 trial that examined the efficacy and safety of darolutamide to treat prostate cancer in the late stage of the disease have been presented at the ASCO GU for the first time. We will put these data into perspective with existing treatment options and discuss how the broadened clinical profile of darolutamide can change the treatment paradigm in prostate cancer in the future. Finally, we will give an update on our further development program and the commercial potential of darolutamide.

I'm delighted that the Coordinating Principal Investigator of the ARASENS study, Dr Matthew Raymond Smith, is joining our webinar today. He will talk you through the study data he presented at ASCO GU yesterday in all detail. A very warm welcome again, Dr Smith, from my end.

Before we dive into ARASENS, Christian Rommel, our Head of R&D at Pharma will kick off this webinar with an overview of Bayer's overall strategy in pharma and the oncology space. Robert LaCaze, our head of the Oncology franchise, will then address the incidence and unmet medical needs in prostate cancer, and darolutamide's position in this market today. Following Matthew's presentation, Robert will then finish up with a summary of the commercial implications of darolutamide's clinical profile and our future ambitions.

Today's webinar is scheduled for one hour. The presentations should be done within, I would think, 35 minutes, roughly, and for the remaining 25 minutes you will then have the chance to raise questions. You will find instructions for the participation in the Q&A session in the Zoom chat, as we normally show the instructions there, and I will remind you of those later again.

As always, before we begin, I would bring your attention to the forward-looking statements included in the materials today and currently on the screen.

[See disclaimer](#)

With that, the floor is yours, Christian.

## **Oncology Overview**

**Christian Rommel**

**Head of R&D, Pharmaceuticals, Bayer AG**

Thank you, Oliver, for your introduction and welcome everyone. At Bayer, our focus is crystal clear: on patients and patients' medical needs. We aim to provide impactful solutions to prevent, diagnose, treat or potentially cure diseases with increased precision and personalization. Cardiovascular diseases, women's health and oncology remain central to our R&D efforts. We bring decades of scientific excellence to the field where, despite significant progress, there remains considerable unmet need. Our recent new drug launches in heart failure, Verquvo, and kidney disease, Kerendia, and in prostate cancer, Nubeqa or darolutamide, each offer significant new treatment options to patients.

We have bold ambitions in oncology, and today we have an opportunity to provide an update on the significant progress we've made with Nubeqa. That said, we are not limited by our traditional strongholds. We apply our expertise wherever we see an opportunity to make the difference to patients across rare diseases, ophthalmology and also in some of the most neurological disorders. Our aim is to address unmet medical needs with innovative, differentiated medicines that reach patients as fast as possible. Precision medicines and more targeted, personalized therapies will feature even more prominently in our future pipeline, not just in the rapidly growing oncology franchise but also across cardiovascular, kidney diseases and, as mentioned, beyond.

Life sciences and healthcare are transforming at an amazing speed and scale. Rapid advances across human genetics, genomics, molecular biology combined with data sciences and the technological progress is driving more personalized medicines and the opportunities to improve health. We are excited to be part of this extraordinary area of scientific and medical progress, and at Bayer we invested boldly in new science and technologies like gene and cell therapies, yet are also building on our leadership in small molecule chemistry and radionucleotide therapies, building on the legacy of Algeta.

Insights into underlying human disease biology drives us to use whichever of these tools is best suited to this challenge. We are inspired and enabled by technology, not constrained by it. We continue to develop our AI and digital health capabilities. Digital tools of course help patients to better manage their conditions, enable more convenient care delivery and are really revolutionizing data collection. Clinical trials can by those means be faster, more targeted and less burdensome for our patients. Rapid analysis of large volumes of data, including real-world data, provides new insights into health and disease.

With this context, let's move into oncology and Nubeqa. We are excited about the opportunity of Nubeqa making a difference to prostate cancer patients, and the impact on our growth strategy and ambition in oncology. Nubeqa builds on our track record delivering innovative cancer medicines in prostate cancer, such as Xofigo, or precision medicines such as Vitrakvi.

There are three areas for us that have the potential to address the remaining unmet need in oncology: targeted radio pharmaceuticals, with a focus on targeted alpha therapies, immunoncology, including cell-based therapies, and precision molecular oncology. Today we are going to show you a powerful example with Nubeqa in that area. However, we also have a

promising early clinical stage asset, with EGF receptor exon 20 inhibitor, which we will continue to work on this year.

Connected to precision molecular technology is also Bayer's recent exciting move of acquiring Vividion Therapeutics, and by this its chemoproteomics platform that can unlock such so far undruggable target spaces. In the area of targeted alpha therapy, there is an emerging class of novel radionucleotide therapies that have the potential to become a powerful tool to help physicians fight cancer types that are rather hard to treat. We are working on novel conjugate approaches, where we combine different alpha radionuclides with different targeting moieties including antibodies and small molecules. An example is the acquisition of Noria and PSMA Therapeutics last year. We invested here further into the area of targeted alpha therapies, expanding our capabilities now to the next generation approaches using actinium and a new small molecule PSMA-targeting technology that has significant potential to reduce some of the off-target toxicities, in for instance salivary glands and in organs like the kidneys that has been observed with other PSMA-targeting molecules.

Our third pillar, immunoncology, here we are harnessing the most powerful tool there is to fight tumor cells: the body's own immune system. One example of our rather focused immunoncology portfolio is a small molecule inhibitor blocking the AHR pathway, which is believed to be a key player in helping the tumor cells to evade immune response or immune escape. The success of our launch products, together with our main inline brands, support our innovation strategy enabling future sustainable growth of our oncology business at Bayer.

Now with some details to the approach and the strategy with Nubeqa. Despite significant advancements in the treatment of prostate cancer patients there's still a high unmet medical need. Targeting the androgen receptor, AR, in prostate cancer, the so-called key oncogenic driver, which means it's consistently and uniformly expressed across cancer cells of the tumor tissue, is a genetically, scientifically and clinically validated therapeutic approach. From a patient's perspective, as shown in the illustration on the left-hand side, this approach typically follows chemical castration with androgen deprivation therapy or surgical castration. Key focus in cancer treatment is to extend overall survival and delay development of metastases, limit additional toxicity burdens and maintain lifestyles and quality of life of often asymptomatic, fit and active men, and manage co-morbidities and limit drug-drug interactions that can lead to changes in the efficacy and safety of patients' ongoing medication as well as combination opportunities. Multiple ways exist to therapeutically target the androgen receptor biosynthesis and signalling axis. Nubeqa is an orally available, highly potent and selective small molecule antagonist, directly inhibiting the gene regulatory activity of the androgen receptor protein in cancer cells. It addresses the need of strong efficacy while at the same time providing an outstanding tolerability profile, which is the result of its unique and differentiated chemical structure.

Let's talk about it in more detail. Today there are three approved small molecule drugs in the market that target the androgen receptor and inhibit the androgen receptor for the activity in prostate cancer cells: apalutamide, enzalutamide and darolutamide. As can be seen from the illustration on the left-hand side of the slide, apalutamide and enzalutamide are very similar in their chemical structures, basically differing only at the two positions that are highlighted here in grey. In contrast, darolutamide, Nubeqa, is a distinctly differentiated compound compared to the other two drugs. It has a different and more flexible chemical structure, with a higher polarity and ligand efficiency, as well as an increased hydrogen bond forming potential. From a medicinal chemistry expertise point of view, it tells us that all these factors are associated with low blood-brain barrier penetration, which is a clinically relevant and a meaningful differentiating feature, and in fact an advantage of darolutamide.

Strong evidence that supports this differentiated blood-brain barrier penetration profile comes from qualitative C14 carbon-labelled in-situ imaging analysis that we show to the right-hand side of this slide. Here you can see the illustrated distribution of darolutamide, apalutamide and enzalutamide, these three molecules in brains of rodents, in this case rats. Blue colour indicates low levels of active ingredients, whereas green, yellow and red indicate higher levels in an ascending order. The results show that brain to blood penetration ratios of enzalutamide and apalutamide were tenfold higher than darolutamide in these pre-clinical models. In addition, concentration of darolutamide in the brain tissue was about fiftyfold lower than enzalutamide and about thirtyfold lower than apalutamide.

In conclusion, darolutamide is a structurally different androgen receptor inhibitor with low blood-brain barrier penetration shown in those preclinical models. My colleague Robert is now illustrating how this translates also in darolutamide's strong and differentiated clinical profile. Robert?

## **Prostate Cancer and ARAMIS**

**Robert LaCaze**

**Head of Oncology, Pharmaceuticals, Bayer AG**

Thank you, Christian, and also a warm welcome from my side to the audience today. I'd like to start my presentation with just some general remarks on prostate cancer overall. As you can see from the pie chart, out of the estimated 10 million cancer patients that were diagnosed globally in 2020, one out of seven actually suffers from prostate cancer, making it the second most common cause of cancer in men worldwide. According to 2018 data from Global Scan, it causes greater than 350,000 deaths per year.

Prostate cancer is usually diagnosed in men over 50. The unmet need, though, is actually a vast one, and while the majority of the men are diagnosed with localised disease, up to 40% of these patients can have relapsed disease that is ultimately incurable over time. There are a fair number of men also who are diagnosed with locally advanced or even metastatic disease upon first diagnosis. Once the disease becomes metastatic, the five-year survival rate really drops to around 30% or so. Therefore, like all other cancers, it's also very important to get this disease diagnosed at an early stage so that respective therapeutic options can be initiated for the patients.

Looking into the diagnosis patterns in more detail, prostate cancer can be separated into early, mid and late stages of the disease. According to the epi numbers, and if you look at it from the US, Japan and the top five countries in Europe, around 145,000 patients are actually treated in the early stage, or the so-called adjuvant and neo-adjuvant setting. In the non-metastatic and the mid-stage setting a total of 130,000 patients are treated each year, of which two third are in the biochemical relapse or the BCR area, and one third are diagnosed with non-metastatic castration-resistant prostate cancer. The biggest portion of patients, 220,000, are in the late state or the metastasis stage of the disease, of which one third suffer from hormone-sensitive and two thirds from castration-resistant prostate cancer.

As Christian has already shown, androgen receptor blockage has become a standard of care to effectively treat prostate cancer, based on the strong clinical data of our first trial, the ARAMIS trial, that led to Nubeqa's first regulatory approval in non-metastatic castration-resistant prostate cancer patients in 2019. In this study, Nubeqa demonstrated a strong metastasis-free survival of more than 40 months, equivalent to a 22-month benefit versus placebo. In addition, it showed a hazard ratio of 0.69 in overall survival compared to placebo, equivalent to a 31% reduction of risk of death. These data have also been published in the *New England Journal of Medicine*, and they compare favourably with the study results observed in the same indication with enzalutamide and apalutamide.

On top of efficacy, Christian also stressed the relevance and the unmet need of a drug's tolerability profile. It's potentially even more important in prostate cancer therapies, due to the long treatment durations and the fact that many of these patients are still very active and the prostate cancer often times is still asymptomatic. For this reason, treatment options with a less likelihood of causing a disruption in the patient's day-to-day life due to side effects of the medication are clearly preferred by both physicians and by their patients. As you can see from the tolerability data in the ARAMIS trial, the side effects of darolutamide are very favourable as compared to the placebo arm, consistently and across all relevant dimensions.

Summing up ARAMIS, it actually revealed darolutamide's strong efficacy profile while at the same time it demonstrated this very positive tolerability profile. These both together make it an ideal treatment choice for patients who suffer from non-metastatic castration-resistant prostate cancer.

Following Nubeqa's approval in major countries, we focused on making Nubeqa available to patients as quickly as possible. In spite of starting many of the launches of the ARAMIS trial in the new indication in the middle of the COVID-19 pandemic, that came with a significant limitation to be able to interact with physicians and payers, but in spite of that Nubeqa has shown a strong, successful market launch. Today, our drug is approved in 65 countries. It's available in 32 commercial markets and additional 24 private markets. Pricing and reimbursement schemes have already been established in 32 countries.

Nubeqa's strong and differentiated profile is also backed by a series of external validations. We were able to achieve approval in China without having local patients. And on top of this, Nubeqa is the only second generation AR to be awarded a considerable benefit rating in the non-metastatic castration-resistant space in Germany by IQWiG and the GB-A. In the US, favourable customer perceptions support the drug's continued uptake.

We have seen a rapid adoption by the payers, with over 90% of the lives covered in managed care. Our market research confirms Nubeqa's strong value proposition for patients and physicians, and the importance of its profile. We find that once physicians use Nubeqa three to four times they see the benefit in their patients, and it becomes their drug of choice for the indication of non-metastatic CRPC. This is also reflected in our sales numbers for 2021, which came in at around €220 million, equivalent to about a quarter of a billion dollars.

I'd like to conclude the first part of my presentation with a reminder that the clinical as well as the commercial profile of Nubeqa until today is only based on the ARAMIS study and the approval in the non-metastatic CRPC cancer setting space.

Now, I am more than happy to hand over to Dr Matthew Smith, who is the Coordinating Principal Investigator of the ARASENS trial and the lead author of the *New England Journal of Medicine* publication on ARASENS. Dr Smith is the Director of the GU Malignancies Program at Mass General Hospital Cancer Center, and he'll walk you through the key data of the ARASENS trial,

our second successful Phase 3 study of Nubeqa. This trial examined Nubeqa's use in patients suffering from metastatic hormone-sensitive prostate cancer. Dr Smith?

## **ARASENS Results**

**Dr Matthew Raymond Smith M.D, Ph.D.**

**Director of the Genitourinary Malignancies Program, Massachusetts General Hospital Cancer Center; Coordinating Principal Investigator of ARASENS**

Thank you, Robert. It's a pleasure to be here and to present the ARASENS data. This is the study design. ARASENS was a global, randomized, controlled trial. ARASENS enrolled 1,306 patients in 286 centres in 23 countries. The study included patients with metastatic hormone-sensitive prostate cancer and an ECOG performance status of 0 or 1, who are candidates for androgen deprivation therapy and docetaxel. Eligible patients were randomised in equal proportions to darolutamide or placebo daily – twice daily, excuse me. And all patients in both arms received the standard of care, which is androgen deprivation therapy and six cycles of docetaxel, the latter starting six weeks after randomization. The primary study endpoint was overall survival, and then there were a number of key secondary endpoints. I think when we designed this trial we took a bold approach saying what would really be important would be to move the needle and improve overall survival, and hence we chose that as the primary study endpoint. Next slide.

Here's the most important data. This is the primary analysis for overall survival. This endpoint was pre-specified and event-driven. There was no interim analysis; this is the final analysis. Compared to placebo, darolutamide significantly reduced the risk of death by 32.5%. The hazard ratio is 0.68, with 95% confidence intervals of 0.57 to 0.80. This was highly statistically significant with a P value of less than 0.001. You'll note, looking at the shape of the curves, that they separate early and continue to widen their separation over time. The median overall survival is 48.9 months in the placebo group and not yet reached in darolutamide. The four-year overall survival rate was 50.4% in the placebo group and improved to 62.7% in the darolutamide group. Next slide.

This clinically important and statistically significant improvement in overall survival was observed despite a high rate of subsequent life-prolonging therapy in the placebo group. One of the general concerns in interpreting trials of this type is that if patients in the placebo group did not have access to subsequent therapies the benefit may not be generalizable to settings where such therapies are available. It's very reassuring here that a high proportion of patients in the placebo group received subsequent life-prolonging therapies. More than 75% of patients in the placebo group received subsequent life-prolonging therapy. The most commonly administered life-prolonging treatments were abiraterone acetate, enzalutamide, cabazitaxel and docetaxel. Two thirds of patients in the placebo group by the data cut-off date had received subsequent life-prolonging therapy with one or more androgen receptor pathway inhibitors. Next slide.

There was consistency of the overall survival benefit in the pre-specified sub-groups. We also saw consistency of the OS benefit by metastatic stage at initial diagnosis. For patients with de novo metastatic disease, meaning metastatic disease diagnosed at the time of initial prostate cancer diagnosis, the hazard ratio was 0.71, and for those with recurrent metastatic disease the hazard ratio was even lower at 0.61. Next slide.

We also saw a benefit across key secondary efficacy endpoints. Time to castration-resistant prostate cancer and time to pain progression were significantly longer in the darolutamide group than in the placebo group, with hazard ratios of 0.36 and 0.79 respectively. Next slide.

Darolutamide also improved time to first symptomatic skeletal event and time to first subsequent antineoplastic therapy, with hazard ratios of 0.71 and 0.39 respectively. Next slide.

Consistent with the clinical experience in other settings, darolutamide had a very favourable safety profile. The rates of any treatment-emergent adverse events, serious adverse events and adverse events leading to permanent discontinuation of study treatments were similar between the darolutamide and the placebo groups. Next slide.

As expected, most of the Grade 3 and 4 adverse events we observed in both arms were attributed to docetaxel chemotherapy. Those included neutropaenia, febrile neutropaenia and anaemia. Importantly, rates of these Grade 3 and 4 AEs were similar between the darolutamide and placebo group. Next slide.

Robert described the specific benefits of darolutamide in terms of its safety relative to other AR pathway inhibitors, but certain adverse events have been associated with AR pathway inhibitors as a drug class, although it's important to note that those rates of AEs of special interest vary considerably for different drugs within that class, and that's specifically true for darolutamide. These AEs of special interest for the class include fatigue, falls, fractures, rash, hypertension, certain cardiac disorders and central nervous system disorders. After adjustment for drug exposure, though, the rates of these AEs of special interest are similar, and really indistinguishable, between the darolutamide and the placebo group, sort of reinforcing the favourable safety profile that was observed in ARAMIS. Next slide.

In summary, darolutamide in combination with ADT and docetaxel significantly improved overall survival in patients with metastatic hormone-sensitive prostate cancer. Darolutamide reduced the risk of death by 32.5%. Darolutamide improved OS despite a high rate of subsequent life-prolonging systemic treatments in the placebo group. And the OS benefit for darolutamide was consistent across the pre-specified subgroups. Darolutamide also demonstrated significant improvements in key secondary efficacy endpoints, including time to castration-resistant prostate cancer, time to pain progression, time to first SSE and time to first subsequent antineoplastic therapy. And then consistent with the prior experience with darolutamide in non-metastatic CRPC, the rates of adverse events were similar between the darolutamide and placebo groups. So I conclude that based on the results of ARASENS, darolutamide in combination with ADT and docetaxel should become a new standard of care for the treatment of patients with metastatic hormone-sensitive prostate cancer.

## **Commercial Implications and Future Ambitions**

### **Robert LaCaze**

Thank you, Dr Smith, for that great overview of the ARASENS data. For those of you who maybe had missed the presentation yesterday, it was also published in the *New England Journal of Medicine* yesterday afternoon as well. Dr Smith is the lead author on that paper as well.

As Dr Smith has shown, this is actually the second large Phase 3 trial for darolutamide that has demonstrated a major overall survival advantage, while at the same time providing a really favourable tolerability profile for the patients.

It's important to stress again the high efficacy and the tolerability hurdles in the ARASENS trial. This is a study where we actually combined ADT therapy in addition to chemotherapy in both arms. None of the existing novel hormonals have demonstrated this level of clinical benefit at Phase 3 trials. Keep in mind that over 75% of the patients which you saw from the data from Dr Smith in the control arm of the ADT and chemotherapy also received additional subsequent life-saving drugs, including enzalutamide, abiraterone and chemotherapy, making the efficacy data of darolutamide in combination with chemo and ADT even more remarkable in this ARASENS study, though the secondary endpoints also were impressive and of note.

It was also discussed a little bit in the discussion yesterday in the presentation, that the time to castration-resistant prostate cancer was reduced by 64%, with a hazard ratio of 0.357. The risk was reduced by 64%. So in the control arm, patients became castration-resistant in a little over a year and a half, or 19.1 months, while patients in the Nubeqa arm still had not reached the average number of months to become castration-resistant, with many of these patients being metastatic for three and a half to four years. By the time of the data cut-off on October 25, 2021, the average length of therapy was 41 months compared to the control group of 16.7 months.

Now, while there was a significant overall survival advantage, as you saw from the presentation, the addition of darolutamide to chemotherapy did not introduce additional major toxicities for the patients beyond chemotherapy. Again, this underpins the ease of use of Nubeqa, even when it's used in combination. With this strong confirmation of efficacy and the tolerability profile in two major studies in two different settings, we feel that darolutamide can become a foundational therapy in prostate cancer across the different stages of prostate cancer given its unique profile.

Now, over the next few years, we'll continue to invest and generate data to allow darolutamide to fulfil this mission of becoming the foundational therapy across a broad spectrum of prostate cancer, as you can see from the development program, which includes five major phase 3 studies. Two of them have already been completed, and three more are in progress. In the adjuvant setting, we're doing the DaSL-HiCap trial, which is expected to show results in the 2028 timeframe. We are also, and this is part of the announcement, doing a Biochemical Relapse study as well, or the BCR study. We plan to start this trial in the second half of this year, with results expected in 2027. And finally, we have an ongoing trial, which is the sister trial to the ARASENS trial. It's called ARANOTE. This is also in the metastatic hormone-sensitive space where Nubeqa is given as a single agent with ADT as compared to placebo and ADT.

So in summary, our investments are aimed at generating data across the early, the non-metastatic, and the metastatic settings, both with and without chemotherapy. As the novel hormonals continue to move in the earlier settings of this disease, it's important to have a profile like darolutamide that combines an efficacy profile with an excellent tolerability profile as most of these patients in this earlier setting will be asymptomatic. Lastly, with darolutamide's combinability profile, we'll also consider additional combination trials with other emergent agents if the science is clear.

So with the confirmation of darolutamide's clinical profile and expansion into the metastatic setting, as well as the investments that we're making in the additional clinical trials, we feel that darolutamide has the potential to generate peak sales of more than €3 billion. The next step for us, though, is to rapidly file the ARASENS data as quickly as possible, and to gain the regulatory approval in the metastatic hormone-sensitive prostate area and extend our existent label in all major markets to make the drug available to patients as soon as possible. As you can see from the chart,

we're just weeks away from simultaneously filing in the US, Japan, and the EU, and China is just a few weeks behind.

So putting today's presentation into a broader context and closing the loop from what Christian started with his remarks at the beginning of the webinar, our ambition is to become one of the top 10 oncology companies by 2030. Over the last five years, we've made decisive steps toward that goal. We've doubled the number of marketed products from three to six and gained more than 75 commercial approvals across multiple indications and tumors. In addition, in terms of innovation, we've seen three FDA breakthrough designations. We have 15 ongoing registrational studies. In addition, we've entered into new platforms such as precision oncology, as Christian stated, which was strengthened by our acquisition of Vividion last summer. We've also expanded our radio-pharmaceutical approaches with the addition of Noria therapeutics and PSMA therapeutics, which occurred last spring. On top of this, we continue to explore the next generation of immune oncology with cell therapy partnerships.

Finally, with the launches of Vitrakvi and Nubeqa, we have translated compelling medical profiles into commercial success. Vitrakvi is the first drug to receive a global tumor agnostic approval in both paediatrics and adults. We're also committed to making Nubeqa the standard of therapy in prostate cancer. With these investments and the continued growth of Nubeqa, oncology is planned to become a key growth driver for Bayer Pharma.

Now, this concludes my part of the presentation, and I'll hand it back over to Oliver to open it up for Q&A. Oliver?

## **Questions & Answers**

### **Oliver Maier**

Thank you so much, Robert, Dr Smith and Christian, all for your presentations. And with that, let's move to the Q&A. Before we start, as always, some housekeeping items on the Q&A session from my end. If you have a question, please click on the 'raise your hand' icon. If your question has been answered or you wish to cancel your request, please click the 'lower your hand' icon. When you will be called to ask your question, you first have to unmute yourself by confirming the corresponding prompt that will appear on your screen.

If you have joined the conference via telephone, the procedure is slightly different. Please press the star followed by the 9 on your telephone to queue for asking a question, and when you're being prompted to ask your question, please press the star followed by the 6 to unmute yourself.

So I see we have the first questions coming in, and I think the first question comes from James Quigley from Morgan Stanley. James, you're next. You're first.

### **James Quigley, Morgan Stanley**

Hello. Thank you for taking my questions. So just in terms of the new peak sales guidance, could you give us a bridge of how you get there from the 1 billion to the 3 billion, and which of the sub-indications are the biggest contributors?

And then also related to that, could you also remind us of when the patent expiry for Nubeqa is? I think, from memory, it's around 2030 in the US. But how are you thinking about the adjuvant and the biochemical relapse setting if they're reading it in '28 and 2027 and how that could impact the peak sales?

### **Robert LaCaze**

Yeah, James, so this is Robert. I'll be happy to address those for you. As we look at this market space, there's a couple of things that's going on here. Obviously, as the patient population continues to age, we know in the epi-numbers there's about 1.5% of new patients coming into the space every year with prostate cancer. We know that, as you look at the compounds as Nubeqa, when you look at the earlier stages of the disease, patients stay on the drug for quite a period of time. And then, when you look at the metastatic disease, we're quite surprised at the overall outcome that we're seeing in the clinical benefit of the program, and patients will stay on the drug for potentially two, three or even four-plus years.

And so, as you look at the – as I've shown at the beginning, and you look at the different segments of the prostate cancer area between the early, the mid and the late stages of the disease, we'll have programs in all of those diseases. I won't necessarily give a comment on which one of those will be the biggest segments because I think some of those segments will continue to evolve over time, but I will say that, if you look at the growth of the market, and then the clinical data that we're generating across all the stages, we're quite comfortable with the \$3 billion.

The \$3 billion, though, is not tomorrow or the next day. It's more towards the end of the '27, '28, '29 timeframe as we do generate the data and the new indications. The patent lives – depending on which country – range from the 2030 to 2034, I believe, or '35 timeframe zone. It does range across depending on which country and which market you're in.

So we're very excited about the data, the second-largest study, and then, obviously, we'll have the – our goal is to try to have every couple of years a new bit of dataset of studies coming out to continue to fuel the clinical profile, which hopefully will translate into the patient benefits, and then eventually into the peak sales.

### **James Quigley**

That's great. I have another question, if that's okay, for Dr Smith. And just thinking about the hormone-sensitive or metastatic hormone-sensitive prostate cancer, your patients, so what role will this chemotherapy play in your treatment decisions? I'm just trying to get a sense of what proportion of your patients are already taking chemotherapy plus androgen deprivation versus that are already on an androgen receptor inhibitor plus androgen deprivation. So just a sense of – are there a bunch of patients where you can add on Nubeqa with chemotherapy quite quickly, or is it going to be more of a deciding which approach would be best? Thanks.

### **Dr Matthew Smith**

Yeah, good question. So the rates of – so currently, the question is, 'Who do you intensify, in which patients do you intensify therapy for metastatic hormone-sensitive disease?' And then the second question is 'Which agent? Is it going to be docetaxel or an AR pathway inhibitor?' And those vary according to geographic region. In the United States, the patients who have intensified initial treatment typically get an androgen receptor pathway inhibitor. It's a smaller group who receive chemotherapy, usually the worst prognosis patients, but let me answer it this way. For a

patient who's going to receive ADT and docetaxel, the addition of darolutamide is the easiest decision in the world. The results of ARASENS are compelling. The magnitude of the benefit probably exceeds, in my opinion, the benefit of giving the patient chemotherapy, so that's easy.

The other knock-on effect of this is going to be that this compelling data from ARASENS confirms the very strong results from ARAMIS. And while these individual disease states have an important role in drug approvals, in regulatory issues, the field is moving away from that because all the consistent data saying, 'intensified androgen deprivation therapy' or 'enhance the androgen deprivation therapy' improves outcomes across the entire spectrum of prostate cancer. And one of the terms used earlier is that 'AR is the key oncogenic driver'. It couldn't be more true, so our approach is going to really be – and the thing that wasn't yet said is, while there are several other drugs in this class, there's tremendous cross-resistance between the agents, so it's really going to be 'Which one do you choose and why do you choose it?'

So now we have two compelling phase 3 studies showing an OS benefit, non-metastatic CRPC, metastatic disease, hormone-sensitive disease, and really compelling safety data that, in my opinion, makes darolutamide best in class, and that will be my go-to drug in patients who I'm going to add an AR pathway inhibitor. And I think that that's the choice that clinicians are going to be making, and you can get very granular, and say, 'This indication, that indication,' but it's the totality of evidence, and really, no other target has shown such consistent results across the entire spectrum of prostate cancer.

### **Oliver Maier**

Fine. Thank you so much, Dr Smith.

### **James Quigley**

Thank you.

### **Oliver Maier**

I think the next question comes from Michael Leuchten from UBS. Michael, you're next.

### **Michael Leuchten, UBS**

Oh, thank you, Oliver. So just going back to that last question, Dr Smith, if we look at the presentation at ASCO GU, I think there was some slides from a discussant saying that only about a third of patients in the hormone-sensitive setting are actually getting duplates at the moment, so it's not a large number of patients relative to what the data like STAMPEDE and LATITUDE would suggest to us. And I think some of the question is, what does chemotherapy really add? So as we think about the upcoming data with the ARANOTE trial, do we get to a point where we actually know what the treatment pathway's going to be in this hormone-sensitive setting?

So that's question number 1, and then there's just a clarification question on the tolerability in the remarks. There was something about adjusted for drug exposure, there were similar rates of adverse events. I just wondered if you could clarify that statement. I didn't quite understand what that meant. Thank you.

**Dr Matthew Smith**

Yeah, so let me start with the second question because it's more straightforward. So I actually, in saying that, I actually understate the safety of darolutamide because the uncorrected rates of those adverse events are remarkably similar across almost all of the AEs of special interests. But just for conciseness, if you had after adjustment, basically every one of those AEs of special interests becomes similar or more or less indistinguishable between the groups. So both the unadjusted and adjusted rates of AEs of special interests are similar between the groups with a couple of minor exceptions. There's a little bit more rash if you don't adjust for exposure, and I think maybe a little tiny bit more of hypertension.

So the other question is – I think the way – again, I'll restate it. AR is a key oncogenic driver in prostate cancer, and I think you're absolutely right that the adoption of intensified systemic treatment for metastatic hormone-sensitive prostate cancer has been slow. That will change over time as the data's accumulated. CHAARTED confused the whole field because the initial intensification was with chemotherapy, and then there was this division between high volume and low volume. There's a lot of confusion in the field, and I think that's contributed to the slow adoption, but with consistent data about improved overall survival, I see that improving over time, and at least in the US, the priority's going to be to add an AR pathway inhibitor. And then the secondary question will be, 'In which patients do you also add docetaxel?'

And as is true in all cases in medicine, we're never going to have all of the data we'd like to make those decisions. Not every decision we make will be perfectly evidence based, but there's a compelling body of data to say that we should be intensifying systemic therapy in the vast majority of patients with metastatic, hormone-sensitive prostate cancer. And at least in the United States, the priority's going to be the addition of an AR pathway inhibitor, and as I have already said, in my practice, my drug of choice is darolutamide.

**Michael Leuchten**

Thank you.

**Oliver Maier**

Alright, thank you so much, Dr Smith. I think the next question comes from Dominic Lunn from Credit Suisse. Dominic, you're next.

**Dominic Lunn, Credit Suisse**

Oh, hi. [Inaudible].

**Oliver Maier**

Dominic, you're hard – sorry to interrupt. You're very hard to understand, Dominic. You're fading in and out. I don't know what kind of mic you're using. I don't know if anybody understood that, but I couldn't.

**Robert LaCaze**

I didn't understand.

**Dominic Lunn**

I'll let you [inaudible].

**Oliver Maier**

Okay, then let's wait for Dominic dialling in again. Let's hear next question from Sachin Jain from Bank of America. Sachin, you're next.

**Sachin Jain, Bank of America**

Sorry. I have two – sorry, Sachin Jain. Sorry, I forgot to unmute myself. So two questions here for Robert, if I may. So firstly, just in the ARAMIS setting, you're three years into launch. Why don't you just give a bit of colour as to the share you've got of the existing agents and how you expect progression of the strong launch you've referenced, the 220 million towards the billion to progress, and what the barriers you've seen to adoption in the ARAMIS setting are?

And I'm relating that question to ARASENS. So would you expect the launch in the ARASENS setting to be quicker given you're the only dataset of this triple with the compelling data that you've seen? Or do the challenges that the doctor speak to suggest to us that there should also be a slower launch that builds over time? Thank you.

**Robert LaCaze**

Thank you, Sachin, for that question. I think there's a couple of different dynamics playing in the marketplace now, as I stated in my opening remarks. As you will recall, the launch of Nubeqa – the initial launch of Nubeqa – happened right in the middle of the pandemic, and our representatives for the most part were not able to get out in how the number of face-to-face type of customer interactions, so we relied a lot on peer-to-peer type of discussions and digital type of outreaches to reach the different customers, etc. I think, as the pandemic begins to wane, and our representatives are able to get out to start having more face-to-face calls to really explain the benefits of the compound, and doctors begin to see it, I think you'll see – because we see this when we talk to physicians that utilize the compound. They really do become adopters of the compound once they use it just a few times.

I think, on the market share question, that is a very difficult question to get at because the data is not always as clear cut as one would see across the different markets because of the, as Dr Smith was saying, the disease itself is almost like a continuation. It is a continuation of prostate cancer, so it's really hard to have market-level segmentation of the data as you do this, but what we see is that we are continuing to trend up in the way that we look at the data, probably in the 20% to 22% range or so, in this non-metastatic setting, and continue to trend upwards. Now, obviously, if you look at this on the total market because the other drugs have broader indications than we have at the current time, it's really hard to put that in the right context because of the, really, smaller segment of the non-metastatic setting. So probably the biggest variant for us is just overcoming some of the issues that most companies have to overcome when you're launching drugs in a pandemic and finding new ways to be able to reach and ensure that you're educating on the benefits of the program.

I think, though, if you look at the compound itself, at really the last year, we – as you know, when you go to Europe, and Japan, and other areas, there's quite a long time from the actual indication to the reimbursement. And so, when you look at really 2021 was the first year that we had a full year

of indications plus reimbursement, it's coming in around the €219 to €220 million segment. So as you look at the ARASENS trial now, I think what this does is begin to build on the confidence level of the compound because now you don't have just one study. You actually have two studies, and if you actually looked at the two studies, they actually showed a greater than 30% reduction of risk, regardless of if you're in metastatic or the non-metastatic setting.

So I think the studies themselves will feed off of each other based on the totality of the data, and then you layer on top of that, regardless of which setting you were in, the tolerability profile was extremely consistent. And so, as doctors now will have the ability to begin to use this drug in the metastatic setting, I think that they will see the true benefits of this compound as they make treatment choices and options for their patients. It's hard to say exactly what the uptake will be as we go into the marketplace, but I think Dr Smith made a comment that anybody right now who are considering chemotherapy for a patient based on this data – it would be very appropriate to immediately add darolutamide to that regimen for this metastatic hormone-resistant indication.

**Oliver Maier**

Great. Thank you, Robert. Does that answer your question, Sachin, or you have a follow-up?

**Sachin Hind**

No, that's perfect. Thank you very much.

**Oliver Maier**

You're welcome. Dominic is back from Credit Suisse. Dominic, let's try it again. You're back.

**Dominic Lunn**

Hi. Can you hear me now?

**Oliver Maier**

Yeah, much better.

**Dominic Lunn**

Perfect. Great. So on ARASENS again, in the past, there's been discussion that the benefit of this indication lies potentially more in having a complete and differentiated label to mark it with instead of a big incremental sales opportunity, given the fact that you're trying to bring chemo earlier into the treatment paradigm in some of the patients, I assume. But the magnitude of the benefit is quite impressive, so did this change your view on the level of adoptions you expect for this regimen? And I ask because, obviously, you are increasing your peak sales by 2 billion at the same time when obviously showing the ARASENS data, but is it correct to assume that the peak is more of a general re-evaluation tied to all indications rather than being solely on the strength of the ARASENS data?

**Robert LaCaze**

Yeah, so Dominic, thanks for that question, and indeed, that's correct. As we look, this second study really confirms the first study in terms of the profile of the compound, and we do have three additional studies including the ARANOTE trial that will read out as a single agent with ADT. And so, when you look at the totality of the entire program, this is where we got to the \$3 billion number. It wasn't on one specific indication, and it's going to be interesting to see, as physicians see a patient in front of them and make treatment options, whether to use this triple combination with intensifying therapy or not, and I think it's going to be very independent based on the physicians, based on the patients. And Dr Smith, maybe you want to comment on how he would think about when to use this more intensifying therapy, but we see this as not just on one indication or two indications, but the \$3 billion number that we put out is more on the totality of the entire program in the clinical development program that we have already put forth.

**Dr Matthew Smith**

Yeah, sure, happy to further comment. So decades ago, this term 'combined androgen blockade' was introduced referring to the addition of a first-generation antiandrogen like casodex or flutamide to standard androgen deprivation therapy with a GnRH agonist. And that was never proven to be helpful, and so the term got dropped.

We're back to combined androgen blockage, but now with drugs that really work. Drugs really work, right? So across the entire spectrum of prostate cancer, we're seeing benefit by addition of a potent AR pathway inhibitor, and I think there will be this generalization. You're going to – and docs are going to choose – they're going to intensify in the vast majority of settings where we're administering ADT. So ADT isn't just going to mean just Lupron, for example, or whatever drug – injectable drug of choice. It's going to be that plus your AR pathway inhibitor of choice, and for the reasons I described, I view this as best in class.

And the data from ARASENS are critically important, right? Not that I ever had any doubts about the strength of the data from ARAMIS, but if there were any doubters, this data should largely silence that, right, because there's this high-risk patient population, poor-prognosis metastatic disease, and you see this very large treatment effect and consistency across all the secondary endpoints.

So I think there will be this, to use your term in the question, generalization across the disease states, and I think that's appropriate because a lot of these labels are a bit outdated, and they're defined in that way for regulatory purposes. But if we focus, say, on the term mCRPC for a moment, it doesn't mean the same thing anymore because almost no one going forward with metastatic disease should be progressing on ADT alone, so when they progress to CRPC, they will have already received an AR pathway inhibitor in addition to their injectable hormonal therapy. So I think it's really going to become an issue of intensifying systemic treatment by addition of an AR pathway inhibitor, and individual physicians are going to make their choice of which agent of choice, and I think this is why the combined data from ARAMIS and ARASENS are so important.

**Oliver Maier**

Great.

**Dominic Lunn**

Thank you. Very helpful.

**Oliver Maier**

Thank you so much, yeah. We have time for maybe one or two more questions, and I have one more question from Harry Sephton from Credit Suisse. Harry, you're next.

**Harry Sephton, Credit Suisse**

Brilliant. No, thank you for taking my question. I just had one, which is a follow-up on the trajectory of your expectations to that 3 billion new guidance. So between now and your passing cliff, you will have Xtandi generics on the market probably about six to seven years prior to your passing cliff. So I just want to understand whether you expect it could be more challenging to gain share in the new-to-brand market as Xtandi generics become available and whether you factor that into your guidance. Thank you.

**Robert LaCaze**

Yes, Harry. So as we think about the genericization of some of the compounds, it's really important to really focus on the differentiation of the compound of Nubeqa. And when you look at Nubeqa, this is the only one that's been able to show this type of data with the ARASENS trial. Keep in mind that abiraterone also went generic and the market still continues to grow as data begins to drive the utilization of these compounds.

And so part of our value proposition, as you saw from Christian's presentation earlier, when you think about the blood-brain barrier and the clean profile of darolutamide, this continues to offer tolerability advantages for these patients. And also, when you look at the way that we are conducting our clinical trials, yes, there will be some genericizations that will occur towards the end of the decade, but our goal is to make sure that this compound is really differentiated based on the clinical profile, the clinical benefit to the patients, and the utilization as the market continues to change.

And I think Dr Smith made a really good point about how even just how the castrate-resistant space, which we're not doing studies in because in that space, by the time you're there, I've already received an AR inhibitor. The only way we would do a study there would be in combination with maybe a new modality, for example. This market will continue to change. It will continue to – these drugs will begin to be utilized in a much, much earlier setting, and as you move these drugs into the earlier settings like we have with the BCR trial and the neoadjuvant and the adjuvant trial, the profile of the compound and the tolerability of the compound really has to be somewhat pristine, because these patients are asymptomatic, and we feel that we have the best in class tolerability profile of the agents that are currently available.

So our \$3 billion number that we have does include some of the changes in the marketplace, but it also includes some of the shifts in the marketplace of these drugs moving, especially Nubeqa, hopefully earlier and earlier in the treatment of disease.

**Oliver Maier**

Thank you, Harry. One more question from Damien. Damien Conover from Morningstar.

**Damien Conover, Morningstar**

Super. Thanks for taking the question and thanks for the presentation. Super helpful. One question I had – there's a great slide – slide 9 – that cross-trial compares Nubeqa to some of the other key molecules in the CRPC market, and as you think about this new data in the HSPC market, how would you characterise some of the cross-trial comparisons? There definitely seems to be a safety benefit, but when you look at some of the efficacy cross-trial comparisons, how do you feel it stacks up, Nubeqa, versus competitors?

**Robert LaCaze**

Maybe I'll ask Dr Smith. From a clinical standpoint he is absolutely the clinical expert here, and then maybe there's additional comments I would add, but maybe I'll ask Dr Smith to take that one on.

**Dr Matthew Smith**

Sure. So the data from ARASENS is the most compelling. The only – by far, I guess I'd say. The other trials that included ADT and Docetaxel as standard of care were a few – ARCHES, TITAN, ENZAMET – were relatively small groups and did not report a benefit of adding their respective drugs onto ADT Docetaxel. And then more recently, in a subgroup analysis of the PEACE1 trial, there was a benefit to adding Abi to ADT and Docetaxel, although the hazard ratio there was, I think, 0.75, so not as favourable as in ARASENS, and there's also a smaller subgroup. So I think the community was not won over by the PEACE1 data because it really is a subset analysis within a larger trial. So to answer your question, ARASENS is best in class for efficacy in this specific disease setting.

**Damien Conover**

Great, thank you.

**Oliver Maier**

Thank you so much, Dr Smith. I think we have one last question from Marietta. Marietta is next.

**Marietta Miemietz**

Yes, thank you very much. Just one quick question on your confidence in the earlier settings. So I absolutely hear you on safety, but just in terms of extrapolating efficacy from the more advanced settings to adjuvant and BCR, can you just speak to your level of confidence that there will actually be a high level of efficacy and the drug will actually succeed in those earlier settings? Just because we've had some examples of cancer drugs that have done phenomenally well in the metastatic setting but failed in the adjuvant settings, and you can debate whether in some cases it might have been due to the drug and in some cases it might have been due to the trial design, but just any thoughts there why maybe in prostate cancer we should look at this differently, why you might have higher confidence. Thank you very much.

**Robert LaCaze**

I'll answer the first part and then I would also welcome Dr Smith if he wants to add any additional comments, but, you know, Christian started the presentation. When you look at this disease, the androgen receptor is the key driver here, and if you can give more intensified therapies earlier on in the disease, the hope would be to be able to provide a better clinical outcome and benefit for the patient. And we've seen that now, and we continue to see that in the non-metastatic setting, and so the next question is: should we go earlier and then also see if we can provide the same additional benefit for patients?

I think when you do that though, the profile of the compound, again as I stated earlier, needs to have a very, very good tolerability profile, because nearly all of these patients will be asymptomatic and it's extremely important that the drug doesn't add burdensome toxicities for the patients.

So the data, I can't predict the outcome, nor will I predict the outcome, but when we combine the fact that we have a very, very good profile in our compound and the fact that the AR inhibitor is the key driver of the disease, I think it's an appropriate question to ask: can we provide better benefit for these patients in this much earlier setting?

And what we're doing also as we look at some of these settings, we're selecting the patients who are at high risk of progressing, so we're not just going to every single patient. We're really being very mindful, from a clinical standpoint, to ensure that we are identifying the patients who are most at risk that may actually progress through their disease.

But anyway, so that's as we think about it on our clinical program, but Dr Smith may have additional comments that he'd like to make just from a broader perspective.

**Dr Matthew Smith**

Yeah, so I'll answer just from the perspective of the class of AR pathway inhibitors. So I have no doubt that AR is a key driver in high-risk localized prostate cancer and in biochemical recurrence after prior-level therapy. I think there's no doubt about the biology there, and I also have no doubt that Nubeqa and these other drugs will work in that setting. So the success or failure of a labelled indication will really be, to your point, dictated by whether the studies are appropriately designed. It's not whether the drugs work; it's whether they're appropriately designed. My prediction is that the many well-designed studies in those earlier disease states will succeed.

**Marietta**

Very clear, thank you.

**Oliver Maier**

Thank you all. I think, with that, that concludes our program for today. I would like to thank all of you for your participation and we hope, and the Bayer team hopes, that you enjoyed this event and found it useful. I'd like to thank you for your continued interest and to stay safe. So look forward to staying in touch. Thanks so much.

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<http://www.ubiquis.com> / [infouk@ubiquis.com](mailto:infouk@ubiquis.com)

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