[music]

**Announcer:** The BioWorld Insider podcast.

**Lynn Yoffee:** This is the BioWorld Insider podcast and I'm Lynn Yoffee. Cervical cancer is a leading cause of cancer morbidity and mortality in women worldwide. With an estimated 447,000 new cases expected this year, it's also the world's second most frequent cancer and the second most common cause of cancer death after breast and lung cancers. Researchers in Sweden last year proved that widespread use of an HPV vaccine is dramatically reducing the number of women who will develop cervical cancers. Where vaccines are common, cases are expected to fall about 9% over the next decade, but the global number of new cases will continue to climb by about 9% as well. The five-year survival rate for women with cervical cancer in the US is about 66%, and before this week, treatment options have been limited to surgery, chemotherapy, radiation, and immunotherapy.

New data just out at a key medical conference showed adding the immunotherapy KEYTRUDA to standard first-line chemo can extend survival for women with cervical cancer by up to eight months, but obviously, that's not enough. More treatment tools are needed. This week a new option arrived. The Danish firm Genmab and its US partner Seagen won accelerated approval for TIVDAK. It's now the world's first and only antibody-drug conjugate to treat women with recurrent or metastatic cervical cancer whose disease has progressed on or after chemo. Today, we're glad to welcome Genmab president and CEO, Jan van de Winkel, as our guest to talk about the approval with BioWorld managing editor, Michael Fitzhugh. Michael, take it away.

**Michael Fitzhugh:** Thanks, Lynn, and thanks for being with us today, Jan. Congratulations on the approval.

**Jan van de Winkel:** Thank you very much. I'm delighted to be here with you, Michael.

**Michael:** In describing TIVDAK's approval on Monday, you framed it as a journey that started nearly two decades ago. That's getting almost all the way back to Genmab's founding in 1999. Can you tell us a little bit about some of the highlights and challenges of the journey along the way?

**Jan:** Absolutely. TIVDAK is a molecule composed of Genmab's antibody targeting tissue factor with ADC with an antibody-drug conjugate technology from Seagen. In 2006, we actually immunized the first mice to really get antibodies targeting tissue factor of antigen. That actually led to the lead candidates being selected soon thereafter. The challenge was actually, Michael, to find an antibody that effectively could kill tumor targets expressing tissue factor the target for TIVDAK, but not impacting coagulation.

That is because we knew that many many years before we started this work, both Genentech which is now Roche, and Centocor, which is now J&J, were working on tissue factor targeted programs that were both stopped because of observed bleeding and use by the antibodies and animal models, so we needed to find the right one. Our lead candidate called Umax tissue factor was binding effectively to tissue factor, had a very, very strong anti-cancer response, but had minimal impact and bleeding models and internalized very effectively. Internalization is one of the characteristics of good antibody-drug conjugates.

We compared the targeting to tissue factor with targeting to EGFR and HER2, also two very well-known targets which are good for antibody-drug conjugate approaches. We actually tested a number of payloads and different linkers and found the MMAE payload from Scheffel genetics and the cleavable linker to be optimal. Then another highlight was a deal with Seattle Genetics in 2010, where we actually agreed to work on this together. We gave them an option to co-own the program following a phase one testing by Genmab.

**Michael:** You are really at the heart of some of this work, originally serving as the Chief Scientific Officer for the company, right?

**Jan:** Exactly. For the first 11 years, I was a CSO for the company. I was overseeing, Michael, this work on targeting tissue factor and creation of TIVDAK.

**Michael:** Horizons are always long in drug development, but it reflects real perseverance along the way. Were there any points there where your faith was shaken or just where you were like, "Oh, are we really going to get there?"

**Jan:** Yes, of course. In any drug development parts, there are moments that you actually are worried that it will not work and get through, but I think this was actually a fairly straightforward route, but it was a lengthy route, as you already indicated. We needed to be very careful with this targeting of tissue-factor because of the history with both genetic and Centocor failing actually targeting the same molecule. We took a very good approach with technology-base to create very good antibodies. In the answer, we found antibody-drug conjugate, Michael, which was very, very effective in killing tissue factor-positive cells.

We saw very early on with all the different cancers we tested, cervical cancer was actually a type of cancer where we had some very, very good results, both in the laboratory, as well as in animal models. Then we moved the molecule into the clinic and very recently actually got an approval for the antibody-drug conjugates, so we are super pleased with that.

**Michael:** One of the reasons why I wanted to talk to you was because of, not only this first-in-class aspect of the ADC and cervical cancer, but also TIVDAK seems to be arriving at a time of evolution for the standard of care in cervical cancer, at least in developed markets. Can you tell me a little bit about how you see the medicine fitting into the market in the near term and even the longer term?

**Jan:** Absolutely. We initially have a label, of course, in second and third line, which is a setting, Michael, but there is very, very few treatment options for cervical cancer patients. Actually, available therapies before TIVDAK showed response rates smaller than 15% in that setting. We actually have much better data for TIVDAK, but there is a need for new therapies for patients with cervical cancer. Right now, we are doing a large phase three year study in order to basically confirm the data we observed in the phase two study. We also have just presented at ESMO, a small really good combination therapy data with TIVDAK and either chemotherapy or an anti-PD-1 antibody, pembrolizumab.

There is a very good, and sound rationale to combine TIVDAK with either chemo or with immune checkpoint targeted molecules, like pembrolizumab. That is very much needed to improve the prospects for patients with cervical cancer, so TIVDAK will likely be moved into frontline setting for clinical testing fairly soon. We’re actually thinking about quadruplets and triplets types of therapy, and we will soon come with what we think would be the right approach to move that work into frontline therapy for cervical cancer.

Of course, we will also try to combine TIVDAK with other therapeutic agents in other types of cancer. We also will also soon cover the updates on that to broaden the base where TIVDAK can be used in the coming years, Michael.

**Michael:** One of the headline issues lately in our industry, of course, is drug pricing and talking about combos and triplets, even priced in my mind just because, obviously, with a lot of this, real through innovation comes to costs for patients. Can you tell me a little bit about the price of TIVDAK and just how you see the reimbursement environment?

**Interviewee:** The price of TIVDAK, which we have agreed with Seagen, is coming to a workable wholesale acquisition cost of between $90,000 and $120,000 per treatment for this setting or $34,000 per month. This is very much in line with other antibody-drug conjugates. Since this is a first-in-class option for patients where there's a real high unmet medical need, we believe that that's a realistic price for this medicine. Of course, we see the challenges with the reimbursement. I think there will be discounts given, depending on which patients and the payer mix we get behind this type of medicine, but new medicines, Michael, are really, really needed. This is an appropriate price for this type of medicine

**Michael:** During the testing of TIVDAK, there were some eye-related adverse reactions in 60% of patients treated with the drug, but it's my understanding that that's a common risk with ADCs as well. How are you thinking about those risks versus the potential benefits there?

**Jan:** There's definitely a risk there for eye toxicity. We have also observed that, Michael, in about 60% of the patients, we saw patients experiencing ocular toxicity. However, these, in general, are quite mild, so only 3.8% of the patients had a grade three-type of toxicities. The good part of the story is that with the pop-over eye care, we have put a very good plan in place with eyedrops and with cooled eye pads, and very good care by eye Dr. Stutter. We actually see that, in a majority of patients, the toxicity was found to be reversible.

Actually, 55% had complete resolution and 30% partial improvement upon the pop-over care. We think it's manageable, Michael. This has been seen before with a number of other antibody-drug conjugates. Iit's basically a matter of really making sure that the patients adhere to the treatment plan that is recommended by their doctor and then is treated appropriately for their cancer.

**Michael:** What sort of impact do you expect TIVDAK to have in terms of your broader goals for Genmab?

**Jan:** This is super important because this is Genmab's first own FDA-approved medicine. It actually signals our first step towards achieving our 2025 vision of transforming cancer treatment to our own innovative products. We have always believed that Genmab in the opportunity to help more patients with our science. We have invested in our capabilities and, at scales with purpose, position, and agility to become a fully integrated, biotechnology company. This is an important moment, I think, in our history, in our journey towards becoming an end-to-end integrated innovative biotech innovation powerhouse, so this is a super proud moment for the whole team of Genmab, Michael.

We actually, in parallel, are also going to progress a very strong, differentiated product pipeline to push us to the forefront of the industry, so this is a very important landmark event for the company.

**Michael:** Thinking about the notion of a fully integrated company, it's something that people seem to be pursuing less and less. Partnerships seem to be divvying up responsibilities. There's lots of licensing activity. Why did you choose to go in that direction? Tell me a little bit more about why that was important for the company.

**Jan:** I see it, Michael, as a journey. We have many partnerships. We have 23 partnerships, seven with pharma companies and then the rest with biotech or tech companies. We are one of the companies which really embraces partnering. Sometimes you really need a partnership when you want to maximize the potential of medicine. A good example is DARZALAX, so there are two **[unintelligible 00:13:28]** here partnered with Janssen, part of the NGA. We could have never put this massive clinical program in place years ago which Janssen did, now making DARZALAX one of the most successful medicines ever in the treatment of multiple myeloma.

We will continue to partner I can assure you, but we also realized that we really want to actually bring our own medicines to patients ourselves because we are a super innovative company. We have an amazing track record, Michael. We filed 39 INDs in the 22 years that we exist together with our partners. Today, 24 of these molecules are still in active clinical development, and then five are on the market as marketed products, so we have an amazing track record and we think that we can actually apply that innovative thinking. That's a spirit to really continuously push boundaries also to our own medicines by bringing actually medicines more effectively to patients ourselves, Micheal.

We believe it's a logical next step to commercialize the molecules ourselves. That also has, of course, as an added advantage that we have our own stock developers sitting at the table and deciding basically themselves how to most effectively and quickly move the medicine towards patients, so we believe that this is a logical step for the company and to actually, make us even more successful in the near future.

**Michael:** In that very near feature beyond TIVDAK's launch, what are some of the key elements of moving toward that 2025 goal that you talked about and just in [chuckles] the waning months of this year and the year ahead, what are you going to be up to?

**Jan:** The first priority is to actually bring our own medicines to patients. As I just discussed, in addition to TIVDAK launch, we're working with AbbVie on accelerating a development program for a molecule called abciximab. That is a bispecific antibody that targets CD21 B cells with fantastic early clinical data. We're now putting into place a massive clinical development plan together with AbbVie and we are making very rapid progress there. In parallel, we're also building a differentiated product pipeline which is second to none.

We look forward to present data in the coming months from different investigational therapies that we co-develop at BioNTech. You know that company because of the vaccine for coronavirus. That is two bispecific programs called DuoBody's PD-L1 4-1bb and DuoBody CD 40x4-1bb, where we actually expect to see data at SITC in November.

In order to become a leading integrated biotech innovation powerhouse, we're also very rapidly growing our presence in the US and Japan, which are two focus areas. Michael. We're also witnessing milestones being achieved by four Genmab-created products that are in development by our partners, DARZALEX, KESIMPTA, **[unintelligible 00:16:45]**, which will ensure a growing and increasing income stream for the company.

Genmab is only at the beginning of a very exciting future and this week's approval of TIVDAK marks a very key step in our journey towards becoming one of the leading biotech innovation powerhouses.

**Michael:** Fabulous, Jan. Thank you so much for sharing Genmab's story with us today, and all the background on the approval. It's really interesting.

**Jan:** Thank you, Michael, and thank you for giving us the floor. We're delighted to keep in touch.

**Lynn:** Thank you, Jan and Michael. As always, BioWorld will continue to keep you informed of all the most important scientific, clinical, and business updates in the field. That's our show for today. If you need to track the development of drugs, turn to BioWorld.com. Follow us on Twitter or email us at newsdesk@BioWorld.com. If you're enjoying the podcast, don't forget to subscribe. Thanks for joining us.

[background music]

**Announcer:** BioWorld, published by Clarivate, is a subscription-based news service-- but all of our COVID-19 content- more than 5000 articles and data entries since the start of the pandemic are freely accessible.

**[00:18:05] [END OF AUDIO]**