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ZYME.N - Zymeworks Inc at UBS Global Healthcare Conference

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CORPORATE PARTICIPANTS

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PRESENTATION

Unidentified Analyst

Good afternoon, and thank you for coming to the 2018 UBS Global Healthcare Conference. My name is [Among Sanghai], and I'm happy to be your host for this session. Our next presenter will be Ali Tehrani, the CEO of Zymeworks. A breakout session in Julliard will follow immediately after the presentation. Thank you. Ali?

Ali Tehrani - *Zymeworks Inc. - Co-Founder, President, CEO & Director*

Thank you. Good afternoon, everyone. Thank you to the UBS team for organizing a great conference. It's my pleasure to introduce Zymeworks to you. Naturally, what we need to start as a public company is get through the legal disclaimers. So there is that for you.

And the place to introduce the company to you would be to talk a little bit about what we're focused on. Zymeworks is focused on the development of the next wave of biologics, and we believe the next wave will be focused on multifunctional biologics, bispecific antibodies, bispecific antibody drug conjugates, essentially, more than just antibodies that are good for blocking. We believe there's a lot of room in antagonists and agonists, both in terms of naked and conjugated antibodies. Antibodies that can go the distance in waking up the immune system and being able to be better at the job of defeating disease. We've developed platforms, and we developed pipelines to that effect. And today, I'll be walking you through that.

In terms of our business model, in terms of how our business has been progressing, this slide captures essentially the entire story. And if you were going to remember one slide, this is the one I encourage you to take away and focus on. At the very bottom, you see our collaborations with pharma. There are 6 active collaborations with pharma: Lilly, Merck, Celgene, GSK, Daiichi Sankyo and J&J. And in total, these deals could bring up to $6.17 billion, plus royalties, for Zymeworks assuming success. The key things about this is that all of these partners have tech transferred in-licensed, nonexclusively different platforms of Zymeworks for the development of bispecifics and multifunctional antibodies. We have not done any targeted exclusivity, we have not done any indication exclusivity, we have not licensed any of our therapeutic assets. These are just tech transfer of our technologies that are believed to be industry-leading for the development of multifunctional biologics.

Then in the middle is our preclinical pipeline. We have not talked much about this. But in later this year, in the fall, we hope to have an Analyst Day where we talk about what else we're working on, what other targets, what other biologies beyond what's in the clinic currently.

What's in the clinic currently is ZW25. ZW25 has been selected for an oral presentation at the upcoming ASCO Conference we'll be presenting on Friday, June 1. Dr. Funda Meric-Bernstam from MD Anderson will the presenter. ZW25 is a bispecific, most specifically a biparatopic antibody that I will be talking to you about in just a second.

ZW49 and is the next asset we intend to IND this year. It is the same backbone antibody as ZW25, except it is conjugated. So it's an ADC. And it benefits from a proprietary linker payload that we call Zymelink. There was a lot of information about ZW49 at the most recent AACR conference, and there are posters on our website, which you can take a look at.

So I talked about our platforms and the fact that they form the backbone of our collaboration with pharma. What are these platforms? Azymetric is the flagship platform enable the development of bispecific antibodies in a full length IgG setting. We also have Zymelink, which, again, as I discussed in terms of ZW49, it provides with us with proprietary linker payload technology. As a note, the initial linker -- or rather the payload that we have built ZW49 around is an auristatin-based drug conjugate. Our EFECT platform enables effective function modulation through CH2 engineering. This is where you get to up or down regulate antibody-dependent cell cytotoxicity, along with other effector functions. And AlbuCORE is an example of nonantibody or antibody alternative multifunctional biologics that we're very much interested in.

One of the questions we often get is how does your bispecific technology compare to ours, why does it stand out, what's so differentiating about it. And the takeaway from this slide is in the world of bispecifics, irrespective of Zymeworks or what have you, we believe there is no one-size-fits-all. There is no one bispecific geometry or solution that addresses all needs. It really depends on geometry. It really depends on modality. And we have the most comprehensive set of solutions in terms of heterodimeric antibody, common light-chain hybrids and even one arms in those best-known scFvs. This best enables drug developers to focus on biology rather than the geometry they're restricted by. So if you're unsure which geometry is right for your 2 targets, you get to screen against all the different geometries that are available to you through the Azymetric platform, such that you find the best geometry in terms of a lead and backup to that lead versus being restricted by a singular geometry.

Together, all of these platforms give us the ability to research and develop drugs, fit-for-purpose biologics. We have the capability that starts with target-discovering antibody generation. We have a lot of capability for antibody and drug optimization, which, ultimately, when you put it through this engine, gives you that highly customized fit-for-purpose therapeutic.

Today, we'll focus on underserved oncology using ZW25 and 49. In the medium term, we want to expand our footprint in oncology, and in the medium to long haul, we want to expand beyond oncology into autoimmune inflammation and other areas. And again, all of this is built upon and grounded by all of the platforms and the capabilities we've developed in-house from the ground up.

It's worth noting that Zymeworks is over 160 employees. When the company was founded, there were only 2 individuals. The company has grown significantly to be able to support all of its aspirations.

A little bit about ZW25, our clinical program that is in a adaptive Phase I, though it does have all of the hallmark and benefits of a Phase Ib/IIa. ZW25, as you see it, binds to 2 different epitopes of HER2: one arm, the shorter arm, the blue arm, binds to ECD4, which is the epitope trastuzumab or Herceptin binds to; and the green arm binds to ECD2, which is the same epitope pertuzumab or PERJETA binds to. Essentially, the pieces behind this asset is that 1 plus 1 equals 5. We've combined 2 clinically validated approved drug into one bispecific, and our objective was to see a better outcome than the combination of those 2 monospecific antibodies. And I'm happy to say, so far, things have been doing really well.

The design of this adaptive Phase I has a standard dose escalation, followed by cohort expansion, single agent and then combination cohorts. And the dose escalation has finished. We had previously presented data for it at ASCO 2017, ESMO 2017 and San Antonio Breast Cancer 2017. And now the cohort expansion is the subject of what will be presented at ASCO 2018. The cohorts that make up the cohort expansion are HER2-high breast cancer, HER2-intermediate breast cancer, HER2-high gastric cancer, HER2-intermediate gastric cancer and a basket cohort.

The data as of December 2018, i.e., San Antonio -- or December 2017, I should say, apologies, i.e., San Antonio Breast Cancer Conference look like this. If you're unfamiliar with the waterfall, each bar is a patient, and every time the bar goes down, the tumor in the respective patient is decreasing. Here, you're looking at different doses for breast and gastric patients, pardon me. And the takeaway based on this data was that there were 6 partial responses, PR, out of 14 patients, total of 19, that were response variable as 14 who have measurable disease. And at the ASCO abstract that was just recently presented, 6 PRs had increased to 9 PRs. So the data continues to get better. The response continues to get better. And of course, there will be an update in terms of more patients across all of the cohorts that I mentioned at the upcoming oral presentation, which is Friday, June 1, coming up. So we are very encouraged by this anti-tumor activity.

We are further very encouraged by the safety profile of ZW25. Essentially, the adverse events can be summarized as no more than grade 1, grade 2 AEs, typically just being a diarrhea. There were some minor infusion reactions, but only limited to the first time infusion and nothing more, very easy to take care of. Nothing else was seen. One of the questions that we often get is, "With HER2, was there anything seen with cardiomyocytes or cardiac cells?" Again, no concerns there. No AEs to report there. This data will be updated at ASCO, and we're very excited about that.

In terms of the patient background, which creates that excitement, I want to draw your attention to Column 4 of this table, and this is breast cancer patients. The breast cancer patients previously were all treated with some combination of trastuzumab, pertuzumab or Kadcyla. That's what the H, P and K are. H is for Herceptin, P is for PERJETA and K is for Kadcyla. And as you can see, some of the patients were treated with lapatinib. And beyond H, P, K and L, the patients were also treated with other experimental therapies. So essentially, the patient population, when it came to breast cancer was, true salvage line. Enrollment in our study require that they had been treated by the standard of care and any approved therapy

that was available and have become resistant refractory, and of course, they're metastatic. So to enroll in our study and to be able to see the study, the result that we saw in terms of the partial responses was extremely encouraging and very valuable to us.

Similarly, the gastric patients were treated with Herceptin, including other treatments, such as chemo. Again, it's noteworthy that the need in gastric cancer is extremely high. Typically, the PFS is about 3 months, and Herceptin is the only large molecule in the context of HER2 gastric cancer that is utilized.

As far as the time of study goes, the swimmer's plot gives you that. You can see our time of study based on different doses, 5 mgs per kg, 10 mgs per kg, 15 and 20. You can see that at the very top of the graph that we had a patient on our lowest dose as a PR that was on study for almost 1 year, and you have a number of patients that are crossing the 6 months' line. We're very, very encouraged by these data. And just as a note. For those patients that came off study, almost every single time, it wasn't because of the primary tumor. It was that these patients are metastatic. They come on study extremely sick and is due to other new lesions and not their primary tumor.

How does it work? On the right-hand side, you see a cartoon where you either have trastuzumab or pertuzumab as blue-blue chains of antibody interacting with HER2. On the left-hand side, you see how ZW25 works. And essentially, one arm binds to one location on one HER2 while the other arm binds to another location on a different HER2, i.e., it bind in trans. And this creates a cluster. This creates a sort of a -- as I like to call it, "chain gang", where HER2, on the surface, start to get clumped and clustered, being kept together by our antibody and working against "escape." HER2 -- or as part of that HER2 resistance could come as a result of 2 HER2s homodimerizing or HER2 heterodimerizing with another member of the ERBB family. Our antibody stops that, essentially builds a fishnet on the surface, such that when that cluster is formed, all the HER2s are captured and held on place, such that they can't escape, and ultimately, they're internalized and then they're destroyed.

One of the questions we often get is, "Why couldn't you do this with a combination of trastuzumab and pertuzumab?" And the simple answer is antibodies don't bind for dear life. As an antibody interacts with the receptor, it likes to come off. It touches and it goes. As soon as either tras or pert come off receptor, it provides the opportunity for escape. It provides the opportunity for HER2 to interact with another receptor and essentially make it unrecognizable by the drug. In our case, because you have this trans binding, one HER2 is linked to another HER2 linked to another kind of shackled by "their hand and their feet." And when they get internalized because of the clustering on the surface, because of the increased surface density, you get them destroyed.

It's worth noting that we have somewhere between 1.5 to 2x more antibody on surface. It's worth noting that our internalization compared to Herceptin is 7x higher. So we have a lot more antibody on surface that is quite active in capturing HER2, stopping it, potentially stopping escape and having it destroyed through internalization. And also, our SC domain is wild type. So having more antibody on surface naturally means more effective function enablement. And we do see that and we've seen that in our preclinical studies where there's increased ADCC.

In terms of where we're going next. We have already started enrolling in combination cohorts, specifically, at this time, what is known in safety cohorts involving chemo combinations. The information is on clinicaltrials.gov. And our objective is to be able to study the added advantage of chemo plus ZW25 versus the single agent and earlier lines of treatment for gastric cancer and for breast cancer. And our aspiration, our vision is to be in multiple Phase II/III studies as early as next year.

The market is big, it's broad, and we're very much -- at this point, ZW25's focus is in HER2-high all lines. However, we're very much excited about bringing in ZW49 into IND at this year-end and, soon after, bringing it into the clinic, where it gets positioned for HER2-intermediate and potentially HER2-low. So together, ZW25 and ZW49 are meant to provide new solutions, more effective solutions with not only HER2-high patients, but also HER2-intermediate and HER2-low. And again, recall that ZW49 is the antibody drug conjugate version of ZW25.

In terms of highlights and what is to come next. This year, we announced, obviously, a platform deal with J&J Janssen. We also just recently announced the platform licensing deal with Daiichi Sankyo, so about $68 million worth of nondilutive financing came through that. We also received an undisclosed payment for our expansion of the deal that we have with Celgene. Recall that Celgene and Eli Lilly are investors also in Zymeworks. So we had a lot of positive progress when it comes to our platform partnering side of the business, and we also are very excited about the progress of ZW25 as far.

As far as what is to come, naturally, we continue to update the world when it comes to ZW25, so obviously at ASCO and other opportunities. But more importantly, we are excited about an R&D Day, as I said, in the latter half of this year, where we talk about non-HER2 bispecific programs that we've been working on. Also, what can be expected are additional platform deals, which provide nondilutive financing for the company. Recall, we do not provide exclusivity, and we do not do any work in these deals. It's just basically a tech transfer, so any money that comes in is pure upside for us. And we're also excited about our existing pharma partners advancing programs in the clinic, which we hope to announce in 2018.

With that, I'm happy to take a couple of questions as we have a couple of minutes left. Thank you.