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ZYME.N - Zymeworks Inc. - Special Call

EVENT DATE/TIME: JUNE 04, 2018 / 12:30PM GMT

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PRESENTATION

Operator

Welcome to the Zymeworks webcast and conference call relating to the recent ZW25 clinical data presented at ASCO. (Operator Instructions) And the conference is being recorded. (Operator Instructions) I would now like to turn the conference over to Dr. Ryan Dercho. Please go ahead, sir.

Ryan Dercho

Good morning, everyone. My name is Ryan Dercho, Head of Investor Relations and Corporate Communications at Zymeworks. It is my pleasure to welcome you to the conference call and webcast to discuss the ZW25 Phase I data presented Friday afternoon at the American Society of Clinical Oncology's Annual Meeting. As a side note, the slides we are using this morning, as well as the audio transcript of the call, will be available on the Zymeworks website later today, specifically on the Events page within the Investors section.

Providing opening remarks will be Dr. Ali Tehrani, Zymeworks' President and Chief Executive Officer. Joining Ali to discuss the data will be Dr. Diana Hausman, Zymeworks' Chief Medical Officer.

Before we start, I would like to remind you that we will be making forward-looking statements during the call, including statements relating to our plans and expectations. Forward-looking statements can be identified by words such as will, may, expect, intend, believe, outlook, plan and other similar words. Forward-looking statements are based upon our current expectations and assumptions that are subject to the usual risks and uncertainties associated with companies in our industry and at our stage of development. For discussion of these risks and uncertainties, we refer you to our 10-K for the year ended December 31, 2017, as well as our other filings with the SEC.

I will now turn the call over to Ali.

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

Thank you, Ryan, and welcome to everyone on the call. It is a pleasure to be speaking with you today. Before discussing the recent data, let's take a moment to talk more broadly about Zymeworks and our vision of serving patients with serious diseases, beginning with ZW25.

As a company with deep expertise in protein engineering, we have built an extensive platform of proprietary complementary technologies intended to create new medicines for patients. Our Azymetric platform, which is used to make bispecific antibodies, incorporates a number of special properties, which I will expand upon in a moment. In addition to our own pipeline, we also have established partnerships with 6 global pharmaceutical

companies to support their research and development initiatives. To date, 5 of these partnerships have been expanded, providing further evidence of the potential and promise of our technology engine, and it's worth noting that the sixth one was only recently signed. Today, our discussion will focus on our lead clinical compound, ZW25, a bispecific antibody that we are developing for patients with HER2-expressing cancers.

Why are we initially focusing on HER2-expressing cancers? Certainly, with the advent of HER2-targeted agents, we have seen outcomes significantly improve in select groups of patients. However, despite this progress, there's still much to be done for patients at various points in their disease and with tumor expressing different levels of HER2. The challenge in front of us is how to overcome resistance to currently approved HER2 agents and achieve meaningful disease control while maintaining an acceptable safety profile. Why do we think ZW25 can meet this challenge? ZW25's multifunctional activity results from targeting 2 separate nonoverlapping binding sites on the HER2 receptor, an achievement made possible by our proprietary Azymetric technology. We believe the unique biparatopic binding that occurs facilitates additional and novel mechanisms of action to help combat cancer. While we believe there are several mechanisms of action at work to achieve the high level of anti-tumor activity we have observed, I would like to highlight a few of them.

In the case of ZW25, it is designed to bind simultaneously to 2 HER2 epitopes, specifically ECD4 and ECD2, the locations of HER2 where trastuzumab and pertuzumab bind. We have shown experimentally that tumor cells can be bound by almost twice as much ZW25 compared to a typical HER2-targeted antibody.

Not only do you have high levels of binding, you also have cross-linking of multiple HER2 receptors. These actions are so pervasive that they result in dense antibody clustering. This can prevent HER2 from dimerizing with nearby receptors, which is believed to be one of the mechanisms of resistance to existing HER2-targeted therapies. We believe this dense clustering enables ZW25 to block significantly larger percentages of HER2 receptors, which is advantageous for the treatment of patients whose tumors express lower levels of HER2.

We have also demonstrated increased internalization of ZW25 as a result of receptor clustering. This results in the removal of HER2 receptors from the cell surface and receptor degradation rather than recycling, which limits the potential for HER2 escape and can lead to direct apoptosis in HER2-driven cancer cells. We believe ZW25, with its diverse and multi-mechanisms of action, has the potential to be an effective and well-tolerated anticancer agent when administered as a single agent and when combined with other anticancer agents. Moreover, the data we have generated to date supports this belief.

Now I will turn the call over to Diana, who will describe the ongoing clinical study and review that data was presented on Friday at ASCO.

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

Thank you, Ali, and good morning, everyone. Since our last update in December, we continued to see good tolerability and encouraging anti-tumor activity for ZW25. As you may recall, previously, we reported data on 22 patients, of whom 17 were response-evaluable. In today's data set, we have almost doubled that number, with 42 inpatients enrolled, of whom 33 were response-evaluable at the time of data cutoff. Enrollment is continuing, and as of today, trial enrollment has reached 50 patients.

As the data set has grown, we continue to see a disease control rate of over 50%. While we remain impressed with the breast cancer data in these heavily pretreated patients, we are also excited to see the increasing number of responses in gastroesophageal patients as well as in patients with other HER2-expressing cancers.

But before moving to the anti-tumor data, let me first give you a brief overview of the study design and patient demographics. This is the first-in-human Phase I dose escalation study designed to evaluate the safety and anti-tumor activity of single-agent ZW25 and to identify a recommended dose for future study. To be eligible, patients had to have a HER2-expressing cancer with progression after all prior therapies known to confirm clinical benefit, including HER2-targeted agents for breast and gastroesophageal cancer patients. HER2 status was determined based on tumor biopsies, which were tested for HER2 expression locally and at a central lab. Other evaluations included standard safety and efficacy assessment. For efficacy, we used RECIST 1.1 criteria and performed tumor restaging every 8 weeks.

In the dose-escalation portion of the study, both a weekly and every other week dosing regimen were evaluated. Patients were enrolled in 3 sequential cohorts evaluating doses of 5, 10 or 15 milligrams per kilogram weekly and 20 milligrams per kilogram given once every 2 weeks. The dose-escalation portion of the study is complete with no dose-limiting toxicities observed. And the recommended single-agent dose for further study is 20 milligrams per kilogram once every 2 weeks.

We are now enrolling patients in multiple single-agent expansion cohorts in different disease indications as well as in chemotherapy combination cohorts. As of the date of cutoff date in mid-April, a total of 42 patients had been enrolled in the study, including 22 patients from dose escalation and 20 patients from the single-agent expansion cohorts. Consistent with earlier data, patients in this study were heavily pretreated, having received a median of 5 prior systemic treatment regimens. This includes treatment with trastuzumab in over 90% of patients, pertuzumab in almost half of the patients and T-DM1 in over 40%. About half the patients had HER2 high breast cancer, either IHC 3+ or IHC2+ and FISH positive, approximately 1/3 had HER2 high or HER2 intermediate, defined as IHC2+ and FISH-negative gastroesophageal cancer, and the remaining patients had a variety of other HER2-expressing cancers, including colorectal cancer.

ZW25 was well tolerated across all dose levels. Most adverse events were Grade I or Grade II in severity. Treatment-related Grade III events occurred in only a single patient in the 10 milligram per kilogram cohort. This patient had reversible Grade III low levels of phosphate, arthralgia and fatigue. There were no discontinuations due to treatment-related toxicities. The most common adverse events were infusion reactions and diarrhea, which were all Grade I or II and readily managed.

Antitumor activity was seen across all dose levels and in multiple cancer types. Overall, 68% of patients with measurable disease and at least 1 tumor restaging had a decrease in the size of their target lesion with an overall disease control rate of 55%, defined as the best response of PR, with partial response, or SD or stable disease at any time on study. Best overall response in these heavily pretreated patients included partial response in 12 or 36% of patients. This included a 44% response rate in gastroesophageal cancer, a 33% response rate in breast cancer and a 33% response rate in other HER2-expressing tumors, including colorectal cancer and gallbladder cancer.

Looking more closely at the breast cancer patients. These were heavily pretreated individuals with progressing cancers despite having received a median of 6 prior systemic regimens overall with a median of 5 prior HER2-targeted regimens for metastatic disease. A 100% of breast cancer patients had received prior trastuzumab, 95% prior T-DM1, 85% prior pertuzumab, 50% prior lapatinib and 30% prior investigational HER2-targeted agents. Of the 17 breast cancer patients evaluable for change in their tumor size, 7 had tumor shrinkage greater than 30%. We saw systemic control of disease for over 6 months in a number of patients. Six patients were still active on study at the time of the data cutoff and enrollment of new patients is ongoing. Notably, of patients who experienced disease progression, 4 have progression in their brain while maintaining stable disease or deepening tumor shrinkage outside of the central nervous system. Several other patients who developed progressive disease also continue to have shrinkage of their target lesions, but progressed due to appearance of new sites of disease. One of these patients had a biopsy of their liver lesions prior to starting therapy on our study and she was actually found to have HER2-negative disease.

Given the very advanced stage of disease in these patients and the number of prior regimens, the reported response rate and disease control rate are very encouraging, especially in the context of single-agent treatment without a cytotoxic component. As a comparator, consider the early response rates of less than 20% for single-agent trastuzumab in patients with HER2-overexpressing breast cancer with progression after prior chemotherapy.

In the context of chemotherapy in later lines of HER2-targeted treatment, such as was reported for the control arm in the TH3RESA trial of T-DM1 versus physician's choice. Trastuzumab in chemotherapy was associated with an overall response rate of only 9% and a median progression-free survival of 3.3 months. In this context, we are very encouraged by the level of activity we are seeing, not only with ZW25 as a single agent, but also with the potential antitumor effects we may see when it is combined with other agents, including chemotherapy.

Looking at the patients with gastroesophageal cancers, these individuals had received a median of 4 prior systemic regimens with trastuzumab in all. Tumor shrinkage was observed in the majority of the 9 response-evaluable patients. Four patients had partial responses, including a patient with intermediate HER2 expression on the biopsy obtained right before study entry, for an overall response rate of 44%. In addition, one patient who'd just missed the cutoff for PR with a 29% decrease in target lesions had stable disease for over 6 months. We were encouraged by these results, especially given the high unmet need for an active and well-tolerated regimen in this patient population. Reflecting the extent of this need,

pembrolizumab was recently approved as a therapy for selected patients in a similar third-line setting with only a 13.3 response rate in a single-arm study of 143 PD-L1-positive patients.

Patients with other HER2-type cancers in the ZW25 Phase I study included those with colorectal, salivary gland and gallbladder cancers. Although the overall numbers are small and we are still actively enrolling patients, we have seen encouraging results, including in patients whose tumors had progressed after prior treatment with other HER2-targeted agents. The disease control rate to date in these patients is 67% with partial responses seen in 1 patient each with colorectal and gallbladder cancer. At the time of data cutoff, 6 of 9 patients were active on study with 2 patients not yet restaged.

In summary, we observed single-agent ZW25 to be well tolerated across all dose levels in very heavily pretreated patients. Meaningful anticancer activity was observed in the absence of a cytotoxic agent across multiple tumor types, including breast, gastroesophageal, colorectal and other tumors. These results validate our Azymetric platform with a biparatopic approach and support the further development of ZW25, both as a single agent and in combination with chemotherapy and other anticancer agents.

Moving forward, we anticipate continued investigation of ZW25, focusing on 3 different settings: first, as a single-agent treatment for advanced HER2 high gastroesophageal cancer in patients who have received prior trastuzumab therapy as well as another HER2 high expressing cancers, such as colorectal cancer, were HER2-targeted agent has not yet been approved. Second, in combination with selected chemotherapy agents in earlier lines of therapy for gastroesophageal and breast cancers. And third, in combination with other anticancer agents in patients, including those with lower HER2-expressing cancers. Our initial priority will be to focus on advanced gastroesophageal cancer with a potential Phase II/III study beginning as early as the second half of next year, pending discussions with the FDA and other regulatory agencies. In addition, new studies to evaluate combination beyond those in the ongoing Phase I study are planned to start later this year.

Now I'd like to turn the call back over to Ali for closing comments.

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

Thank you, Diana. We're excited by the data we have generated to date with ZW25 administered as a cytotoxin-free single agent for patients with HER2-expressing cancers. In addition to being well tolerated, it is delivering meaningful anticancer activity in very heavily pretreated patients as we continue to expand our clinical footprint and accelerate towards a first registration-enabling trial in order to get this promising agent to patients in need.

Not only do we have a compelling active single agent, ZW25, but our pipeline also includes is ZW49, a next-generation bispecific antibody drug conjugate. ZW49 uses ZW25 as its base to take advantage of its ability to induce internalization and deliver our proprietary [toxin] into tumor cells. We reiterate that our anticipated filing and investigational new drug application for this ZW49 is this year and that we see ZW25 and ZW49 as complementary agents designed to be used at different stages in the disease process.

Beyond HER2-expressing cancers, we also have a number of exciting initiatives underway. We will share some preclinical data associated with our earlier-stage programs later this year at our investor and analyst R&D day in New York.

Taken together, we see tremendous opportunities ahead based on our technology platform, our pipeline and our roster of pharmaceutical partners.

Before concluding our prepared remarks, I would like to thank the patients, their families and the clinicians who participated in this study. Without their involvement in clinical trials, new disease treatments would be impossible. We salute your courage, dedication and persistence in helping develop different and even more effective medicines.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) The first question comes from Nochomovitz Yigal with Citigroup.

Yigal Dov Nochomovitz - *Citigroup Inc, Research Division - Director*

This is Yigal Nochomovitz. I guess, the main conceptional question I have is, is it the case that there's somewhat of a pivot in the clinical development strategy away from breast and towards gastric? I guess, I was under the impression initially that you're going to take the -- take ZW25 forward into breast cancer, but it seems that you're moving them to the gastric now.

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

Yigal, this is Ali. No, there is no pivot. As you heard, we've set a priority list, not an exclusive list, and we are very conscious of our efforts, our resources. And we're executing on a plan that has a priority to it. We still believe that HER2 is a huge area of unmet need, and ZW25 has a broad potential of addressing many different needs, but we are executing on a prioritized plan and we do intend to bring ZW25 out to meet the needs of many different cancer types, as shown by our data.

Yigal Dov Nochomovitz - *Citigroup Inc, Research Division - Director*

Okay. So there is the potential to do a late registration study in breast at some point? That is -- that's still in the game plan?

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

Yes, that is correct. There is a lot of complementarity between the different disease areas. But again, being very aligned with the sentiments with our investor group, with the shareholders, we want to have a prioritized plan. And we're executing on that. Again, as Diana highlighted in the development plan, we're looking at both gastric and breast, but our starting point from a faster market strategy starts with gastric.

Yigal Dov Nochomovitz - *Citigroup Inc, Research Division - Director*

Okay. And speaking of faster market, obviously, you're doing the studies in the United States and Canada. Obviously, gastric is a big problem in Asia and specifically China. Are you considering a global study that might incorporate Chinese patients?

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

Our strategy has always been global, and we've always looked at the entire need around the world. So we are certainly considering that. That is certainly on our radar, and we hope to provide future guidance on that at a future point. But for now, I will leave it at it is definitely on our radar.

Yigal Dov Nochomovitz - *Citigroup Inc, Research Division - Director*

Okay, got it. And just on ZW49, I'd be curious on your comments regarding how you see that agent as potentially differentiated from one of the competitors we saw this weekend at ASCO -- or on Friday at ASCO, which appeared to have some pulmonary toxicities that related to the HER2 expression and how you see ZW49 as potentially avoiding that?

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

Two comments, Yigal. One, as we were developing ZW49, we are all very aware of all the other ADCs that were being developed. So one of our key strategies was heavily focused on tolerability. We looked at all of the necessities associated with tolerability. So tolerability first, potency second. And then, the second unique aspect that enables us to do tolerability first, potency second, is the proprietary link or payload, also known as Zymelink. Together, this asset has a large therapeutic window, which again provides optionality to clinicians, to doctors, as opposed to a very limited window. This is supported by the data that we presented recently at the AACR conference, where one of the key focal points was the large therapeutic window. So not all ADCs are the same. Not all ADCs are developed the same. And here at Zymeworks, we very much believe in the fact that ADCs can be very powerful, but their power needs to be controlled. And that's where we put a lot of emphasis in developing this asset with tolerability first, potency second.

Yigal Dov Nochomovitz - *Citigroup Inc, Research Division - Director*

Okay, great. And when might we expect to see the first cut for the ZW49 program?

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

As just mentioned in our prepared remarks, we do plan to have this asset IND-ed this year, and we hope to go from there and provide an update after that. But for now, where we want to leave it is that we'll be submitting an IND application for it to the FDA or our plan is to submit an IND for it to the FDA this year.

Operator

The next question comes from David Novak with Raymond James.

David Novak - *Raymond James Ltd., Research Division - MD & Healthcare Research Analyst*

Congrats on the fantastic results. So first, just starting with the patient cohort in aggregate. Could you guys provide the days on drug range and average duration that we're seeing right now?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So the range, do you have the slide we've set up? I mean, it ranges from less than 2 weeks for some patients who came on who had unrelated adverse events -- actually, day 2 on study, 2 at the time of data cutoff, a patient who was on study for, I think, about 15 months. So the average time on study is a moving number because we're still enrolling patients and patients are still active on therapy. It depends on -- and it's really hard to say for the other cancers. For breast cancer, right now, I think the average, if you look at the time on treatment, is around 2 months. But again, that includes a number of patients who are still active, and again, we are enrolling additional patients. For gastric -- yes, sorry, for the gastroesophageal cancers, again, all the same caveats. There's -- shortest time on study again were patients who had unrelated AEs. Another patient had asymptomatic brain metastases at day 7 on study and we did call that patient progressive disease. But we also had patients who are on study, single-agent ZW25, no cytotoxic agent for 10 treatment cycles.

Operator

The next question will be coming from the line of Gena Wang with Barclays.

Gena Wang - *Barclays Bank PLC, Research Division - Research Analyst*

So I just followed the previous questions. Wondering, what is the duration of response for overall patients and also specifically for the breast cancer and also gastric cancer?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So we have not yet calculated the median duration of response because there's still patients active with PRs and again with new patients coming on. Patients with partial response in the breast cancer cohort certainly had a trend towards being on study longer, and we anticipate that we will continue to see that similar incidence for the gastric cancer patients. So you can see there's a patient with PR who was still active at the time of data cutoff, another patient -- actually, several patients who are still active. So we do plan on updating these data later this year, both for the patients already reported as well as new patients enrolled.

Gena Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Okay. Just maybe follow-up. Wanted to ask again, I think if -- when I look at the slides, I do see there is one PR patient still on, and then seems that all the other PR patients are already off. Can you share with us those patients already off the drugs? What is the median -- what is the, like, average duration of response?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

Average duration of response would probably be 2 to 4 months. I'd have to do the math. I'm just looking at the days, same as you are. I do want to note, though, that 2 of the patients who came off with PRs did not have progressive disease at the time that they came off of the study. So we actually, again, have very small numbers and can't, at this time, I think, accurately represent the median duration of PR. There were 2 patients who were taken off because of physician decision. One patient, I think, lived far away from the clinic. And I don't really know the other reason why the patient came off. So I think that does change how you interpret those data.

Gena Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Okay. And then another question is going to the gastric cancer. You comment that in the late-stage HER2 high, wanted to do monotherapy. I'm wondering, have you thought about a competitive arm -- control arm, active control arm? And then, what kind of a -- the active profile you have in mind that make you feel confident that monotherapy will work -- will show superiority?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

Sure. So I think it depends on which line of therapy you're talking about. Certainly, in patients who progressed, and again, of use of pembrolizumab label also, I acknowledge it's a different type of drug. I mean, that -- those -- that was basically approved based on a single-agent uncontrolled study out in patients who had progressed after 2 prior lines of therapy. And so I would imagine that if we took ZW25 into a similar third-line setting, that the control arm is really either no control arm or best supportive care. Of course, we have to confirm that with regulatory agencies. In a second-line trial, we would most likely have an active comparator arm that would be most likely chemotherapy alone because there is no approved HER2-targeted agent after trastuzumab.

Gena Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Okay. Maybe just ask one more questions. So the third line, gastric, if it's -- whatever standard of care, what will be the, say, overall response and the duration of response? And then for the second line, what will be also the comparator arms, like you think that, that will be also in terms of overall response and the duration of response?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So again, I'll start with third line. I think the response rates are less than 15%. Again, pembrolizumab was approved -- conditional response on a response rate of 13.3%. The response rates in second line are also low. I think the most important number there, if you look at the recent GATSBY trial in HER2-high-expressing patients, the median progression-free survival for -- actually both arms, it was a negative study. It was less than 3 months. So that's, I think, the bar that we would be potentially benchmarking. Though, of course, we'll be working again with regulators and experts in that disease area.

Operator

(Operator Instructions) The next question is from the line of Arlinda Lee with Canaccord.

Arlinda Anna Lee - *Canaccord Genuity Limited, Research Division - Analyst*

Congratulations on the data. Can you -- I was curious about the HER2-negative patients, if you wouldn't mind providing additional color on that patient. And as well, given the focus on tumor-agnostic drug approvals as with ASCO, I'm wondering if you could provide any thoughts on that.

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

Sure. So with regard to the patients who had HER2-negative tumor biopsy, this is a patient who actually previously was known to be HER2 high based on earlier biopsy result. She'd been treated with several lines of prior HER2-targeted therapy, including T-DM1, and she'd had a response on T-DM1 for over a year. At the time of -- she came on study, we are trying to get new biopsies on patients and this is a really good example as to why. She had progressive disease. She -- her target lesions were only in her liver. Her biopsy was from a liver lesion. And again, that was reviewed at a central lab, actually at USC by Dr. Mike Press, who literally writes the papers on HER2 testing. And she was completely HER2-negative, IHC 0, FISH negative. And not unexpectedly, this patient progressed, and actually, her progression was new lesions in her liver. Yes. Sorry. And then with regard to tumor-agnostic approach, I think that's something that we're keeping in mind. It's one of the reasons we're very excited about our basket cohort and by the activity that we're seeing in the patients who are being treated in this cohort and particularly in those who've even had prior HER2-targeted therapies. And we are trying to get new biopsies at the time of study entry in all of these patients to help support that tumor-agnostic approach.

Operator

The next question is from the line of David Novak with Raymond James.

David Novak - *Raymond James Ltd., Research Division - MD & Healthcare Research Analyst*

I had a couple of more questions here. So just looking at the waterfall plot, it begs the question, looking for it, how do you start think about stratifying responders versus nonresponders? Are you currently collecting screening data from the case, for example, PTEN, BRCA, BRAF? What are you thinking about in that respect?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So I think that's a great question. And to answer that, we are starting to collect data, not only in those patients where we get new biopsies, but also collecting circulating tumor DNA. So it's, I think, early for us to be presenting that, but we are actively looking at that data and we certainly hope to build up a sufficient data set and report that in the future. And we will use those data to guide development in the future, too.

David Novak - *Raymond James Ltd., Research Division - MD & Healthcare Research Analyst*

Okay, great. And moving on to gastric. Looking at this intermediate response, I always find intermediate expressors to be a difficult concept. For example, is this on the low range of HER2 high? Is it on the high range of HER2 low? How should I be thinking about this particular patient? And more importantly, would HER2 expression be uniform across the tumor cells?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So I think -- again, another very good question. So I think, for gastric cancer, I think that's, in particular, HER2 expression is quite heterogeneous, which I think may in part be why prior trials have not been successful in later lines of treatment. So just to focus on this patient. When we say HER2 intermediate, that means they are not -- at least the sample that we looked at or had evaluated was non-gene amplified, so it was just expressing HER2 just on the surface of the protein. For this particular patient, they had actually a borderline positive call previously on an older biopsy that we were not able to obtain for review. They were treated with prior HER2-targeted therapy, although it was always in the context of chemotherapy, so it's hard to know whether the chemotherapy or the HER2-targeted agent was contributing. And this patient had a new biopsy, again, right before they came on study, reviewed by Dr. Mike Press at USC. There was 2 plus -- IHC2+ protein expression on the surface, but again, FISH negative, no gene amplification. And this patient did have a very robust response and is active on study -- or was active on study at the time of data cutoff.

David Novak - *Raymond James Ltd., Research Division - MD & Healthcare Research Analyst*

Got you. So when you say HER2 expression is more heterogeneous in the gastric population, I mean, is there any sort of redirect could make here into other indications? For example, in breast cancer, is it perhaps more homogenous? Or how do I think about other cancer indications? And is there any read-through or is it kind of too early to make that sort of assessment?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So I think, historically, breast cancer has had more homogeneous HER2 expressions. Certainly, at the time of diagnosis, I think it's harder to say in this later-stage patient population, where actually changes in HER2 -- expression levels of HER2 is a resistance mechanism to the approved HER2-targeted agents. And in other cancers, again, there is reportedly more heterogeneity and that is something, as we collect new tumor biopsies, we'll also be looking at.

David Novak - *Raymond James Ltd., Research Division - MD & Healthcare Research Analyst*

Got it. And just 2 more. So thinking on the -- about the current treatment paradigm. In ZW25, we have what is undeniably a safe, chemo-free-targeted therapeutic option, which is showing very compelling activity in heavily pretreated patients. When do we start thinking about using this as a -- in a [NeoLAB] setting?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So I think that's something that we are actively thinking about and that hopefully will be something that in future updates we can talk about.

David Novak - *Raymond James Ltd., Research Division - MD & Healthcare Research Analyst*

Okay. And then just lastly, how do you think about ZW25's unique mechanism of action? How do you think that will impact the pathologic response of adding a chemo? I mean, presumably, 25 is the ideal asset to leverage HER2 addiction. Am I thinking about this correctly?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

That's how we think about it.

David Novak - *Raymond James Ltd., Research Division - MD & Healthcare Research Analyst*

Perfect. So you'd expect sort of a more synergistic effect with 25 plus chemo, then just tras plus chemo or even tras plus pert plus chemo?

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

Yes, David. This is Ali. If you think about that comments that Dr. [Sulaiman] made at our presentation, the one comment that he brought out was that ZW25 appears to have a novel mechanism of action. So we're aligned with this thinking. We've always been aligned with this thinking. And we've always said that in this case, 1 plus 1 equals 5. We really believe this is more than just binding to the same location that trastuzumab binds to and pertuzumab binds to. We really like the fact that our antibody has increased clustering, has a unique geometrical binding property when it comes to HER2 where one side of the antibody binds to one location on one HER2 and the other side of antibody binds to a different location on a different HER2. So there is a lot going on here than just simply dock and block. And we are very much in favor of what this could do on a very meaningful level when certain chemo agents are added or certain other anticancer agents are added where you can take a metastatic patient and really reverse the course of their cancer. We are really focused on the bigger picture and really focused on a bigger picture treatment paradigm as opposed to a quick fix.

Operator

The next question is from Rahul Sarugaser of Paradigm Capital.

Rahul Sarugaser - *Paradigm Capital Inc., Research Division - Analyst of Healthcare and Biotechnology*

Can you hear me okay?

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

Yes.

Rahul Sarugaser - *Paradigm Capital Inc., Research Division - Analyst of Healthcare and Biotechnology*

Great. So on HER2 Herceptin's response rate of 9% in Stage II study, as you know, that rate essentially doubled as it was combined with chemotherapy. So you may have begun to address this when you're talking about the heterogeneity in HER2 gastric patients. But have you progress towards a registration study? Could you please clarify specifically why you're prioritizing monotherapy versus combo with chemo? And that's my only question.

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So I'm sorry, you're referring to gastric cancer?

Rahul Sarugaser - *Paradigm Capital Inc., Research Division - Analyst of Healthcare and Biotechnology*

Correct.

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

Yes. So I think we would want to take a multitiered strategy to the development of ZW25 in any particular indication. I think we're thinking of monotherapy, in part because it's certainly -- we're seeing evidence that it seems to be active and well tolerated and that may represent the fastest path to a marketing approval. That's not to say that we're not going to also be concurrently looking at combinations with chemotherapy, particularly for earlier lines of therapy. And certainly, we're starting to do that with our chemotherapy combinations in our current trial, and we've also said that we are planning to start new trials later this year.

Operator

Our next question is from the line of Gena Wang with Barclays.

Gena Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Just very quick question. Just wondering, what percentage of response you reported or confirmed?

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So if you look -- I don't think we've given that exact number. No, obviously, if a patient's been on study for more than 2 cycles or after they had a confirmed -- or after they have a PR, they're still deriving clinical benefits.

Gena Wang - *Barclays Bank PLC, Research Division - Research Analyst*

So what I meant was confirmed response, like, independent assessment.

Diana F. Hausman - *Zymeworks Inc. - Chief Medical Officer*

So we have not done independent reviews of our radiologic scans. These are all based on investigator assessments.

Operator

This concludes the question-and-answer session. I would like to turn the conference back over to Dr. Ali Tehrani for any closing remarks.

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

Thank you. Thank you, everyone. At Zymeworks, we're making significant progress in the development of novel multifunctional therapeutics to achieve our vision of delivering innovative therapies to patients. This is an exciting time for our company as we determine the next steps to get this potential new medicine to patients as quickly as possible. We thank you for your attention, and we thank you for joining our call today. Have a wonderful day.

Operator

This concludes today's conference call. You may disconnect your lines. Thank you for participating, and have a pleasant day.