Zymeworks' (ZYME) HERIZON-BTC-01 Phase II Trial Results Likely to Indicate Future Approval

Summary

- ZYME's indication for zanidatamab as second-line treatment of HER2-expressing biliary tract cancer (BTC) saw promising phase II topline results with full data to be announced at medical conference in 2023, potentially on June 2-6.
- Zanidatamab for BTC is more safe and potentially more efficacious than pre-existing and other clinical second-line treatments.
- ZYME can follow Taiho Oncology in seeking accelerated approval following phase II results.
- Zanidatamab is very likely to be approved as a second line treatment for HER2-positive metastatic BTC.

ZYME expected to release full data from pivotal phase II clinical trial at upcoming 2023 medical conference

ZYME is a clinical-stage biotechnology company that develops multifunctional therapeutics. Zanidatamab, ZYME's first and lead clinical candidate from their multifunctional drug development platform, is currently in four pivotal stage clinical trials. The four indications are biliary tract cancers (BTC), gastroesophageal adenocarcinomas, gastrointestinal cancers, and breast cancer, with indication for BTC nearing the end of phase II trials.

Biliary tract cancers, including gallbladder cancer and bile duct cancer, are relatively rare but aggressive cancers with 20,000 patients diagnosed per year in the US alone [1,2] and 5-year survival rates for gallbladder cancer and bile duct cancer are at 19% and 10%, respectively [3,4]. In most cases, BTC is diagnosed in later stages when the disease is inoperable [5]. The current standard-of-care for first-line treatment, durvalumab with gemcitabine and cisplatin, is modest at controlling the disease with a 12.8 month (95% CI, 11.1-14.0) overall survival (OS), and 26.7% (95% CI, 22%-32%) overall response rate (ORR) [6].

ZYME is developing a new treatment option for patients that experience disease progression following first line treatment containing gemcitabine. In 4-6% of BTC, the human epidermal growth factor 2 (HER2) is overexpressed, making HER2 a promising target for BTC treatment [7]. ZYME has developed zanidatamab, a bispecific antibody targeting two epitopes of HER2, for treating advanced, HER2-expressing cancers. In recent phase 2 topline data, zanidatamab achieved a 41.3% (95% CI, 30.4%-52.8%) ORR with a 12.9 month (95% CI, 5.95-not reached) median duration of response [8]. Full results from the pivotal trial are expected to be released at a medical conference this year. Based on past conference attendance, the release may be made at the American Society of Clinical Oncology annual meeting dated for June 2-6.

Zanidatamab is more efficacious in treating HER2-expressing BTC than other second-line treatments

The current standard of care for BTC is durvalumab, an antibody that inhibits PD-L1, in combination with gemcitabine and cisplatine, a chemotherapy regimen [9, 10]. For those that experience disease progression, second-line treatments typically include additional chemotherapy regimens [11]. Recently,

however, targeted therapies for BTC were approved and clinical outcomes for these therapies are included below in Table 1.

Table 1 summarizes the treatment endpoints for both clinical stage and approved second-line treatments as well as targeted and non-targeted therapies. To compare zanidatamab against non-targeted therapies, we compare zanidatamab against FOLFOX. For patients treated with FOLFOX (folinic acid, fluorouracil, and oxaliplatin), a chemotherapy regimen, the median OS is 6.2 months (95% CI, 5.4-7.6), the 6-month OS is 50.6% (95% CI, 39.3-60.9), the 12-month OS is 25.9% (95% CI, 17.0-35.8), and the ORR is 5%. While OS is not yet reported for zanidatamab, we do know the ORR is 41.3% (95% CI, 30.4-52.8) and the median duration of response is 12.9 months (95% CI, 5.95-not evaluable). Given that the median duration of response is more than twice the median OS for second-line chemotherapy, we can expect zanidatamab to improve patients' OS over additional chemotherapy.

Zanidatamab is the most promising HER2-targeted therapy for BTC in clinical stage development and there are no approved HER2-targeted therapies for BTC. While zanidatamab, futibatinib, ivosidenib are not necessarily comparable as each target different antigens, it is still worthwhile to compare zanidatamab against futibatinib, since futibatinib achieved accelerated approval following phase II results. The phase II results for futibatinib saw an ORR of 42% (95% CI, 32-52) and a median duration of response of 9.7 months (95% CI, 7.6-17.1). Because the phase II results for futibatinib are similar to zanidatamab, zanidatamab may be able to seek accelerated approval. That said, the most important consideration is whether patients with HER2-expressing BTC are better treated with zanidatamab over all other therapies. Comparing zanidatamab against FOLFOX, that appears to be the case: the ORR for zanidatamab is 41.3% while that for FOLFOX is 5%, and the median duration of response for zanidatamab, 12.9 months, is more than twice the median OS for FOLFOX, 6.2 months. Furthermore, zanidatamab is much safer than FOLFOX with only 2% of patients on zanidatamab experiencing grade 3+ adverse events while 69% of patients on FOLFOX experienced grade 3+ adverse events.

Table 1: Comparison of zanidatamab against other second-line treatments for metastatic BTC.

	Zanidatamab (n=80)	**FOLFOX (n=81)**	**Futibatinib (n=103)**	**Ivosidenib (n=169)**
Clinical/FDA Approved	clinical	clinical	approved	approved
Current Phase or Phase at Approval	2	3	2	3
ClinicalTrials.gov Identifier	NCT04466891	NCT01926236	NCT02052778	NCT02989857
Target	HER2 target	N/A	FGFR inhibitor	IDHI target
mOS		6.2 months (5.4-7.6)		10.3 months (7.8-12.4)
6-month OS		50.6% (39.3-60.9)		
12-month OS		25.9% (17.0-35.8)		

ORR	41.3% (30.4-52.8)	5% (2.2-9.7)	42% (32-52)	3.2% (0.9-8.1)
Median Duration of Response	12.9 months (5.95-NE)		9.7 months (7.6-17.1)	
mPFS		4.0 months (3.2-5.0)		2.7 months (1.6-3.6)
Grade 3+	2%	69%	30%	2%
Inclusion	- Received prior gemcitabine-containing chemo - HER2 positive	- Failed no more than one chemo (gemcitabine or cisplatin)	- iCCA and FGFR2 gene rearrangements (incl fusions) - Received prior gemcitabine and platinum-based chemotherapy - No prior FGFR inhibitor	- Documented IDH1 gene-mutated disease
Exclusion	- Received prior HER2 targeted therapy			- Received a prior IDH inhibitor

Preclinical data for zanidatamab shows increased binding to HER2-expressing cancers and anti-tumor activity

Zanidatamab is a bispecific antibody that targets two epitopes, ECD2 and ECD4, of HER2, which are the same individual domains targeted by monospecific pertuzumab (ECD2) and trastuzumab (ECD4), two antibodies approved for treating HER2 expressing cancers [12, 13]. In preclinical studies, Figures 1-4, zanidatamab was shown to have multiple mechanisms of actions, including increased antibody binding, receptor clustering, removal of HER2 from the cell surface, and potent effector function. In each figure, zanidatamab was compared to pertuzumab, trastuzumab, and a combination of pertuzumab and trastuzumab and in each case, zanidatamab either matched the combination of pertuzumab and trastuzumab or performed better.

The two most significant improvements over the monospecific antibodies are zanidatamab's greater binding and its ability to initiate cell death, both effects demonstrated in Figures 1 and 4, respectively. In Figure 1, zanidatamab binds to the HER2-overexpressing SK-BR-3 cell line, a breast cancer cell line, at the same rate as a combination of pertuzumab and trastuzumab while exhibiting increased binding compared to either monospecific antibody alone. The binding activity was measured using flow cytometry. In Figure 4, zanidatamab is shown to mediate potent complement dependent cytotoxicity (CDC) and inhibit tumor growth. In CDC assays of NCI-N87, a HER2-expressing human gastric carcinoma cell line, BT-474, a HER2-expressing ductal carcinoma cell line, and SK-BR-3, a HER2-expressing breast cancer cell line, zanidatamab mediates CDC, whereas, pertuzumab, trastuzumab, and a combination of pertuzumab and trastuzumab did not aside from the combination of pertuzumab and trastuzumab in

NCI-N87. At the same time, zanidatamab inhibits tumor growth and at a greater rate than either pertuzumab or trastuzumab alone and pertuzumab and trastuzumab in NCI-N87 and SK-BR-3.

The combination of these effects makes zanidatamab a promising candidate for treating HER2 overexpressing cancers, including BTC, gastroesophageal adenocarcinomas, gastrointestinal cancers, and breast cancer. Furthermore, these results are generally consistent with that found in a publication exploring anti-HER2 bispecific antibodies.[14]

Figure 1: Zanidatamab exhibits greater HER2 binding than either pertuzumab or trastuzumab alone. In a flow cytometry experiment of SK-BR-3, a human breast cancer cell line that overexpresses HER2, zanidatamab was found to bind at a similar rate to the combination of pertuzumab and trastuzumab while beating each individually.

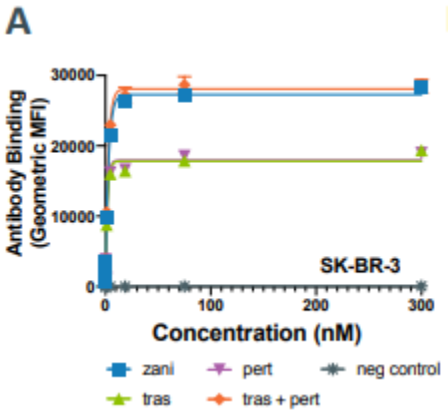


Figure 2: Zanidatamab acts as a linker between HER2 receptors, forming antibody:HER2 clusters. Analytical ultracentrifugation of equimolar antibody:HER2 mixtures indicate that zanidatamab can act as a linker between HER2 molecules to larger complex structures, such as clusters, as compared to pertuzumab and trastuzumab. Mixtures of (pertuzumab + trastuzumab):HER2 can also form antibody:HER2 clusters. On the horizontal axis is the sediment coefficient from analytical centrifugation where larger values indicate larger antibody:HER2 cluster sizes.

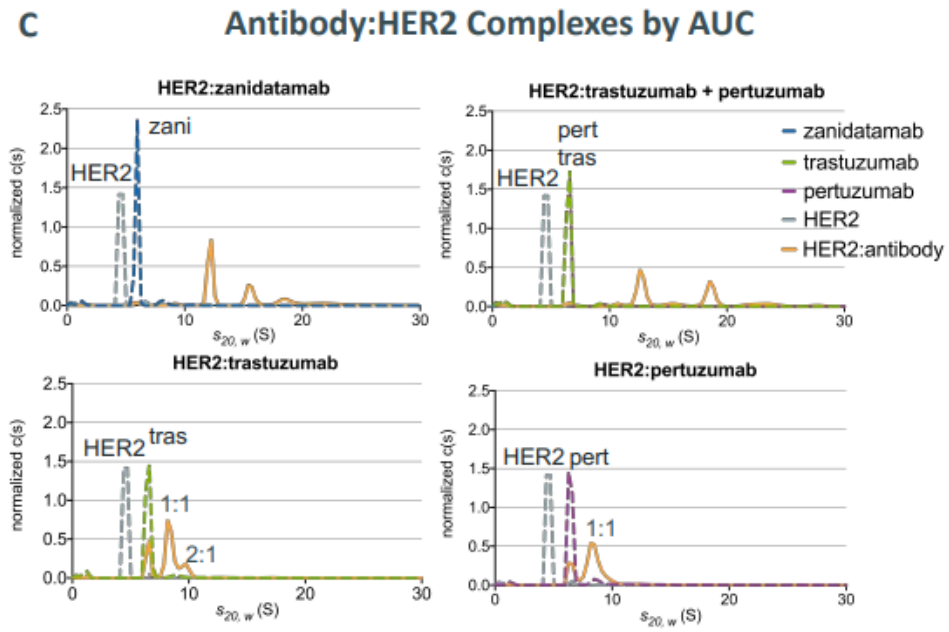


Figure 3: Zanidatamab depletes HER2 count at a greater rate than pertuzumab or trastuzumab alone. In western immunoblotting of SK-BR-3, zanidatamab was shown to have a greater effect of reducing HER2 (24 h) than either pertuzumab or trastuzumab alone.

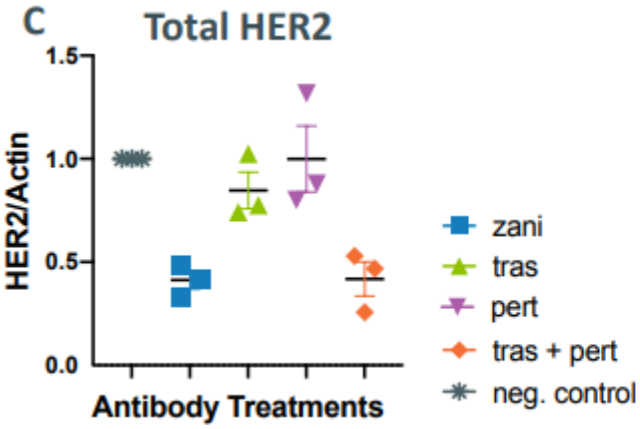
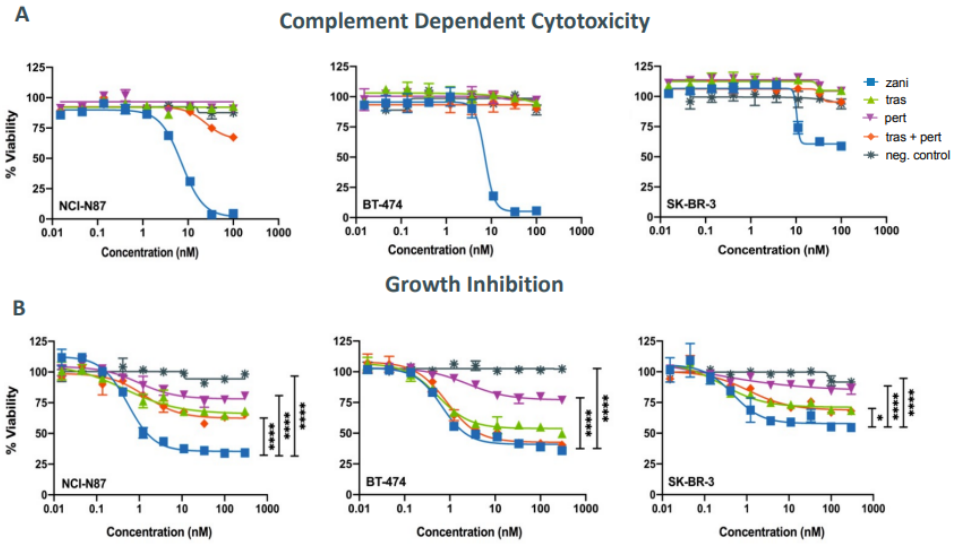


Figure 4: Zanidatamab is able to mediate potent CDC and inhibit tumor growth. In complement dependent cytotoxicity (CDC) assays of NCI-N87, a HER2-expressing human gastric carcinoma cell line, BT-474, a HER2-expressing ductal carcinoma cell line, and SK-BR-3, a HER2-expressing breast cancer cell line, zanidatamab was shown to mediate CDC, whereas, pertuzumab, trastuzumab, and pertuzumab + trastuzumab did not aside from pertuzumab + trastuzumab in NCI-N87. At the same time, zanidatamab inhibits tumor growth and at a greater rate than either pertuzumab or trastuzumab alone and pertuzumab + trastuzumab in NCI-N87 and SK-BR-3.



Phase I and II outcomes suggest zanidatamab can be a powerful second-line treatment for HER2-expressing BTC. Zanidatamab received breakthrough therapy designation for patients with previously treated HER2-amplified biliary tract cancer

Phase I trials tested patients with HER2-expressing cancers for response and safety to zanidatamab. The study was separated into three parts where the objective of part 1 is to identify the recommended dose of zanidatamab, the objective of part 2 is to evaluate the safety and tolerability of zanidatamab as a monotherapy, and the objective of part 3 is to evaluate the use of zanidatamab in combination with chemotherapy and is ongoing.

In part 1 (n=46), no dose-limiting toxicities were detected, and the maximum tolerated dose was not reached. Of the adverse events observed in part 1, diarrhea was the most common at 52%, very few grade 3 events were observed (rate of 2%) and no grade 4 or 5 events were observed.

For part 2, the recommended dose was 20 mg/kg every 2 weeks. For patients with BTC, zanidatamab achieved 38% (95% CI, 18%-62%) objective response, also ORR, and 3.5 month (95% CI, 1.8-6.7) PFS. Patients treated for colorectal cancers (n=26) and other HER2-expressing cancers excluding gastroesophageal and breast cancers (n=36) saw similar ORR to those treated for BTC. Patients enrolled in phase I trials either did or did not receive prior HER2-targeted therapies. Following phase I results, zanidatamab received breakthrough therapy designation for patients with previously treated HER2-amplified biliary tract cancer.

Phase II trial tests zanidatamab as a second-line monotherapy for BTC. Topline data for phase II trials was recently announced on December 19, 2022. 80 patients were enrolled and evaluable with inclusion criteria of HER2-overexpressing (IHC 2+ or 3+) BTC, must have had at least 1 prior gemcitabine-containing chemotherapy regimen, and must not have received a prior HER2-targeted treatment. The confirmed ORR is 41.3% (95% CI, 30.4-52.8) with a median duration of response of 12.9 months (95% CI, 5.95-not reached). The adverse events and safety profile is consistent with what was observed in phase I trials. The increase in ORR and duration of response is likely due to excluding patients that received a prior HER2-targeted treatment. The ORR and duration of response suggest that zanidatamab is a powerful second-line treatment for BTC, especially when compared to other second-line treatments.

The full data will likely be released at a medical conference sometime this year at a medical conference. Given past conference attendance patterns, the announcement may be made at the American Society of Clinical Oncology annual meeting dated for June 2-6. Investors can expect to see additional secondary endpoint data, such as the progression free survival, when the full data will be released, but the primary endpoint, the ORR, is already met.

Taiho Oncology achieved FDA approval for futibatinib following phase II results and ZYME may be able to do the same

Futibatinib was granted accelerated approved as a treatment for metastatic intrahepatic cholangiocarcinoma, a form of BTC, harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements on September 30, 2022.[15] The approval was granted based on ORR and duration of response from phase II results, summarized in Table 1.

Like zanidatamab, futibatinib was granted breakthrough therapy designation. Comparing phase II results of zanidatamab and futibatinib in Table 1, zanidatamab has a similar ORR and greater duration of response, and unlike futibatinib, zanidatamab targets HER2, providing patients with HER2-expressing BTC a strong treatment option.

Because there are no approved HER2-targeted therapies for BTC and because zanidatamab potentially provides greater clinical outcomes (studies are not old enough for OS to be reported) over non-targeted therapies, zanidatamab is likely to be approved. Furthermore, there is precedence with futibatinib for ZYME to seek accelerated approval for zanidatamab following the phase II results.

ZYME raises substantial funding from partnership with Jazz Pharmaceuticals

Following the success of the topline phase II results, ZYME advanced its partnership with Jazz Pharmaceuticals for exclusive rights to develop and commercialize zanidatamab in the US, Europe, Japan and all other territories except for Asia/Pacific territories. The terms of the partnership include a $325 million payment to ZYME in Q4 2022 on top of a prior $50 million in October 2022, a $525 million payment upon reaching certain regulatory milestones, a $862.5 million payment in potential commercial milestone payments, and an additional 10% - 20% royalty fees, summing up to total potential payments of $1.76 billion plus royalty fees.

Conclusion

I think that zanidatamab will be approved as a second-line treatment for HER2-expressing BTC. This conclusion is based on the following two points.

1) Zanidatamab is a well-designed bispecific antibody that is shown to have high binding to HER2 and is able to initiate cell death in cancer cells. The antitumor effect of zanidatamab is confirmed in phase I and phase II clinical trials.
2) Zanidatamab displays greater efficacy than both approved and clinical trial second-line treatments for HER2-expressing BTC. Because zanidatamab is likely to be the best second-line treatment for HER2-expressing BTC, I think that zanidatamab will be approved. Furthermore, it is worth mentioning that futibatinib, a FGFR inhibitor, was also recently approved as a second-line treatment and given the similar phase II clinical results, ZYME can look to Taiho Oncology and futibatinib for seeking accelerated approval for zanidatamab.

3) We think the full dataset will look like X/ and that the OS will be between Z and Y

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