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Zymeworks investors wake up to competition

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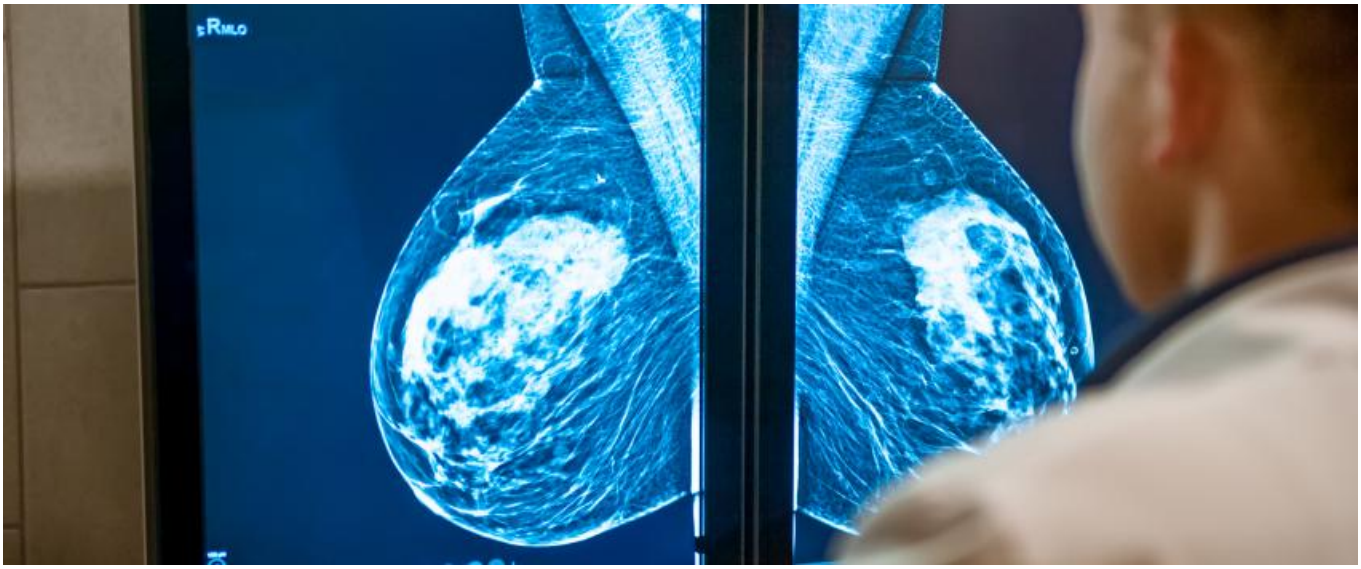

With mounting competition in Her2-directed breast cancer treatment, Zymeworks' latecomer struggles to show that it's better.

At a time when the Her2-positive breast cancer space is celebrating the approval of not one but four new drugs in the past year, any future rival had better differentiate itself. And this is what Zymeworks failed to do yesterday in a convoluted update on its contender ZW49.

To be clear, ZW49 is not Zymeworks' lead; that honour belongs to another Her2-directed asset, zanidatamab, a bispecific the group reckons could displace Roche's Herceptin and Perjeta in the front-line setting. But with so much uncertainty around both assets Zymeworks' stock cooled off 25% overnight.

Zanidatamab is still some way from the market in breast cancer, and its more likely initial use is biliary tract cancer, with filing expected next year. As such, the update of a phase I study of ZW49, an anti-Her2 antibody-drug conjugate, in various tumours was a big focal point for analysts.

Two remissions... and tox

The upshot of yesterday's after-market update, which Stifel analysts described as messy and confusing, was that six subjects in phase I dose escalation are evaluable for efficacy, and two of these have reported partial remissions. While this concerned several Her2-positive tumours, the company did not split these out.

It is likely that more mature data, expected in the second half, will be needed to quantify how competitive ZW49's efficacy is, but Pfizer's rival developmental anti-Her2 ADC, PF-06804103, has yielded a 39% ORR, for example.

Perhaps more concerning was Zymeworks' disclosure of keratitis as an adverse event, though this does not appear to be as serious as the ocular toxicity that led to a boxed warning on the label of Glaxosmithkline's Blenrep. But as keratitis is known to be associated with other ADCs it could make differentiation harder still for ZW49.

The next stage is to progress with three expansion cohorts, which comprise Her2-high breast cancer, Her2-high gastroesophageal adenocarcinoma, and other Her2-positive cancers.

While breast cancer clearly is not the only opportunity it is the most important one. Around 15% of breast and gastric cancers alike are thought to be Her2-high, but Her2-low tumours account for two thirds of the former versus just a quarter of the latter cancer type. Zymeworks argues that current front-line treatments largely cannot address Her2-low patients, but that its more sophisticated Her2-targeting projects can.

Still, Her2-positive breast cancer also happens to have the most competition. Roche has a stranglehold on perioperative, first and second-line settings, and there are four second/third-line Her2-directed newcomers: Puma's Nerlynx, which also hits Her4 and EGFR, Seagen's Tukysa, Macrogenics' Margenza and, most importantly, Astrazeneca/Daiichi's Enhertu.

Selected treatments and projects for Her2-positive breast cancer			
Name	**Modality**	**Company**	**Status**
Herceptin	MAb	Roche (and biosimilars)	Approved neoadjuvant, adjuvant & 1st-line
Perjeta	MAb	Roche	Approved neoadjuvant, adjuvant & 1st-line
Nerlynx	Small molecule	Puma	Approved extended adjuvant & 3rd-line
Kadcyla	ADC	Roche	Approved 2nd-line
Tukysa	Small molecule	Seagen	Approved 2nd-line + Herceptin
Tykerb	Small molecule	Novartis	Approved 3rd-line
Margenza	Fc-optimised MAb	Macrogenics	Approved 3rd-line
Enhertu	ADC	Astrazeneca/Daiichi	Approved 3rd-line
Zanidatamab	Dual epitope bispecific	Zymeworks/Beigene	40% ORR in BTC (n=20), 39% ORR in GEA (n=33)
ZW49	ADC	Zymeworks/Beigene	33% ORR in various cancers (n=6)
PF-06804103	ADC	Pfizer	39% ORR in various cancers (n=31)
PRS-343	Bispecific	Pieris	12% ORR in various cancers (n=33); on clinical hold until 19 Jan
ADC=antibody-drug conjugate; BTC=biliary tract cancer; GEA=gastroesophageal adenocarcinoma. Source: product labels & meeting presentations.			

Meanwhile, Zymeworks' lead asset, zanidatamab, a bispecific hitting two different Her2 epitopes, also has its work cut out.

Pivotal biliary tract and gastroesophageal cancer trials read out in 2022 and 2023 respectively, but in breast cancer it is still early days, with mid-stage studies comprising an Ibrance combination in ER-positive patients and a front-line chemo combo.

The latter might give clues as to how zanidatamab might square up first-line against Herceptin or Perjeta, but as neither Roche drug is available in this trial, which is being run in South Korea and Taiwan, this seems to have little relevance to lucrative western markets.

It is admirable for Zymeworks to aim to displace Herceptin and Perjeta as the foundation of Her2-positive breast cancer treatment, but before it can run it must first learn to walk.