Evaluate Vantage

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Surprise! Macrogenics could have a commercially viable drug

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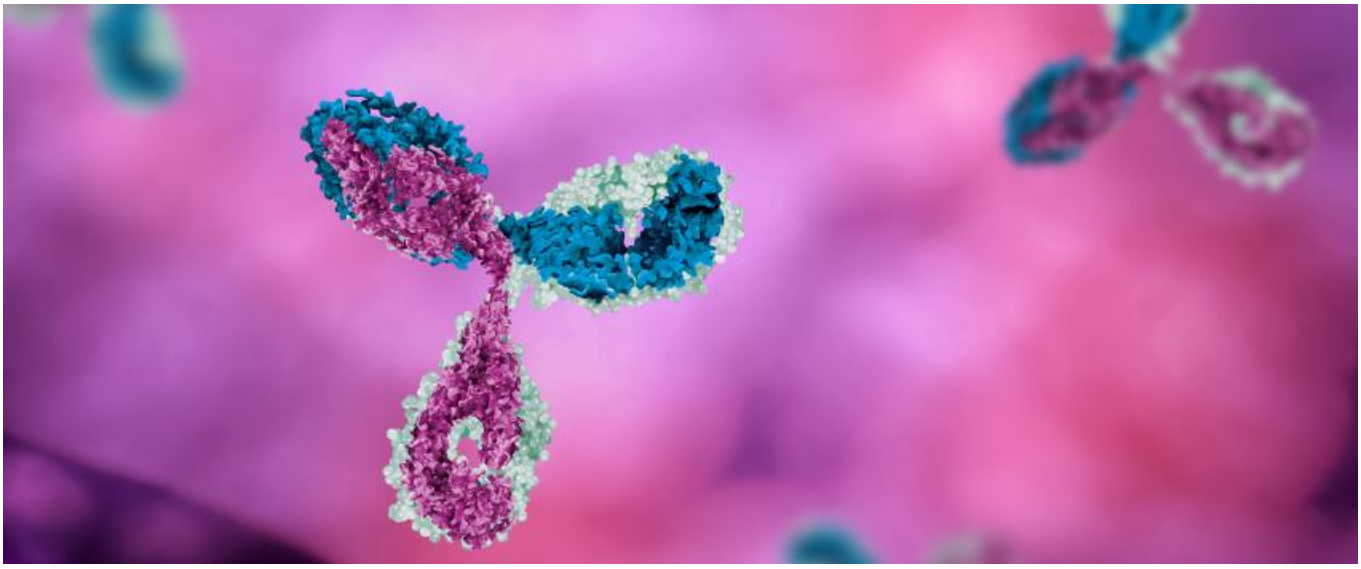

Positive progression-free survival results in breast cancer for the company's lead asset, margetuximab, take the markets by surprise.

The 24% reduction in risk of progression in a trial of Macrogenics' margetuximab might not seem like much, but this morning's 140% surge in the company's stock shows just how low expectations had been.

The phase III Sophia study, testing the Fc-optimised anti-Her2 MAb in breast cancer patients who had progressed on at least two Her2-directed therapies, had been seen as a likely failure, which had put pressure on the stock. As it stands, however, Macrogenics suddenly has an asset with a decent chance of becoming its first commercialised drug.

For now the group is not revealing much beyond Sophia's PFS hazard ratio and p value (0.033), but says the data could be enough to allow margetuximab to be filed for US approval in the second half of the year. Importantly, this would be before the trial's overall survival co-primary endpoint matures.

Turnaround

The success marks a sudden turnaround in Macrogenics' fortunes; the group's stock had lost two thirds of its value over the past year as its anti-B7-H3 bispecific MGD009 was put on clinical hold and several competing bispecifics faced investor scepticism.

Today's share price lift-off partly reflects short positions being covered. Fund managers can hardly be blamed for having shorted Sophia's readout, as the odds were stacked against Macrogenics: Sophia's 530 Her2-positive breast cancer subjects had all failed Roche's standard treatments, Herceptin and Perjeta, and most had also failed Kadcyla.

Macrogenics' argument now is that, through optimisation of the antibody's Fc region, it has designed a better Herceptin. On a call today the company reminded investors that the same Fc optimisation technology was used in its next-furthest advanced asset, the anti-B7-H3 MAb enoblituzumab.

The company also stressed that Sophia's result was driven by patients who carried the CD16A/158F allele, a genetic variant that promotes binding with Fc-optimised MAbs like margetuximab. In the 85% of Sophia subjects who were homozygous or heterozygous for this allele the risk of progression on margetuximab was 32% lower than on Herceptin control (p=0.005).

Macrogenics said there was no approved diagnostic test for this genetic variant, and that in any case it would seek approval in the entire patient population.

Risks

There now remain several risks to the company’s investment case, the most obvious being that overall survival (OS) data fail to replicate the PFS success.

Management said OS was “trending” positively for margetuximab, but the required number of deaths to trigger analysis was far below the required 385, so filing would occur before that. The co-primary endpoints' statistical analysis is hierarchical, meaning that the OS benefit needs to clear nothing stricter than the standard p=0.05 threshold.

The regulator could be troubled by the data in non-carriers of the CD16A/158F allele, and it is even possible that these did worse on margetuximab than on Herceptin in Sophia. Beyond that, the absolute improvement in PFS might be tiny, the positive hazard ratio notwithstanding.

Either way, according to *EvaluatePharma* consensus the sellside expects margetuximab to bring in $268m in 2024 revenue, a forecast that has fallen 40% in the past few months. Stifel analysts today wrote that the Sophia readout could transform Macrogenics from an early-stage platform-focused story into one with tangible commercial prospects.

Investors keeping the faith must now believe that US filing will not depend on OS, and that Macrogenics really has discovered something big rather than simply having got ridiculously lucky. And Macrogenics must pray that the US FDA approves margetuximab before OS data read out.