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Reality bites for Macrogenics

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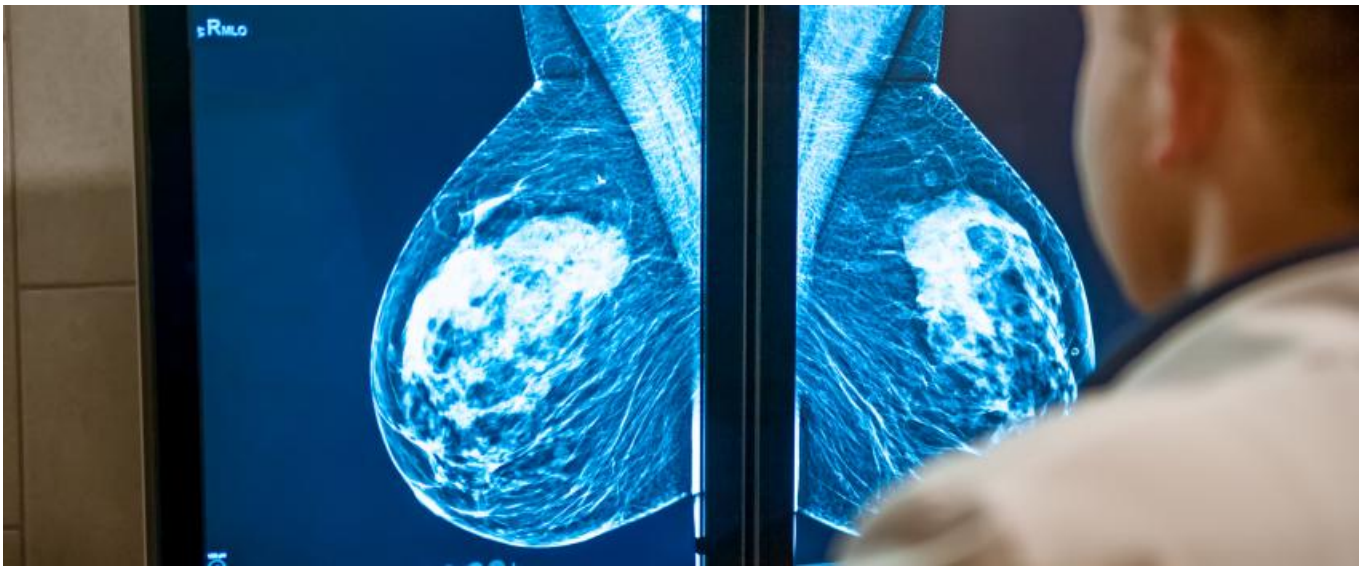


Hopes are fading for margetuximab in breast cancer, which looks unlikely to show an overall survival benefit in the Sophia study.

Investors who bought into Macrogenics' share sale in February are probably feeling pretty peeved. They have been left nursing losses in the wake of a slump in the company's stock yesterday, prompted by a disappointing Asco presentation of full data from the Sophia trial.

Shareholders must now cling to vanishing hopes that the study will ultimately show an overall survival benefit, something that looks highly doubtful given the survival curves Sophia has generated so far. Without this, the commercial prospects for margetuximab in this breast cancer setting look poor.

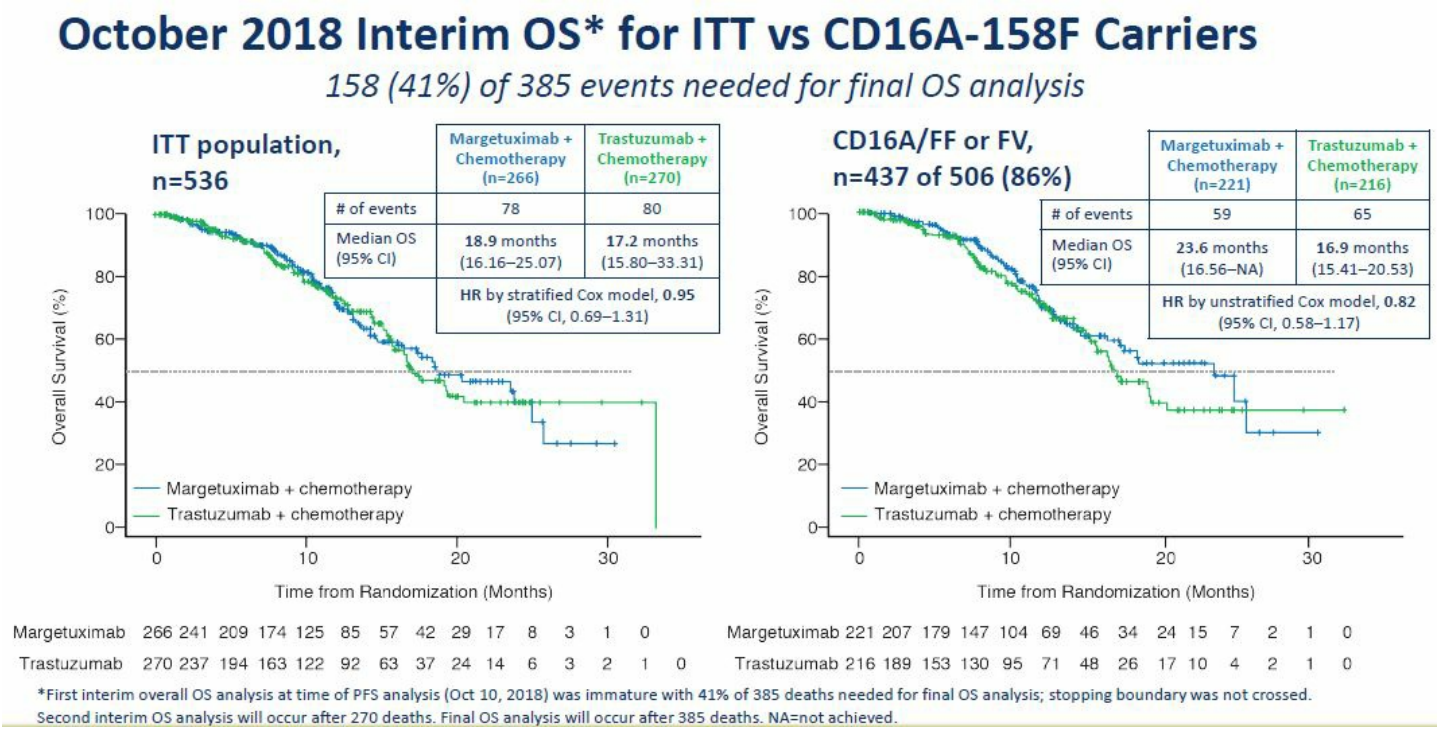
Macrogenics shares dropped 17% to $15.58 yesterday, well below the $20 a share at which the company managed to raise $119m in February. That cash call was launched after the company's stock more than doubled on a press release heralding a hit on progression-free survival for margetuximab in Sophia, a study that had been widely expected to fail (*Surprise! Macrogenics could have a commercially viable drug, February 6, 2019*).

The stock had dwindled to a record low of $11 before the topline Sophia data were released, and the fact that the shares remain above this level will be cold comfort for investors who participated in the fund raising. At the very least, the situation serves as a reminder of how nominally "positive" press releases often have a sting in the tail.

Unattractive curves

The sting in this case came in the form of survival curves; for overall survival this remains an interim look, with only 41% of events occurred so far. But the curves separated relatively late in the analysis and crossed several times; these signals were taken to mean that margetuximab will have a hard time ultimately showing a statistically significant benefit.

This is particularly true for the intent-to-treat population, although a subset of supposedly stronger responders also generated an unimpressive hazard ratio.



There are reasons why this picture could yet improve, Macrogenics executives and the principle investigator of the study argued on a conference call yesterday. A disproportionate contribution is still to come from the better responding CD16A/158F carriers, while T-cell responses take a while to evolve, they said.

But hopes are low and, because Macrogenics insists that it will file on the totality of the data, the performance of the ITT population remains crucial. Chief executive Scott Koenig told *Vantage* yesterday that he did not expect the FDA to approve margetuximab only in the CD16A/158F subset (*Asco 2019 - Macrogenics builds a case for margetuximab, June 5, 2019*).

Approval might be possible based on the hit on PFS, but the company's marketing team will have a considerably harder job if they are unable to boast an OS benefit. Analysts at Stifel took down sales estimates for margetuximab in response to the data; *EvaluatePharma's* sellside consensus sits at $243m in 2024.

A label restricting margetuximab to the high-responding subgroup could salvage something here, although this seems very unlikely, largely because the trial was not powered for a statistical analysis of these patients. Stratification by genotype was exploratory only, with no statistical power assigned.

It is entirely possible that regulators will question the validity of this biomarker in any case. As Asco, the Sophia presentation pointed out that while two retrospective studies have pointed to a role in Fcγ receptor genotype and response to Herceptin, two others found no association. It is thought that the CD16A 158F allele causes lower affinity Fcγ-receptors, which could explain why Herceptin is less effective in carriers.

The company claims that Sophia is the first prospective test of the hypothesis, but the regulator's opinion of the data has yet to be heard. A request for a confirmatory trial would surely be forthcoming for the company to be able to make any claim about subgroup responses, especially as Sophia strongly suggests that the minority of CD16A/158F wild-type subjects fared considerably worse on margetuximab.

Look elsewhere

With Sophia a disappointment, Macrogenics attempted to build a wider case for margetuximab yesterday, revealing new data in gastric cancer and ambitions to test the antibody in earlier breast cancer settings.

Discussions are ongoing with academic groups interested in testing neoadjuvant use of margetuximab. Any further investment by the company here will presumably depend on finding a partner with deeper pockets; should a survival benefit fail to emerge the chance of a deal will also dwindle. The looming prospect of Herceptin biosimilars could also be a major deterrent.

Meanwhile, plans to push forward in gastric cancer, in combination with checkpoint inhibitors, give margetuximab another shot on goal. The company unveiled plans for a phase II/III study called Mahogany yesterday, but results are unlikely to start emerging before the end of 2020.

Shares in the company fell another 5% today as the margetuximab bubble continued to deflate.

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