Evaluate Vantage

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Degrader battle sees Sanofi edged out for now

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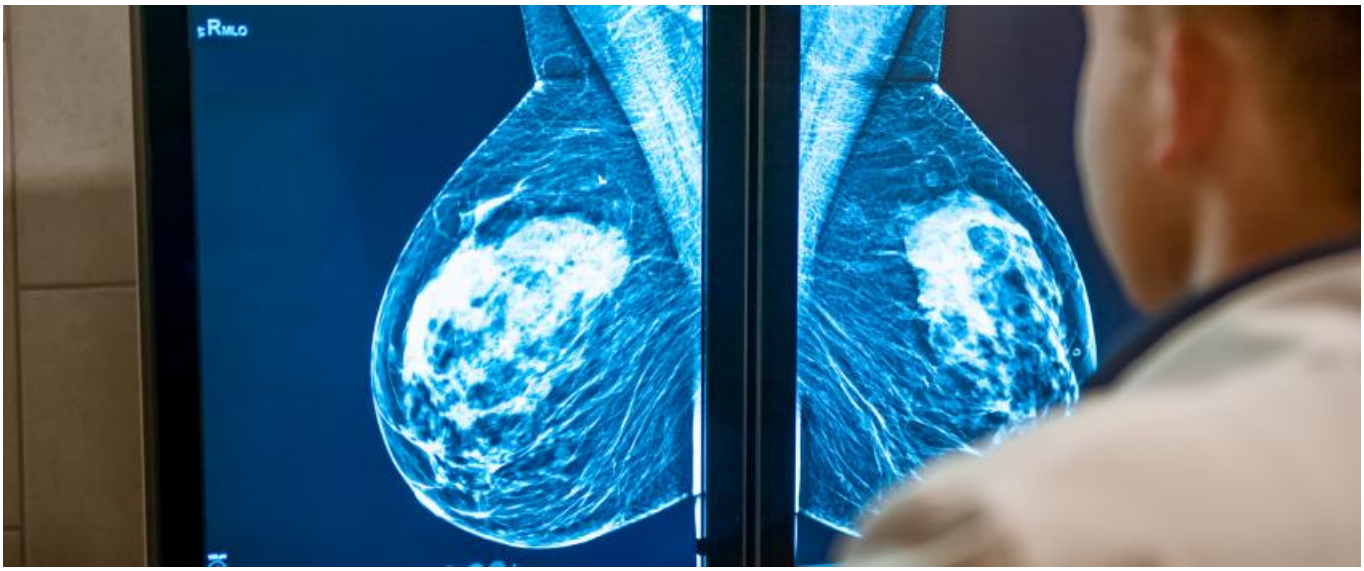

The French group was to have been first to report key Serd data this year, but has suffered delays as Roche and now Radius beat it to the punch.

Just as during yesterday's third-quarter call Roche trumpeted the profile of its Serd giredestrant as being best in class the news broke that Radius/Menarini's rival, elacestrant, had scored in a key phase 3 study.

This made elacestrant the first oral Serd, or selective oestrogen degrader, to hit in a pivotal trial, setting it up for regulatory breast cancer filings next year. This was an approach with which Sanofi's amcenestrant was to have had first-mover advantage, but after delays to the readout of its Ameera-3 study the French company's investors have been left waiting.

True, nothing is known about how convincingly elacestrant performed in the Emerald trial, toplined positive for its co-primary endpoints of progression-free survival versus physician's choice in all-comers as well as ESR1-mutant patients. For the full data investors in Radius, which ended yesterday up 16% after initially surging 40%, will have to check out December's San Antonio Breast Cancer Symposium.

ESR1 key

One obvious question is how important the ESR1 mutation is in this setting of second-line or later ER-positive, Her2-negative breast cancer. Radius's trial was notable for looking prospectively at the ESR1-mutant subgroup as a primary endpoint; ESR1 mutations are a known resistance mechanism to aromatase inhibitors, and 47% of Emerald's population was ESR1 mutant.

At SABCS investors will scrutinise the effect size, and will want to see how elacestrant performed against Faslodex, a first-generation injectable Serd, on one hand and against aromatase inhibitors on the other. Safety, which Radius said was comparable to earlier trials, is also important, since the project has been associated with gastrointestinal and liver toxicities.

All Emerald subjects had to have failed on CDK4/6 inhibitors, which have revolutionised ER-positive, Her2-negative breast cancer. This is important because Sanofi's Ameera-3 trial of amcenestrant allows up to 20% of enrolees to be CDK4/6-naive, which together with the order of therapy makes the outcome of this trial hard to call.

Another key issue is how amcenestrant does in ERS1 mutants – something Jefferies analysts reckon could be key to showing PFS superiority overall.

Ameera-3, whose readout has been delayed from the second to the third and now the fourth quarter of 2021,

will analyse PFS in ESR1 mutants as a secondary endpoint, the sole primary measure being in all-comers. Meanwhile, Roche's giredestrant has earlier shown activity in ESR1 mutants, but its Acelera study focuses on all-comers PFS.

Acelera is not due to read out until mid-2022, but in the meantime Roche has been playing up interim biomarker data presented at Esmo from the phase 2 Coopera trial, in the neoadjuvant setting. Yesterday Roche said giredestrant was seven to 15 times more potent than other Serds, causing immobilisation of the endocrine receptor before its degradation, making it "truly differentiated" and "potentially best in class".

Oral Serds in late-stage development for ER+ve/Her2-ve breast cancer				
Project	Elacestrant	Amcenestrant	Camizestrant	Giredestrant
Company	Radius Health/Menarini	Sanofi	Astrazeneca	Roche
Registrational study	Emerald	Ameera-3	Serena-2	Acelera
Setting	2nd line, postmenopausal	2nd line	2nd line, postmenopausal	2nd/3rd line, pre/peri/ postmenopausal
Comparator	Faslodex or aromatase inhibitor	Faslodex or aromatase inhibitor	Faslodex	Faslodex or aromatase inhibitor
Prior CDK4/6 use	Mandatory	Mandatory for <80%	Not mandatory	Not mandatory
Primary endpoint(s)	PFS in all-comers PFS in ESR1 mutants	PFS in all-comers	PFS in all-comers	PFS in all-comers
Data	Toplined positive 20 Oct 2021; full data at SABCS	Delayed to Q4 2021	Ends Nov 2021 (previously Mar 2022)	Ends Mar 2022
2026e sales ($m)	69	679	166	431
Source: Evaluate Pharma, Asco & company filings.				

Though it is still early days here, early uses – meaning perioperative and/or front-line settings – represent bigger markets than the second or third lines of the current pivotal readouts. Radius's elacestrant is the only one of the leading Serds not to be in a first-line study, though the academic-sponsored Elipse trial does test it preoperatively.

It looks like first-line Serd use is a three-way battle between amcenestrant, giredestrant and Astrazeneca's camizestrant. The last of these is in a second-line study, Serena-2, that is analogous to Roche's Acelera and will read out in a similar timeframe.

And biotech investors are also watching Arvinas and Olema. These two companies' ER degrader assets, ARV-471 and OP-1250 respectively, are both partnered with Pfizer, and updates from their phase 1 studies are keenly awaited.

Sanofi is still in the game, but the competition is closing in.