Evaluate Vantage

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SABCS 2021 – Mutant benefit makes Emerald sparkle

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Trial design comes into focus as late-stage readouts loom for Sanofi, Roche and Astrazeneca.

We already knew that Radius and Menarini's oral selective oestrogen degrader elacestrant had hit in its pivotal breast cancer trial. The question was whether this benefit was driven by a subgroup of patients, those with mutations in the ESR1 gene.

The answer is yes, although it is still unclear to what extent these patients were responsible for the overall benefit. However, it might not matter, with results from the Emerald trial looking strong enough to support approval in all comers. The focus now falls on other companies with late-stage oral Serds, Sanofi, Roche and Astrazeneca, which are set for pivotal readouts next year.

The trials of each of these agents are slightly different, raising questions about whether these projects will be able to replicate elacestrant's success.

Co-primary endpoints

All of these oral Serds are being developed in ER-positive, Her2-negative breast cancer, initially in second-line or later settings. ESR1 mutations are a common resistance mechanism to aromatase inhibitors, the backbone of therapy.

Radius looks canny for designing its study with co-primary endpoints of progression-free survival in all comers and in ESR1 mutants. Full data from Emerald, presented at the San Antonio Breast Cancer Symposium today, showed a 30% reduction in the risk of progression or death versus standard of care in all comers, rising to 45% in ESR1 mutants, who made up 48% of the trial's participants.

Both were statistically significant. As for the result in ESR1 wild-type patients, Dr Aditya Bardia of Massachusetts General Hospital told a press conference that these data were not yet available, but that this analysis would be carried out.

Data from the Emerald trial of elacestrant				
	All comers		**mESR1 patients**	
	Elacestrant	**SOC**	**Elacestrant**	**SOC**
Median PFS (months)	2.79	1.91	3.78	1.87
Hazard ratio	0.70		0.55	
p value	0.0018		0.0005	
Source: Dr Aditya Bardia & SABCS.				

As for adverse events, nausea looked the most problematic, being seen in 35% of elacestrant patients versus 19% of those on standard of care, which included the injectable Serd Faslodex and aromatase inhibitors. Rates of grade 3 or 4 nausea were low, however, at 2.5% and 0.9% in the elacestrant and control arms respectively.

Elacestrant now looks in line to become the first oral Serd to get the nod from the FDA. Regulators will have to weigh whether to plump for a broad label or to restrict approval to ESR1-mutated disease, with the testing burden that the latter would bring.

Serd pipeline

Still, the market could be about to get crowded, with a host of oral Serds in development including three approaching crunch time: Sanofi's amcenestrant, Roche's giredestrant and Astra's camizestrant.

The next to yield data should be amcenestrant, although Sanofi has missed its chance to lead the field; results from the Ameera-3 trial, now due late this year or early next, had originally been expected in the second quarter of this year.

None of these contenders' pivotal trials have PFS in ESR1 mutants as a co-primary; Ameera-3 and the Acelera study of giredestrant list this as a secondary endpoint, while the clinicaltrials.gov entry for camizestrant's Serena-2 trial does not mention ESR1 mutants at all.

Sanofi, for one, does not seem to think this will matter. During the group's third-quarter results call, its head of R&D, John Reed, said that amcenestrant was equally active against both the mutant and wild-type form of the oestrogen receptor, while elacestrant "seems to have a preference for the mutant form".

Meanwhile, Roche has boasted of the best-in-class potential of giredestrant.

Another difference between the trials is prior therapy: Emerald required patients to have received a CDK4/6 inhibitor such as Pfizer's Ibrance, while the giredestrant and camizestrant studies have no such requirement. In Ameera-3 20% of patients are allowed to be CDK4/6 inhibitor naïve.

In the coming months it should become apparent whether these differences in trial design will add up to differences in efficacy.

Oral Serds in late-stage development for ER+ve/Her2-ve breast cancer					
	Elacestrant	**Amcenestrant**	**Giredestrant**	**Camizestrant**	**LY3484356**
Company	Radius Health/Menarini	Sanofi	Roche	Astrazeneca	Lilly
Registrational study	Emerald	Ameera-3	Acelera	Serena-2	Ember-3
Setting	2nd line, postmenopausal	2nd line	2nd/3rd line, pre/peri/ postmenopausal	2nd line, postmenopausal	2nd line
Comparator	Faslodex or aromatase inhibitor	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	Not mandatory
Primary endpoint(s)	PFS in all-comers PFS in ESR1 mutants	PFS in all-comers (PFS in ESR1 mutants is secondary)	PFS in all-comers (PFS in ESR1 mutants is secondary)	PFS in all-comers	PFS in all-comers (PFS in ESR1 mutants is secondary)
Data	All comers 30% reduction; ESR1 mutants 55% reduction in risk of progression/death	Delayed to Q4 2021/Q1 2021	Data due mid-2022	Ends Sep 2022 (previously Mar 2022)	Ends Mar 2023

Source: Evaluate Pharma & clinicaltrials.gov.