Evaluate Vantage

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A blockbuster breast cancer niche has Roche and Sanofi in the lead

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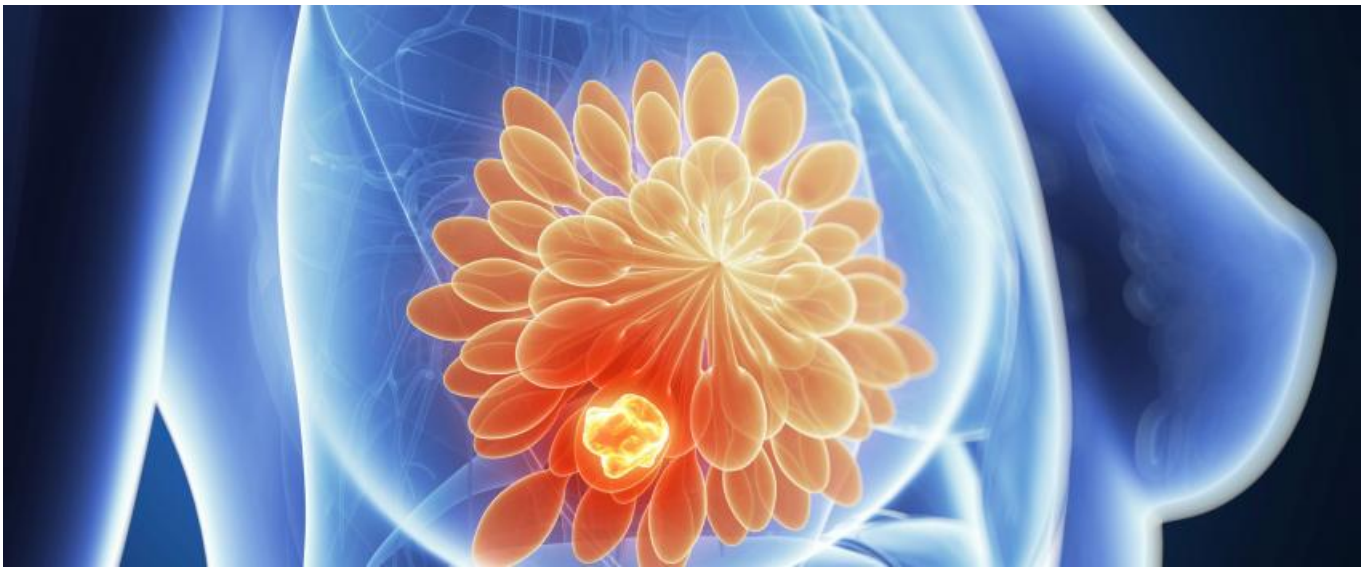

As SAR439859 and RG6171 move into pivotal testing, the Serd approach to treating one form of breast cancer generates renewed interest.

Recent moves by Sanofi and Roche to advance their respective selective oestrogen receptor degraders into pivotal testing has moved analysts to take a second look at this mechanism of action. And perhaps the boldest view was articulated yesterday by Jefferies, which called this “at least a $2-3bn market opportunity”.

This is quite the turnaround for a mechanism of action that, after Roche’s disastrous $725m takeover of Seragon, was set to make a somewhat mediocre addition to the breast cancer armamentarium. What has emboldened developers is the notion that an efficacious drug that is also orally bioavailable could be a real game-changer.

The selective oestrogen receptor degrader (Serd) story was actually begun by fulvestrant, which as Astrazeneca’s Faslodex was launched in 2002, and whose sales just breached the $1bn mark in 2018 – the last full year before its patent expired. It is thought that Faslodex’s poor bioavailability and intramuscular delivery held the drug back, spawning the search for an effective oral.

Her2-negative, ER-positive

The niche that these drugs target is breast cancer that is typically Her2-negative but is driven by oestrogen receptor signalling. Faslodex has a second-line label, after failure on aromatase inhibitors.

The theory is that binding to the oestrogen receptor can change its activity. A first generation of selective oestrogen receptor modulators included tamoxifen, but did not have a blanket effect on all receptor signalling; cue the Serds, which through degrading the receptor could eliminate it and its effects entirely.

Structurally Serds comprise a molecular scaffold to hit the receptor’s ligand-binding pocket, plus a long side chain, known as the “degron”, that causes the receptor’s degradation. Developers have been varying the makeup of both in pursuit of the ideal characteristics, though of course pivotal data will be the ultimate test, Jefferies cautions.

The mechanism was thrust into the spotlight most recently by Sanofi’s new chief executive naming his company’s offering, SAR439859, as one of the group’s top six growth drivers (*Sanofi’s new broom cleans house, December 10, 2019*). A second-line phase II trial could yield data by the end of this year, and allow filing

in 2021.

Roche, meanwhile, last month revealed that RG6171 was entering phase III. While this study has yet to be posted on clinicaltrials.gov, the Swiss firm says it will test the Serd first line, in combination with CDK inhibition.

Two earlier-generation Serds, which Roche acquired along with Seragon, were ditched some time ago, but the group reckons it has found the secret sauce with RG6171, which it calls a best-in-class oral asset with improved efficacy *in vivo* versus other Serds.

Serds in clinical development for ER+ve/Her2-ve breast cancer			
Project	**Company**	**Design**	**Detail**
Phase III			
Elacestrant	Radius Health	2nd-line, postmenopausal, vs SoC	Emerald trial to complete enrolment Q3 2020
RG6171	Roche	1st-line, postmenopausal, CDK combo	Starting imminently
Phase II			
SAR439859	Sanofi	2nd-line, postmenopausal, vs letrozole	Data possible end 2020
AZD9833	Astrazeneca	2nd-line, postmenopausal, vs Faslodex	Serena-2 trial
Phase I			
Rintodestrant	G1 Therapeutics	Postmenopausal	Ibrance combo phase II trial starting in 2020
ZN-c5	Pfizer/Zentalis	2nd-line, peri/postmenopausal, Ibrance combo	Data expected 2020
LSZ102	Novartis	2nd-line, single-agent or various combos	Data expected 2020
D-0502	Inventisbio	2nd-line, pre/postmenopausal, Ibrance combo	Data possible 2021
LY3484356	Lilly	2nd-line, single-agent or Verzenio combo	Study just begun
SHR9549	Jiangsu Hengrui Medicine	3rd-line, single-agent	Study just begun
Source: EvaluatePharma & clinicaltrials.gov.			

This year early data could come from Pfizer/Zentalis's Zn-c5, while G1 Therapeutics' rintodestrant – also, according to that company, a "potential best-in-class Serd" – will start a phase II expansion study, both in combination with Pfizer's CDK inhibitor Ibrance.

The joker in the pack is perhaps Radius's elacestrant, which entered the phase III Emerald study after showing impressive remission rates in subjects who had failed a median three prior therapies.

However, last November Radius decided to focus on endocrine diseases and "explore strategic options" for oncology, and while Emerald is set to complete enrolment later this year the company plans no further investment in it.

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