Evaluate Vantage

July 26, 2021

# The search for a better Faslodex continues

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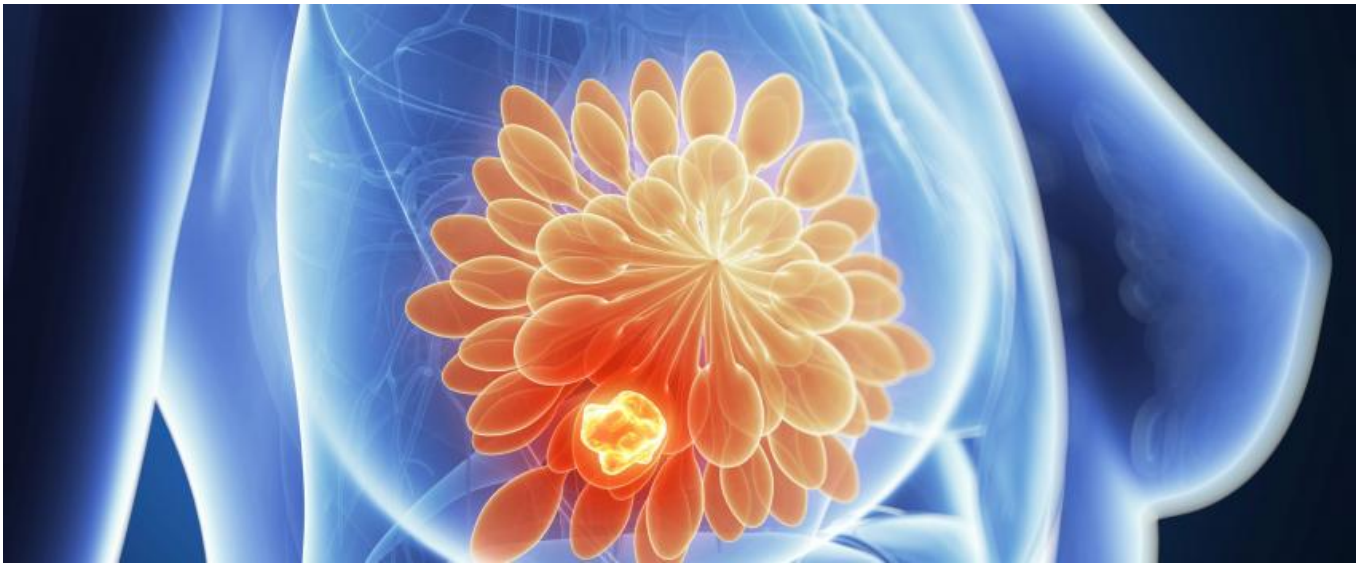

**Selective oestrogen degraders, or Serds, remain in focus as a key period for reporting clinical data approaches.**

Last week's licensing deal between Arvinas and Pfizer, worth an impressive $1bn if its equity element is included, highlighted again the resurgence of selective oestrogen degradation as an approach to treating ER-positive/Her2-negative breast cancer. And, though Pfizer is not the most advanced player, this was its third move into this space in recent years.

The current Serd leaders, Sanofi and Radius Health, will be paying close attention to any newcomer that could muscle its way into this treatment space. This is especially as, after Sanofi's recent delay, the upcoming months could prove key in yielding pivotal data validating this mechanism of action.

Some will point out that the mechanism had already been partly validated by Astra's now off-patent Faslodex, a Serd with efficacy but poor bioavailability and intramuscular delivery. Despite its shortcomings Faslodex did become a blockbuster, showing just how big the market for an even better drug could be.

| Serds in clinical development for ER+ve/Her2-ve breast cancer | | | |
|---|---|---|---|
| **Project** | **Company** | **Design** | **Detail** |
| *Phase 3* | | | |
| Amcenestrant | Sanofi | Ameera-5 (ph3) 1st-line, +Ibrance, vs Femara+Ibrance | Ph2 (2nd-line) registrational Ameera-3 data delayed from Q2 to Q3 2021 |
| Elacestrant | Radius Health | 2nd-line, postmenopausal, vs SoC | Emerald trial data expected Q4 2021 |
| Giredestrant | Roche | 1st-line, +Ibrance, vs Femara+Ibrance | Study began Oct 2020 |
| Camizestrant | Astrazeneca | 1st-line, +Ibrance, vs Femara+Ibrance | Serena-4 trial began Jan 2021 |
| LY3484356 | Lilly | 2nd-line, postmenopausal, vs physician's choice | Ember-3 study beginning Aug 2021 |
| *Phase 1* | | | |
| ARV-471 | Arvinas/Pfizer | 3rd-line, postmenopausal, +/-Ibrance | Further data at SABCS 2021 |
| ZN-c5 | Pfizer/Zentalis | 2nd-line, peri/postmenopausal, Ibrance combo | Early monotherapy data reported Jun 2021; combo data expected H1 2022 |
| Rintodestrant | G1 Therapeutics | +/-Ibrance | Study ends Jan 2022 |
| LSZ102 | Novartis | 2nd-line, single-agent or various combos | Data imminent |
| D-0502 | Inventisbio | 2nd-line, pre/postmenopausal, Ibrance combo | Data possible 2021 |
| OP-1250 | Olema/Pfizer | Single-agent, dose-escalation | Study began Aug 2020; data due later in 2021 |
| ZB716 | Zeno Pharmaceuticals | +/-Ibrance | Study began May 2021 |
| SHR9549 | Jiangsu Hengrui Medicine | 3rd-line, single-agent | Study status unknown |
| *Source: EvaluatePharma & clinicaltrials.gov.* | | | |

Until recently all eyes were on Sanofi's amcenestrant, whose phase 2 Ameera-3 study in third-line ER+ Her2- breast cancer was to have yielded results in the second quarter, potentially paving the way to an immediate US filing.

However, Ameera-3's readout slipped into the third quarter, putting it level with Radius/Menarini's Emerald study of elacestrant. Sanofi also quietly terminated the Ameera-4 study, in preoperative first-line patients, though this was likely down to its decision to start a new trial, Ameera-6, in the adjuvant setting.

Much controversy surrounds Ameera-3, concerning the extent of CDK4/6 inhibition patients might have progressed on, and the possible effect of ESR1 mutation, a resistance mechanism to endocrine therapy. Sanofi looks at PFS in all-comers, while Radius has co-primary endpoints in ESR1-mutant and all-comer patients.

However this plays out, Pfizer likely saw its chance to make a move into Arvinas's approach, whose early data could be extremely important should amcenestrant and/or elacsetrant underwhelm. Results are due to be presented at the San Antonio Breast Cancer Symposium in December.

Last Thursday Pfizer gave Arvinas $650m up front plus a $350m premium-priced equity investment for rights to ARV-471, a Serd that is now Arvinas's most advanced Protac protein degrader. Evercore ISI describes Protacs as heterobifunctional molecules that can trigger multiple rounds of degradation, and are not driven by receptor occupancy.

If Arvinas’s stock movement seemed somewhat muted, rising 9% on Thursday and 13% the following day, maybe this was down to the company committing to funding half of all development costs – for a 50% profit share, of course. Alternatively, perhaps investors were somewhat dismayed by the lack of a full takeover.

**Another foray**

Either way, the deal represented yet another foray into this space for Pfizer, which in 2018 signed a collaboration with Zentalis to study the latter’s Serd ZN-c5 in combination with the US pharma group’s CDK4/6 inhibitor Ibrance. Then, last November, it struck a similar clinical trial tie-up concerning Olema’s OP-1250, which that biotech describes as a “complete ER antagonist and Serd”.

OP-1250 has yet to yield clinical data, though these are expected later this year, while ZN-c5 recently showed two remissions among 21 patients given 150-300mg doses. However, Zentalis says the likely phase 2 dose will be 50mg, which has yet to show any efficacy, suggesting that lack of a therapeutic window is ruling out ZN-c5’s potential as monotherapy.

Last December Arvinas reported initial data from 21 subjects, showing three partial remissions after one monotherapy cycle, though only one of these responses was independently confirmed. One read of last week’s deal is that Pfizer likes the Serd mechanism but is unconvinced by molecules originated by Olema and Zentalis.