

BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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New Approaches to Endocrine Therapy in ER-Positive, HER2-Negative Breast Cancer



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H&O What is standard endocrine therapy in estrogen receptor (ER)-positive breast cancer?

EH The selective estrogen receptor modulator (SERM) tamoxifen, which was first introduced in the 1970s, is the oldest endocrine therapy in use. We also have 3 aromatase inhibitors (AIs) available: the nonsteroidal AIs letrozole and anastrozole and the steroidal AI exemestane. The final option is the ER antagonist fulvestrant, which is administered once a month via an intramuscular injection following a loading dose in the first month. All 5 of these options are considered standard endocrine therapies.

H&O Why does endocrine resistance develop in some patients either during or after endocrine treatment?

EH We do not have a detailed answer, but we view endocrine resistance a bit like antibiotic resistance. If we treat bacteria with an antibiotic for long enough, a lone bacterium will eventually find its way around the antibiotic, and that bacterium is the one that continues to reproduce. Cancer behaves in a similar way; we have therapies that work, but as soon as a mutation develops in a rogue cell that enables the cell to find its way around the treatment, that cell will become the dominant clone and the treatment will no longer work. As a result, we attempt to slow the development of mutations through combination therapy, and to address mutations by switching treatment after resistance develops.

H&O What options are available for patients in whom resistance to AIs or tamoxifen develops?

EH Standard first-line treatment over the past few years has become AIs in combination with CDK4/6 inhibitors. The addition of CDK4/6 inhibition to AIs has been shown to double progression-free survival (PFS) and improve overall survival (OS). We used to rely on fulvestrant for patients whose disease progressed on AIs, but now that we are including CDK4/6 inhibitors in first-line treatment, fulvestrant does not perform as well as it used to. Evidence for this comes from 2 trials: VERONICA and EMERALD.

In the phase 2 VERONICA trial, which was presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting, 103 patients with ER-positive, HER2-negative locally advanced breast cancer that was resistant to endocrine and CDK4/6 inhibitor treatment were randomly assigned to fulvestrant alone or fulvestrant plus the BCL2 inhibitor venetoclax (Venclexta, AbbVie). The addition of venetoclax did not improve the clinical benefit rate or PFS in this study, and notably, a PFS of less than 2 months was observed with fulvestrant in both arms in post-CDK4/6 patients.

The EMERALD study, which was presented at the 2021 San Antonio Breast Cancer Symposium (SABCS), provided the first phase 3 data on an oral selective estrogen receptor degrader (SERD). The study included 477 patients with ER-positive/HER2-negative metastatic breast cancer who had received 1 or 2 prior lines of

endocrine therapy and whose disease had progressed on prior treatment with a CDK4/6 inhibitor. Patients were randomly assigned to receive either the investigational SERD elacestrant or standard therapy with fulvestrant or an AI. At 12 months, PFS was significantly longer in the elacestrant arm than in the standard care arm. In addition, an interim analysis of OS showed a trend in favor of elacestrant. The reduction in the risk for death or disease progression was more pronounced in a subgroup of patients with *ESR1*-mutated tumors than in the overall population: 45% vs 30%, respectively. Despite positive results and proof of concept, the PFS was still short, emphasizing the continued need for more research and better patient selection.

The results of these studies underscore the need for better endocrine therapies for patients who have received CDK4/6 inhibitors. We also want to be able to use oral agents rather than injectables when possible, as they are more patient-friendly.

Ongoing trials are currently looking at the use of SERDs in earlier lines of treatment, such as in combination with CDK4/6 inhibitors in the first-line setting.

H&O What novel SERDs are being investigated?

EH Multiple SERDs are in development (Table). In addition, researchers are developing half a dozen compounds that I refer to as cousins of SERDs: proteolysis-targeting chimeras, often known by the proprietary name PROTACs; selective estrogen receptor covalent antagonists (SERCAs); complete estrogen receptor antagonists (CERANs); and selective estrogen receptor modulators (SERMs). I find it very interesting that we now have more than 15 compounds in development that are new twists on endocrine therapy because our previous endocrine therapies last appeared almost 2 decades ago. Our previous advances in ER-positive disease were targeted agents, such as the CDK4/6 inhibitors and the phosphoinositide 3-kinase (PI3K) inhibitors, but not the endocrine backbones themselves.

H&O Can you discuss these agents in more detail?

EH I presented data at the 2021 SABCs on a phase 1 study of the PROTAC ARV-471, which is being developed by Arvinas. A PROTAC is a special small molecule that binds to a target receptor—in this case the ER—and causes a conformational change that recruits an enzyme to flag the ER cell for destruction. The study looked at women with ER-positive, HER2-negative advanced or metastatic breast cancer who had received at least 1 prior CDK 4/6 inhibitor and at least 2 prior endocrine therapies. These patients were heavily pretreated for ER-positive disease; approximately 83% had received a SERD, and approximately 10% had received a novel oral SERD. The median number of prior agents was 4. Results from 50 patients showed a clinical benefit rate of 40%, so quite a few patients had prolonged benefit. The waterfall plot showed that even some of the patients who had received oral SERDs were responding quite well to PROTACs, so I am encouraged by results with this compound.

Regarding SERCAs, I presented data at the 2021 ASCO Annual Meeting on H3B-6545 in 94 women with ER-positive, HER2-negative advanced breast cancer that was refractory to endocrine therapy. We also saw some data at the 2021 SABCs. The population of this phase 1/2 trial of H3B-6545 was similar to that of the ARV-471 trial; patients had a median of 3 prior therapies for metastatic disease, 85% had received a prior CDK inhibitor, and 72% had received prior fulvestrant. The clinical benefit rate was 32%. H3B-6545 is unique because it is a SERCA; it binds and blocks the ER rather than degrading it. This trial results indicated that we could improve the activity of H3B-6545 if we selected patients who had clonal mutations in *ESR1*, specifically in Y537S and D538G. When we looked at patients with Y537S mutations, the clinical benefit rate increased from 32% to 60%, and the median PFS increased from 5.1 to 7.3 months. Although these results were not statistically significant, they point to ways to enrich for a population that is most likely to respond to these drugs.

Another very exciting compound is Olema's OP-1250, which is a CERAN. In a study of 41 women with ER-positive, HER2-negative metastatic breast cancer that Dr Manish Patel presented in a poster at the 2021 SABCs, among women who received the recommended phase 2 dose of 60 to 120 mg daily, the overall response rate was 17%, and the clinical benefit rate was 46%.

The phase 2 ELAINE trial is looking at the agent lasofoxifene, which is a SERM—the class of compounds to which tamoxifen belongs. Because SERMs have agonist activity in some cells and antagonist activity in other cells, including breast cancer cells, tolerability is increased.

Table. Oral Selective Estrogen Receptor Degraders in Development

Agent	Company	Disease Setting
Amcenestrant (SAR439859)	Sanofi	Advanced/metastatic (untreated and previously treated) Neoadjuvant
Borestrant (ZB716)	Zenopharm	Advanced/metastatic
Camizestrant (AZD9833)	AstraZeneca	Advanced/metastatic (untreated and previously treated) Neoadjuvant
Elacestrant (RAD1901)	Radius Health	Advanced/metastatic
Giredestrant (GDC-9545)	Genentech/ Roche	Advanced/metastatic (untreated and previously treated) Neoadjuvant
Imlunestrant (LY3484356)	Lilly	Advanced/metastatic
Rintodestrant (G1T48)	G1 Therapeutics	Advanced/metastatic
ZN-c5	Zentalis	Advanced/metastatic

SERMs tend to be better tolerated than other endocrine therapies, which often cause menopausal symptoms such as hot flashes, changes in sleep cycle, vaginal dryness, and decreased libido. The ELAINE trial is comparing lasofoxifene vs fulvestrant in women who have advanced or metastatic ER-positive/HER2-negative breast cancer with an *ESR1* mutation (NCT03781063), and ELAINE-2 is studying the combination of lasofoxifene and abemaciclib (Verzenio, Lilly) in the same patient population (NCT04432454). Like the other studies I mentioned, this study is looking at patients who have already received treatment with an AI and in many cases a CDK4/6 inhibitor. Both ELAINE studies have finished enrolling patients, and we hope to see results soon.

H&O What questions would you like to see answered?

EH The biggest question right now is, how can we enrich for a population that will respond to these compounds?

The EMERALD data showed a statistically significant benefit from elacestrant in all comers, and a higher likelihood of benefit among patients who had an *ESR1* mutation. Although we were pleased to see this increase, it was not as large as we were looking for. What factors beyond mutant *ESR1* can tell us which patients are still endocrine-sensitive following CDK4/6 inhibition? In addition, when we examine the curves from the EMERALD trial, we see that disease was progressing in 50% of patients at their first scan, regardless of which arm they were in. What can we do to help these patients, and how can we know when further endocrine therapy is not the answer?

I am pleased to see that ongoing trials are currently looking at the use of SERDs in earlier lines of treatment, such as in combination with CDK4/6 inhibitors in the first-line setting. Other trials are looking at the use of SERDs for higher-risk patients in the adjuvant setting.

Disclosures

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Suggested Readings

Bardia A, Neven P, Streich G, et al. Elacestrant, an oral selective estrogen receptor degrader, vs investigator's choice of endocrine monotherapy for ER+/HER2-advanced/metastatic breast cancer following progression on prior endocrine and CDK4/6 inhibitor therapy: results of EMERALD phase 3 trial [SABCS abstract GS2-02]. *Cancer Res.* 2022;82(4)(suppl).

Hamilton E, Vahdat L, Han HS et al. First-in-human safety and activity of ARV-471, a novel PROTAC® estrogen receptor degrader, in ER+/HER2- locally advanced or metastatic breast cancer [SABCS PD13-08]. *Cancer Res.* 2022;82(4)(suppl).

Hamilton EP, Wang JS, Pluard TJ, et al. Phase I/II study of H3B-6545, a novel selective estrogen receptor covalent antagonist (SERCA), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer [ASCO abstract 1018]. *J Clin Oncol.* 2021;39(15)(suppl).

Lindeman GJ, Bowen R, Jerzak KJ, et al. Results from VERONICA: a randomized, phase II study of second-/third-line venetoclax (VEN) + fulvestrant (F) versus F alone in estrogen receptor (ER)-positive, HER2-negative, locally advanced, or metastatic breast cancer (LA/MBC) [ASCO abstract 1004]. *J Clin Oncol.* 2021;39(15)(suppl).

Patel MR, et al. Preliminary data from a phase I/II, multicenter, dose escalation study of OP-1250, an oral CERAN/SERD, in subjects with advanced and/or metastatic estrogen receptor (ER)-positive, HER2-negative breast cancer. Poster presented at: San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX. Abstract P1-17-12.