BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Novel Endocrine Therapy Agents in ER-Positive, HER2-Negative Breast Cancer

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H&O What types of novel endocrine therapies are being developed for use in estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer?

EH I like to call this the word salad of novel endocrine therapies, because we have 5 classes beyond aromatase inhibitors: selective estrogen receptor degraders (SERDs), selective estrogen receptor modulators (SERMs), proteolysis-targeting chimeras (PROTACs), selective estrogen receptor covalent antagonists (SERCAs), and complete estrogen receptor antagonists (CERANs).

H&O Could you discuss the specific SERDs that are in development?

EH The only SERD that had US Food and Drug Administration approval prior to this year was fulvestrant, which must be injected intramuscularly. In January 2023, elacestrant (Orserdu, Stemline), the first oral SERD, was approved for patients whose tumors have an estrogen receptor 1 (*ESR1*) mutation. We additionally have late-phase data from 4 of the multiple oral SERDs that are in development: elacestrant, giredestrant, amcenestrant, and camizestrant.

We saw results on elacestrant from the phase 3 EMERALD study, which Dr Aditya Bardia presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). In this study, 477 patients with pretreated ER-positive/HER2-negative metastatic breast cancer whose disease had progressed on prior CDK4/6 inhibitor treatment were randomly assigned to elacestrant or to standard therapy with fulvestrant or an aromatase inhibitor. Although the study showed a longer progression-free survival (PFS) in the elacestrant group than in the standard therapy group, the magnitude of benefit was disappointingly low. At the most recent SABCS, we saw updated results (these results have since been published by Bidard and colleagues in the *Journal of Clinical Oncology*) that revealed a greater magnitude of benefit from elacestrant among patients who had remained on a CDK4/6 inhibitor for at least 12 months. This finding was not surprising because patients who discontinue use of a CDK4/6 inhibitor early on in their disease course for progression probably do not have disease that is truly estrogen-driven. The benefit of elacestrant was further amplified among patients with a mutation in *ESR1*, which can cause resistance to aromatase inhibitors. Among the subgroup of patients who had received at least 12 months of CDK4/6 inhibitor treatment and who also had an *ESR1* mutation, the median PFS was 8.61 months for patients taking elacestrant and only 1.91 months for patients receiving standard therapy. This is a large difference, so patient selection is key here.

We saw disappointing results for giredestrant and amcenestrant at the 2022 European Society for Medical Oncology (ESMO) annual meeting. The phase 2 ACELERA trial presented by Dr Miguel Martín Jiménez failed to show an improvement in PFS with giredestrant vs physician's choice of endocrine therapy, and the phase 2 AMEERA-3 trial presented by Dr Sarah Tolaney failed

to show an improvement in PFS with amcenestrant vs physician's choice of endocrine therapy.

At the most recent SABCS, we saw positive data on camizestrant from the phase 2 SERENA-2 trial. This study had 3 arms: fulvestrant at 500 mg, camizestrant at 75 mg, and camizestrant at 150 mg. PFS was significantly higher in both camizestrant arms than in the fulvestrant arm, at more than 7 months vs 3.7 months.

Although 2 of the trials were positive and 2 of them were negative—which could be related to the drugs themselves or to the patient population—it is clear that oral SERDs will eventually become available for clinical use, probably across multiple lines of therapy.

H&O Could you discuss the new SERMs that are in development?

EH Although the SERM tamoxifen has been available for a very long time, researchers are now investigating a newer SERM called lasofoxifene. This agent was originally developed to treat menopausal-type symptoms such as vulvovaginal atrophy and osteoporosis, and has since been shown to have activity against breast cancer. The phase 2 ELAINE-1 trial is looking at the use of lasofoxifene vs fulvestrant in patients with *ESR1*-mutated, ER-positive/HER2-negative metastatic breast cancer. In results that Dr Matthew Goetz presented at the most recent ESMO annual meeting, lasofoxifene did not lead to a statistically significant improvement in PFS compared with fulvestrant, at 6.04 months vs 4.04 months, respectively. We saw more encouraging results from a study of lasofoxifene plus the CDK4/6 inhibitor abemaciclib (Verzenio, Lilly). In results from the open-label, phase 2 ELAINE-2 study that Dr Senthil Damodaran presented at the 2022 ASCO annual meeting, the combination of lasofoxifene and abemaciclib led to median PFS of 13.9 months in patients with ER-positive, HER2-negative metastatic breast cancer and an *ESR1* mutation whose disease had progressed on previous CDK4/6 inhibitors. These findings were highly encouraging, and a randomized trial of the combination called ELAINE-3 is planned (NCT05696626).

H&O What PROTACs are being developed?

EH PROTACs are a new class of drugs that work by degrading the estrogen receptor rather than addressing how much estrogen is in the system. The furthest along of these compounds is ARV-471, which is being developed by Arvinas and Pfizer. Results from the VERITAC expansion trial of ARV-471 were released in November 2022 and presented at the 2022 SABCS. The results showed that ARV-471 had a favorable tolerability profile and a clinical benefit rate of 38%. The clinical benefit rate was even higher among those with an *ESR1* mutation, at 51%. The patients in this study were heavily pretreated, with a median of 4 prior treatments, including CDK4/6 inhibitors in all patients, fulvestrant in 79% of patients, and chemotherapy in 73% of patients. The phase 3 VERITAC-2 trial, which is randomly assigning patients with ER-positive, HER2-negative advanced breast cancer whose disease progressed after prior endocrine therapy, is currently recruiting patients (NCT05654623). Another agent that is being developed is Accutar Biotechnology's AC682, which is being studied a phase 1 trial that is currently recruiting patients (NCT05080842).

I hope to someday have an assay that will tell us which tumors still respond to endocrine agents.

H&O What SERCAs are being developed?

EH At the 2021 ASCO annual meeting, I presented data from a phase 1/2 trial of the SERCA H3B-6545. This study included 94 patients with locally advanced or metastatic ER-positive, HER2-negative breast cancer that was refractory to endocrine therapy. Patients had received a median of 3 prior therapies, with 85% having received a prior CDK4/6 inhibitor and 72% having received prior fulvestrant. This study showed a clinical benefit rate of 32%, and a duration of response of 7.3 months. There was a trend toward improved clinical benefit among patients with an *ESR1* mutation, especially the Y537S variant.

H&O Could you discuss the development of CERANs?

EH Olema's OP-1250 is a CERAN, meaning that it blocks both the AF1 and AF2 domains in the estrogen receptor. Dr Manish Patel presented data on a phase 2 trial of OP-1250 in women with ER-positive, HER2-negative breast cancer at the 2021 SABCS. These patients were heavily pretreated, with 50% having received 3 or more endocrine therapies in the metastatic setting, three-quarters having received chemotherapy, approximately 70% having received fulvestrant, and more than 90% having received CDK4/6 inhibitors. This study found a clinical benefit rate of 38% with OP-1250 and an overall response rate of 18%.

H&O What questions would you like to see answered regarding novel endocrine therapy agents?

EH The first question to answer is, how do we figure out the most appropriate candidates for these therapies? We know that some patients no longer have endocrine-sensitive disease after they have received CDK4/6 inhibitors, which means that simply testing positive for the ER or the progesterone receptor no longer guarantees a response to endocrine therapy. We seem to be able to refine our prediction of which patients will benefit by looking for the *ESR1* mutation, which develops in patients whose tumors are highly dependent on estrogen. However, breast tumors eventually become resistant to endocrine therapy even in patients who have an *ESR1* mutation. We know that *ESR1* mutation status is not the answer, it is just the best enrichment tool we have right now. I hope to someday have an assay that will tell us which tumors still respond to endocrine agents, much like assays such as Oncotype and MammaPrint tell us which patients can avoid chemotherapy. We also want to know which class of agent is most likely to be advantageous in a particular setting, such as a specific mutation profile.

Finally, we need to determine how best to sequence these agents. How does past treatment with one endocrine therapy agent affect the response to a future endocrine therapy agent? I have been lucky enough to use agents from all 5 of these drug classes in patients in our phase 1 unit. For example, I have followed a SERD with a PROTAC and a PROTAC with a CERAN. I have seen patients respond to a drug from another one of these drug classes after progression on a drug from a different class, which is not surprising because we have seen patients with ER-positive breast cancer cycle through tamoxifen to an aromatase inhibitor, then fulvestrant, and then a SERD. I expect that eventually we will be using many of these compounds in sequence and in combination with each other and other targeted therapies.

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Suggested Readings

Arvinas announces ARV-471 achieves a clinical benefit rate of 38% in evaluable patients and continues to show a favorable tolerability profile in its phase 2 expansion trial (VERITAC) [press release]. https://ir.arvinas.com/news-releases/news-release-details/arvinas-announces-arv-471-achieves-clinical-benefit-rate-38. Arvinas; November 22, 2022. Accessed February 9, 2023.

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