

BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Advances in SERDs and Other Novel Endocrine Therapies



Kevin Kalinsky, MD, MS
Associate Professor
Department of Hematology and Medical Oncology
Emory University School of Medicine
Atlanta, Georgia

H&O What are the main challenges with endocrine therapy for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer?

KK The first challenge is providing endocrine therapy that is well tolerated, so that patients can stay on it for the full recommended time. We want patients with newly diagnosed metastatic, HR-positive, HER2-negative disease to remain on endocrine therapy-based treatments, often in combination with targeted therapy, for as long as possible before the need to administer chemotherapy or antibody-drug conjugates.

The second challenge is overcoming resistance. We see the development of *ESR1* mutations in approximately one-third of patients who have prior exposure to aromatase inhibitors. This acquired mutation helps to explain why so many patients experience tumor progression while on an aromatase inhibitor.

H&O What are the various classes of novel endocrine therapies that are currently being evaluated?

KK Although we have various approaches, the target remains the estrogen receptor. The first endocrine therapy that gained widespread use was tamoxifen, a selective estrogen receptor modulator (SERM) that blocks the estrogen receptor. After that came the development of aromatase inhibitors, which decrease the amount of estrogen in the body. Since then, we have seen the development of novel endocrine therapies.

We are excited about the development of new selective estrogen receptor downregulators (SERDs) because they work differently than aromatase inhibitors, which makes them effective for patients with *ESR1* mutations. The only SERD that used to be available was fulvestrant, which needs to be injected. In January of this year, however, the US Food and Drug Administration (FDA) granted accelerated approval to the oral SERD elacestrant (Orserdu, Stemline) for patients with advanced or metastatic HR-positive, HER2-negative disease that has developed *ESR1* mutations. Multiple other oral SERDs are being developed, including camizestrant, giredestrant, and imlunestrant. Researchers are also developing a new SERM called lasofoxifene.

Other novel endocrine therapies include proteolysis-targeting chimeras (PROTACs), which promote the ubiquitination of the estrogen receptor; selective estrogen receptor covalent antagonists (SERCAs), which antagonize the hormone receptor; and complete estrogen receptor antagonists (CERANs), which also antagonize the hormone receptor. Although these drug classes work differently, the goal is the same: to affect the estrogen receptor so the cancer is unable to grow. Another drug class under investigation in breast cancer is selective androgen receptor modulators (SARMs). We know that many HR-positive breast tumors also express the androgen receptor, so the hope is that inhibiting the androgen receptor might halt the growth of breast cancer.

H&O Could you review the design and results of the EMERALD trial that led to the approval of elacestrant?

KK The phase 3, randomized EMERALD study compared elacestrant vs physician's choice of standard endocrine therapy in patients with metastatic, HR-positive, HER2-negative disease that had progressed on prior cyclin-dependent kinase 4/6 (CDK4/6) inhibitor treatment. Standard endocrine therapy consisted of either fulvestrant or an aromatase inhibitor. The researchers found that patients with *ESR1* mutations had the greatest improvements in progression-free survival when using elacestrant vs physician's choice of endocrine therapy. As a result, elacestrant received approval for patients with *ESR1* mutations. The most common side effects associated with elacestrant included fatigue and gastrointestinal symptoms.

In an exploratory analysis of EMERALD that Dr Virginia Kaklamani presented at the San Antonio Breast Cancer Symposium in 2022, patients who had been on a prior CDK4/6 inhibitor for at least 12 months were the ones who seemed to receive the greatest benefit from elacestrant vs physician's choice of endocrine therapy. Elacestrant remains approved for advanced or metastatic, *ESR1*-mutated, HR-positive, HER2-negative disease that has progressed on prior CDK4/6 inhibitor treatment, regardless of the amount of time on the CDK4/6 inhibitor.

I look forward to the possibility of having oral SERDs available for use in the setting of operable breast cancer as well as additional oral SERDs available for use in the metastatic setting.

H&O Could you discuss the ongoing research on elacestrant in combination with other agents?

KK The phase 1b/2 ELEVATE umbrella study is important because it is looking at elacestrant in combination with various agents for patients with HR-positive, HER2-negative advanced or metastatic breast cancer (NCT05563220). These agents include the phosphoinositide 3-kinase inhibitor alpelisib (Piqray, Novartis); the mammalian target of rapamycin inhibitor everolimus; or a CDK4/6 inhibitor, meaning palbociclib (Ibrance, Pfizer), abemaciclib (Verzenio, Lilly), or

ribociclib (Kisqali, Novartis). Patients are eligible for the alpelisib arm if they have a *PIK3CA* mutation. This study is designed to establish safety and gather initial efficacy data.

H&O What are some of the most important ongoing phase 3 trials that are looking at new endocrine agents?

KK This is far from a comprehensive list, but I will highlight some important phase 3 trials. The phase 3 SERENA-4 trial (NCT04711252) is examining whether the oral SERD camizestrant is superior to the aromatase inhibitor anastrozole when added to palbociclib. In addition, the phase 3 SERENA-6 trial (NCT04964934) is looking at patients who have been on an aromatase inhibitor and a CDK4/6 inhibitor for at least 6 months without experiencing disease progression but have developed an *ESR1* mutation. These patients are being randomized to either continue with an aromatase inhibitor and CDK4/6 inhibitor, or switch to camizestrant plus a CDK4/6 inhibitor. This trial is similar in design to what we saw with the PADA-1 trial by Bidard and colleagues, in which switching from an aromatase inhibitor to fulvestrant upon early identification of the *ESR1* mutation was found to double progression-free survival. Other important phase 3 studies include EMBER-3 (NCT04975308) and EMBER-4 (NCT05514054), which are looking at the SERD imlunestrant vs standard endocrine therapy.

Regarding SERMs, the phase 3 ELAINE-3 study randomly assigned patients whose tumors have progressed on an aromatase inhibitor and a CDK4/6 inhibitor and have an *ESR1* mutation to receive either fulvestrant plus abemaciclib or lasofoxifene plus abemaciclib. In addition, phase 3 trials are currently being conducted to see if endocrine therapy can help prevent disease relapse after surgery.

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H&O Do differences exist among the oral SERDs in terms of adverse events?

KK Unlike the aromatase inhibitors, which are viewed as close to interchangeable, the oral SERDs differ in both activity and side effects. For example, some oral SERDs can cause ocular issues, some can cause a decrease in heart rate, some can cause fatigue, and some can cause gastrointestinal issues.

H&O What should future studies of endocrine therapy address?

KK I would like to see comparisons among various novel agents. For example, we do not have a study comparing the various oral SERDs—elacestrant, camizestrant, and giredestrant—against each other. We also do not have studies of novel drug classes against each other, such as CERANs vs PROTACs. We also need to learn the best way to sequence these various agents after they receive FDA approval. Future studies should address these issues.

Disclosures

Dr Kalinsky has served in an advisory or consulting role to Genentech/Roche, Gilead Sciences, Seagen, OncoSec, 4D Pharma, Daiichi Sankyo, Puma Biotechnology, Mersana Therapeutics, Menarini Silicon Biosystems, Myovant Sciences, and Takeda. His spouse has stock in EQRx and is a prior employee of Grail, Array BioPharma, and Pfizer.

Suggested Readings

Bardia A, Bidard FC, Neven P, et al. EMERALD phase 3 trial of elacestrant vs standard of care endocrine therapy in patients with ER+/HER2- metastatic breast

cancer: updated results by duration of prior CDK4/6i in metastatic setting. Paper presented at: San Antonio Breast Cancer Symposium; December 6-12, 2022; San Antonio, TX. Abstract GS3-01.

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).

Bidard FC, Hardy-Bessard AC, Dalenc F, et al; PADA-1 investigators. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2022;23(11):1367-1377.

ClinicalTrials.gov. A comparative study of AZD9833 plus palbociclib versus anastrozole plus palbociclib in patients with ER-positive HER2 negative breast cancer who have not received any systemic treatment for advanced disease (SERENA-4). <https://clinicaltrials.gov/ct2/show/NCT04711252>. Identifier: NCT04711252. Updated April 28, 2023. Accessed May 12, 2023.

ClinicalTrials.gov. Open-label umbrella study to evaluate safety and efficacy of elacestrant in various combination in patients with metastatic breast cancer (ELEVATE). <https://clinicaltrials.gov/ct2/show/NCT05563220>. Identifier: NCT05563220. Updated February 27, 2023. Accessed May 12, 2023.

ClinicalTrials.gov. Phase III study to assess AZD9833+ CDK4/6 inhibitor in HR+/HER2-MBC with detectable ESR1m before progression (SERENA-6). <https://clinicaltrials.gov/ct2/show/NCT04964934>. Identifier: NCT04964934. Updated May 11, 2023. Accessed May 12, 2023.