CLINICAL INSIGHTS

The Latest Breakthrough in Breast Cancer Treatment

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H&O Can you go into the details of elacestrant's US Food and Drug Administration (FDA) approval?

SMT Elacestrant (Orserdu, Stemline) is an oral selective estrogen receptor degrader (SERD) that was recently approved by the FDA for patients who have metastatic, hormone receptor–positive (HR+)/human epidermal growth factor–negative (HER2–) breast cancer with an *ESR1* mutation that has progressed on at least 1 line of endocrine therapy in the metastatic setting. The approval for elacestrant was based on the results of the EMERALD trial. This was a randomized phase 3 study that enrolled patients with metastatic HR+ breast cancer that had progressed on a prior cyclin-dependent kinase 4/6 (CDK4/6) inhibitor and endocrine therapy. Patients were randomized to receive either elacestrant alone or physician's choice of endocrine therapy, which could consist of fulvestrant or an aromatase inhibitor.

What was found was that elacestrant led to an improvement in progression-free survival (PFS). Although that improvement was somewhat modest in the intention-to-treat population, there was a more sizable improvement in PFS when specifically looking at the subset of patients with an *ESR1* mutation, with a difference of about 2 months between the 2 arms. Given this, the FDA decided to restrict the approval to the subgroup of patients with an *ESR1* mutation.

H&O What makes elacestrant an exciting treatment option for patients with breast cancer?

SMT Before the approval of elacestrant, the only approved SERD was fulvestrant. The challenges with fulvestrant are that its bioavailability is not great and that it is given intramuscularly, involving 2 shots at each treatment, 1 in each buttock. These injections are not something that patients are excited about, truthfully. In one way, having an oral option that is a SERD is a significant advancement. Furthermore, based on the results of the EMERALD trial, elacestrant is more effective than fulvestrant. This is not only a convenience because it is oral, but also a testament to its higher efficacy, which could be attributed in part to its superior bioavailability. It is genuinely exciting to have a new endocrine therapy option. We did not have any new endocrine agents approved in breast cancer for more than 20 years, so this is a big deal.

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H&O What are the key findings from the EMERALD study?

SMT The important finding from the EMERALD study was that there was a notable improvement in PFS among the

patients (48%) with an *ESR1* mutation, from 1.9 months to 3.8 months. As I mentioned earlier, this represents nearly a 2-month difference between the 2 arms. The hazard ratio is approximately 0.55, suggesting that elacestrant nearly doubled the PFS in the *ESR1*-mutant group.

The challenge here is that endocrine monotherapy does not work very well in this setting. If you consider the performance of the control arm, with a PFS of 1.9 months, it essentially means that many patients are progressing at their first restaging scan, indicating that they are not benefiting from endocrine therapy alone. That is why the improvement appears somewhat modest; it is because endocrine drugs typically do not work well as monotherapy after patients have progressed on a CDK4/6 inhibitor. However, with elacestrant, we see an improvement in patient outcomes.

There was an interesting subgroup analysis presented at the San Antonio Breast Cancer conference, aiming to identify those who can remain on elacestrant for a prolonged period. When looking at Kaplan-Meier curves for this trial, a noticeable drop-off was evident, with a significant number of patients progressing on both arms of the trial around the 2-month mark. What was discovered was that those who had been on an initial line of CDK4/6 inhibition for more than 12 months and had a tumor with an *ESR1* mutation seemed to have a more prolonged PFS, with a median PFS of approximately 8.5 months.

When contemplating who is best suitable for elacestrant monotherapy, I generally think of individuals who progressed on their upfront CDK4/6 inhibitor and endocrine therapy, having been on it for at least 12 months, and who have a tumor with an *ESR1* mutation. The interesting aspect here is the suggestion that these patients have tumors that are endocrine-sensitive because they were able to be on an endocrine-based treatment for a long time. It indicates a strong dependence on the estrogen receptor within their cancer. This might be a key factor in selecting patients who will gain the most benefit from continued treatment with endocrine monotherapy.

Although it is oral, which is a patient-friendly option, there are some potential side effects. In my experience, elacestrant is generally well tolerated. Some patients may experience mild gastrointestinal side effects, such as nausea. This nausea is usually not severe, but it is something worth noting. Additionally, some patients may experience mild fatigue. One other interesting thing is that it can lead to an increase in triglycerides. This is something we can observe with other endocrine therapies as well.

H&O How will the outcomes of the EMERALD study and advancements in *ESRI* mutation testing shape the future of precision medicine in managing those with breast cancer?

SMT We are entering a phase where we are starting to develop more personalized therapy for patients. It is becoming more critical to understand—particularly in metastatic estrogen receptor–positive (ER+) disease—genomic alterations in the tumor and how those evolve to make therapeutic decisions. In this case, it is critical to assess *ESR1* mutation status at the time of progression on a CDK4/6 inhibitor. We know that between 30% to 50% of patients who have been on an aromatase inhibitor in the metastatic setting and progress on it will develop an *ESR1* mutation. It is essential to check for this mutation after exposure to an aromatase inhibitor to know if the mutation has developed. The standard approach in the clinic is to get a circulating tumor DNA (ctDNA) assay upon progression to determine if the patient is a candidate for elacestrant.

Additionally, knowing if a patient has a phosphoinositide 3-kinase (*PI3K*) mutation is crucial in determining if they are a candidate for alpelisib (Piqray, Novartis). Unlike *ESR1* mutations, *PI3K* mutations are not typically dynamic genomic alterations. If present in the primary tumor, they are likely to be present in the metastatic cancer. It is not usually an acquired alteration, which sets it apart from *ESR1* mutations. Again, this underscores the need for more real-time analysis to see if the *ESR1* mutation is present. Even if it is not initially detected and the patient gets more endocrine therapy, it is advisable to reevaluate, as it could develop later. This shift in approach is guiding us toward an era where more frequent genomic assessments will be crucial for delivering personalized care to our patients.

H&O Could you go into detail about the ELEVATE trial?

SMT What we have learned from EMERALD is that elacestrant monotherapy can work in a subset of patients with *ESR1* mutations, but the benefit is relatively modest. Our focus has shifted toward combining endocrine therapy with targeted agents in the post-CDK4/6 inhibitor setting. The ELEVATE trial is currently looking at the safety of combining elacestrant with various targeted agents, including ribociclib (Kisqali, Novartis), palbociclib (Ibrance, Pfizer), everolimus, and alpelisib. Simultaneously, there is a separate trial called the eLEcTRA trial, which is evaluating the combination of elacestrant with abemaciclib (Verzenio, Lilly). In my view, combination approaches are crucial because when a patient progresses on a CDK4/6 inhibitor, a combination therapy involving a SERD and a targeted agent, is likely to have better outcomes than just single-agent endocrine therapy. However, presently, we do not have the safety data or approval for such combinations. These data will help get us there.

H&O Based on the new ASCO Guidelines and your experience, how have you approached *ESR1* mutation testing in the past, and what about currently?

SMT In the past, we did not have an approved, targeted agent specifically to use in patients with an *ESR1* mutation. Although we knew that patients with this mutation were unlikely to benefit from aromatase inhibition, we now have an agent that is specifically approved for *ESR1* mutations, making it critical to know if it is present. Consequently, our practice patterns have changed, and we need to conduct real-time evaluations of *ESR1* status at the time of progression on CDK4/6 to determine whether a patient is a candidate for elacestrant.

In the current landscape, it is standard to get ctDNA after progression on CDK4/6 inhibition, whereas before the primary concern was often determining *PI3K* mutation status, which was the only actionable mutation at the time, and again, was not dynamic. So, if you had mutational testing from a prior time point, it usually sufficed. There was not as much of a need to continuously monitor for acquired mutations. This shift is changing the way we practice.

H&O How do you decide between liquid biopsy and tissue biopsy?

SMT Both approaches are useful ways to get genomic information. Commonly, we send either tissue or blood off for next-generation sequencing (NGS) to identify mutations in the tumor. One advantage of liquid assays is that they are noninvasive. If a patient has tumor tissue that is not easily or safely accessible for biopsy, for example, then this provides a way to get access to understand the genomics of that patient's tumor. Another advantage is that liquid assays are quick, yielding results within 10 business days of sending a blood sample, whereas obtaining NGS results from tissue may take a bit longer.

The other piece of it is that, when accessing genomics via a tumor biopsy, information is only obtained from the specific spot where the sample was taken. Tumors are heterogeneous, so what if one area of the tumor has a specific genomic alteration while another area does not? A liquid assay can pick up genomic alterations across the entire body, as it detects DNA emitted into the bloodstream from any tumor site. In contrast, a tissue biopsy reflects only the sampled spot. This potential heterogeneity can limit the comprehensive assessment of all areas.

There are pros and cons to both methods. Sometimes a liquid assay may not detect an alteration, but the tissue biopsy does. There can be challenges and limitations with both tests. However, given that we are currently seeking dynamic changes in *ESR1*, a more practical and timely approach post-CDK is to opt for liquid assay. This ensures we get the results much more quickly.

Disclosures

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Suggested Readings

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