Oral selective estrogen receptor degraders: the current status

By Ekaterina Chashnikova, medical writer

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Introduction

Estrogen receptors are identified in more than 70% cases of metastatic breast cancer,[1] and multiple endocrine treatments are now available that target estrogen receptors and help postpone chemotherapy. However, 15–20% of tumors are intrinsically resistant to this treatment, and another 30–40% acquire resistance to endocrine therapy over time.[2]

One of the key causes of endocrine therapy resistance in estrogen-receptor-positive (ER+) breast cancer are mutations in the ESR1 gene that affect estrogen receptors. ESR1 mutations were discovered back in 1997[3] and have been identified as a crucial element of metastatic breast cancer (MBC) resistance to endocrine therapy in 2013.[4] Up until recently, these mutations served purely as a factor of poor prognosis and were not taken into account when selecting treatment. The available endocrine treatment options did not help overcome the resistance, but the situation changed when selective estrogen receptor degrader (SERD) elacestrant was approved in 2023.[5]

This white paper follows the events from the discovery of ESR1 mutations to the approval of elacestrant that significantly improved the progression-free survival in 2+ lines of hormone-resistant HR+/HER2- MBC (see Figure 1). This informative summary can help clinicians stay on top of the recent developments and changes in guidelines and improve the patient survival by timely administration of the latest available treatments. The suggested timing and methods of analysis for ESR1 mutations in clinical practice are also reviewed.

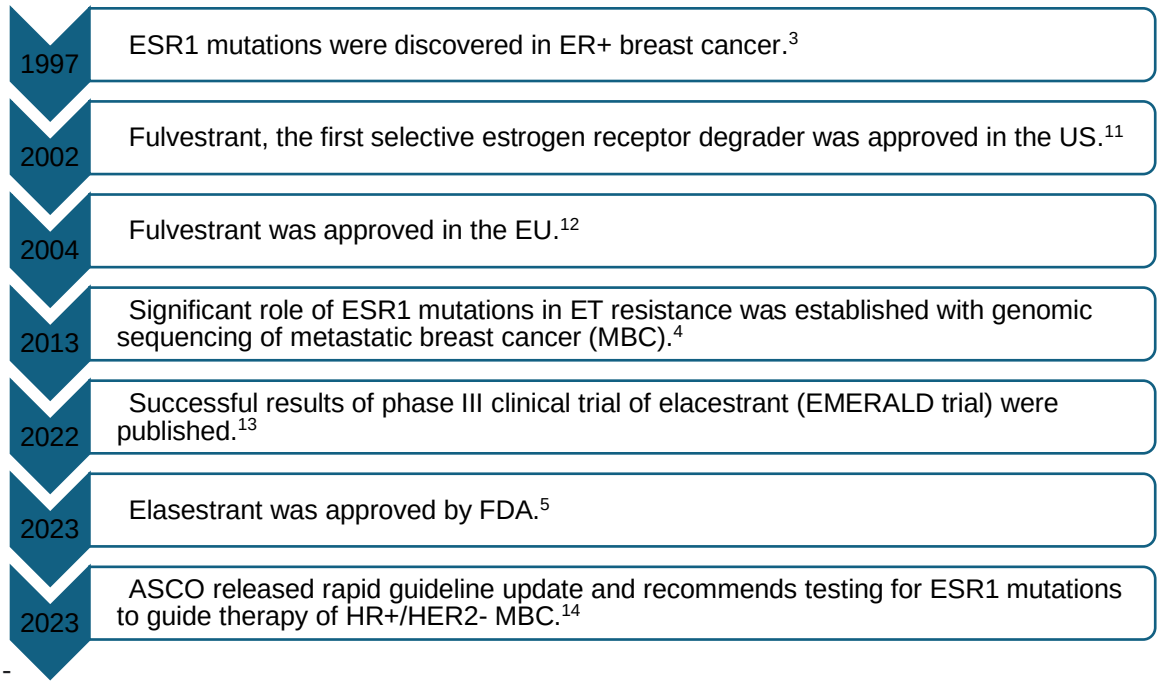

Figure 1. Discovery of ESR1 mutations and development of selective estrogen receptor degraders.

ESR1 mutations in metastatic breast cancer

Mutations in the estrogen receptor 1 (ESR1) gene prevent aromatase inhibitors from depriving the tumor of the estrogen effects that help the tumor grow. They also can make the tumor resistant to other hormone treatments and are associated with a poor prognosis in MBC in general. Considerable knowledge has been accumulated about the mutations over the years.

The most crucial fact is that ESR1 mutations rarely occur in the primary tumor and cannot be excluded at the initial diagnosis, unless it is a newly diagnosed MBC.[4,6] In most cases, mutations develop by the 2+ line of treatment and are identified in at least 39% cases of HR+/HER2- MBC.[4] The most common locations are liver and bones. The other possible sites include pleura, lungs, ovaries, lymph nodes, and thoracic wall.[6]

Genetic studies show that patients with MBC predominantly have the following ESR1 mutations: Y537S, D538G, E380Q, Y537N, Y537C, with Y537S и D538G being the most common.[7-9] About half of the cases present with polyclonal ESR1 mutations.[7-9] This knowledge allows for effective identification of the mutations in clinical practice with next generation genome sequencing (NGS) or droplet digital polymerase-chain reaction (PCR). Although NGS is a well-established method to identify ESR1 mutations in clinical practice, some researchers have looked into PCR as an alternative. More information about the analytical methods is given in the next section.

The accumulated knowledge about ESR1 mutations allows describing a common clinical profile of patients with identified mutations. The mutations are likely to develop in patients with MBC that progressed or relapsed during or after the previous adjuvant treatment of localized disease that included aromatase inhibitors.[7] The rate of ESR1 mutations correlates with resistance to aromatase inhibitors in clinical practice to the extent that prompted some researchers to suggest that AIs can trigger the mutations.[8] Aromatase inhibitors inhibit breast cancer growth by estrogen deprivation and ESR1 mutations allow the tumor to proliferate independently of estrogen.[10]

A study of a prognostic role of ESR1 mutations in patients with relapsed MBC showed a significantly shorter time to progression in patients with the mutations during treatment with AIs as compared to mutation-free patients (3 months vs. 15 months; HR = 3.1; p = 0.017).[6] The mutations clearly being an important prognostic factor, how are they handled in clinical practice?

Sampling and test methods for identification of ESR mutations

To review the available methods, we should answer three questions: when to test for the mutation, which samples to use, and which method of genetic testing to apply. The timing for ESR1 mutation screening can be based on a variety of criteria that are summarized in Figure 2.

Based on the research findings summarized above, the following criteria for ESR1 mutation screening can be assembled:

- Relapse or progression of HR+/HER2- MBC after or during the first or 2+ line of endocrine treatment (with or without CDK4/6 inhibitor),
- Rapid progression during treatment with a CDK4/6 inhibitor,
- Progression during treatment with AIs,
- Appearance of metastases (it makes sense to perform biopsy of the primary metastatic lesion for the mutation),
- Narrow choice of endocrine therapy for MBC due to individual factors.

Figure 2. When to test for ESR1 mutations

When it comes to sampling, two options are available: blood and tumor tissue. The traditional tumor tissue biopsy is a well-established and accurate method, but it is not always feasible in metastatic disease with lesions in hard-to-access locations. Blood test for circulating tumor DNA (ctDNA) is a preferred alternative to tissue biopsy at 2+ treatment lines in MBC patients because of the following benefits:
- high sensitivity,
- identification of the mutation in all metastatic sites,
- less complicated method (no tissue sample is required),
- the possibility to repeat the test at any time point to monitor the treatment.

The American Society of Clinical Oncology (ASCO) recommended ctDNA blood test to screen for ESR1 mutations to guide therapy for HR+ /HER 2- MBC.[14] Experts also suggest combining the blood test with biopsy of the primary metastasis, if possible, because sometimes, soon after the mutation development, it cannot yet be identified in blood but can be found in the primary metastasis.[16]

As for the genetic testing method, next generation genome sequencing is the primary method to identify ESR1 mutations. The PADA-1 trial, which studied efficacy of fulvestrant in combination with palbociclib in ESR1-mutation-positive patients with resistant HR+ HER2+ MBC, applied droplet digital PCR (ddPCR).[15] Although ddPCR is a more selective modification of conventional PCR, NGS seems to be more advantageous because it allows screening for multiple mutations simultaneously.

Treatment options for ESR1-mutation-positive patients

Choice of treatment for MBC is based on multiple factors: immunophenotype of the primary and metastatic lesions, previous adjuvant therapy, remission duration, general state of the patient, including consequences of toxicity of the previous treatment lines.

So, what happens when an ESR1 mutation is identified? The patient is usually on the 2+ line of endocrine treatment and the therapy choice can be limited. Aromatase inhibitors either have already been used or are not considered because of the resistance. The SERD fulvestrant was associated with better outcomes than other endocrine treatments in several studies,[15,17,18] so it counted as an option. Several other treatment options were also considered before the approval of elacestrant. Since elacestrant is not available in some countries yet and might not be suitable for all patients, these options should also be noted.

Results of several studies suggest that it is adequate to continue CDK4/6 inhibitors when the mutation have been identified because these drugs have been associated with positive clinical outcomes.[14] In particular, the PADA-1 study showed that replacing a combination of an aromatase inhibitor with palbociclib with a combination of fulvestrant and palbociclib was associated with significant improvement of progression-free survival (PFS) (from 5.7 months to 11.9 months, $p<0.0040$).[15]

What about chemotherapy? Unfortunately, ESR1 mutations are associated with poor prognosis in all cases.[4,6] The PEARL study compared efficacy of endocrine therapy in combination with a CDK4/6 inhibitor and capecitabine in patients with ESR1 mutation.[19] The combination endocrine therapy was not superior over chemotherapy, and the life duration of patients with confirmed ESR1 mutation did not exceed 30 months, irrespective of the treatment regimen (palbociclib + exemestane, palbociclib + fulvestrant, or capecitabine).[19]

The treatment of hormone-resistant HER2-negative MBC with the estrogen receptor modulator exemestane was also associated with favorable survival rates and was comparable to fulvestrant. The use of exemestane combination with everolimus was accompanied by a significant increase in PFS.[9] A comparative study also showed similar efficacy of exemestane and fulvestrant monotherapy in patients with ESR1 mutations with locally advanced or metastatic BC.[20]

Nevertheless, all those treatment options did not allow considerable prolongation of progression-free survival compared to elacestrant.

Selective estrogen receptor degraders: the current status

The first-generation SERD fulvestrant was associated with favorable outcomes in patients with ESR1 mutations, but not all drug candidates with similar mechanism of action passed phase II. The second-generation drug elacestrant was shown to be superior in phase III specifically in patients with ESR1 mutations and was approved by FDA for this indication. The approval by the European Commission followed shortly.[21] The key phase III clinical trial EMERALD compared elacestrant (Orserdu, Stemline Therapeutics Inc.) and standard endocrine therapy (as chosen by the investigator) for hormone-dependent HER-2-negative advanced breast cancer.[13]

Is elacestrant more effective than the first SERD, fulvestrant? In the EMERALD study, a subset of patients received fulvestrant as standard therapy, and a survival analysis of the elacestrant group compared with the subgroup of patients who received standard therapy with fulvestrant showed a significant difference in favor of elacestrant, especially in patients with a confirmed ESR1 mutation.[13] Post-marketing studies of elacestrant and ongoing studies of other molecules in this class are expected to provide additional comparative data. In particular, the drug

camizestrant (AZD9833, AstraZeneca) showed positive results in the second phase.[22] A phase III study of this molecule (SERENA-6)[23] is currently underway.

The SERD amcenestrant (Sanofi) did not demonstrate sufficiently high efficacy in late-line therapy for hormone-resistant HER2-negative breast cancer in phase III study and its development was canceled.[25] The results of the phase II study of another SERD giredestrant (Roche) were considered favorable enough to move to phase III.[26]

Thus, more options available to drive MBC treatment further might become available before long.

Conclusion

The routine practice of prescribing new targeted therapy drugs (CDK4/6, mTOR, PI3K inhibitors) for HR+ / HER2- MBC in combination with hormonal therapy has led to a counterintuitive deficiency of hormonal therapy in the late lines of treatment. That is, most patients receive hormonal therapy in adjuvant regimens or in the first lines of treatment, and it may be difficult to select another effective combination because many individual factors can limit the choice of hormonal therapy. The development of resistance to hormonal therapy, including the resistance mediated by ESR1 mutations, aggravates this challenge by reducing the treatment options even further. Proactive analysis for mutations in ctDNA in the presence of the outlined warning factors may improve the outcomes of the subsequent treatment lines. The emergence of promising SERDs and the latest approval of elacestrant in the US and EU may also improve survival in this population.

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