Elacestrant Improves Progression-Free Survival After Endocrine Therapy for Estrogen Receptor-Positive Metastatic Breast Cancer

Anne Jacobson, MSPharm, CHCP

Endocrine therapy in combination with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor has emerged as the standard of care for patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. However, most patients will experience disease progression on first-line therapy related to the development of treatment resistance, including resistance secondary to the development of ESR1 mutations.

After progression on first-line therapy, options for patients with ER-positive/HER2-negative metastatic breast cancer include sequential endocrine therapy, with the goal of exhausting available endocrine therapies before switching to chemotherapy. Standard single-agent endocrine therapies such as fulvestrant are associated with poor progression-free survival (PFS), averaging approximately 2 months in the second- and third-line settings.

Elacestrant is an investigational, oral, selective estrogen receptor degrader (SERD) that demonstrates antitumor activity in ER-positive/HER2-negative metastatic breast cancer previously treated with fulvestrant and CDK4/6 inhibition. Elacestrant also shows activity in tumors harboring ESR1 mutations. The phase III EMERALD trial was designed to evaluate elacestrant in patients with estrogen receptor (ER)-positive/HER2-negative metastatic breast cancers that progressed on prior treatment with endocrine and targeted therapies.

Aditya Bardia, M.D., M.P.H., of Mass General Cancer Center, presented results from the EMERALD trial, the first phase III study to examine an oral SERD in advanced breast cancer.

Key Findings

Elacestrant significantly reduced the risk of disease progression or death compared with standard endocrine therapy (Table 2). In the overall study population, the median PFS was 2.79 months in the elacestrant group and 1.91 months in the standard of care group. This represents a 30% reduction in the risk of progression or death with the oral SERD (HR, 0.69; \( p = .0018 \)).

Among patients with tumors harboring \( mESR1 \), elacestrant was associated with a 45% reduction in the risk of progression.

### Table 1. Baseline characteristics of patients with ER-positive metastatic breast cancer

| Characteristic                      | Elacestrant  \( (n = 239) \) | Standard of Care  \( (n = 238) \) |
|------------------------------------|-----------------------------|-----------------------------|
| Median age                         | 63.0 years                  | 63.5 years                  |
| Female patients                    | 97.5%                       | 99.6%                       |
| ECOG performance status            |                             |                             |
| 0                                  | 59.8%                       | 56.7%                       |
| 1                                  | 40.2%                       | 42.9%                       |
| >1                                 | 0%                          | 0.4%                        |
| Visceral metastasis                | 68.2%                       | 70.6%                       |
| Bone-only disease                  | 15.9%                       | 12.2%                       |
| Prior adjuvant therapy             | 66.1%                       | 59.2%                       |
| Number of prior lines of endocrine therapy |                      |                             |
| 1                                  | 54.0%                       | 59.2%                       |
| 2                                  | 46.0%                       | 40.8%                       |
| Number of prior lines of chemotherapy |                           |                             |
| 0                                  | 79.9%                       | 75.6%                       |
| 1                                  | 20.1%                       | 24.4%                       |

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| 1                                  | 20.1%                       | 24.4%                       |
In summary, elacestrant is the first oral SERD to demonstrate a significant improvement in PFS in a phase III trial of patients with ER-positive/HER2-negative metastatic breast cancer, suggesting a potential role for this novel therapy in the second- and third-line treatment settings.

References
1. Bardia A, Kaklamani V, Wilks S, et al. Phase I study of elacestrant (RAD1901), a novel selective estrogen receptor degrader, in ER-positive, HER2-negative advanced breast cancer. J Clin Oncol. 2021;39(12):1360-1370. doi: 10.1200/JCO.20.02272
2. Bardia A, Neven P, Streich G, et al. Elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC) following progression on prior endocrine and CDK4/6 inhibitor therapy: Results of EMERALD phase 3 trial. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). December 7-10, 2021. Abstract GS2-02.

### Table 2. Progression-free survival in patients with ER-positive metastatic breast cancer

| Endpoint | Elacestrant (n = 239) | Standard of Care (n = 238) | HR (95% CI) | p value |
|----------|-----------------------|---------------------------|-------------|---------|
| All patients | 2.79 months | 1.91 months | 0.697 (0.552-0.880) | .0018 |
| Patients with mESR1-positive tumors | 3.78 months | 1.87 months | 0.546 (0.387-0.768) | .0005 |

### Table 3. Adverse events with elacestrant and standard endocrine therapy

| Adverse event | Elacestrant (n = 237) | Standard of Care (n = 229) |
|---------------|-----------------------|---------------------------|
|               | All grades | Grade 3-4 | All grades | Grade 3-4 |
| Nausea        | 35.0% | 2.5% | 18.8% | 0.9% |
| Fatigue       | 19.0% | 0.8% | 18.8% | 0.9% |
| Vomiting      | 19.0% | 0.8% | 8.3% | 0% |
| Decreased appetite | 14.8% | 0.8% | 9.2% | 0.4% |
| Arthralgia    | 14.3% | 0.8% | 16.2% | 0% |
| Diarrhea      | 13.9% | 0% | 10.0% | 0.9% |
| Back pain     | 13.9% | 2.5% | 9.6% | 0.4% |
| Elevated aspartate aminotransferase | 13.1% | 1.7% | 12.2% | 0.9% |
| Headache      | 12.2% | 1.7% | 12.2% | 0.9% |
| Constipation  | 12.2% | 0% | 6.6% | 0% |
| Hot flush     | 11.4% | 0% | 2.6% | 0% |
| Elevated alanine aminotransferase | 9.3% | 2.1% | 10.0% | 0.4% |

or death compared with standard therapy. In this subgroup, the median PFS was 3.79 months with elacestrant and 1.87 months with standard endocrine therapy (HR, 0.54; p = .0005).

Elacestrant was associated with a higher PFS compared with standard therapy at 6 months (34.3% vs. 20.4%) and 12 months (22.3% vs. 9.4%), suggesting a sustained benefit with oral SERD treatment. The observation of higher PFS was consistent for patients with tumors harboring mESR1. In this subgroup, elacestrant demonstrated a higher PFS rate compared with standard therapy at 6 months (40.8% vs. 19.1%) and at 12 months (26.8% vs. 8.2%).

In the safety analysis, elacestrant demonstrated a predictable safety profile consistent with that of other endocrine therapies (Table 3). The most common adverse events in the elacestrant arm included nausea, fatigue, vomiting, decreased appetite, and arthralgia. Adverse events leading to treatment discontinuations were infrequent in the elacestrant and standard-of-care groups (6.3% and 4.4%, respectively).