COMMENTARY

The Emerging Role of Oral SERDs in Early Breast Cancer

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Dear Colleagues,

Endocrine therapy remains the cornerstone of treatment for patients with early, estrogen receptor (ER)-positive, HER2-negative breast cancer.[1] Tamoxifen and aromatase inhibitors (AIs), which have formed the backbone of adjuvant management for decades, substantially reduce recurrence risk and improve long-term survival. Nevertheless, disease recurrence still occurs in a clinically meaningful proportion of patients (approximately 10-20%), particularly among those with higher-risk features.[2,3] Long-term adherence to endocrine therapy is also frequently compromised by treatment-related toxicity, which underscores the need for strategies that improve disease control while remaining tolerable for prolonged use.[4,5]

After more than two decades without major innovation in adjuvant hormonal therapy, emerging evidence suggests that oral selective estrogen receptor degraders (SERDs) might offer both improved efficacy and greater patient convenience in ER-positive, HER2-negative breast cancer. Although their clinical benefit is well established in the metastatic setting,[6-10] their role in early breast cancer has remained uncertain. This landscape is now beginning to change with the emergence of pivotal phase III trials.

The phase III lidERA trial represents the first positive randomized study of an oral SERD in the adjuvant setting. This large study enrolled more than 4,000 patients with stage I–III early ER-positive, HER2-negative breast cancer and compared the oral SERD giredestrant with standard adjuvant endocrine therapy administered for at least five years.[11] In a prespecified interim analysis at a median follow-up of nearly three years, giredestrant significantly improved invasive disease-free survival (iDFS), corresponding to a 30% reduction in the risk of invasive recurrence or death (HR: 0.70 [95% CI: 0.57–0.87]; p=0.0014).[12] Three-year iDFS rates were 92.4% with

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giredestrant and 89.6% with standard therapy. Giredestrant was also generally well tolerated and associated with lower rates of treatment discontinuation. Bradycardia, a recognized class effect of oral SERDs, occurred more frequently with giredestrant (11.3% vs 3.2%), but was predominantly grade 1, asymptomatic and non-serious. While longer follow-up is needed to assess durability and overall survival, lidERA provides the first randomized evidence that an oral SERD can outperform established endocrine therapy in the curative setting.

CAMBRIA-2 is another large, global phase III trial evaluating the oral SERD camizestrant as upfront adjuvant therapy in early-stage, ER-positive, HER2-negative breast cancer at a high risk of recurrence.[13,14] The study plans to randomize approximately 5,500 patients to receive seven years of camizestrant or standard adjuvant endocrine therapy, with abemaciclib permitted in both arms during the first two years. The primary endpoint is invasive breast cancer-free survival. Although efficacy data are not yet available, the scale and robust design of the study indicate strong clinical interest in advancing endocrine strategies to further reduce recurrence and metastatic risk in early disease.

A complementary approach is being explored in the global, multicenter, open-label phase III ELEGANT trial, which evaluates whether switching to the oral SERD elacestrant after several years of conventional adjuvant endocrine therapy can prolong DFS in patients who remain at ongoing risk of recurrence.[15] This study will enroll 4,220 patients with node-positive, ER-positive, HER2-negative early breast cancer at high risk of recurrence who have completed 24–60 months of adjuvant endocrine therapy, with or without a CDK4/6 inhibitor. Patients are randomized 1:1 to continue endocrine therapy or switch to the oral SERD elacestrant for five additional years. While results are pending, ELEGANT addresses important clinical questions regarding the optimal timing and sequencing of oral SERDs in the adjuvant setting. By introducing the SERD after the initial high-risk period, the study acknowledges the temporal heterogeneity of relapse risk and investigates whether late endocrine intervention can further reduce long-term recurrence.

The lidERA, CAMBRIA-2 and ELEGANT trials represent important developments in adjuvant endocrine therapy for early ER-positive, HER2-negative breast cancer. These studies explore complementary strategies, including upfront replacement, combination approaches and treatment sequencing with oral SERDs. While lidERA provides the first evidence of improved clinical outcomes with an oral SERD in the curative setting, results from ongoing studies will be critical to define optimal patient selection, timing and long-term benefit. These efforts mark an important



step toward more effective and individualized endocrine strategies aimed at reducing recurrence and improving long-term outcomes in early breast cancer.

Sincerely,

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Conflict of interest

Marcus Vetter received honoraria for consultancy from GSK, Roche, Novartis, Exact Sciences, Pfizer, Stemline, AbbVie and ASC Oncology. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

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