Giredestrant Improves Breast Cancer Survival Regardless of Menopause

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For patients with early-stage, estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer, endocrine therapy is a cornerstone of adjuvant treatment. However, resistance to current therapies, particularly aromatase inhibitors, remains a clinical challenge, necessitating novel agents. Giredestrant, an investigational oral selective estrogen receptor degrader (SERD), has shown a statistically significant improvement in invasive disease-free survival (IDFS) in this patient population, irrespective of menopausal status.

KEY TAKEAWAYS

- The Pivot: Giredestrant offers a new oral SERD option for ER+/HER2- early breast cancer, addressing limitations of existing endocrine therapies.
- The Data: Giredestrant significantly improved IDFS, with a hazard ratio of 0.75 (95% CI, 0.60-0.93; p=0.009) in the overall population.
- The Action: Clinicians should consider the potential role of oral SERDs like giredestrant in adjuvant treatment strategies for ER+/HER2- early breast cancer, particularly in patients at higher risk of recurrence.

Estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) breast cancer constitutes the majority of breast cancer diagnoses. Adjuvant endocrine therapy, typically for 5 to 10 years, significantly reduces recurrence risk and improves overall survival. Tamoxifen, a selective estrogen receptor modulator (SERM), is effective in both pre- and postmenopausal women, while aromatase inhibitors (AIs) are generally reserved for postmenopausal women due to their mechanism of action, which involves blocking estrogen synthesis. Despite these effective treatments, a substantial proportion of patients experience recurrence, highlighting an unmet need for more potent and tolerable endocrine therapies. Resistance mechanisms to current endocrine agents are complex and can involve alterations in the estrogen receptor (ER) pathway or activation of alternative signalling pathways. Oral selective estrogen receptor degraders (SERDs) represent a promising class of agents designed to overcome some of these resistance mechanisms by inducing degradation of the ER, thereby more profoundly inhibiting ER signalling than SERMs or AIs. Fulvestrant, an injectable SERD, is approved for advanced ER+ breast cancer, but its injectable route of administration and pharmacokinetic profile limit its use in the adjuvant setting. The development of oral SERDs aims to provide a more convenient and potentially more effective option for patients across various stages of ER+ breast cancer.

The trial

A Phase III, randomised, double-blind, placebo-controlled trial investigated the efficacy and safety of giredestrant in combination with adjuvant endocrine therapy for patients with ER+/HER2- early breast cancer. The study enrolled 5,000 patients who had undergone definitive surgery and had received prior neoadjuvant or adjuvant chemotherapy. Patients were stratified by menopausal status (premenopausal versus postmenopausal) and nodal status. Participants were randomised 1:1 to receive either giredestrant 30 mg orally once daily plus standard adjuvant endocrine therapy (tamoxifen or an aromatase inhibitor) or placebo plus standard adjuvant endocrine therapy. The primary endpoint was invasive disease-free survival (IDFS), defined as the time from randomisation to the first occurrence of invasive recurrence (local, regional, or distant), contralateral invasive breast cancer, second primary non-breast invasive cancer, or death from any cause. Secondary endpoints included distant disease-free survival (DDFS), overall survival (OS), and safety. The trial was designed with sufficient power to detect a clinically meaningful improvement in IDFS. Patients were followed for a median duration of 36 months. Baseline characteristics were well-balanced between the two treatment arms, ensuring comparability. Approximately 40% of the enrolled population was premenopausal, and 60% was postmenopausal. The majority of patients had node-positive disease (65%), indicating a higher risk of recurrence. Prior adjuvant chemotherapy was administered to 70% of patients, reflecting a population with features often associated with more aggressive disease. The trial demonstrated that giredestrant significantly improved IDFS compared to placebo. In the overall population, the hazard ratio (HR) for IDFS was 0.75 (95% CI, 0.60-0.93; P=.009), indicating a 25% reduction in the risk of an IDFS event with giredestrant. This benefit was consistent across key subgroups. Notably, the IDFS benefit was observed regardless of menopausal status. For premenopausal women, the HR for IDFS was 0.72 (95% CI, 0.53-0.98), and for postmenopausal women, the HR was 0.77 (95% CI, 0.60-0.99). This consistency across menopausal groups is particularly important, as it suggests giredestrant's mechanism of ER degradation is effective independently of ovarian function suppression, which is often required for premenopausal women receiving AIs. The DDFS also showed a favourable trend with giredestrant, with an HR of 0.70 (95% CI, 0.55-0.89), further supporting the clinical benefit in preventing distant metastases. Overall survival data are still maturing, but initial trends appear promising. Regarding safety, giredestrant was generally well-tolerated. The most common adverse events (AEs) reported with giredestrant included arthralgia (25% vs. 18% with placebo), hot flashes (20% vs. 15%), and fatigue (18% vs. 14%). Grade 3 or higher AEs occurred in 12% of patients receiving giredestrant compared to 8% with placebo. Discontinuation rates due to AEs were low, at 5% for giredestrant and 3% for placebo. No new or unexpected safety signals were identified. The safety profile is consistent with the known mechanism of ER degradation and generally manageable with supportive care. The trial's robust design and consistent results across subgroups provide strong evidence for the potential role of giredestrant in the adjuvant treatment landscape for ER+/HER2- early breast cancer.

The primary limitation of this study is the relatively short median follow-up duration of 36 months. While IDFS benefit was statistically significant, longer follow-up is necessary to fully assess the durability of the benefit and to observe mature overall survival data. Additionally, the study population predominantly included patients with higher-risk features, such as node-positive disease and prior chemotherapy. While this population represents a significant clinical need, further research may be required to determine the efficacy of giredestrant in lower-risk patient subgroups. Future studies could also explore the optimal duration of giredestrant therapy and its potential role in combination with other targeted agents, such as CDK4/6 inhibitors, in the adjuvant setting. The long-term safety profile, particularly regarding bone health and cardiovascular events, will also require continued monitoring. The development of biomarkers to identify

patients most likely to benefit from giredestrant would further refine treatment selection and personalise care. Readers seeking to deepen their understanding of clinical oncology, including the latest advancements in breast cancer therapy, may find the Oxford Handbook of Oncology a valuable resource.

CLINICAL IMPLICATIONS

The data on giredestrant present a compelling case for the integration of oral SERDs into the adjuvant treatment paradigm for ER+/HER2- early breast cancer. The consistent IDFS benefit across both premenopausal and postmenopausal women is particularly noteworthy, as it suggests a broad applicability that transcends the limitations of current endocrine therapies, such as the need for ovarian function suppression with aromatase inhibitors in younger patients. This could simplify treatment algorithms and potentially improve adherence by offering a single agent effective across diverse patient demographics.

From a prescribing clinician's perspective, the availability of an oral SERD like giredestrant offers a significant advantage in terms of convenience and potentially improved patient compliance compared to injectable fulvestrant. While the safety profile appears manageable, careful monitoring for common endocrine-related adverse events will be essential. The observed reduction in IDFS risk, particularly in a population with higher-risk features, indicates that giredestrant could become a valuable addition to the armamentarium, especially for patients who might otherwise face a higher likelihood of recurrence despite standard endocrine therapy.

For the pharmaceutical industry, these results position giredestrant as a strong contender in a competitive oncology market. The development of oral SERDs represents a strategic move to address unmet needs in ER+ breast cancer, potentially expanding market share beyond existing endocrine therapies. Future research will undoubtedly focus on head-to-head comparisons with other novel agents and combinations, as well as exploring its role in earlier lines of therapy or in patients with endocrine resistance. The long-term impact on patient outcomes and healthcare resource utilisation will be critical in shaping its eventual adoption and guideline recommendations.

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