First-line fulvestrant *vs.* anastrozole in hormone receptor-positive advanced breast cancer: insights from the final FALCON trial results

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The management paradigm for hormone receptor-positive (HR^+) advanced breast cancer has evolved dramatically with improvements in endocrine therapy (ET), notably through aromatase inhibitors (AIs), selective estrogen receptor degraders (SERDs), and more recently, the addition of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors (1). Despite the introduction of novel agents and combinations, the choice of first-line ET remains a pivotal decision point for clinicians. The FALCON trial, a landmark phase III study, provides valuable evidence for optimizing therapy selection, comparing fulvestrant with anastrozole in postmenopausal women naïve to prior ET (2).

FALCON enrolled 462 postmenopausal women with HR^+, human epidermal growth factor receptor 2-negative ($HER2^-$) advanced breast cancer who had not previously received systemic ET in the advanced setting. The randomized, double-blind design compared fulvestrant 500 mg with anastrozole 1 mg as first-line ET. Stratification by visceral and nonvisceral metastases allowed granular analysis of how metastatic site influences therapeutic benefit, a factor increasingly recognized as clinically significant. *Tab. 1* summarizes baseline characteristics, confirming balanced demographics (median age 62–64 years), performance status, prior treatments, and distribution of metastatic sites (3).

At the preplanned final analysis (68% events, cutoff July 2022), median follow-up exceeded 3 years per arm. The intention-to-treat cohort revealed no statistically significant difference in median overall survival (OS): 44.8 months for fulvestrant *vs.* 42.7 months for anastrozole [hazard ratio 0.97, 95% confidence interval (CI): 0.77–1.21]. Subgroup analyses, however, tell a more nuanced story. In patients with nonvisceral disease, fulvestrant showed a trend toward improved OS (65.2 *vs.* 47.8 months, hazard ratio 0.85, 95% CI: 0.60–1.20), corresponding to a sizable 17.4-month median OS benefit and a 15% reduction in relative risk of death, though not reaching statistical significance. Exploratory analysis in this nonvisceral population found the greatest absolute OS gain with fulvestrant (65.2 months) compared to those with visceral metastases (37.2 months, hazard ratio 0.62, 95% CI: 0.45–0.85). These results are consistent across multiple subgroups and echo findings from the pivotal FIRST, CONFIRM, MONALEESA, and SWOG S0226/MONARCH 2 trials (4-9).

Long-term safety data in FALCON reaffirm prior reports: both therapies exhibited low rates of serious adverse events, treatment discontinuations, and deaths directly linked to study drugs. No new safety signals emerged over 8 years of monitoring. The health-related quality of life (HRQOL) assessments further support the excellent tolerability of both drugs, with no clinically meaningful differences across arms through prolonged therapy (2,3,10).

Real-world treatment following study therapy progressed

similarly for both arms: about half of the patients received post-study anticancer therapies, including other ET agents, chemotherapy, and radiotherapy. Use of newer agents such as CDK4/6 inhibitors was infrequent overall (<5% per arm), reflecting trial timing and global access trends. *Tab. 3* in the FALCON report provides a comprehensive distribution of these subsequent therapies, showing parallel real-world management across both trial groups (1,11).

Meta-analyses and translational studies have clarified that metastatic site is not a mere reflection of tumor burden, but a proxy for underlying disease biology and endocrine sensitivity. Patients with nonvisceral (bone, skin, breast-only, soft tissue) involvement typically retain higher estrogen receptor (ER) and progesterone receptor (PR) levels, have lower proliferation indices (Ki-67), and fewer pathway mutations driving resistance, correlating with augmented benefit from endocrine monotherapy. Mechanistically, fulvestrant induces near-complete degradation of ER protein, whereas nonsteroidal aromatase inhibitors (NSAIs) suppress estrogen synthesis but leave ER available for possible ligand-independent, phosphorylated ER-driven signaling. Consistent with this concept, Vergote *et al.* reported that anastrozole retained activity as second-line therapy after fulvestrant, supporting the feasibility of sequential fulvestrant-NSAI use in advanced breast cancer (12).

FALCON reinforces this observation by demonstrating substantially higher median OS for nonvisceral disease with fulvestrant therapy, a finding mirrored in earlier subgroup and post hoc analyses (3).

International consensus from the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) similarly recommend initial ET subject to individual patient risk, comorbidities, and metastatic pattern, in endocrine-sensitive, nonvisceral cases, reserving chemotherapy for symptomatic or rapidly progressing disease (6). The landscape of ET continues to shift: while fulvestrant remains a gold-standard SERD for first-line and second-line use, newer oral SERDs such as elacestrant, camizestrant, amcenestrant, giredestrant, and imlunestrant, etc., are changing therapeutic possibilities, with promising data emerging for ET-resistant disease and ESR1-mutant populations (13-15).

Recent advances in CDK4/6 inhibitor therapy have also expanded treatment options. The 2024–2025 literature confirms that CDK4/6 inhibitors combined with fulvestrant remain standard first-line treatment for both premenopausal and postmenopausal women with $HR^+/HER2^-$ advanced breast cancer (16). Moreover, abemaciclib plus fulvestrant has demonstrated significant progression-free survival (PFS) improvement even after disease progression on previous CDK4/6 inhibitor therapy, offering an additional treatment option in the post-CDK4/6 inhibitor setting (17). Yet, not all patients are eligible or able to access CDK4/6 inhibitors or oral SERDs due to cost, comorbidities, or intolerance. Thus, fulvestrant retains a pivotal role for those with ET-sensitive, indolent disease, and especially for nonvisceral metastases where the benefit is most pronounced.

FALCON's strengths include its robust double-blind, randomized international design, long-term follow-up, and prespecified OS analysis. The trial provides some of the longest OS estimates for ET-naïve populations, with median OS near 4 years for both drugs. Limitations include its descriptive rather than powered OS analysis, the timing of therapy sequencing amidst evolving standards, and incomplete subsequent therapy capture post-study. Exploratory subgroup findings, particularly for nonvisceral and visceral populations, generate hypotheses that merit validation in larger, powered prospective cohorts. Real-world studies and meta-analyses, now involving thousands of patients, confirm that fulvestrant and other ET agents produce superior outcomes in nonvisceral *vs.* visceral metastatic disease. For example, Robertson *et al.*'s meta-analysis reports consistently longer OS among bone-only and soft tissue metastasis cohorts compared with liver and lung involvement (18).

As clinical trial evidence converges with real-world data, several key research avenues emerge (4,13):

- Identification and management of *ESR1* mutations, which may predict ET resistance and help tailor optimal sequencing (e.g., oral SERDs for ESR1-mutant).
- Refinement of patient selection, incorporating molecular and genomic profiling to better stratify risk and optimize treatment.
- Ongoing phase III trials evaluating oral SERDs and their partner combinations, including CDK4/6 inhibitors, will define new standards for efficacy, safety, and patient-centered care.

The FALCON trial's final OS analysis indicates that, while first-line fulvestrant and anastrozole did not show a statistically significant difference in OS in ET-naïve $HR^+/HER2^-$ advanced breast cancer, fulvestrant may confer a meaningful survival benefit for patients with nonvisceral metastases, reflecting a biologically indolent and endocrine-sensitive pattern. Its tolerability and favorable HRQOL

underline its enduring value in the contemporary clinical armamentarium. Widespread use of fulvestrant, the rise of CDK4/6 inhibitors, and the imminent arrival of oral SERDs necessitate more sophisticated, personalized treatment algorithms rooted in both biological and clinical risk factors. The international oncology communities will rely increasingly on detailed trial and real-world evidence like FALCON to achieve precision care, improve patient outcomes, and guide the next generation of therapeutic innovations.

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