Elacestrant Monotherapy as a Second-Line Treatment for ER-Positive, HER2-Negative Advanced Breast Cancer with *ESR1* Mutations

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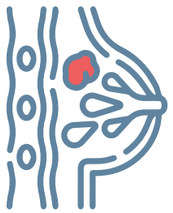
Current Recommendations



- Guidelines recommend testing for *ESR1* mutations in liquid biopsy at each progressionof ER+/HER2- aBC following treatment with endocrine therapy plus CDK4/6 inhibitors, if not detected previously[1-3]
- Archival tumour tissue is not recommended
- Elacestrant is approved and recommended by ASCO, NCCN, and ESMO guidelines for patients with *ESR1* mutations in this scenario, based on data from the EMERALD trial (NCT03778931)[1-6]

Study Design

EMERALD is a Phase III, global, multicenteric, randomised, controlled trial of elacestrant versus SoC endocrine therapy in patients with ER+/HER2- aBC with prior exposure to endocrine therapy and CDK4/6 inhibitors, for which one primary endpoint is PFS in patients with *ESR1* mutation (Figure 1)[5-7]

Figure 1: EMERALD Study Design[5-7]

Patients

- ER+/HER2- advanced/metastatic breast cancer
- 1-2 prior lines of ET in advanced disease
- 1 line of prior CDK4/6i required
- ≤1 line of chemotherapy in advanced disease
- Prior fulvestrant use was allowed
- Primary resistance was allowed

R 1:1 (N=478)

Elacestrant	Investigator's choice (SoC)
345 mg daily*	• Fulvestrant • Anastrozole • Letrozole • Exemestane

Until disease progression

Follow-up

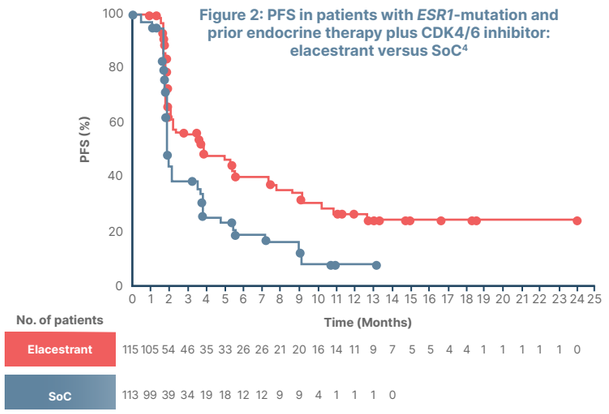
Primary endpoints

- PFS in patient with *ESR1*-mut
- PFS in all patients

*345 mg of elacestrant is equivalent to 400 mg of elacestrant dihydrochloride.

PFS in patients with *ESR1*-mut

Figure 2: PFS in patients with *ESR1*-mutation and prior endocrine therapy plus CDK4/6 inhibitor: elacestrant versus SoC[4]



	Elacestrant (n=115)	SoC (n=113)
mPFS (months)	3.8	1.9
PFS rate at 12 months, % (95% CI)	26.8 (16.2-37.4)	8.2 (1.3-15.1)
Hazard ratio (95% CI)	0.55 (0.39–0.77)	
P-value	0.0005	

- **PFS was significantly prolonged in the elacestrant arm in patients with *ESR1* mutation leading to a 45% reduction in the risk of progression or death (HR 0.55; 95% CI 0.39–0.77; P=0.0005).[4]**
- Because of the initial drop in PFS in both treatment arms (likely due to primary resistance), median PFS may not be a sufficient measure of efficacy; therefore, landmark analyses were conducted[4]

PFS in patients with ESR1-mut and NO prior chemotherapy

Elacestrant showed 5.3 months mPFS vs 1.9 with SOC in patients with ESR1-mut tumors and NO prior exposure to chemotherapy in aBC (HR: 0.535; 95% CI: 0.356-0.799; p=0.00235)

PFS and Duration of Prior CDK4/6 Inhibitor Therapy in Patients with *ESR1*-mut

Figure 3: PFS in patients with ESR1 mutations and longer prior ET + CDK4/6i[7]

- With the intention to evaluate the benefit of elacestrant based on prior ET-based regimen duration (≥12 months), a non pre-specified exploratory subgroup analysis was conducted, concluding that a longer duration of prior ET-based regimen in the metastatic setting was associated with a clinically meaningful improvement in PFS for elacestrant compared to SOC in patients with *ESR1*-mutated tumours.
- In post-hoc analyses of EMERALD data, duration of prior CDK4/6i therapy (as a surrogate marker for endocrine sensitivity) was positively associated with median PFS in patients with *ESR1* mutation
- Among patients with longer duration (≥12 months) of prior endocrine therapy plus CDK4/6i, elacestrant provided a mPFS of 8.61 months versus 1.91 months for SoC (Figure 3)[9]

	Elacestrant	SoC
mPFS, months (95% CI)	8.61 (4.14–10.84)	1.91 (1.87–3.68)
Hazard ratio (95% CI)	0.410 (0.262–0.634)	

PFS in Endocrine-sensitive Tumours with *ESR1* Mutation

Table 1: Across all subgroups evaluated, a clinically meaningful improvement in PFS was associated with elacestrant compared with SoC in those patients with *ESR1*-mutated tumors who received prior ET + CDK4/6i ≥12 months[9]

	mPFS, Months			
Patient Subgroup	n (%)	Elacestrant	SoC	HR (95% CI)
All patients with *ESR1*-mutated tumors	159 (100)	8.6	1.9	0.41 (0.26-0.63)
Bone metastases	136 (86)	9.1	1.9	0.38 (0.23–0.62)
Liver and/or lung metastases	113 (71)	7.3	1.9	0.35 (0.21–0.59)
<3 metastatic sites	82 (52)	9.0	1.9	0.41 (0.23–0.75)
≥3 metastatic sites	53 (33)	10.8	1.8	0.31 (0.12–0.79)
PIK3CA-mutated tumors	62 (39)	5.5	1.9	0.42 (0.18–0.94)
TP53-mutated tumors	61 (38)	8.6	1.9	0.30 (0.13–0.64)
HER2-low expression	77 (48)	9.0	1.9	0.30 (0.14–0.60)
$ESR1^{D538G}$-mutated tumors	97 (61)	9.0	1.9	0.38 (0.21–0.67)
$ESR1^{Y537S/N}$-mutated tumors	92 (58)	9.0	1.9	0.25 (0.13–0.47)

- *ESR1* mutations are associated with poor prognosis[10]
- When tumours with *ESR1* mutation remain endocrine sensitive, the ER pathway could be the main driver of disease progression, in the context of other variables associated with poor prognosis
- A clinically meaningful improvement in PFS favouring elacestrant compared with SoC was consistent across all relevant subgroups with *ESR1* mutation and assumed endocrine-sensitivity (prior CDK4/6i duration ≥12 months; Figure 4)[7]

Safety Profile

Most adverse events were Grade 1-2; no Grade 4 treatment-related adverse events were reported (Table 1)[6,7]

Table 1: Safety profile of elacestrant versus SoC in the EMERALD study[6,7]

Adverse Reaction[a]	Elacestrant (n=237)		SoC (n=230)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[b]	41.0	7.0	39.0	1.0
Gastrointestinal Disorders				
Nausea	35.0	2.5	19.0	0.9
Vomiting[b]	19.0	0.8	9.0	0.0
Diarrhoea	13.0	0.0	10.0	1.0
Constipation	12.0	0.0	6.0	0.0
Abdominal pain[b]	11.0	1.0	10.0	0.9
Dyspepsia	10.0	0.0	2.6	0.0
General Disorders				
Fatigue[b]	26.0	2.0	27.0	1.0
Metabolism and Nutritional Disorders				
Decreased appetite	15.0	0.8	10.0	0.4
Nervous System				
Headache	12.0	2.0	12.0	0.0
Vascular Disorders				
Hot flush	11.0	0.0	8.0	0.0
Treatment-related AEs leading to discontinuation, %				
	3.4		0.9	

[a]Adverse events were graded using NCI CTCAE version 5.0;
[b]Includes other related terms;

Nausea summary[7]	Elacestrant (n=237)	SoC (n=230)
Grade 3 nausea (%)	**2.5**	**0.9**
Dose-reduction rate due to nausea (%)	1.3	N/A
Discontinuation rate due to nausea (%)	1.3	0.0
Antiemetic use (%)	8.0	10.3 (AI) 1.3 (fulvestrant)

Key Takeaways

- Elacestrant demonstrated a statistically significant, clinically meaningful, PFS improvement versus SoC in patients with *ESR1* mutations, with manageable safety, in patients with ER+/HER2- aBC
- Clinically meaningful improvement in PFS favouring elacestrant was consistent across all relevant subgroups with *ESR1* mutations and assumed endocrine-sensitivity (longer prior CDK4/6i duration) inluding visceral metastasis and coexistence of *ESR1* and *PIK3CA* mutations or HER2-low expression
- **These data support the sequencing of single-agent elacestrant therapy in patients with ESR1 mutation, before the use of other targeted therapies, drug combinations, and chemotherapy-based regimens, including antibody-drug conjugates[7]**

Abbreviations

aBC: advanced breast cancer; AE: adverse event; AI: aromatase inhibitor; ASCO: American Society of Clinical Oncology; CDK4/6: cyclin-dependent kinase 4/6; CDK4/6i: CDK4/6 inhibitors; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; ER+: ER-positive; ESMO: European Society for Medical Oncology; ESR1: Estrogen Receptor 1; ESR1-mut: ESR1-mutation; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HER2-: HER2-negative; HR: hazard ratio; mPFS: median progression-free survival; NCCN: National Comprehensive Cancer Network; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PFS: progression-free survival; PIK3CA: p110α subunit of phosphoinositide 3-kinase; R: randomisation; SoC: standard of care; TP53: tumor protein p53.

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