ESR1 testing in oestrogen receptor (ER)-positive HER2-negative locally advanced or metastatic breast cancer guidance document

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Guideline version: 1.0 **Date:** 15 05 25

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1.Background

The gene, ESR1, encodes the oestrogen receptor. Up to 50% of breast cancers treated with endocrine therapy such as an aromatase inhibitor inhibitors develop variants in ESR1 on disease progression. ESR1 variants are a key resistance mechanism to aromatase inhibitors but maintain sensitivity to the selective oestrogen receptor degrading agent, elacestrant (1)

The key clinical-effectiveness evidence for elacestrant came from EMERALD (2). This was a phase 3, open-label, multicentre trial that compared elacestrant with physician's choice of fulvestrant, anastrozole, letrozole or exemestane. It included 478 women who had been through the menopause and men 18 years and over, with histologically or cytologically proven ER-positive HER2-negative locally advanced or metastatic breast cancer. The key inclusion criteria were:

- disease progression during or within 28 days after treatment with 1 to 2 previous lines of endocrine therapy for advanced or metastatic breast cancer, including a CDK 4 and 6 inhibitor with fulvestrant or an aromatase inhibitor
- progression during or within 12 months of adjuvant endocrine therapy, considered as 1 line of endocrine therapy for advanced or metastatic cancer
- up to 1 chemotherapy regimen for advanced or metastatic breast cancer
- ECOG performance status 0 or 1, and measurable disease using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or evaluable bone-only disease.

Randomisation was stratified based on ESR1-variant status, previous treatment with fulvestrant and presence of asymptomatic visceral metastasis. The primary endpoint was progression-free survival

Activating ESR1 variants were detected in 47.8% of patients, In the EMERALD trial population, 228 people had an ESR1 variant, of which 159 people had at least 12 months of previous treatment with endocrine therapy plus a CDK 4 and 6 inhibitor.

For the target population NICE considered 2 post-hoc subgroups from EMERALD:

- Activating ESR1-variant subgroup (n=159; 78 in the elacestrant arm and 81 in the active control arm).
- Dual-mutated activating ESR1-variant and PIK3CA-variant subgroup (n=62; 27 in the elacestrant arm and 35 in the active control arm).

The EMERALD results showed statistically significantly longer progression-free survival in the elacestrant arm (median 8.6 months) compared with the physician's choice arm in the activating ESR1-variant subgroup that included the dual-mutated subset (hazard ratio 0.41, 95% confidence interval [CI] 0.262 to 0.634; p<0.0001; n=159). Statistically significantly longer progression-free survival in the elacestrant arm (median 5.5 months) compared with the physician's choice arm (median 1.9 months) was also observed for the dual-mutated subset (hazard ratio 0.423, 95% CI 0.176 to 0.941; n=62).

2.Objective and scope

The aim of this document is to provide clinical staff with guidance on ESR1 testing in oestrogen receptor (ER)-positive HER2-negative locally advanced or metastatic breast cancer.

The guidance is relevant to all staff involved with the management of adults who are eligible to have their tumour tested for this genetic biomarker.

3.NICE recommendation for Elacestrant

Elacestrant is recommended (1) as an option for treating oestrogen receptor (ER)-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 variant that has progressed after at least 1 line of endocrine treatment plus a cyclin-dependent kinase (CDK) 4 and 6 inhibitor in:

- women, trans men and non-binary people who have been through the menopause, or the patient has undergone ovarian ablation or suppression with LHRH agonist treatment
- trans women and men.

Elacestrant is recommended only if the cancer has progressed after at least 12 months of endocrine treatment plus a CDK 4 and 6 inhibitor.

4.Who to test

All individuals with ER-positive, HER2-negative locally advanced or metastatic breast cancer, including women, trans men, trans women, and non-binary people, should be considered for ESR1 testing.

Patients must have progressed after at least 1 line of endocrine treatment plus a cyclin-dependent kinase (CDK) 4 and 6 inhibitor, that has been given for at least 12 months'.

The Cancer Drug Fund (ver1.354 14-Mar-25) does not allow elacestrant if the patient has had no more than 1 prior line of cytotoxic chemotherapy for advanced/metastatic disease.

5.When to test

On progression.

6.What sample to test

Cell-free DNA (cfDNA) extracted from blood plasma will be used for the detection of ESR1 variants. This cfDNA will contain any circulating tumour DNA (ctDNA) that has been shed by the cancer cells into the bloodstream.

Activating ESR1 variants are rarely present in primary tumours but emerge as a resistance mechanism after exposure to aromatase inhibitors (3). A tissue biopsy from a tumour before expose to AI's may not reflect the current mutational landscape in metastatic disease. Additionally, as ESR1 variants are sub-clonal, single-site tissue biopsy may miss ESR1-mutant subclones, whereas ctDNA provides a more comprehensive, systemic view of all circulating tumour-derived DNA fragments.

There may be very low levels of ctDNA within the sample meaning that any tumour ESR1 variants are undetectable by the test. Result interpretation in the absence of an ESR1 variant will therefore be cautious.

7.Which ESR1 variants confer resistance to aromatase inhibitor but main sensitivity to elacestrant?

Activating variants in ESR1 (e.g., Y537S, D538G, E380Q, L536H/P/R) lead to ligand-independent ER activation, reducing the effectiveness of aromatase inhibitors and tamoxifen but maintaining sensitivity to SERDs like elacestrant.

8.How to request the genomic test

ESR1 testing performed by the All Wales Medical Genomics Service (AWMGS).

All samples for ESR1 testing should be accompanied by Breast Oncology ctDNA request form (see appendix i). The request form can be downloaded from the AWMGS website.

Blood should be collected in **Streck tubes,** which stabilise the sample. Streck tubes are distributed by AWMGS and can be requested by emailing lab.genetics.cav@wales.nhs.uk

Two Streck tubes each containing 10 ml of blood are required.

The samples in Streck tubes should be sent promptly to be received at AWMGS within a maximum of 96 hours. Samples that are delayed in transit may not be suitable for testing.

Do not refrigerate the Streck tubes.

The turnaround time for testing is 14 calendar days from sample receipt in AWMGS.

Samples should be sent to:

All Wales Medical Genomics Service

Canolfan Iechyd Genomig Cymru (CIGC)

Cardiff Edge Business Park

Longwood Drive

Whitchurch

Cardiff

CF14 7YU

9.How to interpret the genomic result report

The AWMGS report will describe the variant identified using professionally recommended nomenclature, HGVS (Human Genome Variation Society), e.g. c.3140A>G p.(His1047Arg).

The following results will be reported by AWMGS**:-**

1. **Clinically relevant ESR1 variant detected**

The AWMGS report will include a therapeutic comment: '*Based on the presence of a clinically relevant ESR1 variant in cfDNA, this patient has an increased likelihood of resistance to aromatase inhibitor but maintained sensitivity to selective oestrogen receptor degraders (SERDs) such as Elacestrant'.*

2. **Variant of uncertain significance detected**

The AWMGS report will include a therapeutic comment: '*An ESR1 variant of uncertain clinical significance has been detected in this patient's cell free DNA sample. During investigation insufficient evidence was found on this variant to allow it to be classified as an actionable variant. This patient's response to treatment with selective oestrogen receptor degraders such as Elacestrant is therefore also uncertain.*'

3. **No ESR1 variants detected**

The AWMGS report will include a therapeutic comment: *Results of this cfDNA testing do not indicate treatment with selective oestrogen receptor degraders (SERDs) such as Elacestrant. No currently actionable variants detected in ESR1.* Additional information on the limitations of cfDNA testing will be provided.

4. **Failed result**

Failed testing reports may also be issued for samples that are unsuitable for testing (i), or have failed to meet laboratory quality metrics during testing (ii). These will be reported with the following conclusions:

i. Insufficient cell free DNA or insufficient quality cell free DNA for NGS testing
ii. Testing has failed for this patient's cell free DNA sample

For either of the above scenarios (i or ii) repeat testing with a new blood sample will be recommended.

10.References

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3. Will, M., Liang, J., Metcalfe, C., & Chandarlapaty, S. (2023). Therapeutic resistance to anti-oestrogen therapy in breast cancer. *Nature reviews. Cancer*, *23*(10), 673–685. https://doi.org/10.1038/s41568-023-00604-3

11.Appendix i: ESR1 Request Form:

AWMGS
All Wales Medical Genomics Service

ESR1 Analysis Breast Oncology ctDNA Request Form

Fill in patient details below, or affix addressograph			
Patient forename(s):		Patient surname:	Lead Consultant:
DoB:	Sex	Hospital (required for report):	Requested by:
Address:			Hospital number:
			Alternative hospital number:
			NHS number:
Postcode:			Date requested:
Email addresses to receive report (*NHS emails only*):			
Date and time of blood draw: dd/mm/yyyy _____ hh:mm _____			

Instructions for sending samples:

- Provide 20ml whole blood in 2 Streck Cell-Free DNA BCT® tubes (Streck tubes available on request from the laboratory, please email lab.genetics.CAV@wales.nhs.uk)
- Invert the tubes gently 8-10 times following blood draw
- Ensure all blood tubes are clearly labelled with the patient's name and DOB and that all details on this form have been completed.
- Samples are to be kept at ambient temperature and dispatched within 24 hours. **Do not refrigerate or freeze.**
- Samples can be received at AWMGS on Monday to Thursday 9am to 5pm, or Friday 9am to 3pm only. This will ensure that the samples can be processed rapidly on receipt to maintain sample integrity.
- If sending samples to the lab on a Friday, please alert the lab team by emailing lab.genetics.CAV@wales.nhs.uk so that processing can be completed promptly upon receipt.

Please send the sample and completed request form to:	**Laboratory contact details for enquiries:**
All Wales Medical Genomics Service Wales Genomic Health Centre Cardiff Edge Business Park Longwood Drive Cardiff CF14 7YU	Phone: 02921 834000 **Email addresses:** For general lab queries and Streck tube requests: lab.genetics.cav@wales.nhs.uk

https://www.medicalgenomicswales.co.uk/