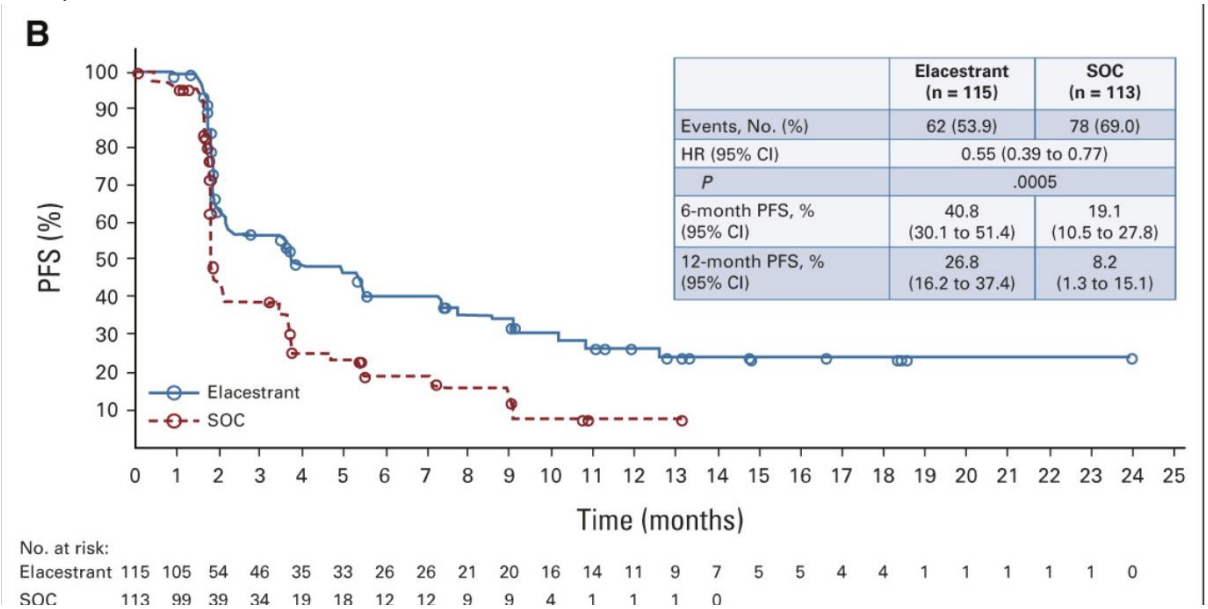
**The Condition**

1) Mutations in the oestrogen receptor (ESR1) are a common mechanism of resistance to hormonal therapies in metastatic breast cancer (potentially in 20-40% of patients).
2) This is potentially a problem in a large number of patients given that ER positive cancer is the most common form of breast cancer, and hormonal therapies in conjunction with CDK 4/6 inhibitor is the most common treatment paradigm in suitable patients.

**The Treatment**

3) Elacestrant is a new class of agent called an ESR1 inhibitor or degrader.
4) It was approved by the MHRA in January 2024.
5) The license is for ER-positive, HER2-negative, metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor.
6) Funding will be available within the terms of the license and if the cancer has progressed after **at least 12 months of endocrine treatment plus a CDK 4/ 6 inhibitor**
7) It was assessed in the EMERALD study[1], which included patients with ER-positive/HER2-negative advanced breast cancer who had one-two lines of endocrine therapy and pretreatment with a cyclin-dependent kinase 4/6 inhibitor regardless of ESR-1 status.
8) A preplanned analysis was performed in patients with tumours with activating ESR1 mutations.
9) Efficacy is this population is shown below. The Hazard ratio for progression or death was 0.55 (95% CI, 0.39 to 0.77) with a **14% improvement** in the percentage of patients with ongoing disease control at **6 months** (34% versus 20%) and **22% increase at 12 months** 41% versus 19%.




| | Elacestrant (n = 115) | SOC (n = 113) |
|---|---|---|
| Events, No. (%) | 62 (53.9) | 78 (69.0) |
| HR (95% CI) | 0.55 (0.39 to 0.77) | |
| *P* | .0005 | |
| 6-month PFS, % (95% CI) | 40.8 (30.1 to 51.4) | 19.1 (10.5 to 27.8) |
| 12-month PFS, % (95% CI) | 26.8 (16.2 to 37.4) | 8.2 (1.3 to 15.1) |

**The Genomic Test**

10) ESR1 mutations are an **acquired resistance** mutation and won't be found in the baseline sample but can be readily detected in **circulating tumour DNA**.
11) Given the wording of the license and accompanying approval by NICE : demonstration of an ESR1 mutation will be **mandatory** to be eligible for this treatment.
12) In the EMERALD study this was performed on plasma ctDNA using **Guardant** technology. This is the technology that has been used via a tech transfer in the North Thames GLH
13) Other technologies including **Foundation Liquid** (forthcoming tech transfer in the North West GLH and Genexus technology: validated in the South East GLH would be capable of providing this.
14) Testing on the tumour by a repeat biopsy may miss this mutation as it can be a sub-clonal event and **will not** be commissioned within the National Test Directory.

**Results**

15) ctDNA results can be challenging to interpret, particularly if a full gene panel is performed (which is what is provided by Guardant and Foundation Liquid).
16) This may include genes which are not standardly commissioned for reporting in the national test directory, and where there are not therapeutic options available.
17) It may also highlight potential germline abnormalities which may or may not be of significance.
18) Reports should be reviewed by an experienced oncologist. Advice as to interpretation can be sought by referral to the genomics tumour advisory board (GTAB).

**Implications**

19) Extensive work will be required around implementation and education.
20) This includes
    a. Provision and storage of consumables
    b. identification of suitable patients (ie patients at time of progression on appropriate hormonal/ CDK 4/6 inhibitors having completed at least 12 months of combination therapy)
    c. Upskilling phlebotomy services to move to a business-as-usual service
    d. Educating clinical teams to understand the results and actions to be taken with both a positive and negative result.
    e. Strategies to deal with other genomic findings if a NGS panel is run on cfDNA. For example somatic findings outside of the national test directory and potential germline findings.

1) Bidard et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338.