NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
November 2022

Elacestrant for treating HER2-negative, ER-positive, advanced breast cancer after endocrine therapy

Company/Developer	Menarini Group

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27136	NICE ID: 11825	UKPS ID: 665793

Licensing and Market Availability Plans

Currently in phase II/III trials.

Summary

Elacestrant is in clinical development for the treatment of oestrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-negative), advanced or metastatic breast cancer in patients who have progressed after prior treatment. Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Cancers that have receptors for the hormone oestrogen are ER+, and HER2-negative means that the cancerous cells do not contain high levels of the protein HER2. Metastatic cancers have spread from where they started to other parts of the body. There is a major unmet need for breast cancer patients who have progressed after receiving standard endocrine therapy and cyclin-dependent kinase 4/6 (CDK4/6) inhibitor.

Elacestrant is a novel, nonsteroidal, selective oestrogen receptor degrader (SERD) that degrades the oestrogen receptor, preventing oestrogen-mediated tumour growth. Elacestrant is administered orally. Elacestrant is the first oral SERD to demonstrate improved efficacy compared with standard of care endocrine therapy in advanced breast cancer. If approved, elacestrant will provide a novel treatment option for patients with ER+, HER2-, advanced or metastatic breast cancer who have had previous endocrine therapy, including treatment with a CDK4/6 inhibitor.

Proposed Indication

Treatment of postmenopausal adults with oestrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-negative), advanced or metastatic breast cancer who had one or two lines of endocrine therapy.[1,2]

Technology

Description

Elacestrant (RAD1901) is a novel, nonsteroidal, oral selective oestrogen receptor degrader (SERD). Elacestrant degrades the ER alpha in a dose-dependent manner and inhibits oestradiol-dependent ER-directed gene transcription and tumour growth in both *in vitro* and *in vivo* preclinical models, including those harbouring *ESR1* mutations associated with endocrine resistance.[1]

Elacestrant is in clinical development for the treatment of ER+, HER2-, advanced or metastatic breast cancer who have had previous endocrine therapy, including treatment with a CDK4/6 inhibitor.[2,3] In the phase III trial (NCT03778931), 400mg elacestrant once daily was administered orally.[2]

Key Innovation

Breast cancer progression after treatment with endocrine therapy, aromatase inhibitors/fulvestrant and a CDK4/6 inhibitor, can be associated with endocrine resistance, which includes development of acquired mutations in a variety of genes such as erb-b2 receptor tyrosine kinase 2 (*ERBB2*), neurofibromin 1 (*NF1*), and oestrogen receptor 1 (*ESR1*). Mutations in *ESR1* result in oestrogen-independent ER activation and, consequently, resistance to aromatase inhibitors (AIs) but not ER inhibitors (e.g., SERDs and selective ER modulators).[1] The clinical activity of endocrine monotherapy in patients who have received prior CDK4/6 or mammalian target of rapamycin (mTOR) inhibition is limited, with a median progression-free survival (PFS) of approximately 2 months, highlighting a major unmet clinical need in the field.[4-6]

In the phase III clinical trial (NCT03778931), elacestrant was associated with a statistically significantly prolonged PFS compared with standard of care (SOC) endocrine therapy in patients with advanced/metastatic ER-positive/HER2-negative breast cancer who had progressed on prior endocrine and CDK4/6 inhibitor therapy. Elacestrant is the first oral SERD to demonstrate improved efficacy compared with SOC endocrine therapy in patients with advanced breast cancer.[1] Nearly two decades have passed since the last endocrine therapy, fulvestrant, was approved in 2002 for patients with ER-positive metastatic breast cancer.[7] If approved, elacestrant offers a new oral endocrine therapy option to patients with previously treated metastatic HR–positive breast cancer, including *ESR1*-mutant breast cancer.[1]

Regulatory & Development Status

Elacestrant does not currently have Marketing Authorisation in the EU/UK for any indication.

Elacestrant is also in currently in phase II and III clinical trials in combination with other drugs for the treatment of breast cancer, as well as in combination with abemaciclib for the treatment of brain metastasis due to HR+/HER2- breast cancer.[8]

Elacestrant has the following regulatory designations/awards:[9]

- An FDA Priority Review in August 2022.
- An FDA Fast Track Designation by the FDA in 2018.

Patient Group

Disease Area and Clinical Need

Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Breast cancer starts in the breast tissue, most commonly in the cells that line the milk ducts of the breast.[10] Cancers that have receptors for oestrogen are ER+ breast cancers.[11] When a breast cancer is HER2-negative, it means that the cancerous cells do not contain high levels of the protein HER2.[12] Metastatic cancers have spread from where they started to other parts of the body. Cancers that have spread are often thought of as advanced when they can't be cured or controlled with treatment.[13] There are several risk factors that can cause breast cancer, including being overweight, drinking alcohol, contraceptive pill, hormone replacement therapy (HRT), ageing, diabetes and dense breast tissue.[14] Symptoms include a new lump or thickening in the breast or armpit, a change in size, shape or feel of the breast, skin changes in the breast such as puckering, dimpling, a rash or redness of the skin, fluid leaking from the nipple in a woman who isn't pregnant or breast feeding and changes in the position of the nipple.[15]

Breast cancer is the most common cancer in the UK, and it is more common in women than men. Around 55,500 women and around 370 men are diagnosed in the UK each year. 1 in 7 women in the UK develop breast cancer during their lifetime. It is more common in older women.[10] HER2-negative breast cancer is the most common type, accounting for about 70% of all breast cancers.[16] Approximately 75% of breast cancers are ER+.[11] There are around 11,500 breast cancer deaths in the UK every year (2017-2019). Around 85% of women diagnosed with breast cancer in England survive their disease for five years or more (2013-2017).[17] Breast Cancer Now estimate that around 35,000 people living with metastatic breast cancer in the UK. In around 5% of women, breast cancer has already spread by the time it is diagnosed.[18] In England (2021-22), there were 244,374 finished consultant episodes (FCE) for malignant neoplasm of the breast (ICD-10 code C50), of which 1,196 were for male patients and 243,116 were for female patients. This resulted in 240,790 admissions, 218,006 day cases and 60,220 FCE bed days.[19]

Recommended Treatment Options

NICE recommend endocrine therapy for patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, following the completion of chemotherapy.[20]

NICE guidelines suggest offering an aromatase inhibitor (either non-steroidal or steroidal) to:[20]

- Postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
- Postmenopausal women with ER-positive breast cancer previously treated with tamoxifen

NICE recommend the following for the treatment of ER+, HER2-, advanced or metastatic breast cancer, who have had prior treatment:

- Abemaciclib plus fulvestrant in adults who have had endocrine therapy only if exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor.[21]
- Ribociclib plus fulvestrant in adults who have had previous endocrine therapy only if exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor.[22]
- Palbociclib with fulvestrant in people who have had previous endocrine therapy only if exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor.[23]
- Everolimus, in combination with exemestane.[24]

Clinical Trial Information

Trial	**EMERALD; NCT03778931;** Elacestrant Monotherapy vs. Standard of Care for the Treatment of Patients With ER+/HER2- Advanced Breast Cancer Following CDK4/6 Inhibitor Therapy: A Phase 3 Randomized, Open-label, Active-controlled, Multicenter Trial **Phase III** – Active, not recruiting **Location(s) –** 10 countries in EU, UK, USA, Canada and other countries **Study completion date –** August 2021
Trial Design	Randomised, parallel assignment, open label
Population	N = 466 (actual); 18 years and older; adenocarcinoma of the breast with evidence of either locally advanced disease not amenable to resection or radiation therapy with curative intent or metastatic disease not amenable to curative therapy; appropriate candidate for endocrine monotherapy; ER+/HER2- tumour status; previously received at least one and no more than two lines of endocrine therapy; received prior treatment with a CDK4/6 inhibitor in combination with either fulvestrant or an aromatase inhibitor
Intervention(s)	Elacestrant, 400mg once daily, orally
Comparator(s)	SOC (One of fulvestrant, anastrozole, letrozole or exemestane)
Outcome(s)	**Primary outcomes** • Progression Free Survival (PFS) in the ESR1-mut subjects [Time frame: from date of randomisation until disease progression or death due to any cause (up to 12 months)] • PFS in all (ESR1-mut and ESR1-WT) subjects [Time frame: from date of randomisation until disease progression or death due to any cause (up to 12 months)] See trial record for full list of other outcomes.
Results (efficacy)	PFS was prolonged in all patients (hazard ratio = 0.70; 95% CI, 0.55 to 0.88; P = .002) and patients with *ESR1* mutation (hazard ratio = 0.55; 95% CI, 0.39 to 0.77; P = .0005).[1]
Results (safety)	Treatment-related grade 3/4 adverse events occurred in 7.2% of patients receiving elacestrant and 3.1% receiving SOC. Treatment-related adverse events leading to treatment discontinuations were 3.4% in the elacestrant arm versus 0.9% in SOC. Nausea of any grade occurred in 35.0% receiving elacestrant and 18.8% receiving SOC (grade 3/4, 2.5% and 0.9%, respectively).[1]

Estimated Cost

The cost of elacestrant is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Sacituzumab govitecan for treating hormone receptor-positive HER2-negative metastatic breast cancer after 2 or more therapies (GID-TA10919). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Entinostat for treating hormone receptor-positive breast cancer after hormonal therapy (GID-TA10309). Expected publication date to be confirmed.
- NICE technology appraisal guidance. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA836). October 2022.
- NICE technology appraisal guidance. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA725). September 2021.
- NICE technology appraisal guidance. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA687). March 2021.
- NICE technology appraisal guidance. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA619). January 2020.
- NICE technology appraisal guidance. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017.
- NICE quality standard. Suspected cancer (QS124). December 2017.
- NICE quality standard. Breast cancer (QS12). June 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. June 2022.[25]
- American Society of Clinical Oncology. Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Update. July 2021.[26]
- European Society for Medical Oncology. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). December 2020.[27]
- NHS England. Clinical Guidelines for the Management of Breast Cancer. 2019.[28]

Additional Information

References

1 Bidard F-C, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, 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. *Journal of Clinical Oncology*. 2022;40(28):3246-56. Available from: https://doi.org/10.1200/JCO.22.00338.

2 ClinicalTrials.gov. *Phase 3 Trial of Elacestrant vs. Standard of Care for the Treatment of Patients With ER+/HER2- Advanced Breast Cancer (EMERALD). Trial ID: NCT03778931*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03778931 [Accessed 17th October 2022].

3 ClinicalTrials.gov. *TREAT ctDNA Elacestrant*. *Trial ID: NCT05512364*. 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT05512364 [Accessed 17th October 2022].

4 Di Leo A, Johnston S, Lee KS, Ciruelos E, Lønning PE, Janni W, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2018;19(1):87-100. Available from: https://doi.org/https://doi.org/10.1016/S1470-2045(17)30688-5.

5 Lindeman GJ, Bowen R, Jerzak KJ, Song X, Decker T, Boyle FM, et al. Results from VERONICA: A randomized, phase II study of second-/third-line venetoclax (VEN) + fulvestrant (F) versus F alone in estrogen receptor (ER)-positive, HER2-negative, locally advanced, or metastatic breast cancer (LA/MBC). *Journal of Clinical Oncology*. 2021;39(15_suppl):1004-. Available from: https://doi.org/10.1200/JCO.2021.39.15_suppl.1004.

6 Turner NC, Kingston B, Kilburn LS, Kernaghan S, Wardley AM, Macpherson IR, et al. Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. *The Lancet Oncology*. 2020;21(10):1296-308. Available from: https://doi.org/https://doi.org/10.1016/S1470-2045(20)30444-7.

7 Bross PF, Cohen MH, Williams GA, Pazdur R. FDA Drug Approval Summaries: Fulvestrant. *The Oncologist*. 2002;7(6):477-80. Available from: https://doi.org/10.1634/theoncologist.7-6-477.

8 ClinicalTrials.gov. *elacestrant | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Phase 2, 3.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?term=elacestrant&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 17th October 2022].

9 Menarini Group. *Menarini Group's Elacestrant Granted Priority Review by the U.S. FDA for Patients with ER+/HER2- Advanced or Metastatic Breast Cancer.* 2022. Available from: https://www.menarini.com/en-us/news/news-detail/menarini-groups-elacestrant-granted-priority-review-by-the-us-fda-for-patients-with-erher2-advanced-or-metastatic-breast-cancer [Accessed 17th October 2022].

10 Cancer Research UK. *What is breast cancer?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 18th October 2022].

11 Cancer Research UK. *Tests on your breast cancer cells.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed/tests-diagnose/hormone-receptor-testing-breast-cancer [Accessed 18th October 2022].

12 Medical News Today. *What to know about HER2-negative breast cancer.* 2021. Available from: https://www.medicalnewstoday.com/articles/326099 [Accessed 18th October 2022].

13 American Cancer Society. *Understanding Advanced and Metastatic Cancer.* 2020. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html [Accessed 18th October 2022].

14 Cancer Research UK. *Risk factors.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/risks-causes/risk-factors [Accessed 18th October 2022].
15 Cancer Research UK. *Breast cancer symptoms.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/symptoms [Accessed 18th October 2022].
16 National Institute for Health and Care Excellence. *NICE recommends step-change targeted treatment for people with early breast cancer.* 2022. Available from: https://www.nice.org.uk/news/article/nice-recommends-step-change-targeted-treatment-for-people-with-early-breast-cancer [Accessed 18th October 2022].
17 Cancer Research UK. *Breast cancer statistics.* 2022. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer [Accessed 18th October 2022].
18 Breast Cancer Now. *Facts and statistics 2021.* 2021. Available from: https://breastcancernow.org/about-us/media/facts-statistics [Accessed 18th October 2022].
19 NHS Digital. *Hospital Admitted Patient Care Activity 2021-22: Diagnosis.* 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 18th October 2022].
20 National Institute for Health and Care Excellence. *Advanced breast cancer: diagnosis and treatment.* 2017. Available from: https://www.nice.org.uk/guidance/cg81/chapter/Recommendations [Accessed 7th November 2022].
21 National Institute for Health and Care Excellence. *Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy.* 2021. Available from: https://www.nice.org.uk/guidance/ta725/chapter/1-Recommendations [Accessed 7th November 2022].
22 National Institute for Health and Care Excellence. *Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy.* 2021. Available from: https://www.nice.org.uk/guidance/ta687/chapter/1-Recommendations [Accessed 7th November 2022].
23 National Institute for Health and Care Excellence. *Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer.* 2022. Available from: https://www.nice.org.uk/guidance/ta836 [Accessed 7th November 2022].
24 National Institute for Health and Care Excellence. *Everolimus with exemestane for treating advanced breast cancer after endocrine therapy.* 2016. Available from: https://www.nice.org.uk/guidance/ta421/chapter/1-Recommendations [Accessed 7th November 2022].
25 Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2022;20(6):691-722. Available from: https://doi.org/10.6004/jnccn.2022.0030.
26 Burstein HJ, Somerfield MR, Barton DL, Dorris A, Fallowfield LJ, Jain D, et al. Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Update. *Journal of Clinical Oncology.* 2021;39(35):3959-77. Available from: https://doi.org/10.1200/JCO.21.01392.
27 Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5).

Annals of Oncology. 2020;31(12):1623-49. Available from: https://doi.org/10.1016/j.annonc.2020.09.010.

28 NHS England. *Clinical Guidelines for the Management of Breast Cancer*. 2018. Available from: https://www.england.nhs.uk/mids-east/wp-content/uploads/sites/7/2018/02/guidelines-for-the-management-of-breast-cancer-v1.pdf [Accessed 18th October 2022].

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.