

Health Technology Briefing May 2024

Abemaciclib with fulvestrant for HR+/HER2- locally advanced or metastatic breast cancer after CDK4/6 inhibitor and endocrine therapy

Company/Developer

Eli Lilly and Company Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 38330

NICE ID: Not available

UKPS ID: 673603

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Abemaciclib with fulvestrant is in clinical development for the treatment of patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer with evidence of disease progression or recurrence following cyclin-dependant kinases (CDK) 4/6 inhibitor and endocrine therapy. Breast cancer is when abnormal cells in the breast begin to grow in an uncontrolled way and eventually form a tumour. Locally advanced breast cancer is where cancer has spread from the breast to areas close to the breast or to the chest wall. Metastatic breast cancer is where the cancer has spread to other parts of the body. HR+ breast cancer is a type of breast cancer that expresses either progesterone or oestrogen or both hormone receptors. HER2- breast cancers have low or no expression of the HER2 protein in cancer cells. Despite advances in the understanding of origin breast cancer, precise treatment of locally advanced HR+/HER2- breast cancer remains an unmet need.

Abemaciclib is a medicinal product taken orally. It works by blocking the activity of certain enzymes known as CDK 4 and 6, which play a key role in regulating the way cells grow and divide. Fuvestrant blocks oestrogen receptor in breast cancer cells. If licenced, Abemaciclib with fulvestrant may provide a new treatment option for patients with HR+/HER2- locally advanced or metastatic breast cancer with evidence of disease progression or recurrence after previous CDK 4/6 inhibitor and endocrine therapy.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Treatment of patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer following progression on cyclin-dependent kinases (CDK) 4/6 inhibitor and endocrine therapy.¹

Technology

Description

Abemaciclib (Verzenios) is a potent and selective inhibitor of CDK 4 and 6, and most active against Cyclin D1/CDK4 in enzymatic assays.² CDK4 and 6, play a key role in regulating the way cells grow and divide. In some cancers, including HR-positive breast cancer, the activity of CDK4 and CDK6 is increased, which helps the cancer cells to multiply uncontrollably. By blocking CDK4 and CDK6, abemaciclib slows the growth of HR-positive breast cancer cells.³

Fulvestrant, is an anti-oestrogen. It blocks the receptors for oestrogen on cells and causes the number of oestrogen receptors to fall. As a result, the cancer cells are not stimulated to grow by oestrogen, and this slows down the growth of the tumour.⁴

Abemaciclib with fulvestrant is currently in clinical development for the treatment of patients with HR+/HER2- locally advanced or metastatic breast cancer with evidence of disease progression or recurrence after CDK4/6 inhibitor and endocrine therapy. In the phase III clinical trial (NCT05169567), patients receive 150mg daily oral abemaciclib and intramuscular fulvestrant.¹

Key Innovation

Despite advances in the understanding of genomic nuances of breast cancer, targeted therapies remain an unmet need for the treatment of locally advanced breast cancer aside from HER2-positive tumours.⁵

Endocrine therapy is the recommended treatment option for HR+/HER2- metastatic breast cancer.⁶ However, the majority of patients develop resistance to endocrine therapy.⁷ Abemaciclib blocks the activity of CD4/CD6 enzymes and thereby slows the growth of HR-positive breast cancer cells. The addition of abemaciclib to fulvestrant, an oestrogen receptor blocker, may further slowdown the growth of cancer cells and provide effective treatment in patients with HR+/HER2- locally advanced or metastatic breast cancer.^{3,8}

If licenced, abemaciclib with fulvestrant may provide a new treatment option for patients with HR +/HER2- locally advanced or metastatic negative breast cancer with evidence of disease progression or recurrence after previous CDK4/6 inhibitor and endocrine therapy.

Regulatory & Development Status

Abemaciclib is currently has Marketing Authorisation in the UK for:²

- the treatment of women with HR+, HER2- locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.
- in combination with endocrine therapy for the adjuvant treatment of adult patients with HR+/HER2-, node positive early breast cancer at high risk of recurrence.

Fulvestrant currently has Marketing Authorisation in the EU/UK for a number of indications:⁹

- As a monotherapy for the treatment of oestrogen receptor positive, locally advanced, or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy, or with disease relapse on or after adjuvant antioestrogen therapy, or disease progression on antioestrogen therapy.
- In combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy. In pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

Abemaciclib with fulvestrant is also in phase II/III development for other types of breast cancer, endometrial cancer and malignant neoplasms of female genital organs.¹⁰

Patient Group

Disease Area and Clinical Need

Breast cancer most commonly starts in the cells that line the milk ducts of the breast. It is the most common cancer in the UK and mainly affects women.¹¹ Some breast cancers are sensitive to the body's naturally occurring female hormones – oestrogen and progesterone.¹² If the cancer cell has one or both hormone receptors above, the term hormone-receptive positive (also called hormone positive or HR+) may be used.¹³ HER2 is a protein that helps breast cancer cells grow quickly.¹⁴ If breast cancer cells produce low level of HER2 proteins, the breast cancer is considered HER2- negative.¹⁵ Symptoms of breast cancer include a lump or thickened area of breast tissue, changes in the size of one or both breasts, discharge from the nipples, lumps or swelling underneath the armpits, changes in the look or feel of the skin of the breast, and changes in the overall appearance of the nipple (e.g. becoming sunken into the breast).¹⁶ The causes of breast cancer are not always clear, however there are risk factors known to affect the likelihood of developing breast cancer which include age, family history, previous breast cancer or lump, dense breast tissue and other lifestyle factors like being overweight and drinking alcohol.¹⁷

Breast cancer is the most common type of cancer in the UK, accounting for 15% of all new cancer cases (2016-2018), with about 1 in 7 women diagnosed with breast cancer during their lifetime, and less commonly, men can also be diagnosed.^{11,18} The age standardised incidence rate of breast cancer in England is 1.3 and 169.2 per 100,000 amongst males and females respectively.¹⁹ Between 2017 and 2019, there were 9,509 and 69 deaths from breast cancer in England for females and males respectively. The age standardised mortality rate per 100,000 population in England was 32.8 and 0.3 for females and males respectively.²⁰ In England (2022-23), there were 259,866 finished consultant episodes (FCEs) and 256,441 admissions for malignant neoplasm of the breast (ICD10 code C50), which resulted in 233,521 day cases and 61,787 FCE bed days.²¹ For patients diagnosed between 2013 and 2017, the 1-year and 5-year age-standardised survival rates for stage III (locally advanced) breast cancer were 95.5.0% and 72%

respectively. In addition, the 1-year and 5-year age-standardised survival rates for stage IV (metastatic) breast cancer were 66.0% and 26.2% respectively.²²

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for the treatment of locally advanced or metastatic HR+/HER2- breast cancer after endocrine therapy.²³⁻²⁵

- Abemaciclib with Fulvestrant
- Palbociclib-Fulvestrant
- Ribociclib-Fulvestrant

Clinical Trial Information

Trial	<p>postMONARCH, NCT05169567: A Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy of Abemaciclib Plus Fulvestrant to Placebo Plus Fulvestrant in Participants With HR+, HER2-, Advanced or Metastatic Breast Cancer Following Progression on a CDK4 & 6 Inhibitor and Endocrine Therapy</p> <p>Phase III- active, not recruiting</p> <p>Location(s): Ten EU countries, USA, and other countries</p> <p>Primary completion dates: February 2024</p>
Trial Design	Randomised, parallel assignment, double-masked
Population	N=368; Adult patients with a diagnosis of HR+, HER2- locally advanced or metastatic breast cancer who have radiologic evidence of disease progression or recurrence on or after CDK4/6 inhibitor and endocrine therapy.
Intervention(s)	Oral abemaciclib plus intramuscular fulvestrant.
Comparator(s)	Matched placebo plus intramuscular fulvestrant
Outcome(s)	<p>Primary outcome: Progression-Free Survival (PFS) [Time frame: Randomization to the date of first documented progression of disease or death from any cause (estimated as up to 3 years)]</p> <p>See trial record for full list of other outcomes</p>
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative prices (hospital only) for 28 and 56 tablets of 50mg, 100mg and 150mg abemaciclib are £1,475 and £2,950 respectively.²⁶

The NHS indicative price for fulvestrant two 250mg/5ml pre-filled disposable injections ranges from £261.21 to £522.41.²⁷

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment (GID-TA 11513). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Imlunestrant for treating oestrogen receptor-positive HER2 negative advanced breast cancer after endocrine therapy (GID-TA11439). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Datopotamab deruxtecan for previously treated hormone receptor-positive HER2-negative unresectable or metastatic breast cancer (GID-TA11402). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Vepdegestrant for treating hormone receptor-positive HER2-negative metastatic breast cancer after endocrine treatment (GID-TA11400). Expected date of issue to be confirmed.
- 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 date of issue to be confirmed.
- NICE technology appraisal guidance. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016
- NICE guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). June 2023.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015 (Last updated: October 2023).
- NICE clinical guideline. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). June 2013 (Last updated: November 2023).
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 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

- Chacón López-Muñiz, J. I., de la Cruz Merino, L., Gavilá Gregori, J., Martínez Dueñas, E., Oliveira, M., Seguí Palmer, M. A., et al. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). *Clinical and Translational Oncology*. 2019.²⁸
- Gradishar, W. J., Anderson, B. O., Abraham, J., Aft, R., Agnese, D., Allison, K. H., et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. April 2020.²⁹
- ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. 2021.³⁰

Additional Information

References

- 1 Clinicaltrials.gov. *postMONARCH: A Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy of Abemaciclib Plus Fulvestrant to Placebo Plus Fulvestrant in Participants With HR+, HER2-, Advanced or Metastatic Breast Cancer Following Progression on a CDK4 & 6 Inhibitor and Endocrine Therapy*. 2021. Available from: <https://classic.clinicaltrials.gov/ct2/show/NCT05169567> [Accessed 27 March 2024].
- 2 Electronic Medicine Compendium (emc). *Verzenio 100 mg film-coated tablets*. 2024. Available from: <https://www.medicines.org.uk/emc/product/11046/smpc> [Accessed 27 March 2024].
- 3 European Medicines Agency. *Verzenio*. 2024. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/verzenio> [Accessed 27 March 2024].
- 4 European Medicines Agency. *Fulvestrant Mylan*. 2024. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/fulvestrant-mylan> [Accessed 27 March 2024].
- 5 Costa R, Hansen N, Gradishar WJ. 63 - Locally Advanced Breast Cancer. In: Bland KI, Copeland EM, Klimberg VS, Gradishar WJ, eds. *The Breast (Fifth Edition)*. Elsevier; 2018: 819-31.e6 Available from: <https://www.sciencedirect.com/science/article/pii/B9780323359559000635>.
- 6 Simon J, Chaix M, Billa O, Kamga AM, Roignot P, Ladoire S, et al. Survival in patients with HR+/HER2- metastatic breast cancer treated with initial endocrine therapy versus initial chemotherapy. A French population-based study. *British Journal of Cancer*. 2020;123(7):1071-7. Available from: <https://doi.org/10.1038/s41416-020-0979-3>.
- 7 Başaran GA, Twelves C, Diéras V, Cortés J, Awada A. Ongoing unmet needs in treating estrogen receptor-positive/HER2-negative metastatic breast cancer. *Cancer Treatment Reviews*. 2018;63:144-55. Available from: <https://doi.org/10.1016/j.ctrv.2017.12.002>.
- 8 Neven P, Rugo HS, Tolaney SM, Iwata H, Toi M, Goetz MP, et al. Abemaciclib plus fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in premenopausal women: subgroup analysis from the MONARCH 2 trial. *Breast Cancer Res*. 2021;23(1):87. Available from: <https://doi.org/10.1186/s13058-021-01463-2>.
- 9 Electronic Medicine Compendium (emc). *Faslodex 250 mg solution for injection*. 2023. Available from: <https://www.medicines.org.uk/emc/product/68/smpc> [Accessed 28 March 2024].
- 10 Clinicaltrials.gov. *Abemaciclib with fulvestrant phase II/III clinical development indications*. Available from: https://classic.clinicaltrials.gov/ct2/results?cond=abemaciclib+and+fulvestrant&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&ead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 28 March 2023].
- 11 Cancer Research UK. *What is breast cancer?* 2023. Available from: <https://www.cancerresearchuk.org/about-cancer/breast-cancer/about> [Accessed 28 March 2024].

- 12 Mayo Clinic. *Breast cancer types: What your type means*. 2022. Available from: <https://www.mayoclinic.org/diseases-conditions/breast-cancer/in-depth/breast-cancer/art-20045654> [Accessed 28 March 2024].
- 13 American Cancer Society. *Breast Cancer Hormone Receptor Status*. 2021. Available from: <https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html> [Accessed 28 March 2024].
- 14 American Cancer Society. *Breast Cancer HER2 Status*. 2021. Available from: <https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html> [Accessed 28 March 2024].
- 15 Healthline. *What's the difference between HER2-negative and HER2-positive breast cancer?* 2022. Available from: <https://www.healthline.com/health/breast-cancer/her2-positive-vs-her2-negative> [Accessed 28 March 2024].
- 16 National Health Service (NHS). *Symptoms of breast cancer in women*. 2024. Available from: <https://www.nhs.uk/conditions/breast-cancer-in-women/symptoms-of-breast-cancer-in-women/> [Accessed 28 March 2024].
- 17 National Health Service (NHS). *Causes of breast cancer in women*. 2024. Available from: <https://www.nhs.uk/conditions/breast-cancer-in-women/causes-of-breast-cancer-in-women/> [Accessed 28 March 2024].
- 18 Cancer Research UK. *Breast cancer incidence (invasive)*. 2024. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero> [Accessed 28 March 2024].
- 19 Cancer Research UK. *Breast cancer incidence (invasive) statistics*. 2024. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero> [Accessed 28 March 2024].
- 20 Cancer Research UK. *Breast cancer mortality statistics*. 2024. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality#heading-Zero> [Accessed 28 March 2024].
- 21 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-2023*. 2023. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23> [Accessed 28 March 2024].
- 22 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2019. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed> [Accessed 28 March 2024].
- 23 National Institute for Health and Care Excellence (NICE). *Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy*. Available from: <https://www.nice.org.uk/guidance/ta725> [Accessed 23 March 2024].
- 24 National Institute for Health and Care Excellence (NICE). *Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy*. Available from: <https://www.nice.org.uk/guidance/ta687> [Accessed 23 March 2024].
- 25 National Institute for Health and Care Excellence (NICE). *Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy*. Available from: <https://www.nice.org.uk/guidance/ta836> [Accessed 28 March 2024].
- 26 British National Formulary (BNF). *Verzenio 50mg, 100mg and 150mg tablets*. 2024. Available from: <https://bnf.nice.org.uk/drugs/abemaciclib-specialist-drug/medicinal-forms/> [Accessed 28 March 2024].

- 27 British National Formulary (BNF). *Fulvestrant 250mg/5ml solution for injection pre-filled syringes*. 2024. Available from: <https://bnf.nice.org.uk/drugs/fulvestrant/medicinal-forms/> [Accessed 28 March 2024].
- 28 Chacón López-Muñiz JI, de la Cruz Merino L, Gavilá Gregori J, Martínez Dueñas E, Oliveira M, Seguí Palmer MA, et al. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). *Clinical and Translational Oncology*. 2019;21(1):31-45. Available from: <https://doi.org/10.1007/s12094-018-02010-w>.
- 29 Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2020;18(4):452-78. Available from: <https://doi.org/10.6004/jnccn.2020.0016>.
- 30 Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆. *Annals of Oncology*. 2021;32(12):1475-95. <https://www.sciencedirect.com/science/article/pii/S0923753421044987>.

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