NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
September 2023

Imlunestrant with or without abemaciclib for treating ER-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine therapy

Company/Developer	Eli Lilly and Company Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 33651	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Imlunestrant with or without abemaciclib is in development for the treatment of patients with locally advanced or metastatic oestrogen receptor positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer. 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. ER+ breast cancer is a type of breast cancer that expresses the oestrogen hormone receptors. HER2- breast cancers have low or no expression of the HER2 protein in cancer cells. Targeted therapies remain an unmet need in the treatment of ER+/HER2- metastatic breast cancer due to the development of resistance to existing hormonal treatment.

Imlunestrant is a medicinal product that is given orally. It works by binding into a specific part of the cancer cells, called the oestrogen receptor, causing a change in the shape of the receptor, leading to its breakdown. By doing this, imlunestrant disturbs the growth and survival mechanism of cancer cells that express the oestrogen receptors. In preclinical trials, imlunestrant had enhanced efficacy when combined with abemaciclib in ER+ models. If licenced, imlunestrant with or without abemaciclib could provide a new treatment option for patients with locally advanced or metastatic ER+/HER2- breast cancer.

Proposed Indication

For the treatment of adult patients with oestrogen receptor positive (ER+) and human epidermal receptor 2-negative (HER2-) locally advanced or metastatic breast cancer previously treated with endocrine therapy.[1]

Technology

Description

Imlunestrant (LY-3484356) is an orally bioavailable selective oestrogen receptor degrader (SERD) and ER antagonist. Imlunestrant has been specifically designed to deliver continuous ER target inhibition throughout the dosing period and regardless of oestrogen receptor gene (ESR1) mutational status.[2]
Upon oral administration, imlunestrant specifically targets and binds to the ER and induces a conformational change that results in ER degradation. This prevents ER-mediated signalling and inhibits both the growth and survival of ER-expressing cancer cells.[3]

Imlunestrant as monotherapy and in combination with abemaciclib is currently in clinical development for the treatment of patients with ER+/HER2- locally advanced or metastatic breast cancer previously treated with endocrine therapy (EMBER-3; NCT04975308). In phase III clinical trial, patients receive imlunestrant 400 mg orally once daily (QD) continuously in 28-day cycles as monotherapy, or in combination with abemaciclib administered orally.[1,4]

Key Innovation

Targeted therapies remain an unmet need for the treatment of locally advanced breast cancer, aside from HER2-positive tumours.[5] For metastatic HR+/HER2- breast cancer, endocrine therapy remains the recommended treatment option according to available international guidelines.[6-9] However, there are several cases of patients developing resistance to endocrine therapy.[10]
As the ER is the key therapeutic target for patients with ER+/HER2- breast cancer, novel degraders of ER have showed their ability to overcome endocrine therapy resistance while providing consistent oral pharmacology and convenience of administration.[2] Imlunestrant has pure antagonistic properties resulting in sustained inhibition of ER-dependent gene transcription and cell growth. In a phase 1a/b trial (EMBER, NCT04188548), imlunestrant monotherapy demonstrated a favourable safety profile with pharmacokinetic exposures that exceeded standard of care endocrine therapy. It also showed single agent efficacy in patients with ER+, HER2- metastatic breast cancer, including in patients with baseline ESR1 mutations.[4] Preclinically, imlunestrant has favourable efficacy and pharmacokinetic properties, including antitumor activity in ER 1-mutant models, along with enhanced efficacy when combined with abemaciclib.[11] If licenced, imlunestrant with or without abemaciclib will offer an additional treatment option to patients with ER+/HER2- locally advanced or metastatic breast cancer after endocrine therapy.

Regulatory & Development Status

Imlunestrant as a monotherapy or in combination does not currently have marketing authorisation in the EU/UK for any indication.

Abemaciclib is marketed in the EU/UK in combination with other technologies for the following indications:[12]

- Adjuvant treatment of adult patients with hormone receptor positive, HER2-, node-positive early breast cancer at high risk of recurrence
- Hormone receptor positive, HER2-, locally advanced or metastatic breast cancer as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

Imlunestrant is also currently in phase III clinical development for early breast cancer that is ER+/HER2-.[13]

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.[14] Cancers that have receptors for oestrogen are ER+ breast cancers.[15] When a breast cancer is HER2-negative, it means that the cancerous cells do not contain high levels of the protein HER2.[16] 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 cannot be cured or controlled with treatment.[17] 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.[18] 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 is not pregnant or breast feeding and changes in the position of the nipple.[19]

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.[14] HER2-negative breast cancer is the most common type, accounting for about 70% of all breast cancers.[20] Approximately 80% of breast cancers are ER+.[15] There are around 11,500 breast cancer deaths in the UK every year (2017-2019). It is predicted that around 75.9% women diagnosed with breast cancer in England survive their disease for ten years or more (2013-2017).[21] Breast Cancer Now estimate that around 61,000 people are living with metastatic breast cancer in the UK. In around 5% of women, breast cancer has already spread by the time it is diagnosed.[22] 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.[23]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following for the treatment of hormone receptor positive, 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. [24]

- 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.[25]
- 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. [26]
- Everolimus, in combination with exemestane.[27]

Clinical Trial Information

Trial	**EMBER-3**: NCT04975308, EudraCT 2021-000079-35; A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant Plus Abemaciclib in Patients With Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated With Endocrine Therapy **Phase III**- recruiting **Location(s):** 9 countries in EU, Australia, USA, and other countries **Primary completion date**: April 2024
Trial Design	Randomised, parallel assignment, open label
Population	N=860 (planned); Patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with endocrine therapy with a CDK4/6 inhibitor; aged 18 years and older
Intervention(s)	• Receive imlunestrant 400 mg orally QD continuously in 28-day cycles[4] • Receive Imlunestrant plus abemaciclib administrated orally
Comparator(s)	Investigator's Choice of Endocrine Therapy; Exemestane and Fulvestrant
Outcome(s)	**Primary outcomes** • Progression free survival (PFS) -Time Frame: from randomization to the date of first documented progression of disease or death from any cause (estimated as up to 3 years) • PFS in the oestrogen receptor 1 (ESR1)-mutation detected population Time Frame: from randomization to the date of first documented progression of disease or death from any cause (estimated as up to 3 years) See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of imlunestrant is not yet known.

The NHS indicative price (hospital only) for 28 tablets of 50mg, 100mg and 150mg abemaciclib are all £1,475.[28]

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. 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.[29]
- European Society for Medical Oncology. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). December 2020.[30]
- NHS England. Clinical Guidelines for the Management of Breast Cancer. 2019.[31]

Additional Information

Eli Lilly and Company Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *A Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant Plus Abemaciclib in Participants With ER+, HER2- Advanced Breast Cancer (EMBER-3). Trial ID: NCT04975308*. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04975308?term=NCT04975308&draw=2&rank=1 [Accessed 01/08/2023].

2 Eli Lilly and Company. *News Release: Lilly Announces Details of Presentations at 2022 American Society of Clinical Oncology (ASCO) Annual Meeting*. Press release. Available from: https://investor.lilly.com/news-releases/news-release-details/lilly-announces-details-presentations-2022-american-society [Accessed 26/07/2023].

3 National Center for Biotechnology Information. *PubChem Compound Summary for CID 146603228, Imlunestrant*. 2023. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Imlunestrant [Accessed 26/07/2023].

4 Smyth; Joyce O'Shaughnessy KJNHPAS-BKXPCSGCMCXAWSRLYL. Abstract OT2-11-01: EMBER-3: A randomized phase 3 study of LY3484356, a novel, oral selective estrogen receptor degrader vs investigator's choice of endocrine therapy of either fulvestrant or exemestane, in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer previously treated with endocrine-based therapy. *American Association for Cancer Research (AACR)*. 2022. https://aacrjournals.org/cancerres/article/82/4_Supplement/OT2-11-01/680272/Abstract-OT2-11-01-EMBER-3-A-randomized-phase-3.

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 Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Annals of Oncology*. 2018;29(8):1634-57. Available from: https://doi.org/10.1093/annonc/mdy192.

8 Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, et al. Chemotherapy and Targeted Therapy for Women With Human Epidermal Growth Factor Receptor 2–Negative (or unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*. 2014;32(29):3307-29. Available from: https://doi.org/10.1200/jco.2014.56.7479.

9 Gradishar WJ, Anderson BO, Blair SL, Burstein HJ, Cyr A, Elias AD, et al. Breast Cancer Version 3.2014. *Journal of the National Comprehensive Cancer Network*. 2014;12(4):542-90. Available from: https://doi.org/10.6004/jnccn.2014.0058.

10 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. https://www.sciencedirect.com/science/article/pii/S0305737217302049.

11 Muralidhar KJH-CWCMELJJTLMJ-YPRPYJGY-SL. Abstract PD13-12: PD13-12 Imlunestrant, an oral selective estrogen receptor degrader, in combination with

abemaciclib with or without an aromatase inhibitor, in estrogen receptor-positive advanced breast cancer: Results from the phase 1a/b EMBER study *American Association for Cancer Research (AACR)*. 2023;83(5). https://aacrjournals.org/cancerres/article/83/5_Supplement/PD13-12/716791/Abstract-PD13-12-PD13-12-Imlunestrant-an-oral.

12 Electronic Medicines Compendiom (EMC). *Verzenios 50 mg film-coated tablets*. Last Update Date: May 2022. Available from: https://www.medicines.org.uk/emc/product/9532/smpc#gref [Accessed 21/09/2023].

13 ClinicalTrials.gov. *Imlunestrant | Phase 2, 3*. Available from: https://classic.clinicaltrials.gov/ct2/results?term=Imlunestrant&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 04/08/2023].

14 Cancer Research UK. *What is breast cancer?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 02/08/2023].

15 Cancer Research UK. *Tests on your breast cancer cells*. 2021. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed/tests-diagnose/hormone-receptor-testing-breast-cancer [Accessed 02/08/2023].

16 MedicalNewsToday. *What to know about HER2-negative breast cancer*. 2021. Available from: https://www.medicalnewstoday.com/articles/326099 [Accessed 04/08/2023].

17 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 04/08/2023].

18 Cancer Research UK. *Risk Factors for breast cancer*. 2020. Available from: https://www.cancer.org/cancer/managing-cancer/advanced-cancer/what-is.html [Accessed 04/08/2023].

19 Cancer Research UK. *Breast cancer symptoms*. 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/symptoms [Accessed 04/08/2023].

20 National Institute for Health and Care Excellence(NICE). *NICE recommends step-change targeted treatment for people with early breast cancer*. Available from: https://www.nice.org.uk/news/article/nice-recommends-step-change-targeted-treatment-for-people-with-early-breast-cancer [Accessed 26/07/2023].

21 Cancer Research UK. *Breast Cancer statistics*. 2022. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer [Accessed 01/08/2023].

22 Breast Cancer Now. *Facts and Statictics 2023*. 2023. Available from: https://breastcancernow.org/about-us/media/facts-statistics [Accessed 04/08/2023].

23 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 03/08/2023].

24 National Institute for Health and Care Excellence(NICE). *Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy*. Last Update Date: September 2021. Available from: https://www.nice.org.uk/guidance/ta725/chapter/1-Recommendations.

25 National Institute for Health and Care Excellence(NICE). *Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy*. Last Update Date: March 2021. Available from: https://www.nice.org.uk/guidance/ta687/chapter/1-Recommendations [Accessed 26/07/2023].

26 National Institute for Health and Care Excellence(NICE). *Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy*. Last Update Date: October 2022. Available from: https://www.nice.org.uk/guidance/ta836 [Accessed 29/07/2023].

27 National Institute for Health and Care Excellence(NICE). *Everolimus with exemestane for treating advanced breast cancer after endocrine therapy*. Last Update Date: December 2016. Available from: https://www.nice.org.uk/guidance/ta421/chapter/1-Recommendations [Accessed 04/08/2023].

28 British National Formulary(BNF). *Abemaciclib*. Available from: https://bnf.nice.org.uk/drugs/abemaciclib-specialist-drug/medicinal-forms/ [Accessed 21/09/2023].

29 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. *Journal of the National Comprehensive Cancer Network*. 2022;20(6):691-722. Available from: https://doi.org/10.6004/jnccn.2022.0030.

30 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.

31 NHS England. *Clinical Guidelines for the Management of Breast Cancer*. 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 02/08/2023].

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.