Health Technology Briefing
January 2022

Giredestrant with palbociclib for previously untreated advanced or metastatic breast cancer

Company/Developer	Roche Products Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30524	NICE ID: 30524	UKPS ID: 663265

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Giredestrant combined with palbociclib is in clinical development for previously untreated oestrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2)-negative locally advanced (recurrent or progressed) or metastatic breast cancer. Breast cancer arises from the tissues of the breast and most commonly originates in the cells that line the milk ducts. This kind of ER-positive cancer has receptor cells for the hormone oestrogen, meaning the cancer often responds to treatment with endocrine therapy. Other therapies for this patient population are administered via intravenous injection which can be uncomfortable for the patient and costly. In addition, prolonged treatment and risk of relapse can represent significant challenges for patients; therefore, a need remains for more effective and acceptable treatment options.

Giredestrant is a selective oestrogen receptor degrader (SERD). Giredestrant is administered orally and works by blocking this receptor to prevent the action of oestrogen, and in the process causes the receptor to be degraded, leading to cancer cell death. If licensed, giredestrant would provide a more comfortable, less costly, and possibly more effective treatment option for this patient population compared to therapies administered intravenously.

Proposed Indication

Patients with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer.[1]

Technology

Description

Giredestrant (GDC-9545) is a selective oestrogen receptor degrader (SERD). Oestrogen encourages HR-positive breast cancer cells to grow by attaching to the ER. A breast cancer is classified as HR-positive if its cells have receptors for the hormones estrogen and progesterone. Giredestrant works by blocking this receptor to prevent the action of oestrogen, and in the process causes the receptor to be degraded, leading to cancer cell death.[1]

Giredestrant combined with palbociclib is in clinical development for adult patients with ER-positive, human epidermal growth factor receptor-2 (HER2)-negative locally advanced (recurrent or progressed) or metastatic breast cancer. In the phase III trial (NCT04546009), giredestrant is taken orally once per day on days 1-28 of each 28-day treatment cycle.[2]

Key Innovation

Prolonged treatment durations and risk of relapse can represent significant challenges for patients; therefore, a need remains for more effective and tolerable treatment options in those with HER-2 positive breast cancer. The mainstay of treatment for ER-positive, HER2-negative breast cancer is to block oestrogen, but the side effects of this have a very significant impact on quality of life and can greatly affect treatment adherence. Giredestrant may provide a more tailored, more effective and less debilitating treatment for HR (hormone receptor)-positive breast cancer.[1]

Orally given, giredestrant delivers a strong clinical efficacy and safety profile and has shown superior pre-clinical potency over other SERDs in development. The oral administration of giredestrant has the potential to transform the treatment experience for patients, offering greater convenience and a less painful option compared to therapies administered via intramuscular injection.[1]

Regulatory & Development Status

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

Giredestrant in combination with other therapies is in phase II and III clinical trials for early stage, and locally advanced or metastatic breast cancer.[3]

Patient Group

Disease Area and Clinical Need

Breast cancer arises from the tissues of the breast and most commonly originates in the cells that line the milk ducts of the breast.[4] Breast cancers with receptors for the hormone oestrogen are ER-positive breast cancers.[5] HER-2 is a protein found in some cancerous cells. HER2- negative breast cancer refers to disease that does not overexpress HER-2.[6] Advanced or metastatic (stage IV) breast cancer refers to disease that has spread to other parts of the body.[7] The causes of breast cancer are not completely understood, however a number of factors are known to increase its likelihood, such as exposure to radiation, increased

alcohol consumption, being taller, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors. Breast cancer is normally characterised by a lump or thickened tissue in the breast area. Other features include a change in breast size or shape, discharge from the nipple (which may include blood), lumps/swelling in armpits, dimples on the skin of the breast, a rash around the nipple area and pain in the breast or axilla.[8]

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-2018).[9] In England, the European age-standardised incidence rate per 100,000 of the population was 169.2 amongst females and 1.3 amongst males (2016-2018).[10] Breast cancer incidence is strongly related to age, with higher incidence rates observed with increasing age. In the UK, 24% of new breast cancer cases were in people aged 75 and older. The highest incidence rates were observed in those aged 90 years and older amongst females and 85-89 amongst males.[11] In England and Wales (2020-21), there were 202,340 finished consultant episodes (FCE) for malignant neoplasm of the breast (ICD-10 code C50), of which 955 were for male patients and 201,314 were for female patients. This resulted in 199,266 admissions, 172,062 day cases and 47,613 FCE bed days.[12] In England (2017), there were 2,372 patients diagnosed with stage IV (metastatic) breast cancer. In England and Wales (2017), there were 10,219 deaths where malignant neoplasm of the breast was recorded as the underlying cause; in England (2017) the directly age-standardised registration of death from malignant neoplasm of the breast for females was 33.3 per 100,000 and 0.3 per 100,000 for males.[13,14] For adult women in England diagnosed with stage IV breast cancer between 2013 and 2017 and followed up to 2018, the 1-year and 5-year age-standardised survival rate was 66.0% and 26.2% respectively.[15]

Recommended Treatment Options

For previously untreated advanced ER-positive HER-2 negative breast cancer, NICE recommends endocrine therapy as first-line treatment for the majority of patients. Chemotherapy is offered as first-line treatment for patients whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, provided they understand and are prepared to accept the toxicity.[16]

Endocrine therapy recommendations include:[19]

- An aromatase inhibitor (either non-steroidal or steroidal) to postmenopausal women with medium to high risk of disease reoccurrence
- Tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women who are at low risk of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated.
- Ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression
- Tamoxifen as first-line treatment to men with ER-positive advanced breast cancer.

Chemotherapy recommendations include:[19]

- Docetaxel monotherapy for patients with advanced breast cancer who are not suitable for anthracyclines
- Abemaciclib with an aromatase inhibitor
- Palbociclib with an aromatase inhibitor
- Ribociclib with an aromatase inhibitor

Clinical Trial Information

Trial	**persevERA Breast Cancer,** NCT04546009, 2020-000119-66; A Phase III Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of GDC-9545 Combined With Palbociclib Compared With Letrozole Combined With Palbociclib in Patients With Estrogen Receptor-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer **Phase III** - recruiting **Location(s):** 11 EU countries, UK, USA, Canada, and other countries **Primary completion date:** April 2024
Trial Design	Randomised, parallel assignment, double blind, placebo-controlled
Population	N = 978; women who are premenopausal or perimenopausal, and men, with locally advanced or metastatic adenocarcinoma of the breast, with a documented ER-positive tumour and HER2-negative tumour; aged 18 years and older
Intervention(s)	• Giredestrant (oral) once daily on days 1-28 of each 28-day treatment cycle. • Letrozole-matched placebo (oral) once daily on days 1-28 of each 28-day treatment cycle • Palbociclib 125 mg (oral) once daily on days 1-21 of each 28-day treatment cycle • Luteinizing hormone releasing hormone (LHRH) agonist on day 1 of each 28-day treatment cycle
Comparator(s)	• Giredestrant-matched placebo (oral) once daily on days 1-28 of each 28-day treatment cycle. • Letrozole 2.5 mg (oral) once daily on days 1-28 of each 28-day treatment cycle. • Palbociclib 125 mg (oral) once daily on days 1-21 of each 28-day treatment cycle • LHRH agonist on day 1 of each 28-day treatment cycle
Outcome(s)	• Progression-Free Survival (PFS), as determined by the Investigator according to RECIST v1.1 See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of giredestrant is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Ribociclib in combination with endocrine therapy and goserelin for previously untreated hormone receptor-positive, HER2-negative advanced breast cancer in premenopausal women (ID1307). Expected date of issue to be confirmed.

- NICE technology appraisal guidance. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA563). February 2019.
- NICE technology appraisal guidance. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA495). December 2017.
- NICE clinical guidance. Advanced breast cancer: diagnosis and treatment (CG81). February 2009. Updated August 2017

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

- ASCO Guideline Update. Chemotherapy and targeted therapy for patients with HER2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor–negative. July 2021.[17]
- European School of Oncology (ESO) and European Society for Medical Oncology (ESMO). 5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5). 2020.[18]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4. 2017, NCCN Clinical Practice Guidelines in Oncology. 2018. [19]

Additional Information

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