

Health Technology Briefing January 2023

Palbociclib with trastuzumab with or without pertuzumab and endocrine therapy for HR+/HER2+ metastatic breast cancer

Company/Developer

Pfizer Limited (UK)

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 29341

NICE ID: 10670

UKPS ID: 651841

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Palbociclib in combination with trastuzumab with or without pertuzumab and endocrine therapy is currently in clinical development for use as a maintenance therapy for patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer who have had prior treatment. Breast cancer occurs when abnormal cells in the breast begin to grow and uncontrollably divide, and eventually form a growth (tumour). Metastatic breast cancer is cancer that has spread beyond the breast to other parts of the body, and usually cannot be treated with surgery. HR+/HER+ breast cancer is a particularly aggressive subtype of breast cancer. Affected patients often experience disease progression after standard treatment.

Palbociclib is administered orally in combination with intravenous trastuzumab with or without intravenous pertuzumab and oral endocrine therapy. It works by blocking the activity of certain enzymes known as cyclin-dependant kinases 4 and 6, which play a key role in regulating the way cells grow and divide. By blocking these enzymes, palbociclib slows the growth of breast cancer cells, and has been shown to be tolerable to patients over an extended period. If licensed, palbociclib in combination with trastuzumab and endocrine therapy will provide an additional treatment option for HR+/HER2+ metastatic breast cancer patients who have received induction therapy.

Proposed Indication

Palbociclib in combination with trastuzumab and endocrine therapy as a treatment for hormone receptor positive (HR+) and human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer patients after they have received induction therapy.¹

Technology

Description

Palbociclib (Ibrance) is a highly selective, reversible, inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation. Through inhibition of CDK4/6 complex activity, palbociclib reduces cellular proliferation, blocking cell cycle progression from G1 into S phase.² Testing of palbociclib in a panel of molecularly profiled breast cancer lines showed a high reactivity against HR+, particularly oestrogen receptor (ER-positive) cancers.²

Palbociclib in combination with trastuzumab with or without pertuzumab and endocrine therapy is currently in phase III trial (NCT02947685) for adults with HR+/HER2+ metastatic breast cancer who had induction therapy. In the trial, patients received palbociclib at a dose of 125mg taken orally once daily, day 1 to day 21 followed by 7 days off treatment in a 28-day cycle.¹

Key Innovation

There is a lack of definite guidelines for the treatment of metastatic breast cancer in patients who are both HR+/HER+. Therefore, there remains an unmet need for specific treatment options for patients with this breast cancer subtype, who typically have poor prognosis.³ The recent introduction of CDK4/6i in combination with endocrine therapy has had significant impact in the treatment of advanced HR+/HER2-disease, and there is early evidence to suggest promising outcomes in patients with HER2+ disease.⁴⁻⁶ In a phase II trial (NCT02448420), palbociclib in combination with trastuzumab was shown to be safe and exhibited promising survival outcomes patients with HER2+ metastatic breast cancer.⁷

If licensed, palbociclib in combination with trastuzumab with or without pertuzumab and endocrine therapy will provide an additional treatment option for HR+/HER2+ metastatic breast cancer patients who have received induction therapy.

Regulatory & Development Status

Palbociclib is currently licensed in the EU/UK for the treatment of HR+, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer the following indications:^{8,9}

Palbociclib is indicated:

- in combination with an aromatase inhibitor
- in combination with fulvestrant in women who have received prior endocrine therapy
- in pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.⁹

Palbociclib is also currently in phase II and/or III development for several other indications including:¹⁰

- Ovarian cancer

- Liposarcoma
- Colon cancer
- Brain cancer
- Lymphoma
- Prostate cancer
- Liver cancer
- Renal cancer
- Bladder cancer

Patient Group

Disease Area and Clinical Need

Breast cancer starts in the breast tissue, most commonly in the cells that line the milk ducts of the breast.¹¹ The causes of breast cancer are not completely understood, however several factors are known to increase its likelihood, such as exposure to radiation, increased alcohol consumption, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors.¹² Metastatic breast cancer is a type that has spread to other parts of the body including the lungs, liver, bones or brain.¹³ Breast cancers can be categorised according to whether or not they respond to certain hormones in the body and the specific genes or proteins that the tumour cells express.¹⁴ Breast cancers with receptors for hormones are HR+ breast cancers while HER2+ breast cancer is the type that express HER-2 protein.³ Most HR+ breast cancers are estrogen receptor positive (ER+).¹⁵ About 10% of patients have breast cancers which express receptors for hormones (HR+) and also express HER2 proteins (HER2+).¹⁶

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-2018).¹⁷ In England, there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the directly age-standardised rates per 100,000 population were 166.7 among females and 1.3 among males.¹⁸ In 2021-22, there were 205,082 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 201,297 admissions resulting in 48,154 bed days and 174,668 day cases.¹⁹ In England (2017) there were 9,569 deaths due to malignant neoplasm of the breast; the directly age-standardised rates per 100,000 population of registrations of death from malignant neoplasm of the breast were 33.3 and 0.3 for females and males respectively.¹⁸ For adult women in England diagnosed with stage IV breast cancer between 2013 and 2017, the 1-year and 5-year age-standardised survival rate was 66% and 26.2% respectively.²⁰

Recommended Treatment Options

For metastatic breast cancer patients who are both HR+ and HER2+ there is no current specific National Institute for Health and Care Excellence (NICE) treatment recommendations.³ However, there are recommendations for metastatic breast cancer patients who are either ER+ or HER2+.

NICE recommends endocrine therapy as first-line treatment for majority of patients with ER+ advanced breast cancer. Chemotherapy is recommended for patients whose disease is imminently life threatening or requires early relief of symptoms. For patients with ER+ advanced breast cancer who have been treated with chemotherapy as their first-line treatment, endocrine therapy is offered.²¹

Endocrine therapy recommendations include:²¹

- Ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression
- An aromatase inhibitor to postmenopausal women with ER+ breast cancer and no prior history of endocrine therapy or previously treated with tamoxifen
- Tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER+ advanced breast cancer not previously treated with tamoxifen
- Tamoxifen as first-line treatment to men with ER-positive advanced breast cancer

Chemotherapy recommendations include:^{3,21,22}

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine.

NICE also recommends lapatinib or trastuzumab in combination with an aromatase inhibitor for treating metastatic HR+ breast cancer that overexpresses HER2 in adults.³ Also, pertuzumab with trastuzumab and docetaxel is recommended for treating HER2+ breast cancer.²²

Clinical Trial Information

<p>Trial</p>	<p>PATINA; NCT02947685; A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy vs. Anti-HER2 Therapy + Endocrine Therapy After Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer Phase III – Active, not recruiting Location(s): Four EU countries, USA, Australia, and New Zealand Primary completion date: May 2023;</p>
<p>Trial Design</p>	<p>Randomised, parallel assignment, open label</p>
<p>Population</p>	<p>N=496 (estimated): 18 years and older; patients must have histologically confirmed invasive breast cancer; patients must have histologically confirmed HER2+ and HR+, metastatic breast cancer.</p>
<p>Intervention(s)</p>	<p>Palbociclib 125 mg daily + AntiHER2 Therapy (trastuzumab/pertuzumab) q3wks + Endocrine Therapy (letrozole, anastrozole, exemstane OR fulvestratnt) until confirmed disease progression</p>

Comparator(s)	AntiHER2 Therapy (trastuzumab/pertuzumab) q3wks + Endocrine Therapy (letrozole, anastrozole, exemstane OR fulvestrant) until confirmed disease progression
Outcome(s)	Primary outcome measured: Progression-free survival as assessed by investigator [Time frame: 24 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Palbociclib is already marketed in the UK for HR+/HER2 negative locally advanced or metastatic breast cancer.⁸ The NHS indicative price for palbociclib tablets is as follows:²³

- Palbociclib 125 mg; 21 tablets cost £2950
- Palbociclib 125 mg; 63 tablets cost £8850

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane (GID-TA10804). Expected date of issue February 2023.
- NICE technology appraisal. Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies (TA786). April 2022.
- NICE technology appraisal. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (TA704). May 2021.
- NICE technology appraisal. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). March 2018.
- NICE technology appraisal. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). November 2017.
- NICE technology appraisal. Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (TA257) June 2012.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and treatment (NG101). July 2018.
- NICE clinical guideline. 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

- European Society of Medical Oncology (ESMO). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. December 2021.²⁴
- American Society of Clinical Oncology. Management of Advanced Human Epidermal Growth Factor-2 positive Breast Cancer and Brain Metastasis: ASCO Guideline Update. May 2022.²⁵
- American Society of Clinical Oncology. Current and Future Management of HER2-Positive Metastatic Breast Cancer. October 2021.²⁶
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Additional Information

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