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HEALTH TECHNOLOGY BRIEFING
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Palbociclib for breast cancer - post neo-adjuvant therapy

NIHRIO ID	9760	**NICE ID**	9774
Developer/Company	Pfizer Ltd (UK)	**UKPS ID**	644865

Licensing and market availability plans	Currently in phase III clinical trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Palbociclib is in clinical development for treatment of women with high-risk early breast cancer, as a treatment after main cancer treatment to reduce cancer cell spread. Women are classified as high-risk if they have a greater than 30% chance of developing breast cancer in their lifetime, this is a result of number of physiological and environmental factors, such as age. Early breast cancer is where the disease is limited to the breast region and has not spread to other parts of the body.

Palbociclib is an oral cancer medicine. It works by blocking the activity of certain enzymes known as cyclin-dependant kinases (CDK) 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 of time. If licenced, palbociclib will provide an additional treatment option for adults with invasive early breast cancer.

PROPOSED INDICATION

Post neoadjuvant treatment of women with high-risk early breast cancer.[a]

TECHNOLOGY

DESCRIPTION

Palbociclib (Ibrance, PD-0332991) is a highly selective, reversible, small-molecule 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 inhibits the phosphorylation of retinoblastoma protein, blocking cell cycle progression from G1 into S phase. Palbociclib molecular testing showed a high reactivity against HR+, HER-negative cancer, particularly estrogen receptor (ER-positive) cancers, however in a follow-up study with fresh tumour samples no response was observed.[1]

Palbociclib is currently in phase III clinical development for the post neoadjuvant treatment of women.[2] In Phase III clinical trials (NCT01864746) patients received palbociclib at a dose of 125 mg taken orally once daily, day 1 to day 21 followed by 7 days off treatment in a 28-day cycle.[2]

INNOVATION AND/OR ADVANTAGES

Palbociclib shows to be tolerable for most patients for an extended duration of treatment, this could be beneficial as side-effects could reduce the quality of a patients daily life.[3,4] With palbociclib showing high activity against HR+, HER-negative cancer this would provide an additional option for post neoadjuvant treatment of women with high-risk early breast cancer.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Palbociclib is currently licenced in the EU/UK for hormone receptor postive (HR+), human epidermal growth factor receptor negative (HER2-negative) locally advanced or metastatic breast cancer in one of the following combinations:[5]

- With an aromatase inhibitor
- With fulvestrant in women who have received prior endocrine therapy

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.[5]

The most common side-effects with palbociclib (which may affect more than 1 in 5 people) are neutropenia, infections, leucopenia, tiredness, nausea, stomatitis, anaemia, diarrhoea, alopecia and thrombocytopenia. Additional common side effects (which may affect up to 1 in 50 people) are neutropenia, leucopenia, infections, anaemia, tiredness and increased blood levels of liver enzymes (aspartate and alanine transaminases).[6]

Palbociclib is in phase II and phase III development, as a monotherapy or in combination therapy, for several indications including breast cancer, squamous cell lung cancer, pancreatic neuroendocrine cancer and ovarian cancer.[7]

[a] Information provided by Pfizer Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common cancer in the UK, and mainly affects women, although men can also have the condition. It usually starts in the cells that line the ducts of the breast.[8] Early stage breast cancer is defined as disease confined to the breast with or without regional lymph node involvement and the absence of distant metastatic disease.[9] There are different immune/pathological subtypes of breast cancer subtypes of breast cancer, among which is HER2. HER2 is a transmembrane receptor protein that is overexpressed in about 20% of breast cancers and associated with more aggressive disease in the absence of HER2 directed therapy. HER2 plays a role in cell growth and differentiation.[10]

The exact aetiology is unknown, but family history is a strong risk factor (hereditary factors).[11] Other risk factors for breast cancer include increased age, reproductive history and hormone exposure, lifestyle factors, medical history and radiation exposure.[12]

One of the first noticeable symptom of breast cancer amongst women is a lump or an area of thickened tissue in their breast. Other common signs and symptoms include a change in the size or shape of one or both breasts, nipple discharge, dimpling on the skin of your breasts, and a rash on or around the nipple.[13,14]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK in 2017, breast cancer was the most common cancer accounting for 15% of all new cancer cases.[15] In England, in 2017 there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the direct age-standardised rate per 100,000 population was 166.7 among females and 1.3 among males.[16] Incidence rates among females are projected to rise by 2% in the UK between 2014 and 2035, from 205 per 100,000 (54,833 cases) to 210 per 100,000 (71,022 cases).[17]

In England, in 2018-19 there were 219,885 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 215,644 admissions resulting in 80,435 bed days and 183,828 day cases.[18]

In England in 2017, there 10,219 registrations of death from malignant neoplasm of breast,[19] and the direct age-standardised death rate per 100,000 population was 0.3 and 33.3 among males and females respectively.[16]

The latest published survival statistics for breast cancer for women in England (patients diagnoses 2013-2017) reported a 1-year survival rate of 95.8% and a 5-year survival rate of 85% (age-standardised).[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of breast cancer should be carried out in specialised breast units/centres and provided by a multidisciplinary team specialised in breast cancer, consisting of at least medical oncologists, breast surgeons, radiation oncologists, breast radiologists, breast pathologists and breast nurses (or similarly trained and specialised health care practitioners).[21]

The management of breast cancer requires different approaches and involves the use of different therapies. The main treatments for breast cancer include surgery, radiotherapy, chemotherapy, hormone therapy, biological therapy (targeted therapy). Patients may have one of these treatments or a combination. The type or combination of treatments will depend on how the cancer was diagnosed and the stage of the disease.[22]

Adjuvant systemic therapy should be started without undue delays, as data show an important decrease in efficacy when it is administered >12 weeks after surgery. The decision on adjuvant systemic therapies should be based on an individual's risk of relapse (which depends on tumour burden and tumour biology), the predicted sensitivity to particular types of treatment, the benefit from their use and their associated short- and long-term toxicities, the patient's biological age, general health status, comorbidities and preferences.[21]

CURRENT TREATMENT OPTIONS

The following are recommended in the treatment of early breast cancer:[23-25]

Chemotherapy

- A regimen which contains both a taxane and anthracyclin is recommended for people of sufficient risk that chemotherapy is indicated

Radiotherapy

- Whole-breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins
- Partial breast radiotherapy (as an alternative to whole-breast radiotherapy) for women who have had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins
- Adjuvant postmastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins

Surgery

- Breast-conserving surgery involves a local excision to remove the cancerous area with a small amount of surrounding breast tissue
- Mastectomy is complete removal of the breast, which may be completed as a preventative measure or in cases where breast-conserving surgery has been unsuccessful in halting cancer cell spread into neighbouring tissue

Bisphosphonate therapy

- Zoledronic acid or sodium clodronate as adjuvant therapy for postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence

Endocrine therapy

- Tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER-positive breast cancer

- Aromatase inhibitor as the initial adjuvant endocrine therapy for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence
- Ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer
- Extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years

PLACE OF TECHNOLOGY

If licenced, palbociclib will provide an additional option, with a favourable safety profile, for post neoadjuvant treatment of women with high-risk early breast cancer.[2,4]

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**(PENELOPE-B), NCT01864746, 2013-001040-62; Phase III Study Evaluating Palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in Patients With Hormone-receptor-positive, HER2-normal Primary Breast Cancer With High Relapse Risk After Neoadjuvant Chemotherapy "PENELOPEB"** **Phase III – Active, not recruiting** **Location(s): EU (incl UK), USA, Canada and other countries** **Primary completion date: December 2020**
Trial design	Randomised, quadruple masked (participant, care provider, investigator, outcomes assessor), parallel assignment
Population	n = 1250; women aged 18 and older; histologically confirmed unilateral or bilateral primary invasive carcinoma of the breast; HR-positive/HER2-normal primary breast cancer; patients must have received neoadjuvant chemotherapy of at least 16 weeks.
Intervention(s)	Palbociclib capsule at a dose of 125 mg taken orally, once daily, day 1 to day 21 followed by 7 days off treatment in a 28-day cycle.
Comparator(s)	Matched placebo
Outcome(s)	Invasive disease free survival (iDFS) for palbociclib vs. placebo in patients with high CPS-EG score after neoadjuvant chemotherapy receiving standard adjuvant endocrine therapy for HR-positive/HER2-normal primary breast cancer. [Time frame: time-to-event outcome measure. Final analysis on the primary endpoint and secondary efficacy endpoints (except for OS) Analysis will be conducted when 255 events observed. Assessed until approx. Dec 2020.] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Palbociclib is already marketed in the UK.[26]The NHS indicative price for palbociclib capsules is as follows:[26]

- Palbociclib 125 mg; 21 capsules (prescription only medicine) cost £2950 (Hospital only)
- Palbociclib 125 mg; 63 capsules (prescription only medicine) cost £8850 (Hospital only)

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Intrabeam radiotherapy system for adjuvant treatment of early breast cancer (TA501). January 2018
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018
- NICE quality standard. Breast cancer (QS12). June 2016
- NICE diagnostics guidance. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (DG34). December 2018

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 for Medical Oncology. Early breast cancer. ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2019[21]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice guidelines in Oncology. 2018[27]

ADDITIONAL INFORMATION

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