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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Inavolisib with palbociclib and fulvestrant for treating hormone receptor-positive HER2-negative PIK3CA-mutated locally advanced or metastatic breast cancer after adjuvant endocrine treatment [ID6425]

Final scope

Final remit/evaluation objective

To appraise the clinical and cost effectiveness of inavolisib with palbociclib and fulvestrant within its marketing authorisation for treating hormone receptor-positive HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer that has progressed on or within 12 months after completing adjuvant endocrine treatment.

Background

Breast cancer arises from the tissues of the ducts or lobules of the breast. The cancer is said to be 'advanced' if it has spread to other parts of the body such as the bones, liver, and lungs (metastatic cancer), or if it has grown directly into nearby tissues and cannot be completely removed by surgery.

In 2022 in England, 50,980 people were diagnosed with breast cancer.[1] Approximately 15% of people with breast cancer in England in 2022 had advanced stage disease (stage III or IV) when they were diagnosed.[1,2] The 1-year survival rate for adults diagnosed at stage IV (metastatic breast cancer) in England is 67%.[2] Around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis.[3]

Current treatments for advanced breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with minimal adverse events. Treatment depends on whether the cancer cells have particular receptors, the extent of the disease, and previous treatments, which may include surgery for early and locally advanced disease. The most prevalent type of breast cancer is hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative disease.[4] PIK3CA gene mutations are found in 30% to 40% of oestrogen receptor positive, HER2-negative tumours.[5]

Adjuvant therapy is used to reduce the risk of the cancer coming back after surgery. NICE guideline 101 recommends adjuvant endocrine therapy (tamoxifen or aromatase inhibitors such as anastrozole and letrozole) for hormone receptor-positive early breast cancer. It also recommends considering ovarian function suppression for premenopausal women and extended endocrine therapy (total duration of endocrine therapy of more than 5 years). Adjuvant chemotherapy (a regimen containing both a taxane and an anthracycline), adjuvant radiotherapy and adjuvant bisphosphonate therapy (for post-menopausal women) are also recommended for early breast cancer.

- NICE technology appraisal guidance 810 recommends abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive,

HER2-negative, node-positive early breast cancer in adults whose disease is at high risk of recurrence, defined by the following clinical and pathological features:

- at least 4 positive axillary lymph nodes, or
- 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:
- grade 3 disease (defined as at least 8 points on the modified Bloom–Richardson grading system or equivalent), or
- primary tumour size of at least 5 cm.

NICE technology appraisals 495, 496 and 563 recommend cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors (palbociclib, ribociclib and abemaciclib respectively) in combination with an aromatase inhibitor (a type of endocrine therapy) for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults.

- The choice of endocrine therapy for advanced breast cancer is guided by NICE clinical guideline 81 (CG81). In people who have been through the menopause, endocrine therapies include non-steroidal aromatase inhibitors (anastrozole and letrozole) or tamoxifen, if aromatase inhibitors are not tolerated or are contraindicated. People who are before menopause or around menopause will have first-line treatment with tamoxifen and ovarian suppression if they have not previously received tamoxifen. Men may receive tamoxifen as a first-line endocrine treatment.
- For people whose disease is life-threatening or requires early relief of symptoms, CG81 recommends chemotherapy first, followed by endocrine therapy.

For people whose hormone receptor-positive, HER2-negative advanced breast cancer has recurred or progressed after previous endocrine therapy:

- NICE technology appraisals 687, 725 and 836 recommend abemaciclib, ribociclib and palbociclib, all in combination with fulvestrant, for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine therapy and only if, exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor. In clinical practice in the NHS a CDK 4/6 inhibitor in combination with fulvestrant may be used as initial treatment in people whose breast cancer is not expected to be sensitive to aromatase inhibitor-based endocrine therapy. Where a CDK 4/6 inhibitor in combination with an aromatase inhibitor was used as first-line treatment, re-treatment with a CDK 4/6 inhibitor would be unlikely to occur.

For people whose hormone receptor-positive, HER2-negative advanced breast cancer has recurred or progressed after a non-steroidal aromatase inhibitor:

- NICE technology appraisal 421 recommends treatment with everolimus plus exemestane.

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- Where the breast cancer has a PIK3CA mutation, NICE technology appraisal 816 recommends alpelisib plus fulvestrant for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer when the condition has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.

The technology

Inavolisib (brand name unknown, Roche) does not currently have a marketing authorisation in the UK for hormone receptor-positive HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer after adjuvant endocrine therapy. Inavolisib plus palbociclib and fulvestrant has been studied in a clinical trial compared with placebo plus palbociclib and fulvestrant for the treatment of hormone receptor-positive HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer that has progressed during treatment or within 12 months after adjuvant endocrine treatment in people who have not received prior systemic therapy for metastatic disease.

Intervention(s)	Inavolisib with palbociclib and fulvestrant
Population(s)	People with hormone receptor-positive HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer that has progressed on or within 12 months after completing adjuvant endocrine treatment
Comparators	CDK 4/6 inhibitors (abemaciclib, ribociclib or palbociclib) in combination with fulvestrant
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • duration of response • adverse effects of treatment • health-related quality of life.

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Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of inavolisib with palbociclib and fulvestrant is conditional on the presence of a PIK3CA mutation. The economic modelling should include the costs associated with diagnostic testing for a PIK3CA mutation in people with locally advanced or metastatic breast cancer after adjuvant endocrine treatment who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: Introduction to health technology evaluation | NICE health technology evaluations: the manual | Guidance | NICE.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related technology appraisals:** Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (2022) NICE technology appraisal guidance 836. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer (2022) NICE technology appraisal guidance 816. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence (2022) NICE technology appraisal guidance 810. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (2021) NICE technology appraisal guidance 725. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after

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	endocrine therapy (2021) NICE technology appraisal guidance 687. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (2019) NICE technology appraisal guidance 563. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (2017) NICE technology appraisal guidance 496. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (2017) NICE technology appraisal guidance 495. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (2016) NICE technology appraisal 421. Fulvestrant for the treatment of locally advanced or metastatic breast cancer (2011) NICE technology appraisal guidance 239. **Related NICE guidelines:** Advanced breast cancer diagnosis and treatment (2009; updated 2017) NICE guideline CG81 Early and locally advanced breast cancer: diagnosis and management (2018; updated 2024) NICE guideline NG101 Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (2013; updated 2019) NICE guidance CG164 Improving outcomes in breast cancer (2002; reviewed 2014) NICE guideline CSG1 MammaTyper in vitro diagnostic test for determining breast cancer subtypes (2018) NICE Medtech Innovation Briefing 135 **Related NICE guidelines in development:** Advanced breast cancer: diagnosis and treatment (Partial update) NICE guideline. Publication date to be confirmed Breast cancer guidelines. NICE guideline. Publication date to be confirmed Early and locally advanced breast cancer: diagnosis and management - Neoadjuvant chemotherapy and ovarian function suppression (update). NICE guideline. Publication expected March 2025

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	Lymphoedema: prevention and management in people with early, locally advanced, and advanced breast cancer (update). NICE guideline. Publication date to be confirmed **Related quality standards:** Breast cancer (2011; updated 2016) NICE quality standard 12.

References

1. NHS Digital (2024) Cancer registration statistics, England, 2022. Accessed November 2024.

2. Cancer Research UK (2022) Early diagnosis data hub. Accessed November 2024.

3. Dewis R and Gribbin J (2009) Breast cancer: diagnosis and treatment, an assessment of need. Cardiff: National Collaborating Centre for Cancer. Accessed November 2024.

4. Jin X, Zhou YF, Ma D, et al. (2023) Molecular classification of hormone receptor-positive HER2-negative breast cancer. Nature Genetics 55:1696-1708.

5. Kratz J, Burkard M, O'Meara T, et al (2018) Incorporating Genomics Into the Care of Patients With Advanced Breast Cancer. American Society of Clinical Oncology. Volume 38, 56-64. Accessed November 2024.