

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

**Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer**

**Final scope**

**Remit/appraisal objective**

To appraise the clinical and cost effectiveness of alpelisib within its marketing authorisation for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer.

**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 2017 in England, around 46,109 people were diagnosed with breast cancer.<sup>1</sup> In 2018 there were 9,640 deaths from breast cancer in England.<sup>2</sup> Approximately 13% of women with breast cancer have advanced disease (stage III or IV) in England when they are diagnosed.<sup>3</sup> The 1-year survival rate for adults diagnosed at stage IV (metastatic breast cancer) in England is 66%.<sup>4</sup> Around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis.<sup>5</sup>

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. Most (80%) breast cancers are hormone-receptor positive and around two-thirds are oestrogen receptor positive. Human epidermal growth factor receptor 2 (HER2) is present in about 10-15% of breast cancers.<sup>6</sup> Approximately 64% of women with metastatic breast cancer in the UK have hormone-receptor positive, HER2 negative disease.<sup>7</sup> PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutations have been found in 30% to 40% of oestrogen receptor positive, HER2-negative tumours.<sup>8</sup>

NICE clinical guideline 81 (CG81) recommends first-line treatment with endocrine therapy for most people with advanced hormone receptor-positive breast cancer. For people whose disease is life-threatening or requires early relief of symptoms, CG81 recommends chemotherapy. The endocrine therapies used in clinical practice in postmenopausal women include aromatase inhibitors (anastrozole and letrozole), or tamoxifen, if aromatase inhibitors are not tolerated or are contraindicated. Women who are

premenopausal or perimenopausal will receive first-line treatment with tamoxifen and ovarian suppression if they have not previously received tamoxifen, while men will receive tamoxifen as a first-line endocrine treatment. NICE technology appraisals 495, 496 and 563 recommend cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors (palbociclib, ribociclib and abemaciclib respectively) in a combination with an aromatase inhibitor for treating hormone receptor positive, HER2-negative, locally advanced or metastatic breast cancer as initial endocrine based therapy in adults. Fulvestrant is not recommended for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer (NICE technology appraisal 503).

For people who receive first-line treatment with anastrozole or letrozole, second-line treatment may be either tamoxifen, exemestane, or everolimus and exemestane (NICE technology appraisal 421). NICE technology appraisal 687 recommends ribociclib in combination with fulvestrant as an option for hormone receptor-positive, HER2-negative, advanced breast cancer in people who have had previous endocrine therapy if exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor. NICE technology appraisals 579 and 619 recommend abemaciclib and palbociclib respectively in the same population for use within the Cancer Drugs Fund.<sup>a</sup> Subsequent treatment options also include chemotherapy for some people. Fulvestrant monotherapy is not recommended for use following anti-oestrogen therapy, as an alternative to aromatase inhibitors (NICE technology appraisal 239), however, it is sometimes used after exemestane and tamoxifen in people who would otherwise receive chemotherapy.

### The technology

Alpelisib (Piqray, Novartis) is a phosphoinositide 3-kinase (PI3K) alpha inhibitor. It inhibits the activation of the PI3K signalling pathway. This may result in inhibition of tumour cell growth and survival in breast cancer cell lines with PIK3CA gene mutations (PIK3CA-mutated). It is administered orally.

Alpelisib in combination with fulvestrant has a marketing authorisation in the UK for treating hormone receptor-positive, HER2-negative breast cancer following endocrine therapy.

<b>Intervention(s)</b>	Alpelisib in combination with fulvestrant
<b>Population(s)</b>	People with advanced hormone-receptor positive HER2-negative, PIK3CA-mutated breast cancer that has progressed after prior endocrine therapy (in the neo/adjuvant or advanced setting)

<sup>a</sup> Products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. [NICE's position statement](#).

<b>Comparators</b>	<ul style="list-style-type: none"> <li>• CDK4/6 inhibitors in combination with fulvestrant <ul style="list-style-type: none"> <li>○ ribociclib</li> <li>○ abemaciclib (subject to ongoing NICE appraisal)</li> <li>○ palbociclib (subject to ongoing NICE guidance)</li> </ul> </li> <li>• Everolimus and exemestane</li> <li>• Exemestane</li> <li>• Tamoxifen</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rate</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the comparator technologies will be taken into account.</p> <p>The use of alpelisib is conditional on the presence of PIK3CA mutation. The economic modelling should include the costs associated with diagnostic testing for PIK3CA mutation in people with advanced hormone-receptor positive, HER2-negative breast cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. <a href="#">See section 5.9 of the Guide to the Methods of Technology Appraisals.</a></p>

<p><b>Other considerations</b></p>	<p>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.</p>
<p><b>Related NICE recommendations and NICE Pathways</b></p>	<p>Related Technology Appraisals:</p> <p><a href="#">Palbociclib with fulvestrant for treating hormone-receptor positive, HER2-negative, advanced breast cancer</a> (2020) NICE technology appraisal guidance 619. Next review date to be confirmed.</p> <p><a href="#">Ribociclib with fulvestrant for treating hormone-receptor positive, HER2-negative, advanced breast cancer</a> (2021) NICE technology appraisal 687. Next review date 2024.</p> <p><a href="#">Abemaciclib with fulvestrant for treating hormone-receptor positive, HER2-negative, advanced breast cancer after endocrine therapy</a> (2019) NICE technology appraisal 579. Next review date December 2021.</p> <p><a href="#">Abemaciclib with an aromatase inhibitor for previously untreated, hormone-receptor positive, HER2-negative, locally advanced or metastatic breast cancer</a> (2019) NICE technology appraisal 563. Next review date 2022.</p> <p><a href="#">Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer</a> (2018). NICE technology appraisal 503. Next review date to be confirmed.</p> <p><a href="#">Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer</a> (2017). NICE technology appraisal 496. Next review date 2020.</p> <p><a href="#">Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer</a> (2017). NICE technology appraisal 495. Next review date 2020.</p> <p><a href="#">Everolimus with exemestane for treating advanced breast cancer after endocrine therapy</a> (2016) NICE technology appraisal 421. Next review 2019.</p> <p><a href="#">Fulvestrant for the treatment of locally advanced or metastatic breast cancer</a> (2011). NICE Technology Appraisal 239. Review date Nov 2014. Review decision, static list</p> <p><a href="#">Gemcitabine for the treatment of metastatic breast</a></p>

	<p><a href="#">cancer</a> (2007). NICE technology Appraisal 116. Review date, May 2010. Review decision, static list.</p> <p>Appraisals in development (including suspended appraisals):</p> <p><a href="#">Abemaciclib with fulvestrant for treating hormone-receptor positive, HER2-negative, advanced breast cancer after endocrine therapy</a> [ID2727] NICE technology appraisal guidance. Publication date to be confirmed</p> <p><a href="#">Taselisib for previously treated ER-positive, HER2-negative, PIK3CA-positive breast cancer in postmenopausal women</a> Proposed NICE technology appraisal [ID1401]. Publication date to be confirmed</p> <p><a href="#">Entinostat for treating hormone receptor-positive breast cancer after hormonal therapy</a> [ID1260] NICE technology appraisal guidance. Publication date to be confirmed</p> <p>Related Guidelines:</p> <p><a href="#">Advanced breast cancer: diagnosis and treatment</a> (2009, updated 2017). NICE clinical guideline 81. Surveillance check in January 2018.</p> <p><a href="#">Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer</a> (2013, updated 2019). NICE clinical guideline 164. Surveillance check in November 2019.</p> <p>Related Quality Standards:</p> <p><a href="#">Breast cancer</a> (2011, updated 2016). NICE quality standard 12.</p> <p>Related NICE Pathways:</p> <p><a href="#">Advanced breast cancer</a> (2020) NICE Pathway</p> <p><a href="#">Familial breast cancer</a> (2020) NICE Pathway</p>
<b>Related National Policy</b>	<p>The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018) <a href="#">Manual for Prescribed Specialised Services</a> 2018/19. Chapter 105, Specialist Cancer services (adults)</p> <p>Department of Health (2016) <a href="#">NHS Outcomes Framework 2016-2017</a>. Domains 1 and 2.</p>

### References

- 1 Office for National Statistics (2019) [Cancer registration statistics, England, 2017](#). Accessed January 2020.
- 2 Nomis (2020) Office for National Statistics. [Mortality statistics – underlying cause, sex and age](#): 2018 data. Accessed January 2020.
- 3 Cancer Research UK (2020) [Breast cancer incidence statistics](#): England 2014 data. Accessed January 2020
- 4 Cancer Research UK (2020) [Breast cancer survival statistics](#): adults diagnosed 2013-2017, followed up to 2018. Accessed January 2020.
- 5 Dewis R and Gribbin J (2009) [Breast cancer: diagnosis and treatment, an assessment of need](#). Cardiff: National Collaborating Centre for Cancer. Accessed August 2018
6. NIHR Evidence Briefing (2017) [Alpelisib in combination with fulvestrant for advanced HR positive, HER2-negative breast cancer in men and postmenopausal women](#). Accessed September 2018.
- 7 NICE (2017) [Resource impact report: Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor positive, HER2-negative, locally advanced or metastatic breast cancer \(TA495\)](#). Accessed September 2018.
- 8 Kratz J, Burkard M, O’Meara T, Puztai L, Veitch Z, Bedard PL (2018) [Incorporating Genomics Into the Care of Patients With Advanced Breast Cancer](#). American Society of Clinical Oncology. Volume 38, 56-64. Accessed September 2018.