

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**Single Technology Appraisal****Everolimus with exemestane for treating HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (review of TA295)****Draft scope****Remit/appraisal objective**

To appraise the clinical and cost effectiveness of everolimus in combination with an aromatase inhibitor within its marketing authorisation for the treatment of human epidermal growth factor 2 (HER2) negative, oestrogen receptor positive locally advanced or metastatic breast cancer after prior endocrine therapy.

Background

Breast cancer arises from the tissues of the ducts or lobules of the breast. Locally advanced cancer describes tumours that are larger than 5 cm in size, and may have grown into the skin or muscle of the chest or nearby lymph nodes. Metastatic breast cancer describes disease that has spread to another part of the body, such as the bones, liver, or lungs.

Over 44,800 people were diagnosed with breast cancer in England in 2013, and there were approximately 9800 deaths from breast cancer in 2012^{1,2}. The 5-year survival rate for people with metastatic breast cancer in England is 15%³. Approximately 16% of women with invasive breast cancers have locally advanced or metastatic disease when they are diagnosed⁴, and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer^{5,6}.

Current treatments for locally advanced and metastatic breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with few adverse events. Treatment may depend on whether the cancer cells have particular receptors (hormone receptor status or HER2 status), the extent of the disease, and previous treatments.

NICE Clinical Guideline 80 recommends that locally advanced hormone receptor-positive breast cancer is treated with surgery (to remove the tumour) followed by systemic adjuvant endocrine therapy to reduce the risk of the cancer coming back. For people with metastatic hormone receptor-positive breast cancer, NICE Clinical Guideline 81 recommends first-line treatment with endocrine therapy for most people. In clinical practice, people who are post-menopausal with hormone receptor-positive metastatic breast cancer often receive first-line treatment with anastrozole or letrozole. The NICE clinical guideline advises that chemotherapy should be offered as first-line

treatment for people with hormone-receptor positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.

For post-menopausal people who receive first-line treatment with anastrozole or letrozole, second-line treatment may be either tamoxifen or exemestane, followed by third-line treatment with exemestane or tamoxifen depending on the previous treatment received. Fulvestrant is not recommended for use following anti-oestrogen therapy, as an alternative to aromatase inhibitors (NICE [technology appraisal guidance 239](#)). If the disease progresses after endocrine therapy in people with hormone-receptor-positive, HER2-negative advanced breast cancer, NICE Clinical Guideline 81 recommends sequential chemotherapy, starting with an anthracycline-based regimen. If anthracyclines are not suitable (because they are contraindicated or because of prior anthracycline treatment), systemic chemotherapy should be offered in the following sequence: docetaxel monotherapy, followed by single agent capecitabine or vinorelbine, and then either vinorelbine or capecitabine depending on the previous treatment received. NICE recommends gemcitabine in combination with paclitaxel as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate (NICE [technology appraisal guidance 116](#)).

NICE is reviewing the [technology appraisal guidance 295](#) following publication of mature survival data from the BOLERO-2 study.

The technology

Everolimus (Afinitor, Novartis Pharmaceuticals UK) is an orally administered inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells.

Everolimus has a marketing authorisation in the UK for treating hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

Intervention(s)	Everolimus in combination with exemestane
Population(s)	Post-menopausal people with hormone-receptor-positive, HER2-negative, advanced breast cancer, without symptomatic visceral disease, that has progressed after a non-steroidal aromatase inhibitor

Comparators	<ul style="list-style-type: none"> • Exemestane • Tamoxifen
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</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 intervention or comparator technologies will be taken into account.</p>
Other considerations	<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>
Related NICE recommendations and NICE Pathways	<p>Related Technology Appraisals:</p> <p>Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (2013) NICE Technology Appraisal guidance 295. Review ongoing, publication date TBC.</p> <p>Eribulin for the treatment of locally advanced or metastatic breast cancer (2012). NICE Technology Appraisal 250. Review ongoing, publication date TBC.</p> <p>Fulvestrant for the treatment of locally advanced or metastatic breast cancer (2011). NICE Technology Appraisal 239. Review date Nov 2014. Review decision,</p>

	<p>static list</p> <p>Gemcitabine for the treatment of metastatic breast cancer (2007). NICE technology Appraisal 116. Review date, May 2010. Review decision, static list.</p> <p>Appraisals in development (including suspended appraisals):</p> <p>Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer. NICE Technology Appraisal guidance [ID319]. Suspended.</p> <p>Sunitinib in combination with a taxane within its licensed indication for the first line treatment of advanced and/or metastatic breast cancer. NICE Technology Appraisal guidance [ID58]. Suspended.</p> <p>Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer). NICE Technology Appraisal guidance [ID20]. Suspended.</p> <p>Bevacizumab for the second line treatment of HER2 negative metastatic breast cancer. NICE Technology Appraisal guidance [ID488]. Suspended.</p> <p>Proposed Technology Appraisals:</p> <p>Palbociclib for treating metastatic, hormone receptor-positive, HER2-negative breast cancer Proposed NICE technology appraisal [ID915]. Publication date to be confirmed.</p> <p>Related Guidelines:</p> <p>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 (2013). NICE guideline CG164 Review date: December 2015</p> <p>Advanced breast cancer: diagnosis and treatment (2009). NICE guideline 81 This guidance replaces previous Technology Appraisals No. 30, 54 and 62. Review date December 2015.</p> <p>Breast cancer (early and locally advanced): diagnosis and treatment (2009). Clinical Guideline No. 80. Review decision date December 2015.</p> <p>Related Quality Standards:</p> <p>Quality Standard No. 12, September 2011, 'Breast cancer'. Update in progress, publication expected June</p>
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	<p>2016.</p> <p>Related NICE Pathways:</p> <p>Advanced breast cancer (2015) NICE pathway</p> <p>Familial breast cancer (2015) NICE pathway</p> <p>Early and locally advanced breast cancer (2014) NICE pathway</p>
<p>Related National Policy</p>	<p>NHS England, Manual for prescribed specialised services 2013/14: Chapter 105. Specialist Cancer services (adults)</p> <p>http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf</p> <p>Department of Health, Improving Outcomes: A Strategy for Cancer, third annual report, Dec 2013</p> <p>https://www.gov.uk/government/publications/the-national-cancer-strategy-3rd-annual-report--2</p> <p>Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1, 2, 4 and 5</p> <p>https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf</p>

Questions for consultation

Which treatments are considered to be established clinical practice in the NHS for treating hormone-receptor-positive, HER2-negative, advanced breast cancer without symptomatic visceral disease that has progressed after a non-steroidal aromatase inhibitor?

- Are the comparators listed in the table appropriate?
- Should everolimus be compared with chemotherapy? If so, which regimens would be used at the same point in the treatment pathway?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom everolimus in combination with exemestane is expected to be more clinically effective and cost effective or other groups that should be examined separately

Where do you consider everolimus in combination with exemestane will fit into the existing NICE pathways ([Early and locally advanced breast cancer](#) [2014] and [Advanced breast cancer](#) [2015])?)

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which everolimus in combination with exemestane are licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider everolimus in combination with exemestane to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of everolimus in combination with exemestane can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>)

References

- 1 Office for National Statistics (2015) [Cancer registration statistics, England, 2013](#). Accessed January 2016.
- 2 Cancer Research UK (2014) [Breast cancer mortality statistics](#). Accessed January 2016.

3 Cancer Research UK (2014) [Breast cancer survival statistics](#). Accessed January 2016.

4 Cancer Research UK (2015) [Breast cancer incidence statistics](#). Accessed January 2016.

5 NICE (2009) [Costing report for clinical guideline 81: advanced breast cancer](#). Accessed January 2016.

6 Dewis R and Gribbin J (2009) [Breast cancer: diagnosis and treatment, an assessment of need](#). Cardiff: National Collaborating Centre for Cancer. Accessed January 2016.