NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA263; Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer

This guidance was issued in August 2012.

The review date for this guidance is June 2015.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of bevacizumab in combination with capecitabine within its licensed indication for the first-line treatment of metastatic breast cancer.

3. Current guidance

1.1 Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months.

1.2 People currently receiving bevacizumab in combination with capecitabine that is not recommended according to 1.1 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

4. Rationale[1]

No significant new evidence has been identified that would be likely to change the current recommendation in TA263. It is therefore appropriate to transfer this guidance to the 'static guidance list'.

5. Implications for other guidance producing programmes

The Centre for Clinical Practice note the proposal to move the guidance to the static list. CG81 (Advanced breast cancer (update): Diagnosis and treatment) is scheduled

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

to be considered for review in 2015. Any potential future updated versions of this guidance could potentially incorporate the recommendations from TA263.

6. New evidence

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from November 2011 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisation for bevacizumab for treating metastatic breast cancer has not changed since the previous guidance. In addition, the marketing authorisations for the comparators, capecitabine monotherapy, and vinorelbine, have also not changed since the previous guidance.

The cost of bevacizumab has not changed since publication of TA263, that is, £242.66 and £924.40 100 mg and 400 mg vials, respectively.

In TA263, the Committee concluded that bevacizumab plus capecitabine improved progression-free survival relative to capecitabine plus placebo, but that there was no robust evidence that it improved overall survival and that its effects on health-related quality of life had not been captured (because the main trial had not collected quality of life data). The literature review found the interim results of 1 relevant clinical trial (TURANDOT) published since TA263 was issued. TURANDOT is an open-label, non-inferiority, phase 3 trial comparing first-line bevacizumab plus either capecitabine or paclitaxel in adults with metastatic breast cancer. The primary objective was to show non-inferior overall survival with bevacizumab plus capecitabine compared with bevacizumab plus paclitaxel. This study was excluded from the clinical effectiveness evidence in TA263 because it was ongoing and no efficacy data was available. Interim analysis from this study was published by Lang et al. in 2013 in which overall survival results were inconclusive and efficacy results in both groups were consistent with previous reports. Based on these interim results, there is still no evidence that bevacizumab improves overall survival. There is also still no evidence reported for its effect on health-related quality of life. In addition, a recent meta-analysis by Fang et al. (2015) showed that although bevacizumab combined with chemotherapy significantly improves progression-free survival, it did not improve overall survival.

In summary, the new evidence is unlikely to lead to a change in the recommendations of the original guidance, given the uncertainties that remain with overall survival, health-related quality of life, and the fact that the cost of bevacizumab has not changed.

8. Implementation

There is no submission from Implementation, as the technology is not recommended.

9. Equality issues

No equality issues were identified during the appraisal.

GE paper sign off: Helen Knight, Associate Director – 26 May 2015

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (2013) NICE technology appraisal 295.

Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (2012) NICE technology appraisal 257.

Eribulin for the treatment of locally advanced or metastatic breast cancer (2012) NICE technology appraisal 250.

Fulvestrant for the treatment of locally advanced or metastatic breast cancer (2011) NICE technology appraisal 239.

Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (2011) NICE technology appraisal 214.

Gemcitabine for the treatment of metastatic breast cancer (2007) NICE technology appraisal 116.

Trastuzumab for the treatment of advanced breast cancer (2002) NICE technology appraisal 34.

Advanced breast cancer (update): Diagnosis and treatment (2014) NICE guideline CG81.

Improving outcomes in breast cancer (2002) NICE cancer service guidance CSGBC.

In progress

Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) NICE technology appraisals guidance. Publication date to be confirmed. *"Please note that the NICE Decision Support Unit (DSU) are undertaking a discussion paper for assessing technologies that are not cost effective at a zero price." June 2014. NB this is on the current Cancer Drugs Fund (March 15) list for 'advanced breast cancer'.*

Breast cancer (HER2 positive, unresectable) - trastuzumab emtansine (after trastuzumab & taxane) NICE technology appraisals guidance. Publication date to be confirmed. *"The Committee discussion for trastuzumab emtansine for treating HER2-positive, locally advanced or metastatic breast cancer that was due to take place on 28 May 2014 has been cancelled. This is due to the consideration of a commercial arrangement proposed by the manufacturer."*

Suspended/terminated

Breast cancer (ErbB2 HER2, metastatic) - lapatinib (with paclitaxel, 1st line) NICE technology appraisals guidance. Publication date to be confirmed. *"The Institute has now been informed by the manufacturer that it has withdrawn its application for a centralised marketing authorisation for lapatinib in combination with paclitaxel, which was based on the results of the EGF104535 study." Suspended March 2012.*

Breast cancer (HER2 negative, metastatic) - bevacizumab (2nd line) NICE technology appraisals guidance. Publication date to be confirmed. *"The Institute has now been informed by the manufacturer that it has decided not to apply for a centralised marketing authorisation for this indication. NICE has therefore decided to suspend this appraisal on its current work programme for the time being." November 2011.*

Breast cancer (metastatic) -trastuzumab (as monotherapy and in combination with a taxane) NICE technology appraisals guidance. Publication date to be confirmed. *"A scoping workshop was held in June 2010, where potential changes to the remit of this appraisal were proposed. These proposals were put the Department of Health, who are currently in the process of considering the request to amend the remit. There are a complex set of issues to be discussed regarding the suggested changes to the remit and these need to be explored further before the Department of Health can take a decision."*

Breast cancer (advanced or metastatic) – lapatinib NICE technology appraisals guidance. Publication date to be confirmed. *Postponed October 2010.*

Breast cancer (advanced and/or metastatic) - sunitinib (in combination with capecitabine) NICE technology appraisals guidance. Publication date to be confirmed. *"The manufacturer of sunitinib has advised us that regulatory approval for this technology is not being sought at this time following the receipt of trial data. The Institute has therefore decided to remove this appraisal from its current work programme." April 2010.*

Breast cancer (locally advanced or metastatic) – ixabepilone NICE technology appraisals guidance. Publication date to be confirmed. *"The manufacturer recently received a negative CHMP opinion for Ixabepilone for locally advanced or metastatic breast cancer. Consequently this appraisal will be suspended until we receive an update from the manufacturer on the status of regulatory approval." December 2008.*

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"Bevacizumab in combination with capecitabine has a marketing authorisation for 'first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine'." "Bevacizumab is available in 100 mg and 400 mg vials at net prices of £242.66 and £924.40, respectively (excluding VAT; 'British national formulary' [BNF] edition 63)."	The indication and price remains the same, in eBNF March 2015.

Registered and unpublished trials

Trial name and registration number	Details
A Randomized Phase III 2-arm Trial of Paclitaxel Plus Bevacizumab vs. Capecitabine Plus Bevacizumab for the First-line Treatment of HER2-negative Locally Recurrent or Metastatic Breast Cancer. NCT00600340; CECOG/BC1.3.005 *In the original guidance TA263, it says: "The TURANDOT trial was excluded because it is ongoing and no efficacy data are available."*	Phase III, ongoing not recruiting. No results published on the trial record. Estimated enrolment: 560 Primary completion date: February 2015. *Two interim publications have been found for this trial: Lang et al (2013) and Brodowicz et al (2014).*

References

Fang Y, Qu X, Cheng B et al. (2015) The efficacy and safety of bevacizumab combined with chemotherapy in treatment of HER2-negative metastatic breast cancer: a meta-analysis based on published phase III trials. Tumour Biology 36 (3): 1933-1941.

Lang I, Brodowicz T, Ryvo L et al. (2013) Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic

breast cancer: interim efficacy results of the randomised, open-label, non-inferiority, phase 3 TURANDOT trial. The Lancet Oncology 14 (2): 125-133.