NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA214; Bevacizumab in combination with a taxane for the first line treatment of metastatic breast cancer

This guidance was issued in February 2011

The review date for this guidance is July 2013

1. Recommendation

TA214 should be transferred to the 'static' guidance list. That we consult on this proposal.

2. Original remit

To appraise the clinical and cost effectiveness of bevacizumab in combination with a taxane within its licensed indication for the first-line treatment of HER2-negative metastatic breast cancer (to include a re-initiation of terminated appraisal TA147).

3. Current guidance

1.1. Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer.

1.2. Patients currently receiving bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

4. Rationale[1]

A systematic review published in 2012 (Wagner et al.) found only one additional study that was not included in the original appraisal. This study was a randomised double-blind, assessing the efficacy of another investigational anti-VEGF drug, motesanib placebo-controlled trial versus placebo and open-label bevacizumab (Martin et al., 2011). In an accompanying editorial, it was noted that "weekly paclitaxel resulted in a higher response rate and longer control of disease than was noted in the E2100 clinical trial; and the addition of bevacizumab did not significantly improve response rates or progression-free survival" (Buzdar, 2011). The results of the meta-analysis including this study would not change the Committee's original conclusion that bevacizumab may improve progression-free survival relative to taxanes alone, but that there is no robust evidence that bevacizumab improves overall survival.

[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

A randomised, double-blind, placebo-controlled, study to evaluate the efficacy and safety of bevacizumab, and associated biomarkers, in combination with paclitaxel compared with paclitaxel plus placebo as first-line treatment of HER2-negative metastatic breast cancer is not expected to complete until the end of 2018.

Given that there is no new evidence to suggest that the guidance should change, it is proposed that this guidance moves to the static list.

5. Implications for other guidance producing programmes

The clinical guideline on diagnosis and treatment of advanced breast cancer (CG81) was published in February 2009. The guideline provides recommendations on systemic disease-modifying therapy, including biological therapy, but does not currently have any recommendations on use of bevacizumab.

A review of CG81 was conducted in February 2012. The review recommendation was that the guideline should not be considered for an update but should cross-refer to new Technology Appraisals (including TA214) that were previously not mentioned in the guideline. The proposal to transfer TA214 to the static list is not likely to impact on CG81.

The next review of CG81 will be in April 2015 which will take into to account relevant Technology Appraisals which have been published since the guidelines publication.

The Centre for Clinical Practice are also commencing a rapid update work stream which will include elements of advanced breast cancer, this work is due to commence in October 2013.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from February 2010 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 original submission for technology appraisal 214 was based on a single trial (E2100) that compared bevacizumab plus paclitaxel with paclitaxel alone. The trial demonstrated a statistically significant increase in median progression-free survival of 5.5 months (hazard ratio 0.48, 95% confidence interval [CI] 0.39 to 0.61), and a non-statistically significant increase in median overall survival of 1.7 months (hazard ratio 0.87, 95% CI 0.72 to 1.05). A study that compared bevacizumab plus docetaxel to docetaxel alone (AVADO) was excluded from the main submission on the basis that the docetaxel regimen was not consistent with UK clinical practice. The clinical experts who attended the Committee meeting did not agree with this as a basis for exclusion. The results of AVADO, along with results of another study (RIBBON-1) were provided by the manufacturer after consultation on the appraisal consultation document. In the AVADO trial, there was a statistically significant improvement in

progression-free survival by 1.9 months (hazard ratio 0.77, 95% CI 0.64 to 0.93), and a non-statistically significant reduction in median overall survival by 1.7 months (hazard ratio 1.03, 95% CI 0.70 to 1.33). The RIBBON-1 trial was a randomised double-blind placebo controlled trial of standard chemotherapy with or without bevacizumab.

The most plausible incremental cost-effectiveness ratio (ICER) for bevacizumab plus paclitaxel versus weekly paclitaxel was between £110,000 and £259,000 per QALY gained and the ICER for bevacizumab plus paclitaxel versus docetaxel was considered to be greater than £115,000 per QALY gained. The Committee concluded that bevacizumab is likely to improve progression-free survival compared with paclitaxel or docetaxel, but it was not persuaded that the additional costs of treatment justify the additional benefits.

The literature search for this review identified a meta-analysis of randomised controlled trials (RCTs) evaluating the clinical effectiveness of VEGF-targeting therapies in patients with hormone-refractory or hormone-receptor negative metastatic breast cancer (Wagner et al., 2012). Trials in both the first- and second-line settings were considered eligible for inclusion. Progression-free survival was selected as the primary outcome of the analysis, with overall survival as a secondary outcome. All the included trials used bevacizumab in the intervention arm. For the comparison of first-line bevacizumab plus chemotherapy compared with chemotherapy alone, the analysis comprised a total of 2886 patients from 4 RCTs: Martin et al. (2011), AVADO, E2100 and RIBBON-1. Patients in the trials had either locally recurrent or metastatic breast cancer. Bevacizumab was compared with weekly paclitaxel in Martin et al. (2008) and the E2100 trial, and with docetaxel every 3 weeks in the AVADO trial. In the RIBBON-1 trial, bevacizumab in combination with standard chemotherapy was compared with standard chemotherapy alone. For the outcome progression-free survival, the overall hazard ratio was 0.67 (95% CI 0.61 to 0.73), which demonstrated a statistically significant benefit for patients treated with bevacizumab (the heterogeneity between the trials was moderate). The analysis of overall survival included data from AVADO, E2100 and RIBBON-1 only because survival data were not reported in Martin et al. (2011). The hazard ratio was 0.93 (95% CI 0.84 to 1.04), reflecting a non-statistically significant estimate (small heterogeneity).

During the course of the appraisal, the Committee noted the clinical specialist's comment that further research into whether there are any clinical or biological subgroups (such as subgroups by biological markers) for whom bevacizumab is particularly beneficial would be useful. The literature search for this review identified 1 study reporting biomarker results from the AVADO trial (Miles et al., 2013). The most consistent potential predictive effect was observed with plasma vascular endothelial growth factor A and vascular endothelial growth factor receptor 2. In addition, the literature search identified a trial the objective of which is to evaluate the efficacy and safety of bevacizumab, and associated biomarkers, in combination with paclitaxel compared with paclitaxel plus placebo as first-line treatment of patients with HER2-negative metastatic breast cancer. The study started in August 2012, with an estimated primary completion date of July 2018.

The Committee recommended further research designed to investigate differences in health-related quality of life and the clinical effectiveness of bevacizumab in

subgroups, such as those with prior taxane exposure, but no studies that would address the Committee's recommendation have been identified in this review.

Overall, the new evidence on the treatment effect of bevacizumab for the first-line treatment of metastatic breast cancer is in line with the evidence considered by the Committee in formulating its recommendations. A recent meta-analysis of major RCTs of bevacizumab corroborated the evidence presented to Committee for progression-free survival. However, as noted during the appraisal, the progression-free survival benefit does not translate into overall survival, and the benefit of bevacizumab in terms of extending life remains uncertain. No large studies in patients who had received prior taxane therapy were published recently, or are ongoing. The evidence for biomarkers to identify patients who would benefit most from bevacizumab is immature. In view of that, the new evidence does not warrant a review of the guidance.

8. Implementation

A submission from Implementation is included in Appendix 3.

9. Equality issues

The Committee noted information from the manufacturer's submission relating to the potential for worse outcomes in lower socioeconomic groups or by ethnicity. The Committee heard from the clinical specialist that there may be differences in overall treatment outcomes between these groups, but that they are likely to result from factors such as lower uptake of screening or later presentation of disease rather than differences in treatment. The Committee concluded that there was no evidence of differences in access to treatment or response to treatment by socioeconomic status or ethnicity in patients with disease at the metastatic stage.

GE paper sign off: Janet Robertson, 26 June 2013

Contributors to this paper:

Information Specialist:	Sadia Mughal
Technical Lead:	Ahmed Elsada
Implementation Analyst:	Rebecca Lea
Project Manager:	Andrew Kenyon
CCP input:	Katie Perryman Ford

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.	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.	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.	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
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

Options	Consequence	Selected – 'Yes/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

Advanced breast cancer: diagnosis and treatment. Clinical Guideline CG81. Issued: February 2009. The Institute decided not to update this guideline in March 2012, however this decision will be reviewed again in 2013 to enable relevant Technology Appraisals, which are due to be published in 2012, to be taken into consideration.

Early and locally advanced breast cancer: Diagnosis and treatment. Clinical Guideline CG80. Issued February 2009. Review decision date March 2012: It has been decided not to update this guideline at this stage. This guideline will be reviewed for update again in 2015.

Gemcitabine for the treatment of metastatic breast cancer. Technology Appraisal TA116. Issued January 2007. Static guidance.

Fulvestrant for the treatment of locally advanced or metastatic breast cancer. Technology Appraisal TA239. Issued: December 2011. Review date: August 2014.

Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. Technology Appraisal TA257. Issued: June 2012. Review date: June 2015.

Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer .Technology Appraisal TA263. Issued: August 2012. Review date: June 2015.

Breast cancer. Quality Standard QS12. Issued: September 2011. Review date: September 2016.

In progress

Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523]. Technology Appraisal. Expected date of issue: November 2013.

Breast cancer (HER2 negative, oestrogen receptor positive, locally advanced or metastatic) - everolimus (with an aromatase inhibitor) [ID538]. Technology Appraisal. Expected date of issue: July 2013.

Breast cancer (metastatic hormone-receptor) - lapatinib and trastuzumab (with aromatase inhibitor) [ID344]. Technology Appraisal. Expected date of issue: June 2012.

Suspended/terminated

Breast cancer (advanced or metastatic) - lapatinib [ID20]. Suspended Technology Appraisal. NICE's Guidance Executive decided that, whilst the Department of Health is considering NICE's request to extend the review of technology appraisal guidance 34 (Trastuzumab, as monotherapy and in combination with a taxane, for the

treatment of metastatic breast cancer), to include the appraisal of continued use of trastuzumab post progression in the metastatic setting and to possibly also include the review of the lapatinib appraisal, publication of the guidance on the use of lapatinib is not in the interests of patients or the efficiency of the NHS and should therefore be postponed (October 2010).

Breast cancer (locally advanced or metastatic) - ixabepilone [ID377]. Suspended Technology Appraisal. Suspended following negative opinion on ixabepilone from the CHMP (December 2008).

Breast cancer (advanced and/or metastatic) - sunitinib (in combination with capecitabine) [ID319]. Suspended Technology Appraisal. The manufacturer of sunitinib has advised NICE that, following the receipt of trial data, regulatory approval for this indication is not being sought.

Breast cancer (ErbB2 HER2, metastatic) - lapatinib (with paclitaxel, 1st line) [ID517]. Suspended Technology Appraisal. 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, following the receipt of trial data.

Breast cancer (first line treatment) - sunitinib (in combination with a taxane) [ID58]. Suspended Technology Appraisal. The manufacturer of sunitinib has advised NICE that, following the receipt of trial data, regulatory approval for this indication is not being sought.

Breast cancer (metastatic) -trastuzumab (as monotherapy and in combination with a taxane) [ID345]. Suspended Technology Appraisal. Remit not clear so appraisal has been suspended until further notice.

Details of changes to the indications of the technology

Indication considered in original appraisal	**Proposed indication (for this appraisal)**
First-line treatment of patients with metastatic breast cancer.	Unchanged

Details of new products

Drug (manufacturer)	**Details (phase of development, expected launch date,)**
Afatinib (Boehringer Ingelheim Pharmaceuticals, Inc.)	Advanced, 1st or 2nd line, HER2+ breast cancer. Phase III UK launch anticipated [redacted].

Drug (manufacturer)	Details (phase of development, expected launch date,)
Everolimus (Novartis)	Advanced, HER2+ve 1st-line breast cancer (with trastuzumab & paclitaxel). Phase III UK launch anticipated [redacted].
Trastuzumab emtansine (Roche)	Metastatic HER2+ve, first-line breast cancer. Phase III UK launch anticipated [redacted].

Registered and unpublished trials

Trial name and registration number	Details
Paclitaxel, Paclitaxel Albumin-Stabilized Nanoparticle Formulation, or Ixabepilone With or Without Bevacizumab in Treating Patients With Stage IIIC or Stage IV Breast Cancer NCT00785291	Status: Ongoing Estimated Enrolment: 900 Estimated Completion date: Dec 2013
Bevacizumab and Paclitaxel or Bevacizumab, Cyclophosphamide, and Capecitabine as First-Line Therapy in Treating Women With Locally Advanced, Recurrent, or Metastatic Breast Cancer NCT01131195	Status: Recruiting Estimated Enrolment: 142 Estimated Completion date: Oct 2015
1st Line Treatment of Bevacizumab-Taxane vs Bevacizumab-Exemestane in Metastatic Breast Cancer NCT01303679	Status: Recruiting Estimated Enrolment: 198 Estimated Completion date: May 2018
A Study of Avastin (Bevacizumab) in Women With HER2 Negative Metastatic Breast Cancer NCT00333775	Status: Ongoing Estimated Enrolment: 737 Estimated Completion date: Dec 2013
A Study of Avastin (Bevacizumab) in Combination With Herceptin (Trastuzumab)/Docetaxel in Patients With HER2 Positive Metastatic Breast Cancer. NCT00391092	Status: Ongoing Estimated Enrolment: 424 Estimated Completion date: Dec 2013

Trial name and registration number	Details
Study To Evaluate the Efficacy and Safety Of Bevacizumab, and Associated Biomarkers, In Combination With Paclitaxel Compared With Paclitaxel Plus Placebo as First-line Treatment Of Patients With Her2-Negative Metastatic Breast Cancer NCT01663727	Status: Recruiting Estimated Enrolment: 480 Estimated Completion date: Jan 2019
A Study Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy in Untreated Metastatic Breast Cancer (RIBBON 1) NCT00262067	Status: Ongoing Estimated Enrolment: 619 Estimated Completion date: Dec 2013
2-arm Trial of Paclitaxel Plus Bevacizumab vs. Capecitabine Plus Bevacizumab NCT00600340	Status: Ongoing Estimated Enrolment: 560 Estimated Completion date: Nov 2013
"An open randomized phase III study to compare 8 continuous cycles of chemotherapy with 8 cycles of intermittent (2 times 4 cycles) chemotherapy in first line treatment, in combination with bevacizumab, and second line treatment of patients with HER2/neu negative, incurable, metastatic or unresectable locally advanced breast cancer" EudraCT Number: 2010-021519-18	Status: Ongoing Estimated Enrolment: 420 Estimated Completion date: Not known
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 EudraCT Number: 2007-005828-32	Status: Ongoing Estimated Enrolment: 560 Estimated Completion date: Not known

Additional information

Drug safety:

Bevacizumab (Avastin): hypersensitivity and infusion reactions

Medicines and Healthcare products Regulatory Agency, 14 September 2010

Drug Safety Update: Volume 3, Issue 11, June 2010

Medicines and Healthcare products Regulatory Agency, 07 June 2010

References

Buzdar AU (2011) Anti-angiogenic therapies in metastatic breast cancerGÇöan unfulfilled dream The Lancet Oncology 12 (4) : 316-318.

Martin M, et al. Motesanib, or open-label bevacizumab, in combination with paclitaxel, as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncology 2011; Vol. 12, issue 4:369–76.

Miles, D. W., De Haas, S. L., Dirix, L. Y., Romieu, G., Chan, A., Pivot, X., Tomczak, P., Provencher, L., Cortes, J., Delmar, P. R., and Scherer, S. J. Biomarker results from the AVADO phase 3 trial of first-line bevacizumab plus docetaxel for HER2-negative metastatic breast cancer. British Journal of Cancer.108 (5) (pp 1052-1060), 2013.

Wagner AD, Thomssen C, Haerting J, Unverzagt S. Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD008941. DOI: 10.1002/14651858.CD008941.pub2.

Appendix 3 – Implementation submission

Implementation feedback: review of NICE technology appraisal guidance 214

NICE Technology Appraisal 214 Breast cancer - bevacizumab (in combination with a taxane)
Implementation input required by 07/05/2013
Please contact Rebecca Lea regarding any queries rebecca.lea@nice.org.uk

Contents

1 Routine healthcare activity data

The NICE implementation programme has not been able to identify any routinely collected data to determine the uptake of this technology appraisal guidance.

2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

2.1 ***Richards, M (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE.***

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.