NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA257; Breast cancer (first-line treatment of metastatic hormone-receptor positive) - lapatinib and trastuzumab (in combination with an aromatase inhibitor)

This guidance was issued in June 2012.

The review date for this guidance is June 2015.

1. Recommendation

TA257 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 lapatinib and trastuzumab in combination with an aromatase inhibitor within their licensed indications for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses ErbB2 (HER2) receptor.

3. Current guidance

1.1 Lapatinib in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2).

1.2 Trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone receptor-positive breast cancer that overexpresses HER2.

1.3 Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor that is not recommended according to 1.1 or 1.2 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

4. Rationale

No new evidence has been found that would be expected to change the recommendations in TA257.

A subcutaneous version of trastuzumab is available, but it is not anticipated that this formulation would be significantly more cost effective than the intravenous version.

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 to be considered for review in 2015. Any potential future updated versions of this guidance could potentially incorporate the recommendations from TA257.

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 April 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

This review did not identify any new evidence that is likely to lead to a change in the recommendations of the original guidance. It identified a randomised controlled trial comparing an aromatase inhibitor in combination with lapatinib, trastuzumab or both in postmenopausal people with hormone-receptor-positive, HER2-positive metastatic breast cancer who received prior trastuzumab and endocrine therapies (NCT01160211). Although this trial would provide head-to-head data on the efficacy of lapatinib plus an aromatase inhibitor relative to trastuzumab plus an aromatase inhibitor, this would not be in the same population for which trastuzumab in combination with an aromatase inhibitor has a marketing authorisation. This is because the marketing authorisation stipulates that patients should have not have received trastuzumab, whereas patients in the trial must have received trastuzumab.

In TA257, the Committee was particularly uncertain about the increase in overall survival with lapatinib or trastuzumab in combination with an aromatase inhibitor (see sections 4.3.5 and 4.3.10 of the guidance). No new evidence that would address this uncertainty has been identified in this review.

An extension to the product licence was received for a subcutaneous formulation of trastuzumab from the European Medicines Agency in September 2013. The extension was granted in the same therapeutic indications for the subcutaneous formulation of trastuzumab as for the intravenous formulation. No new evidence in this indication was generated for the licence extension.

The list prices of trastuzumab and lapatinib have not changed since the guidance was published. The cost of the new subcutaneous formulation of trastuzumab is similar to that of the intravenous formulation which was appraised (£26,888 and £24,852, respectively, assuming a mean treatment period of 15 months; see below for further details). Therefore, the cost effectiveness of trastuzumab in combination with an aromatase inhibitor is unlikely to change as a result of introducing the new formulation.

There are biosimilars to trastuzumab currently being developed, but none is yet on the market.

8. Implementation

No submission was received from Implementation, as the technologies are not recommended.

9. Equality issues

Comments from consultees indicated that a small population of older patients who are not fit enough to receive chemotherapy may not have access to an alternative treatment and so may be disadvantaged. The Committee agreed that this was not an issue of age discrimination because other factors can also affect whether people are fit enough to receive chemotherapy, such as comorbidities. The Committee concluded that there was no need to change or add to its recommendations.

GE paper sign off: Janet Robertson, Associate Director – 4 June 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

Guidance on the use of trastuzumab for the treatment of advanced breast cancer (2003) NICE Technology Appraisal 34

Gemcitabine for the treatment of metastatic breast cancer (2007) NICE Technology Appraisal 116

Bevacizumab in combination with a taxane for the first line treatment of metastatic breast cancer (2011) NICE Technology Appraisal 214

Fulvestrant for the treatment of locally advanced or metastatic breast cancer (2011) NICE Technology Appraisal 239

Eribulin for the treatment of locally advanced or metastatic breast cancer (2012) NICE Technology Appraisal 250

Bevacizumab in combination with capecitabine for the first line treatment of metastatic breast cancer (2012) NICE Technology Appraisal 263

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

Improving outcomes in breast cancer (2002) NICE Cancer Services Guidance

Breast cancer quality standard (2012) NICE Quality Standard 12

In progress

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy – in development, publication date tbc

Trastuzumab emtansine for treating unresectable metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane – in development, publication date tbc

Suspended/terminated

Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer –in development, publication date tbc

Lapatinib for breast cancer (for use in women previously treated advanced or metastatic breast cancer – in development, publication date tbc

Lapatinib in combination with paclitaxel for the first-line treatment of metastatic breast cancer which over expresses ErbB2 (HER2) receptor – in development, publication date tbc

Sunitinib in combination with a taxane within its licenced indication for the first line treatment of advanced and/or metastatic breast cancer – in development, publication date tbc

Ixabepilone for locally advanced or metastatic breast cancer – in development, publication date tbc

Trastuzumab as monotherapy and in combination with a taxane for the treatment of metastatic breast cancer – in development, publication date tbc

Details of changes to the indications of the technology

Indication and price considered in original appraisal	**Proposed indication (for this appraisal) and current price**
Lapatinib is 'indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2); in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy'. The summary of product characteristics (SPC) states that 'patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor'. Lapatinib is administered orally at a dosage of 1500 mg (six tablets) per day. The net price per pack of 84 tablets is £965.16 (excluding VAT; British national formulary [BNF], edition 62).	The indication remains the same. Source: SPC, last updated 11 March 15. The dosage and price remain the same. Source: eBNF April 2015 (edition 69).

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Trastuzumab is indicated for the treatment of patients with HER2+ metastatic breast cancer 'in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab'. The recommended dosage of trastuzumab is either a loading dose of 4 mg/kg by intravenous infusion followed by a weekly maintenance dose of 2 mg/kg until disease progression, or a loading dose of 8 mg/kg by intravenous infusion followed by 3-weekly maintenance doses of 6 mg/kg until disease progression. The net price per 150 mg vial is £407.40 (excluding VAT; BNF 62).	Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer: -in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable. - in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. - in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab. The dosage remains the same. Source: SPC, last updated 2 April 15. The price remains the same. Source: eBNF April 2015 (edition 69).

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Trastuzumab biosimilar (BCD-022): Biocad	In phase III for metastatic breast cancer[redacted]
Trastuzumab biosimilar (CT-P6; credima): Hospira	In phase III for early, and metastatic, breast cancer. Approved in South Korea [redacted]
Trastuzumab biosimilar (PF-05280014): Pfizer	In phase III for breast cancer. The trial compares 'efficacy, safety, pharmacokinetics and combination with paclitaxel versus trastuzumab sourced from the European Union (trastuzumab-EU) with paclitaxel in female patients with HER2-

Drug (manufacturer)	Details (phase of development, expected launch date,)
	positive, metastatic breast cancer in the first-line treatment setting.’ [redacted]

Registered and unpublished trials

Trial name and registration number	Details
A Phase III Trial to Compare the Safety and Efficacy of Lapatinib Plus Trastuzumab Plus an Aromatase Inhibitor (AI) vs. Trastuzumab Plus an AI vs. Lapatinib Plus an AI as 1st- or 2nd- Line Therapy in Postmenopausal Subjects With Hormone Receptor+, HER2+ Metastatic Breast Cancer (MBC) Who Received Prior Trastuzumab and Endocrine Therapies. NCT01160211 (other id: 114299)	Phase III, currently recruiting. Estimated enrolment: 525. Primary completion date: December 2017. [redacted]
Clinical Trial to Evaluate Patient´s Preference of Subcutaneous Trastuzumab (SC) Versus Intravenous (IV) Administration in Patients With HER2 Positive Advanced Breast Cancer (ABC) Who Have Received Intravenous Trastuzumab at Least 4 Months and Without Disease Progression. NCT01875367 (other id: GEICAM/2012-07)	Phase III, currently recruiting. Estimated enrolment: 160. Primary completion date: June 2015.