

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA208; Trastuzumab for the treatment of HER2-positive metastatic gastric cancer

This guidance was issued in November 2010.

The review date for this guidance is August 2013.

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 trastuzumab within its licensed indication for the treatment of HER2 positive advanced gastric cancer.

3. Current guidance

1.1 Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with human epidermal growth factor receptor 2 (HER2)-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:

- have not received prior treatment for their metastatic disease and
- have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).

1.2 People who are currently receiving treatment with trastuzumab for HER2-positive metastatic gastric cancer who do not meet the criteria in 1.1 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

4. Rationale¹

Since the publication of TA208, no significant new clinical evidence has been identified that is likely to lead to a change in the current guidance. Although the cost effectiveness would be affected by taking account of the average prices that the NHS pays for generic medicines, the impact of this is not expected to be significant

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

enough to change the recommendation in TA 208. It is therefore appropriate that the guidance should be transferred to the 'static guidance list'.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal

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 2008 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

Trastuzumab has a marketing authorisation in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anticancer treatment for their metastatic disease. The marketing authorisation specifies use only in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by immunohistochemistry (IHC)2 positive and a confirmatory silver in situ hybridisation (SISH) or fluorescence in situ hybridisation (FISH) positive result, or IHC3 positive, as determined by an accurate and validated assay. The marketing authorisation for trastuzumab was revised on August 6, 2010 to include SISH testing as an alternative method to FISH testing for confirming HER2 overexpression. Because of the timing of the revision, SISH testing was not considered in the original guidance TA 208. It is not anticipated that this alternative testing method is likely to impact on the current guidance.

The price of trastuzumab (Herceptin) is still listed in the British National Formulary as £407.40 for a 150 mg vial. The patent protection for trastuzumab is anticipated to expire in July 2014. This potentially provides the opportunity for increased competition, in the form of biosimilars, to enter the market. Any such biosimilars will be considered through NICE's topic selection function, as appropriate. The patent protection for capecitabine is anticipated to expire in November 2013 and the availability of generic capecitabine is not expected to have an impact on the recommendation in TA 208 because capecitabine was part of the triple regimen considered in both the trastuzumab group and the epirubicin group. Fluorouracil, cisplatin and oxaliplatin were all available in generic forms at the time of the original guidance and the non-proprietary prices have remained the same. Although generic epirubicin was available at the time of the original guidance, the prices for the different formulations have changed slightly since the publication of TA 208. It is not expected that these changes in the non-proprietary price of epirubicin will have a significant impact on the ICER for the IHC3 positive subgroup for whom the trastuzumab regimens were recommended. Although the average prices that the NHS pays for generic medicines are lower than the list prices, the impact of the price

difference on the ICER is not expected to be significant enough to change the recommendation in TA 208.

A current literature search for this review proposal identified a phase 3, randomised controlled trial – LOGIC, with 545 participants assessing the efficacy and safety of lapatinib or placebo in combination with capecitabine and oxaliplatin for treating HER2 positive, metastatic, unresectable gastric, oesophageal or gastro-oesophageal cancer. The new drugs online website states that the LOGIC study did not meet its primary endpoint of overall survival and it is unlikely to be filed for marketing approval. This study is still on going and is expected to be completed fully in February 2015.

A phase 3 study assessing the efficacy and safety of different doses of trastuzumab in combination with cisplatin and capecitabine and a phase 4 single arm study of trastuzumab in combination with standard chemotherapy were also identified from the literature review. These studies are still at the recruitment phase and will be completed in June 2020 and August 2018 respectively.

A meta-analysis of overall survival consisting of 35 studies with 5726 participants was also identified. The study was a review of different chemotherapy regimens for gastric cancer. Although the meta-analysis did not focus on targeted therapies, the authors concluded that trastuzumab should be added to a standard fluoropyrimidine and cisplatin regimen for people with HER2 positive tumours. The literature review also identified a Japanese cost effectiveness study which showed that trastuzumab was cost effective for treating HER2 positive gastric cancer in the IHC3 positive population.

The literature search for this review proposal did not identify any other studies directly relevant to the decision problem for TA 208. In conclusion, no new clinical evidence has been identified that is likely to lead to a change in the recommendations of the original guidance.

8. Implementation

A submission from Implementation is included in Appendix 3. Hospital Pharmacy Audit Index cost and volume data for trastuzumab show that uptake of trastuzumab has been fluctuating since TA 208 was published in November 2010. There was a sharp decrease in volume from July 2011 to October 2011, which was followed by a greater increase of approximately 165,000 units from October 2011 to January 2012. However, it is not possible to draw any firm conclusions about the use in gastric cancer from these data because the audit encompassed trastuzumab's multiple indications (including early and advanced HER2 positive breast cancer).

9. Equality issues

The Committee heard that the incidence of gastric cancer is increased in certain social classes but did not consider that the recommendations would lead to differential access to the technology according to social class.

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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.	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.	<p>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.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No.

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline.	<p>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.</p> <p>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).</p>	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

Capecitabine for the treatment of advanced gastric cancer TA191. Issued July 2010.
Review proposal May 2013: move to static.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
<p>Trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anticancer treatment for their metastatic disease. Trastuzumab is approved for use only in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by immunohistochemistry (IHC)2 positive and a confirmatory fluorescence in situ hybridisation (FISH) positive result, or IHC3 positive, as determined by an accurate and validated assay.</p> <p>On 6 August 2010, the marketing authorisation for trastuzumab was revised to include silver in situ hybridisation (SISH) testing as another method for confirming HER2 overexpression. Because of the timing of the revision, SISH testing was not considered in this appraisal.</p>	<p>Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.</p> <p>Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used.</p> <p><i>The indication is the same, but includes the SISH testing.</i></p> <p><i>The cost of trastuzumab remains the same as in the original appraisal.</i></p>

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Ramucirumab (Eli Lilly)	Phase III for metastatic gastric cancer or gastro-oesophageal junction cancer.
Tegafur (Nordic Pharma)	Tegafur in combination with gimeracil and oteracil is licensed for the treatment of advanced gastric cancer when used in combination with cisplatin. Launched 2012. The SMC has produced guidance

Drug (manufacturer)	Details (phase of development, expected launch date,)
	(September 2012).
Trastuzumab emtansine (Roche)	Phase III for HER2-positive advanced gastric cancer – see trial NCT01641939 , below.

Registered and unpublished trials

Trial name and registration number	Details
A Randomized, Multicenter, Adaptive Phase II/III Study To Evaluate The Efficacy And Safety Of Trastuzumab Emtansine (T-DM1) Versus Taxane (Docetaxel Or Paclitaxel) In Patients With Previously Treated Locally Advanced Or Metastatic Her2-Positive Gastric Cancer, Including Adenocarcinoma Of The Gastroesophageal Junction. NCT01641939	Phase III RCT, currently recruiting. Estimated enrolment: 412 Estimated primary completion date: September 2015.
HELOISE Study: A Study of Herceptin (Trastuzumab) in Combination With Cisplatin/Capecitabine Chemotherapy in Patients With HER2-Positive Metastatic Gastric or Gastro-Esophageal Junction Cancer. NCT01450696	Phase III RCT, currently recruiting. Estimated enrolment: 400 Estimated primary completion date: June 2020.
An Open-label, Multicentre Phase IV Study of Trastuzumab in Combination With the Standard Therapy (as Per Routine Clinical Practice) as First-line Therapy in Patients With HER2 Positive Metastatic Gastric Cancer. NCT01260194	Phase IV non randomised study, currently recruiting. Estimated enrolment: 30 Estimated primary completion date: August 2018.
A double-blind, placebo-controlled, randomized, multicenter Phase III study evaluating the efficacy and safety of Pertuzumab in combination with Trastuzumab and chemotherapy in patients with HER2-positive metastatic gastroesophageal junction or gastric cancer. NCT01774786	Phase III RCT, currently recruiting. Estimated enrolment: 780 Estimated primary completion date: June 2015.

Trial name and registration number	Details
A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma. NCT01196390	Phase III RCT, currently recruiting. Estimated enrolment: 480 Estimated primary completion date: August 2018.

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No.208; Trastuzumab for the treatment of HER2-positive metastatic gastric cancer

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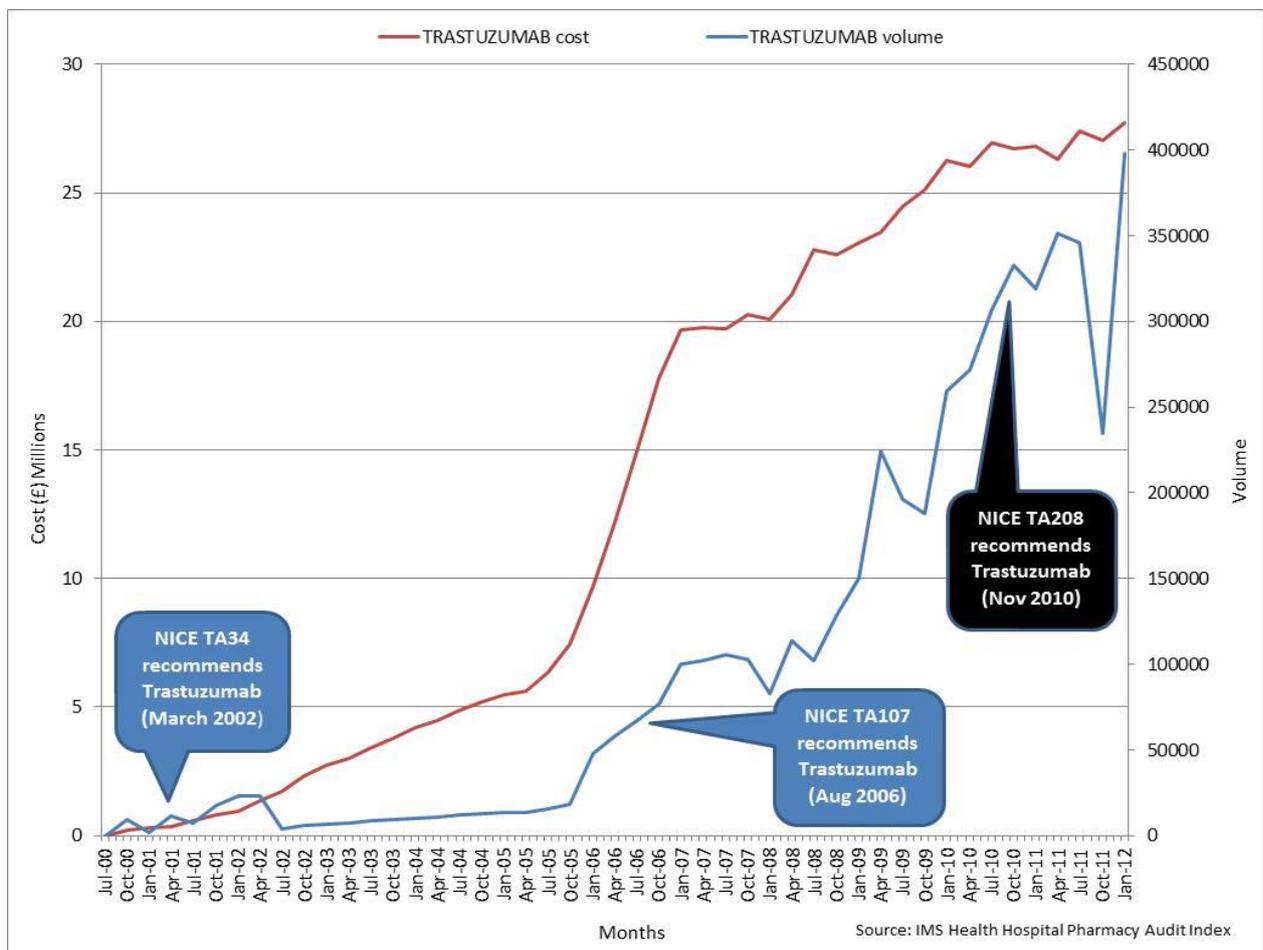
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Routine healthcare activity data

1.1. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the cost and volume of Trastuzumab prescribed and dispensed for use in hospitals in England between July 2000 and January 2012. These data need to be treated with caution as there is more than one indication for Trastuzumab; it is also recommended for people with breast cancer.

Figure 1 Cost and volume of Trastuzumab prescribed and dispensed in hospitals in England



2. Implementation studies from published literature

Information is taken from the uptake database ([ERNIE](#)) website. Nothing specific to add.

3. Qualitative input from the field team

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

Nothing specific to add.

Appendix A: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.