

Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Comments submitted by [REDACTED] on behalf of:

Name of your organisation: NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by [REDACTED]

Are you (tick all that apply):

- Y- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

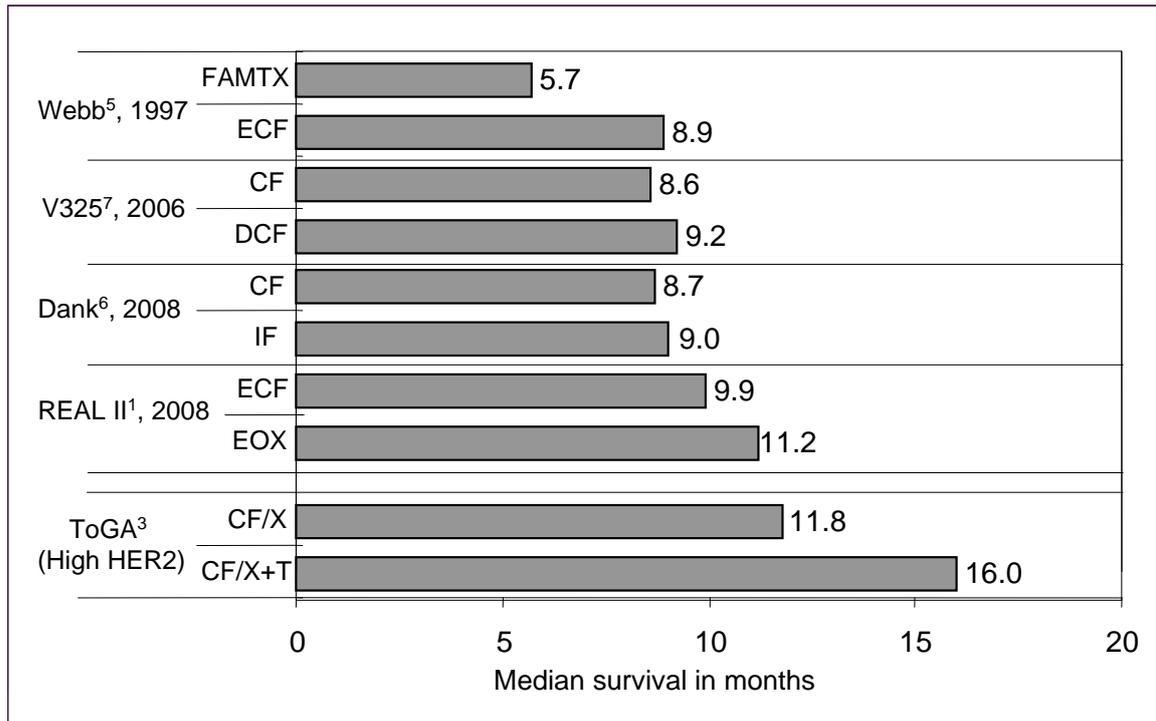
In the context of UK practice, the standard of care for patients with inoperable tumours of the stomach or gastro-oesophageal junction consists of palliative combination chemotherapy utilising platinum (cisplatin/oxaliplatin), fluoropyrimidine (5-fluorouracil/capecitabine) with or without the addition of epirubicin (E). The specific choice of regimen in an individual patient may be influenced by the presence of co-morbid conditions or concern over specific toxicities. Based on the findings of the UK NCRI REAL II study¹ the combination of epirubicin, oxaliplatin and capecitabine (EOX) is considered the optimal regimen for patients of good performance status.

With regard to the cytotoxic regimen adopted in the ToGA study, it is important to consider that there is no international consensus as to a 'standard regimen'. The incremental survival gain achieved through the addition of epirubicin to the doublet combination of cisplatin/fluoropyrimidine (CF/X) has not been evaluated in large randomised studies and although meta-analysis indicates a modest benefit², the use of CF/X as a comparator in the ToGA study can be considered as appropriate and applicable to UK practice. Furthermore, the addition of trastuzumab to a chemotherapy backbone incorporating epirubicin would not have been appropriate, given the potential increased risk of cardiac toxicity when trastuzumab is co-administered with anthracyclines.

The ToGA study demonstrated a differential benefit for the addition of trastuzumab according to the level of tumoral HER2 expression (Low HER2: HR 1.07 95%CI 0.7-1.6 versus High HER2: HR 0.65 95%CI 0.51-0.83)³. As a consequence the EU approval is limited to those patients with tumours expressing high levels of HER2 protein (IHC 3+ or IHC 2+ & FISH +ve). The use of trastuzumab would be applicable to all patients meeting this criteria other than those with significant co-morbid conditions that would contra-indicate the use of trastuzumab i.e. significant cardiac disease. In addition to the survival data presented at ASCO 2009, recently presented

quality of life (QoL) data has provided evidence that the improvement in survival achieved with the addition of trastuzumab was achieved without compromising QoL⁴.

Since the introduction of ECF chemotherapy into practice almost 15 years ago⁵, the incremental survival gains achieved through the use of modern chemotherapeutics including irinotecan⁶, docetaxel⁷ and oxaliplatin¹ have been relatively modest (see figure below). In view of the significant survival advantage demonstrated in the ToGA study, it is likely that trastuzumab will gain universal acceptance as a standard of care for patients with inoperable HER2 overexpressing tumours of the stomach and oesophagogastric junction.



FAMTX (5-FU, doxorubicin, methotrexate); ECF (epirubicin, cisplatin, 5-FU); CF (cisplatin, 5-FU); DCF (docetaxel, cisplatin, 5-FU); IF (irinotecan, 5-FU); EOX (epirubicin, oxaliplatin, capecitabine); CF/X (cisplatin, 5-FU/capecitabine).

Trastuzumab can be delivered within oncology units/centres with no specific need for additional professional input.

Trastuzumab is not currently available within the NHS and treatment guidelines are yet to be updated⁸.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

UK oncology centres have significant experience of delivering trastuzumab therapy which has been widely used in the management of breast cancer for a number of years.

CF/X chemotherapy is widely used in current practice and gastrointestinal oncology specialists will be familiar with the delivery of this treatment and management of its associated toxicities. The ToGA study indicated that the addition of trastuzumab to CF/X is well tolerated with a comparable toxicity profile to that seen with CF/X. In view of the wealth of trial data relating to the use of trastuzumab in breast cancer we can be confident that unexpected adverse events are unlikely to become apparent during routine practice in the gastric cancer patient population.

The main areas where the introduction of trastuzumab will impact on clinical services are:

1. Histopathology: HER2 immunohistochemistry (IHC) and FISH.

The delivery of trastuzumab will require gastrointestinal oncology units to introduce routine HER2 testing on diagnostic biopsy specimens for patients with advanced gastric cancer. Although HER2 testing is widely utilised in the management of breast cancer the assessment and scoring system used for gastric cancer differs significantly⁹. The provision of a reliable HER2 tumour testing service would be best facilitated by the identification of regional histopathology centres with the requisite expertise. National quality control procedures that are already in place for HER2 testing of breast cancer will need to be expanded to incorporate gastric cancer.

2. Cardiac monitoring:

As is routine practice for patients receiving trastuzumab, cardiac assessment (MUGA or ECHO) will be required at baseline and every 3 months whilst on treatment. These services are available to all oncology centres and although an increase in service use will occur it is expected that this would be manageable in view of the relatively small patient population that will be suitable for trastuzumab therapy.

When considering the implication of delivering trastuzumab it should be noted that the available data suggest only 15 - 18% of patient presenting with inoperable tumours of the stomach will demonstrate high tumour HER2 expression^{3;9;10}. Of these it would be expected that a further proportion will not be suitable for treatment.

As previously stated trastuzumab is in general well tolerated however its use is associated with an increased risk of cardiac failure. This toxicity is a major concern when trastuzumab is delivered in combination with other cardiotoxic chemotherapy agents, most notably the anthracycline doxorubicin.

Within the ToGA study no concerning cardiac toxicity was observed. The proportion of patients that experienced a decline in cardiac function (> 10% drop in ejection fraction to <50%) was noted to be non-significantly higher in the trastuzumab arm (4.6% vs 1.1%). However, rates of serious cardiac events were low and comparable between the arms (3% CF/X arm versus 1% CF/X+T arm).

A decline in cardiac function whilst receiving trastuzumab will necessitate the discontinuation of trastuzumab therapy. In many cases recovery will be seen potentially allowing for the re-institution of treatment¹¹.

The ToGA study recruited patients from five continents including a significant proportion (56%) from Asia. Consequently the data are not directly comparable to the UK patient population. Most notably the use of second-line chemotherapy in the ToGA study was significantly higher than would be anticipated in UK practice with 41% of patients receiving second-line treatment. Second-line chemotherapy is not a standard of care in the NHS setting and data from the UK REAL II study indicate only 14% of patients receive second-line treatment¹. The higher proportion of second-line chemotherapy administered within the ToGA study should not have influenced the comparative outcomes as treatment was balanced between the arms. Furthermore the hazard ratio for overall survival in the European population in the ToGA study (n = 190; HR = 0.63) was comparable with that for the entire study population (n = 584, HR = 0.74) and superior to the Asia population (n = 319; HR = 0.82).

The ToGA study stipulated the delivery of CF/X for a total of 6 cycles. In the UK, providing there is ongoing benefit, chemotherapy may be continued for up to 8 cycles (6 months). This variation in practice is not considered to alter the relevance of the results to the UK setting. Indeed within the REAL II study the median number of cycles delivered was 6 (maximum 8).

Based on these data, trastuzumab should be considered in combination with CF in patients with FISH+ and IHC 2+/ IHC 3+ disease. Patients with low HER2 expression should continued to be offered chemotherapy alone or be considered for ongoing studies such as REAL-3.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Not applicable.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Please see previous comments.

Reference List

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Ref Type: Abstract

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- (7) Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; 24(31):4991-4997.
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- (9) Hofmann M, Stoss O, Shi D, Buttner R, van d, V, Kim W et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008; 52(7):797-805.
- (10) Park D, Yun J, Park J, Oh S, Kim H, Cho Y et al. HER-2/neu Amplification Is an Independent Prognostic Factor in Gastric Cancer. *Digestive Diseases and Sciences* 2006; 51(8):1371-1379.
- (11) Martin M, Esteva FJ, Alba E, Khandheria B, Perez-Isla L, Garcia-Saenz JA et al. Minimizing Cardiotoxicity While Optimizing Treatment Efficacy with Trastuzumab: Review and Expert Recommendations. *Oncologist* 2009; 14(1):1-11.