Trastuzumab for the treatment of HER2 positive advanced gastric cancer
Appraisal Consultation Document (ACD)

Comments submitted by Dr Patrick Cadigan, RCP registrar on behalf of:

NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by Dr David Watkins

We do not consider that the ACD provides a reasonable interpretation of the evidence and fails to appreciate the clinical significance of the ToGA trial results in this patient population.

Clinical Effectiveness – The significance of trastuzumab to this patient population

The ToGA study represents a truly significant advance in the management of this patient group. The survival benefit in the licensed patient population was greater than 4 months, for a disease with a median survival of less than 12 months, and with a Hazard Ratio of 0.65. This is the largest survival benefit recorded in a high quality randomized clinical trial for any single agent or combination in advanced gastric cancer and represents a major advance in this disease. Oesophagogastric cancer is considered among the tumour types with the highest level of medical need. The survival outcomes in this disease are amongst the poorest of all the common cancers with little progress made over recent decades (figure 1). Modern cytotoxic agents have failed to result in significant gains and overall survival in this disease setting has stagnated at 9-11 months over the previous 15 years (figure 2). As such, it is vital that where there are clear opportunities for progress, as is the case for trastuzumab, that investment in to improving patient outcomes is made.

Cost Effectiveness – The evaluation of ECX/EOX as a comparator

The use of a triplet chemotherapy regimen comprising epirubicin, platinum and capecitabine (ECX/EOX) has evolved in the UK over two decades of sequential randomized controlled clinical trials. ECF was initially developed as a triplet regimen based on evidence of single agent activity for each individual agent, and in comparison with the previous triplet regimen in use, rather than as a step-wise addition of epirubicin to existing doublet regimens. The specific benefit of epirubicin to the CX/OX doublet has never been robustly studied and hence can not be reliably estimated. In the cost-effectiveness model the benefit of epirubicin has been overstated with a Hazard Ratio as significant as 0.77 based on the Wagner meta-analysis[1]. As indicated at the initial appraisal meeting this meta-analysis was felt to significantly over state the benefit of epirubicin and its use in cost effectiveness model is inappropriate. A Hazard Ratio of 0.77 is far in excess of the observed benefit demonstrated in successive randomized clinical trials for any single chemotherapy intervention in this disease. The value of the meta-analysis is further debated given that the included studies used regimens with lower doses and lower dose-intensity of cisplatin &/or fluoropyrimidine than used in the ToGA comparator regimens. In addition, none of the studies utilised capecitabine containing regimens which may influence the relative benefit of epirubicin. Epirubicin is considered to provide some additional benefit to CF/CX and in the absence of any more active alternative therapies epirubicin containing triplet regimens should remain the standard of care in HER2 negative gastric cancer. However for HER2 positive gastric cancer the addition of trastuzumab to a CF/CX backbone has demonstrated a clear

survival benefit with a favourable toxicity profile and should be the standard of care in this disease setting.

End-of-life Criteria – Rational for inclusion of the breast cancer population

This submission fails to meet the end–of–life criteria solely because trastuzumab is already licensed for breast cancer. Herceptin is licensed for both early and advanced breast cancer, and the median survival of patients with early breast cancer treated with adjuvant herceptin is of the order of several years. It is surprising and inappropriate that this patient group should influence the end–of–life treatment decisions of patients with gastric cancer, a clearly distinct patient population. The end-of-life rules as applied have the consequence of disadvantaging patients with rarer tumours, often with more limited therapeutic options and poorer overall survival, as is the case in gastric cancer. In addition, we believe that, the application of end-of-life criteria in this way results in the nonsensical position where if trastuzumab had been licensed in gastric cancer prior to breast cancer the outcome of a NICE appraisal would likely be more favourable. During the committee meeting it was implied that this situation was acceptable and that the manufacturer would be expected to in some way support the adoption in rarer indications. We are uncertain as to how NICE envisage this being facilitated and further consideration and clarification with regard to the application of the end-of-life criteria appears necessary. The number of patients the current appraisal will apply to is small and comfortably within the end-of-life criteria thresholds. Additionally, the availability of generic formulations of trastuzumab in the medium term will reduce the cost of this therapy and as such the overall impact on NHS budgets will be modest.

Impact on UK Research Practice

Through undertaking pivotal studies such as OEO2[2], MAGIC[3] and REAL-II[4], the UK has played a central role in shaping international standards of care in oesophagogastric cancer. Trastuzumab represents a further significant advance in the treatment of gastric cancer and is a globally accepted standard of care in the management of HER2 positive disease. As such, we believe that, the rejection of funding for trastuzumab across England and Wales amounts to a retrograde step for gastric cancer care in the UK. Furthermore, ongoing academic and commercial clinical research would be hindered without access to the accepted standard of care in this patient group. Current research practice is focused on identifying patient/tumour characteristics associated with response &/or resistance to targeted therapies, with the aim of improving the cost/benefit ratio of treatment. The strategy of defining a response enhanced biological sub-group is at the core of all NCRI research strategy and indeed Pharma research strategy going forward. A NICE position not supporting this approach may be difficult to maintain in the long term.

To summarise the outcome of the first Appraisal Committee meeting. The Appraisal Committee felt that the use of trastuzumab in combination with cisplatin and fluoropyrimidine chemotherapy was likely to offer a survival benefit over the current UK standard of care in HER2 over-expressing gastric cancer. It was noted that the survival gain was likely to be achieved without compromising quality of life. In addition, no resource or infrastructure related barriers to the adoption of HER2 testing or the introduction of trastuzumab therapy were identified. Trastuzumab was not recommended based on the committee's conclusion that the estimated cost to the NHS exceeded what could be considered a reasonable use of NHS resources. In view of the concerns highlighted above it is felt that further evaluation of trastuzumab is required in this indication where the benefits have been clearly defined.

Figure 1

Ten-year survival (%) for adults (15-99) diagnosed with cancer during 1971-72 and predicted survival for adults diagnosed in 2007

CANCER TYPE	1971-72	2007 (predicted)
Bladder	34.6%	48.9%
Bowel - Colon	22.6%	50.4%
Bowel - Rectum	23.9%	49.3%
Brain	**5.7%**	**9.4%**
Breast (women)	38.9%	77.0%
Cervix	48.4%	63.0%
Hodgkin's lymphoma	49.0%	77.9%
Kidney	22.2%	43.5%
Larynx (men)	50.5%	59.6%
Leukaemia	8.1%	33.2%
Lung	**3.2%**	**5.3%**
Melanoma	49.3%	83.2%
Myeloma	5.3%	17.1%
Non-Hodgkin's lymphoma	21.8%	50.8%
Oesophagus	**3.6%**	**10.0%**
Ovary	18.0%	35.4%
Pancreas	**1.9%**	**2.8%**
Prostate	20.4%	68.5%
Stomach	**4.6%**	**13.5%**
Testis	67.4%	96.5%
Uterus	55.2%	74.5%
ALL CANCERS	23.7%	45.2%

Data for England and Wales
Source: Cancer Research UK.

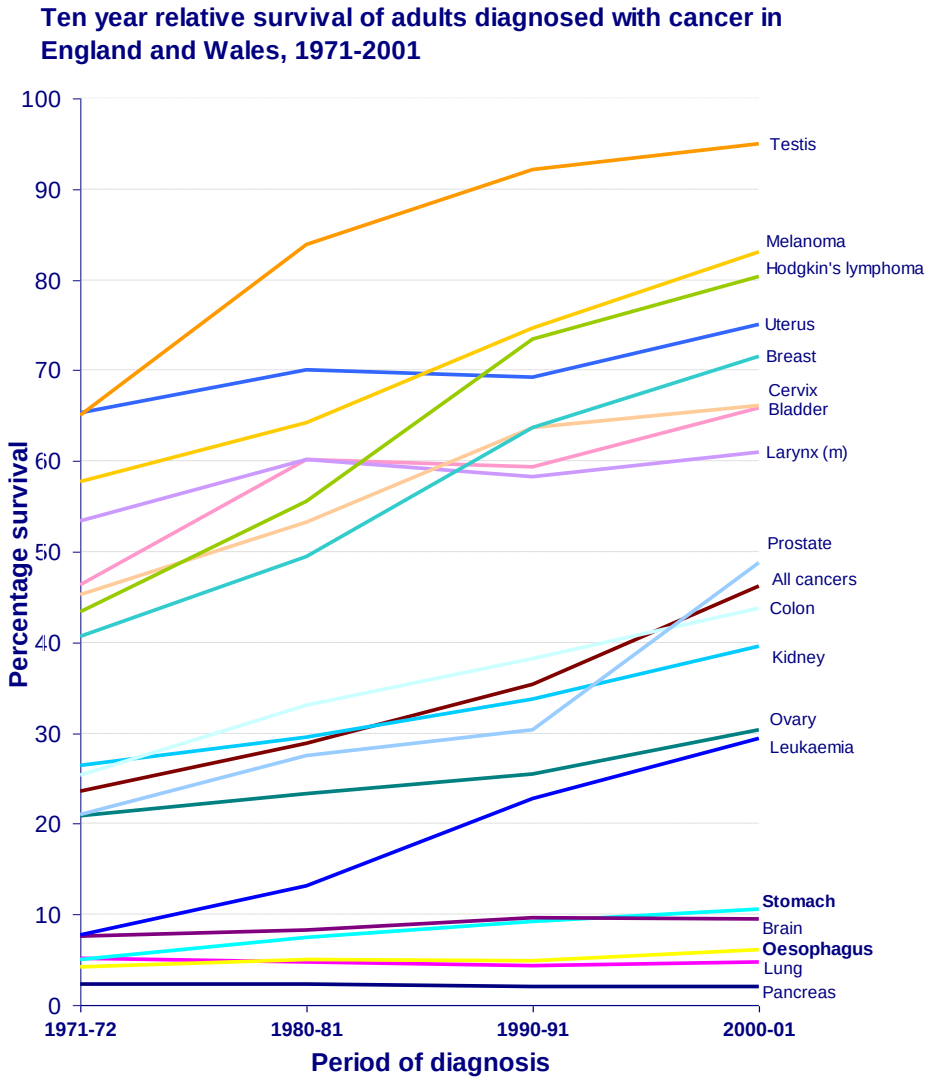
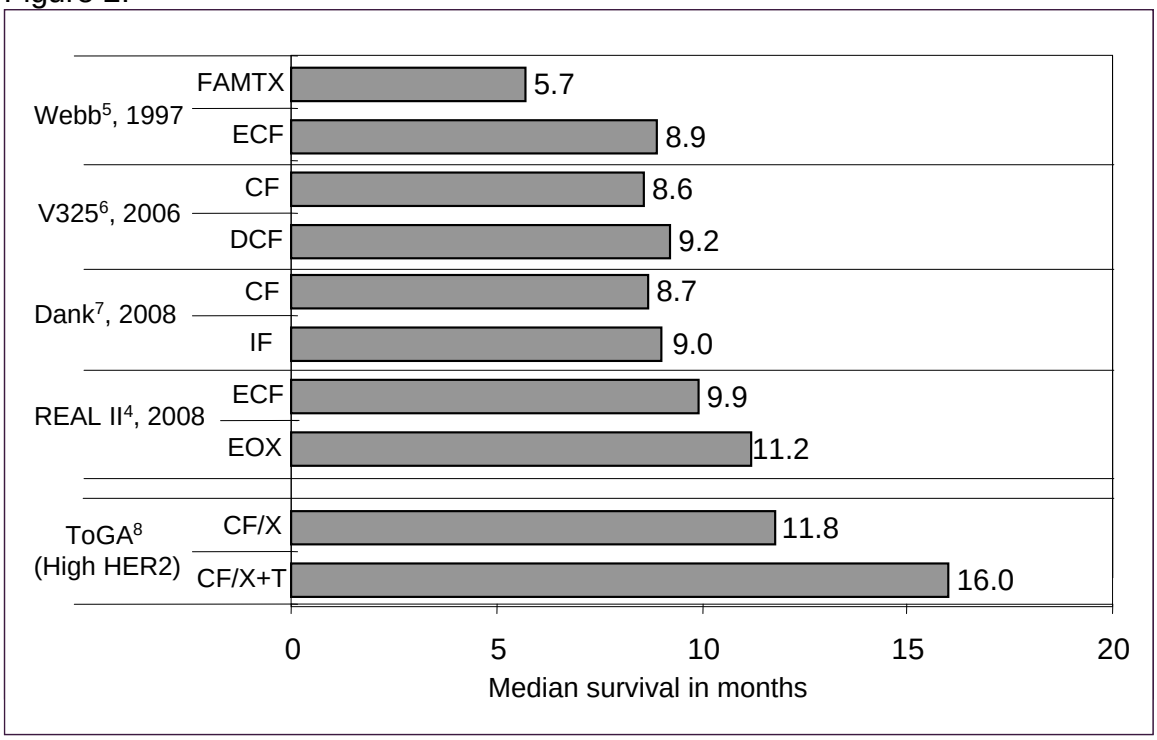


Figure 2.



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).

Reference List

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