

## Social Values and Health Priority Setting Case Study

<b>Title of Case Study</b>	<b>Trastuzumab for the treatment of HER-2 positive advanced and/or metastatic gastric cancer</b>
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<b>Case Summary (approx. 350 words)</b>  Please include information here about why the case is of particular interest	<p>Trastuzumab was assessed under NICE's end of life criteria. It is a case in which, whilst all the end of life criteria were met, nonetheless the treatment was not approved for the whole patient population on the grounds that, even with the end of life weightings, the treatment was still too expensive and did not provide sufficient benefits to justify its costs. However, the greater benefits which it provided to one patient sub-group meant that it was approved for that particular group only, once end of life criteria were taken into account.</p> <p>This case raises questions around one of the end of life criteria in particular. Part of the logic of the end of life criteria is that the patient groups involved may well be small and therefore treatments for them will likely be more costly: the end of life criteria seek to take account of this. However, the 'small population size' criterion is interpreted as the cumulative population across all diseases for which the treatment has a marketing authorization, rather than just for the patient population covered by the individual appraisal.</p> <p>Trastuzumab is licensed for use (although not all uses are approved by NICE) in several different cancers, making its <i>cumulative</i> population relatively large and technically just over the 7000 limit for what is considered a 'small' population, even though each <i>single</i> patient population numbers far less than 7000. Two appraisal committees differed in opinion on the matter of population size in the case of trastuzumab, raising questions about the definition of what constitutes a 'small' population. Issues of fairness may also arise around justifying denial of access to smaller subgroups when they belong to a cumulatively 'too large' patient population and are thus prevented from benefiting from the QALY weightings afforded by end of life criteria.</p>
<b>1. Facts of the case</b>	<b>Facts of the case</b>
Please include information on as many of the following as are relevant to the case: <ul style="list-style-type: none"> <li>• At what condition is the intervention, program or service aimed?</li> <li>• What are its effects? Eg. Is it curative, preventative, palliative, life-prolonging, rehabilitative?</li> <li>• Is there a relevant comparator? If so how does this intervention, service or program compare to the alternative? Include ICER estimates/QALY costs if relevant.</li> </ul>	<p>Trastuzumab is a treatment for advanced and metastatic cancer. It has a marketing authorization specifically for the treatment of patients whose tumours overexpress the human growth factor receptors ErbB2 (HER2), and who have not received prior treatment for their metastatic disease. Trastuzumab is a recombinant humanised IgG1 monoclonal antibody directed against HER2 and it is administered as an intravenous infusion.</p> <p>Current NHS treatment for metastatic gastric cancer is a triple regimen of an anthracycline, a platinum agent and a fluoropyrimidine. Chemotherapy is associated with overall survival of 11.8 months (based on the chemotherapy alone group in the ToGA trial) and reduces disease symptoms.</p> <p>The net price of a 150-mg vial of trastuzumab is £407.40. On average, four vials are required for the first loading dose and three vials for each subsequent</p>

<ul style="list-style-type: none"> <li>• What are the significant features about the condition and/or about the patient population in this case? Eg. patient population is very young, very old, condition is rare, life-threatening, life-limiting etc.</li> <li>• How are the benefits of the intervention distributed across the patient population and/or across time?</li> <li>• What is the cost or budget impact of the intervention/service/ programme?</li> <li>• What is the nature and strength of the evidence about the outcomes of the intervention, service or programme? Eg. randomized clinical trials, evidence on patient-related outcomes.</li> <li>• How did the issue about this case arise - for example, from clinical practice, from a policy setting, from a topic selection process?</li> </ul>	<p>dose. Assuming that excess trastuzumab is wasted, the drug cost of eight infusions of trastuzumab (the median number of infusions in the regulatory trial) is £10,185.</p> <p>The ToGA trial randomised 594 people to receive either chemotherapy (n = 296) or trastuzumab plus chemotherapy (n = 298). From the full population of 594 in the ToGA trial, 446 people (75%) had tumours that met the narrower IHC3 definition. Of this subgroup, 218 people received treatment with chemotherapy alone and 228 people received treatment with trastuzumab plus chemotherapy.</p> <p>The hazard ratio for overall survival in the EMA subgroup was 0.65 (95% confidence interval [CI] 0.51 to 0.83) corresponding to a median survival for the trastuzumab plus chemotherapy group of 16 months compared with 11.8 months for the chemotherapy alone group (4.2-month improvement in survival). A median survival of 13.8 months was reported for the total trial population receiving trastuzumab plus chemotherapy compared with 11.1 months in the chemotherapy alone group (2.7-month improvement in survival).</p> <p>The manufacturer reported the results for secondary outcomes including progression-free survival and overall response rate. For the IHC3 subgroup the hazard ratio for progression-free survival was 0.64 (95% CI 0.51 to 0.79), corresponding to a median progression-free survival for the trastuzumab plus chemotherapy group of 7.6 months compared with 5.5 months for the chemotherapy alone group (a 2.1-month improvement in progression-free survival). Results for overall response rate were reported for the total trial population only, and demonstrated a statistically significantly higher overall response rate in the trastuzumab plus chemotherapy group (47.3%) compared with the chemotherapy alone group (34.5%), odds ratio 1.70 (95% CI 1.22 to 2.38, p = 0.002).</p> <p>For the whole population, the incremental analysis of all interventions resulted in an ICER of £63,081 per QALY (deterministic) and £71,463 per QALY (probabilistic) for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus oxaliplatin and capecitabine.</p> <p>For the IHC3 subgroup, the ICER ratio was between £49,970 and £51,934 per QALY gained for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine.</p> <p>(NICE, 2010)</p>
<p><b>2. Policy decision: process</b></p>	<p><b>Policy decision: process</b></p>
<p>Please include information on as many of the following as are relevant to this case:</p> <ul style="list-style-type: none"> <li>• What stages/institutions were involved in the decision making process?</li> <li>• Is legal context important in this case? If so, in what way?</li> <li>• Who was involved? Eg. key</li> </ul>	<p>Trastuzumab was assessed according to the NICE Single Technology Appraisal Process.</p>

<p>stakeholders, the public, professionals, industry, patients, governmental or non-government policy actors.</p> <ul style="list-style-type: none"> <li>• How were they involved, and at what stages of the process?</li> <li>• Was there disagreement between any of the parties involved in the decision process?</li> <li>• Do any rules or frameworks exist to guide decision making? If so, were they followed in this instance?</li> <li>• Do mechanisms exist for challenging the decision at any stage of the process?</li> <li>• How, if at all, is the decision process or the decision itself publicized?</li> </ul>	
<p><b>3. Policy decision: content</b></p> <p>Please include information on as many of the following as are relevant to this case:</p> <ul style="list-style-type: none"> <li>• What decision was made about the intervention, service or program, if any?</li> <li>• What values were relevant in the case or in the decision itself? For example, values of cost-effectiveness, clinical effectiveness, justice/equity, solidarity or autonomy. How did they affect the decision itself?</li> <li>• Was the way in which these values were balanced affected by any specific features of the case? For example, end of life considerations, age of patients, impact on carers, disease severity, innovative nature of the intervention, social stigma or cultural sensitivity?</li> <li>• Did the case challenge established guidance or 'decision rules'? Eg. on cost-effectiveness, cost thresholds, age discrimination etc. If so, in what way?</li> <li>• Were any health system-wide considerations influential in the decision? For example, displacement of old technologies, professional practice issues, or infrastructure/feasibility considerations.</li> </ul>	<p><b>Policy decision: content</b></p> <p>The following were taken into consideration in the Committee's decision making:</p> <p><i>Treatment alternatives</i></p> <p>The Committee noted comments from consultation that no treatment options for metastatic gastric cancer currently target HER2 overexpression, and that trastuzumab offers a new option for this patient group.</p> <p><i>Clinical effectiveness</i></p> <p>The Committee discussed the clinical effectiveness of the trastuzumab regimens presented in the ToGA trial. It noted that, compared with cisplatin plus either capecitabine or 5-fluorouracil, trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil provided a 4.2-month gain in overall survival and a 2.1-month gain in progression-free survival. The Committee concluded that the ToGA trial demonstrated trastuzumab plus cisplatin and capecitabine or 5-fluorouracil offers clinical benefit.</p> <p>The Committee discussed the clinical effectiveness of trastuzumab for the IHC3-positive subgroup. It noted the efficacy in the trial was greater for this subgroup than for the whole population. The Committee discussed the biological plausibility of greater benefit in the IHC3-positive subgroup and considered that greater effectiveness may be experienced with higher levels of HER2. The Committee concluded it was an appropriate subgroup and discussed the clinical evidence. It noted that the hazard ratio of overall survival for the trastuzumab plus chemotherapy group compared with the chemotherapy alone group was 0.57, corresponding to a median survival for the trastuzumab plus chemotherapy group of 18 months compared with 12.4 months for the chemotherapy alone group (a 5.6-month gain in survival). The Committee concluded that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil is clinically effective in the IHC3-positive subgroup.</p>

### *Cost effectiveness*

The Committee agreed that the ICER for the whole population covered by the marketing authorisation probably lay between £63,100 per QALY gained and £71,500 per QALY. The Committee concluded that the ICER for the whole population covered by the marketing authorisation was in excess of the range normally considered cost effective.

The Committee also discussed the ERG's exploratory analyses for the IHC3-positive subgroup and agreed that the most plausible estimate of cost effectiveness of trastuzumab plus cisplatin and capecitabine lay between £45,000 and £50,000 per QALY gained for this subgroup. The Committee concluded that this ICER was higher than would normally be considered cost effective.

### *End of life considerations*

First, the Committee considered the life expectancy of people with HER2-positive metastatic gastric cancer. It understood that the ToGA trial reported a median 11.8 months overall survival for people receiving cisplatin plus either capecitabine or 5-fluorouracil. Therefore, the Committee was persuaded that trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil met the criterion for short life expectancy.

The Committee then considered whether trastuzumab offers an extension to life of at least an additional 3 months. It noted that the median overall survival gain for the licensed population from the ToGA trial was 4.2 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone. This produced a modelled mean overall survival gain of 4.8 months for people treated with trastuzumab plus cisplatin and capecitabine compared with people treated with epirubicin plus cisplatin and capecitabine.

The Committee further noted that the median overall survival gain for the subgroup of people whose tumours were IHC3-positive in the ToGA trial was 5.6 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone. This produced a modelled mean overall survival gain of 7.4 months for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine. The Committee considered that this was subject to uncertainty because of the absence of appropriate UK practice comparator data. However, on balance the Committee was persuaded that the addition of trastuzumab to chemotherapy would result in an extension to life of more than 3 months. The Committee therefore considered that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil met the criterion for life extension.

The Committee considered the size of the patient population. Treatment with trastuzumab would be suitable for approximately 7000 people (7158) who have one of the diseases for which trastuzumab is licensed (that is, HER2-positive metastatic gastric cancer, HER2-positive early and locally advanced breast cancer and HER2-positive metastatic breast cancer). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary end of life advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-

	<p>of-life was applicable. (However, see also Discussion section below for details of the view on population size taken by a later Appraisal Committee assessing trastuzumab for metastatic breast cancer).</p> <p>Thus, the Committee agreed that trastuzumab met all of the criteria for consideration as an end of life intervention.</p> <p><i>Overall assessment</i></p> <p>The Committee discussed the cost effectiveness of trastuzumab plus cisplatin and capecitabine for the whole population covered by the marketing authorisation, taking into account the end-of-life criteria. It agreed that the most plausible estimate was between £63,100 per QALY gained and £71,500 per QALY gained.</p> <p>The Committee therefore considered that, even when taking the end-of-life considerations into account, the ICER ratios exceeded what could be considered a reasonable use of NHS resources. Therefore the Committee concluded that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil could not be recommended as an appropriate use of NHS resources for the whole population covered by the marketing authorisation.</p> <p>The Committee then discussed the cost effectiveness of trastuzumab plus cisplatin and capecitabine for the subgroup of people whose tumours are IHC3 positive, taking into account the end-of-life criteria. It agreed that the ICER was between £45,000 and £50,000 per QALY gained. The Committee considered that, the magnitude of end of life weight required for the ICER to be in a range normally considered cost effective in the NHS was acceptable.</p> <p>The Committee therefore concluded that trastuzumab plus cisplatin and capecitabine (or 5-fluorouracil) should be recommended as an option for people with HER2-positive, gastric cancer who have not received prior treatment for their metastatic disease and whose tumours are IHC3 positive.</p>
<p><b>4. Discussion</b></p>	<p><b>Discussion</b></p>
<p>Please use this space to reflect on, for example:</p> <ul style="list-style-type: none"> <li>• The reasons or values explicitly used in making the decision. Do these reflect any institutional decision rules or statements of value, for example commitments to equality, non-discrimination or fairness? Do they reflect wider social, moral, cultural, religious values, and if so how?</li> <li>• Considerations not explicitly taken into account in the decision, but which may nonetheless have been important ‘background’ factors. These might include, for example, public opinion, political sensitivity, moral sensitivity, and international reputation, as well as cultural, social, moral, religious or</li> </ul>	<p>There are questions around the end of life criterion around small population size in relation to this case, and especially in light of a later appraisal of trastuzumab as a treatment for metastatic breast cancer.</p> <p>As noted above, the Appraisal Committee commented that 7000 was at the upper end of what could be considered a ‘small population’, but nonetheless allowed this criterion to be applied to trastuzumab with its estimated patient population of 7158 across all the indications for which the drug is licensed. That is, the patient population that must be taken into account is a cumulative one across all diseases for which the treatment is licenced rather than just the population covered by any given appraisal. So, the cumulative population for trastuzumab includes those with metastatic gastric cancer, metastatic breast cancer, and early or locally advanced breast cancer, even though the appraisal at hand relates only to the population with metastatic gastric cancer. The cumulative population interpretation of the ‘small population’ criterion has been influential in negative appraisals of several other drugs including bevacizumab (Avastin) for breast, colorectal and renal cell cancer, and cetuximab for head/neck cancer and colorectal cancer, and erlotinib for lung</p>

<p>institutional norms.</p> <ul style="list-style-type: none"> <li>• The impact of the decision making process on the decision itself, if any.</li> <li>• Any issues relating to implementation. For example, whether access may be restricted by capacity issues, even if the intervention, service or programme is provided on a 'universal' basis.</li> <li>• Anything else you think significant or interesting about the decision.</li> </ul>	<p>cancer, and panitumumab for colorectal cancer.</p> <p>The logic of the end of life criterion around small population size is that manufacturers are expected to reserve exceptionally high prices for drugs with a small market. One NICE Appeal Panel opinion often quoted by Appraisal Committees is that “Sufficient regard should be given to recognition of the desirability of developing new treatments in smaller disease areas and that higher prices, and therefore reduced cost effectiveness, were more likely to be justified given the need to recoup costs of development of the product from more limited licences” (see NICE, 2011; para. 4.21). It has been noted by NICE that some commentators would prefer the population size criterion to mean just the population covered by the appraisal (NICE, 2009b; para. 2.5). However, “arguably any population could be considered ‘small’ if divided into subgroups” (ibid.). It is possible that this kind of subdivision could then make a nonsense of the logic of the small population criterion.</p> <p>Whilst the pragmatic logic for the criterion is clear, there are perhaps questions around how the cumulative populations interpretation is justified to subgroups who are denied access to a treatment because they have the misfortune to be part of a larger population for which that treatment is indicated.</p> <p>There may also be questions around how the size ‘limit’ of 7000 is interpreted and/or justified. For example, a later Appraisal Committee assessed trastuzumab for the treatment of metastatic breast cancer, and commented as follows on the matter of population size for the drug, noting a difference of opinion with the Committee who assessed the drug for gastric cancer:</p> <p>“The Committee considered whether trastuzumab met the criterion for a small population. The Committee examined the estimates provided by the manufacturer of the number of patients diagnosed annually with conditions for which trastuzumab is indicated. It noted that the total number (7158) had previously been accepted as fulfilling the criterion for a small population by another Committee. It also noted that on that occasion, the other Committee had accepted that patients in clinical trials could be excluded from the calculation of population size. The Committee was not persuaded that a population of over 7000 was small, or that it was valid to exclude patients in clinical trials from the calculation of population size. The Committee recognized that these different conclusions from those of a previous Committee were matters of judgement. However in the interest of fairness to this patient population, the Committee agreed not to differ from the other Committee's conclusion on this occasion. On this basis the Committee accepted that trastuzumab plus an aromatase inhibitor fulfilled the small population criterion.” (NICE, 2012; para 4.3.15)</p> <p>It is also interesting to note that in the case of another end of life drug, Sunitinib, which was one of the first to be assessed under the end of life criteria, the Appraisal Committee noted that:</p> <p>“although sunitinib was to be aimed at more patient groups than just people with Renal Cell Carcinoma, such as people with gastrointestinal stromal tumours, this was the first indication for which it was being appraised. It therefore considered that for this appraisal, sunitinib should be regarded as meeting this criterion for an end-of-life treatment.” (NICE, 2009c)</p>
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	<p>There are also questions about what happens when the marketing authorizations are increased for a treatment <i>after</i> it has been approved for one indication on the basis of the small patient population criterion. If it is to remain consistent in applying the small population criterion, should NICE review existing guidance where the cumulative population is increased due to subsequent marketing authorizations? (See NICE, 2009b: para. 2.5).</p>
<p><b>5. References/Links to relevant documents</b></p>	
	<p>NICE (2012) <i>Lapatinib or trastuzumab in combination with aromatase inhibitors for the first line treatment of metastatic hormone receptor positive breast cancer that overexpresses HER2</i>. Available at: <a href="http://www.nice.org.uk/nicemedia/live/13777/59707/59707.pdf">http://www.nice.org.uk/nicemedia/live/13777/59707/59707.pdf</a></p> <p>NICE (2011) <i>Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer</i>. Available at: <a href="http://www.nice.org.uk/nicemedia/live/13497/55122/55122.pdf">http://www.nice.org.uk/nicemedia/live/13497/55122/55122.pdf</a></p> <p>NICE (2010) <i>Trastuzumab for the treatment of HER2 positive advanced and/or metastatic gastric cancer</i>. Available at: <a href="http://www.nice.org.uk/nicemedia/live/13275/51681/51681.pdf">http://www.nice.org.uk/nicemedia/live/13275/51681/51681.pdf</a></p> <p>NICE (2009a) <i>Supplementary advice on appraising life-extending, end of life treatments</i>. Available at: <a href="http://www.nice.org.uk/media/88A/F2/SupplementaryAdviceTACEoL.pdf">http://www.nice.org.uk/media/88A/F2/SupplementaryAdviceTACEoL.pdf</a></p> <p>NICE (2009b) <i>Update Report on the Application of the End of Life Supplementary Advice in Health Technology Appraisals</i>. Available at: <a href="http://www.gserve.nice.org.uk/media/835/8E/ITEM7EndOfLifeTreatments.pdf">http://www.gserve.nice.org.uk/media/835/8E/ITEM7EndOfLifeTreatments.pdf</a></p> <p>NICE (2009c) <i>Sunitinib for the treatment of advanced and/or metastatic renal cell carcinoma</i>. Available at: <a href="http://guidance.nice.org.uk/TA169">http://guidance.nice.org.uk/TA169</a></p>