Appendix 1

A 1.1 Supporting data for relevant comparators and patient populations

Quantifying the extent to which existing therapies are used within the relevant patient population continues to be problematic due to the non-availability of local or national NHS audit data. GSK has therefore employed two different approaches:

- A review of patient treatment records submitted to the IMS Oncology Analyzer MBC Enhanced Tumour Study database by UK breast oncologists. As described in GSK's Manufacturer Submission to NICE (Appendix 9.4), the IMS Oncology Analyzer database is the largest, most comprehensive commercially available oncology patient-record database. In the absence of national audits of NHS patient treatment, the IMS Oncology Analyzer is arguably the most reliable source available for studying treatment pathways in metastatic breast cancer (MBC).
- A survey with consultant oncologists with a specialist interest in breast cancer with Cegedim Dendrite. In this study clinicians were asked to estimate the proportions of their patients that receive various therapies. Figures retrieved from this piece of research are supporting evidence for the data derived from the IMS Oncology Analyzer but should not be used in isolation; clinician estimates (and all surveys that are not diary-derived) are subject to a small degree of respondent error.

The methodologies employed in these studies, and the results obtained are described in the following sections.

A1.1.1 IMS Oncology Analyzer and the MBC Enhanced Tumour Study

GSK's submission to NICE in April 2007 used the most current IMS Oncology Analyser dataset available at that time (January 2004 to September 2006) at which time the database reported case histories from 1,410 UK patients that had metastatic disease. Over the last two years IMS has expanded the Oncology Analyzer database by developing the Metastatic Breast Cancer Oncology Analyzer Enhanced Tumour Study (MBC-OA-ETS), with the objective to better enable the study of treatment pathways in the MBC setting. In this study additional cases relating to patients receiving therapy for the treatment of MBC were collected and incorporated with data collected as part of the standard IMS Oncology Analyzer. As with the IMS Oncology Analyzer, all patient records are completed by physicians treating breast cancer. The names of clients subscribing to the database are not disclosed to the respondents, and as such the case history reporting should be seen as unbiased.

The MBC-OA-ETS database uses logic to define progression on trastuzumab; progression is defined as:

- One or more chemotherapeutic agent(s) added to what was originally trastuzumab monotherapy and/or
- A chemotherapeutic switch in a trastuzumab-containing regimen.

Trastuzumab was deemed to have been continued as maintenance therapy (and not trastuzumab beyond progression) if the trastuzumab monotherapy commenced within 28 days of the end date of the previous trastuzumab-containing regimen.

In the two year period ending Q4 2007 the MBC-OA-ETS database reported case histories from 2,815 UK patients with metastatic disease, of which 98 had progressed on trastuzumab in the metastatic setting (using the logic above) after prior treatment with a taxane and an anthracycline. Table 1 shows the relative proportion of therapies received by these patients

at point of progression on trastuzumab for MBC. Trastuzumab-containing regimens are highlighted in bold. Over this two year period, trastuzumab was used past progression in 55.1% of the 98 patients and, of the trastuzumab-containing regimens, 38.9% were administered in combination with capecitabine and 37.0% in combination with vinorelbine. This 55.1% figure is approximately 10% higher than the estimate used in GSK's April 2007 Manufacturers Submission which was based on only 24 patient records. It is also apparent that our April 2007 estimate of capecitabine usage as monotherapy was over-estimated; the current two-year, 98-patient record study estimates capecitabine usage in 31.6% of patients, approximately 15 % lower than our earlier estimate.

Table 1. Therapies use beyond progression on trastuzumab-containing therapy for MBC (with prior treatment with anthracycline plus taxane). Source: IMS-OA-ETS (MAT Q4 2006 plus MAT Q4 2007).

Therapeutic regimen	# of patients receiving regimen	% of patients receiving regimen
Capecitabine	31	31.6
Trastuzumab + capecitabine	21	21.4
Trastuzumab + vinorelbine	20	20.4
Vinorelbine	5	5.1
Letrozole	4	4.1
Trastuzumab + capecitabine + anastrazole	3	3.1
Trastuzumab monotherapy	2	2.0
Trastuzumab + anastrazole	2	2.0
Anastrazole	2	2.0
Trastuzumab + capecitabine + exemestane	1	1.0
Trastuzumab + docetaxel	1	1.0
Trastuzumab + gemcitabine + paclitaxel	1	1.0
Trastuzumab + gemcitabine	1	1.0
Trastuzumab + exemestane	1	1.0
Trastuzumab + letrozole	1	1.0
Bevacizumab + paclitaxel	1	1.0
Capecitabine + letrozole	1	1.0
Any trastuzumab beyond progression	98	55.1

Comparators for lapatinib plus capecitabine

The therapies listed in Table 1 are all potential comparators for lapatinib plus capecitabine. As part of GSK's response to the ACD we have performed an analysis to demonstrate the overall cost effectiveness of lapatinib plus capecitabine against the three major existing therapeutic options currently employed within the NHS (capecitabine monotherapy, trastuzumab in combination with capecitabine or vinorelbine). This involves generating a cost effectiveness estimate for lapatinib plus capecitabine compared with a 'blended' comparator consisting of a weighted average of both the costs and effectiveness of the three key treatment options. In order to determine the final proportions of relevant comparators for lapatinib plus capecitabine in this blended analysis, and to ensure that all the above patients including those receiving the less commonly used interventions were represented, we used the following logic to group those that did not receive capecitabine monotherapy or trastuzumab either with capecitabine and vinorelbine (26 patients) with those that did (72 patients).

Table 2 describes how patients were reallocated and the number of patients reallocated into each broad group.

Table 2. Logic used to reallocate patients for the economic analysis

Therapeutic regimen	Patient numbers reallocated to:	Patients re-allocated
Single agent chemotherapy, or single agent hormonal therapy, or chemotherapy plus hormonal therapy	single agent capecitabine bucket	12
trastuzumab monotherapy, or trastuzumab plus chemotherapy, or trastuzumab plus hormonal, or bevacizumab plus paclitaxel	trastuzumab plus vinorelbine and trastuzumab plus capecitabine buckets (split proportionately)	14

The relative proportions of patients receiving trastuzumab plus capecitabine or trastuzumab plus vinorelbine is 0.51:0.49 (Table 1). This ratio was used to reallocate the 14 patients receiving "other" trastuzumab- (or bevacizumab-, n=1) containing regimens, as described in Table 2, to either trastuzumab plus capecitabine or trastuzumab plus vinorelbine groups. The final re-allocation of patients in this analysis is shown at Table 3. In this re-distributed patient set, the trastuzumab-containing groups represent a total of 55 patients, or 56.1% of all regimens used.

Table 3. Final allocation of patients for the economic analysis.

Therapeutic regimen	Original # patients identified in IMS Analysis (Table 1)	New # with patients re-allocated	% of patients receiving "regimen"
Single agent capecitabine	31	43.0	43.9%
Trastuzumab plus capecitabine	21	28.2	28.8%
Trastuzumab plus vinorelbine	20	26.8	27.3%
Total trastuzumab beyond progression	**41**	**55.0**	**56.1%**

The availability of the expanded IMS-OA-ETS dataset has enabled us to track changes in the levels of trastuzumab usage beyond progression over the 2006-2007 period. Table 4 shows changes in the relative proportion of therapies used at point of progression on trastuzumab for MBC after prior treatment with an anthracycline and a taxane. The numbers of relevant patient records is also shown. Data are reported as moving annual totals (MATs); one MAT contains all data for the previous 12 months. Levels of usage of trastuzumab beyond progression in the metastatic setting have remained reasonably constant over the period of the analysis (varying between 54.7 % and 61.6 %). Levels of usage of capecitabine monotherapy, and trastuzumab used in combination with capecitabine or vinorelbine, have also remained reasonably constant.

Table 4 Variance of therapies used beyond progression on trastuzumab-containing therapy for MBC (with prior treatment with anthracycline plus taxane) over the period MATQ12007-MATQ42007.

Therapeutic regimen	MATQ1 2007 n=35	MATQ2 2007 n=60	MATQ3 2007 n=73	MATQ4 2007 n=86	2 years ending Q4 2007 n=98
Capecitabine	28.6	28.3	26.0	31.4	31.6
Trastuzumab + capecitabine	22.9	21.7	24.7	20.9	21.4
Trastuzumab + vinorelbine	17.1	21.7	26.0	22.1	20.4
Vinorelbine	5.7	5.0	4.1	5.8	5.1
Letrozole	0.0	5.0	5.5	4.7	4.1
Trastuzumab + capecitabine + anastrazole	0.0	3.3	4.1	3.5	3.1
Trastuzumab monotherapy	2.9	1.7	1.4	1.2	2.0
Trastuzumab + anastrazole	5.7	3.3	2.7	2.3	2.0

Anastrazole	5.7	3.3	1.4	1.2	2.0
Trastuzumab + capecitabine + exemestane	2.9	0.0	0.0	0.0	1.0
Trastuzumab + docetaxel	2.9	1.7	0.0	0.0	1.0
Trastuzumab + gemcitabine + paclitaxel	0.0	0.0	0.0	1.2	1.0
Trastuzumab + gemcitabine	2.9	1.7	1.4	1.2	1.0
Trastuzumab + exemestane	2.9	1.7	1.4	1.2	1.0
Trastuzumab + letrozole	0.0	0.0	0.0	1.2	1.0
Bevacizumab + paclitaxel	0.0	0.0	0.0	1.2	1.0
Capecitabine + letrozole	0.0	1.7	1.4	1.2	1.0
Any trastuzumab beyond progression	60.0	56.7	61.6	54.7	55.1

Distribution of respondents in the MBC-OA-ETS database

Due to issues relating to patient confidentiality, IMS does not disclose the hospital, cancer network, or strategic health authority in which the participating physicians work. IMS does, however, report the geographical region in which respondents are based. In the period 2006-2007, 117 physicians submitted metastatic breast cancer case histories to the database, and the distribution of these throughout the UK is shown at Table 5. In addition, 38% of physicians described their place of work as a "University Hospital", 56% described it as a "non-University hospital", and 6% said they worked in both "University" and "non-University" hospitals. There is a slight bias in the data towards the Greater London region, but this unsurprising due to the relatively larger population of patients and clinicians in this geography. Therefore, the MBC-OA-ETS data should not be seen as being over-representative of any particular UK region, or any particular type of hospital.

Table 5. Distribution of responders submitting patient case histories to the IMS-OA-ETS database 2006-2007.

Region	% of responders
Eastern	12.7
Greater London	24.6
North & Yorkshire	11.9
North Western	10.3
Northern Ireland	0.8
Scotland	7.1
South & West	5.6
South East	7.1
Trent	5.6
Wales	5.6
West Midlands	8.7
Total	100.0

A 1.1.2 Dendrite Primary Market Research Study

In order to further investigate the rates of trastuzumab beyond progression in the UK, GSK commissioned an independent Market Research survey from Cegedim Dendrite (http://www.cegedimdendrite.com/En/Pages/default.aspx) in the months April to June 2008. The survey, which contained no reference to GlaxoSmithKline as a sponsor, was completed by 92 consultant oncologists in the UK with a specialist interest in breast cancer.

Participants were asked the question:

"Consider your NHS patients that have progressed on trastuzumab in the metastatic setting and have been previously treated with an anthracycline and a taxane for either early stage or metastatic breast cancer. What % of these patients receive the following therapies?"

1. Aromatase inhibitor monotherapy
2. Capecitabine monotherapy
3. Capecitabine plus trastuzumab
4. Capecitabine plus trastuzumab plus aromatase inhibitor
5. Trastuzumab monotherapy
6. Trastuzumab plus aromatase inhibitor
7. Vinorelbine monotherapy
8. Vinorelbine plus trastuzumab
9. Vinorelbine plus trastuzumab plus aromatase inhibitor
10. Other

The average responses from the 92 consultant breast cancer physicians are shown at Table 6. Although the level of evidence is lower than that presented in the OA-MBC-ETS study (the study is based on physician perceptions rather than a review of patient notes), figures from both studies agree remarkably closely. The Cegedim Dendrite study estimates levels of trastuzumab beyond progression in this setting at 48.2%. Levels of usage of other regimes also agree well.

Table 6. Percentage of patients receiving various regimens at point of progression on trastuzumab for MBC after prior treatment with anthracycline plus taxane. Source: Cegedim Dendrite Physician Survey fielded April-June 2008.

Regimen	% of patients estimated to receive this regimen
Capecitabine monotherapy	32.2%
Capecitabine plus trastuzumab	22.8%
Vinorelbine monotherapy	11.8%
Vinorelbine plus trastuzumab	11.6%
Capecitabine plus trastuzumab plus aromatase inhibitor	6.5%
Aromatase inhibitor monotherapy	6.3%
Vinorelbine plus trastuzumab plus aromatase inhibitor	3.1%
Trastuzumab plus aromatase inhibitor	2.3%
Trastuzumab monotherapy	1.9%
Other (of which trastuzumab- containing)	1.4% (0.0%)
Trastuzumab beyond progression	48.2%

The Cegedim Dendrite study was specifically designed to obtain a UK-wide picture of prescribing in this setting and recruitment of multiple respondents from the same cancer network was avoided. The distribution of respondents is shown at Table 7; physicians from 30 cancer networks in the UK completed the survey; no single cancer network makes up more than 9% of the total responses and the mean number of responders per cancer network was 3. Table 7 shows the mean responses per cancer network for the question outlined above. It is apparent that levels of trastuzumab beyond progression vary widely in the UK, and can be as high as 100% and as low as 0%. The mean and median response values agree well (48.2% and 50.0%, respectively.)

Table 7. Distribution of responders and mean responses per cancer network from the Cegedim Dendrite study

		% of all regimens										
Cancer Network	% responders from each network	capecitabine monotherapy	vinorelbine monotherapy	capecitabine + trastuzumab	vinorelbine + trastuzumab	trastuzumab monotherapy	capecitabine + trastuzumab + aromatase inhibitor	vinorelbine + trastuzumab + aromatase inhibitor	trastuzumab + aromatase inhibitor	aromatase inhibitor monotherapy	other	Sum of all trastuzumab-containing regimens
South West London Cancer Network	2%	0.0	0.0	50.0	35.0	0.0	0.0	5.0	10.0	0.0	0.0	100.0
Humber & Yorkshire Coast Cancer Network	3%	6.7	0.0	31.7	3.3	0.0	33.3	10.0	15.0	0.0	0.0	93.3
Mount Vernon Cancer Network	1%	10.0	0.0	70.0	0.0	0.0	20.0	0.0	0.0	0.0	0.0	90.0
Sussex Cancer Network	2%	0.0	0.0	75.0	15.0	0.0	0.0	0.0	0.0	0.0	10.0	90.0
Avon, Somerset & Wiltshire Cancer Network	4%	7.5	2.5	37.5	15.0	10.0	15.0	3.8	5.0	1.3	2.5	86.3
South West Wales Cancer Network	2%	5.0	5.0	30.0	25.0	15.0	10.0	0.0	0.0	10.0	0.0	80.0
Arden Cancer Network	2%	5.0	5.0	20.0	45.0	5.0	0.0	0.0	5.0	15.0	0.0	75.0
Thames Valley Cancer Network	4%	16.8	12.0	47.6	14.6	0.5	2.4	3.7	2.4	0.0	0.0	71.2
Central South Coast Cancer Network	3%	13.3	3.3	33.3	33.3	0.0	0.0	0.0	0.0	16.7	0.0	66.7
West London Cancer Network	7%	24.2	5.8	24.2	15.8	1.7	14.2	1.7	6.7	1.7	4.2	64.2
West of Scotland Cancer Network	4%	27.5	5.0	35.0	15.0	12.5	0.0	0.0	0.0	5.0	0.0	62.5
Yorkshire Cancer Network	3%	27.8	0.0	47.2	8.3	0.0	0.0	0.0	5.6	5.6	5.6	61.1
Greater Manchester & Cheshire Cancer Network	3%	13.3	6.7	13.3	6.7	1.7	13.3	25.0	0.0	18.3	1.7	60.0
Kent & Medway Cancer Network	2%	30.0	5.0	5.0	2.5	2.5	40.0	2.5	0.0	12.5	0.0	52.5
Lancashire & South Cumbria Cancer Network	2%	30.0	20.0	5.0	10.0	0.0	10.0	25.0	0.0	0.0	0.0	50.0
South East Wales Cancer Network	3%	43.3	0.0	20.0	0.0	0.0	13.3	13.3	3.3	3.3	3.3	50.0
Northern Ireland Cancer Network	4%	46.1	3.7	12.5	20.0	0.0	10.0	0.0	1.3	6.2	0.3	43.7
Greater Midlands Cancer Network	8%	33.8	20.6	22.1	14.7	2.9	1.5	0.0	1.5	0.0	2.9	42.7
Pan Birmingham Cancer Network	1%	60.0	0.0	20.0	20.0	0.0	0.0	0.0	0.0	0.0	0.0	40.0
South East London Cancer Network	2%	45.0	12.5	20.0	20.0	0.0	0.0	0.0	0.0	2.5	0.0	40.0
Merseyside & Cheshire Cancer Network	4%	37.5	16.3	20.0	3.8	0.0	12.5	0.0	0.0	7.5	2.5	36.3
3 Counties Cancer Network	3%	10.0	55.0	10.0	20.0	2.5	0.0	0.0	0.0	2.5	0.0	32.5
Peninsular Cancer Network	4%	51.3	12.5	7.5	7.5	5.0	0.0	0.0	1.3	15.0	0.0	21.3
Anglian Cancer Network	9%	60.0	11.3	16.3	3.1	1.3	0.0	0.0	0.0	8.1	0.0	20.6
North Trent Cancer Network	3%	61.7	10.0	6.7	5.0	1.7	3.3	1.7	0.0	10.0	0.0	18.3
North of England Cancer Network	3%	51.7	21.7	6.7	6.7	0.0	0.0	0.0	0.0	13.3	0.0	13.3
North London Cancer Network	2%	65.0	5.0	0.0	10.0	0.0	0.0	0.0	0.0	20.0	0.0	10.0
Mid Trent Cancer Network	1%	50.0	50.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
North East London Cancer Network	3%	46.7	46.7	0.0	0.0	0.0	0.0	0.0	0.0	6.7	0.0	0.0
North Wales Cancer Network	1%	70.0	20.0	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.0

A 1.1.3 Quantifying levels of "3-weekly" versus "weekly" trastuzumab administration and intravenous medication wastage

In order to quantify the levels of 3-weekly vs. weekly trastuzumab usage and IV medication usage in MBC, GSK sponsored a market research study undertaken by Taylor Nelson Sofres in the first week of July 2008. Respondents individually answered a series of questions via an internet portal; no reference to GSK's sponsorship of the study was made in any way. The panel was made up of 24 oncology pharmacists from 17 UK cancer networks. Eleven respondents described themselves as "Lead Oncology Pharmacists", 10 as "Oncology Pharmacists", 2 as "Clinical Trial Pharmacists" and 1 as a "Network Oncology Pharmacist". All were personally responsible for the dispensing of trastuzumab in their hospital. No single cancer network contributed more than 12.5% of the total sample. The distribution of respondents is shown at Table 8.

Table 8. Distribution of responders participating in the Taylor Nelson Sofres online research questionnaire (July 2008).

Cancer Network	respondents per cancer network	%
Anglian Cancer Network	1	4%
Avon, Somerset & Wiltshire Cancer Network	1	4%
Central South Coast Cancer Network	3	13%
Essex Cancer Network	1	4%
Greater Manchester & Cheshire Cancer Network	1	4%
Kent & Medway Cancer Network	2	8%
Merseyside & Cheshire Cancer Network	1	4%
North East London Cancer Network	2	8%
North London Cancer Network	1	4%
North Trent Cancer Network	1	4%
Pan Birmingham Cancer Network	2	8%
South West Wales Cancer Network	1	4%
Surrey, West Sussex & Hampshire Cancer Network	1	4%
Sussex Cancer Network	3	13%
Thames Valley Cancer Network	1	4%
West London Cancer Network	1	4%
West of Scotland Cancer Network	1	4%
Grand Total	24	100%

Participants were asked the question:

"Thinking specifically about your metastatic breast cancer patients, we are interested in how Herceptin is prescribed in combination with certain agents or in certain regimens. Specifically, I would like to understand the relative proportion of Herceptin doses that would be prescribed weekly or 3-weekly during a course of treatment.
For each of the following regimens, please indicate the % of doses that would be administered weekly and the % that would be administered 3-weekly. It's just the Herceptin regimen we're interested in – please don't give details of how the chemotherapy partner is administered.
Mean responses from the 24 participants are given at Table 9. Approximately 12% of trastuzumab, when administered as dual therapy with capecitabine or vinorelbine, is given in a weekly schedule.

Table 9. Oncology pharmacists' estimates of the relative proportions of trastuzumab delivered as weekly or 3-weekly regimens in their hospital.

Regimen	Administration schedule	% MBC trastuzumab delivered in this schedule
Trastuzumab plus capecitabine	Weekly	11.7
	3-Weekly	88.3
Trastuzumab plus vinorelbine	Weekly	11.5
	3-Weekly	88.5
Trastuzumab plus docetaxel	Weekly	9.8
	3-Weekly	90.2
Trastuzumab plus paclitaxel	Weekly	13.8
	3-Weekly	86.2
Trastuzumab monotherapy	Weekly	20.2
	3-Weekly	79.8

Respondents were also asked the question:

"Consider all of the Herceptin doses that are delivered to metastatic breast cancer patients treated in your hospital or by any aligned home healthcare providers your hospital may use". What proportion of all Herceptin doses are made up by the following healthcare personnel?

- *Nurses preparing the dose on a ward*
- *Pharmacists preparing the dose in an aseptic facility*
- *Home healthcare provider services preparing the dose in their own aseptic facility*
- *Home healthcare provider services preparing the dose in a patient's home*

Mean responses from the 24 participants are given at Table 10. Approximately 78% of all trastuzumab doses are dispensed by pharmacists in their own aseptic facility.

Table 10. Oncology pharmacists' estimates of the proportions of trastuzumab dispensed by various healthcare personnel

Healthcare personnel dispensing trastuzumab for MBC	% of all trastuzumab dispensed in this way
Nurses preparing the dose on a ward	13.7
Pharmacists preparing the dose in an aseptic facility	77.9
Home healthcare provider services preparing the dose in their own aseptic facility	7.9
Home healthcare provider services preparing the dose in a patient's home	0.5

Respondents were also asked:

"*Do you have a policy for multiple (repeat) use of IV vials? By multiple/repeat we mean those vials that are used more than once (re-punctured)".* Forty six percent of respondents said they had a policy relating to the repeat use of IV vials and considered all to be single use. Thirty three percent claimed they had a policy and considered some IV vials for multiple use (where possible). The remainder stated that they did not have a policy relating to repeat use of IV vials.

Finally, respondents were asked: *"What proportion of total Herceptin used for the treatment of metastatic breast cancer patients under the care of your hospital (or aligned home healthcare providers) do you estimate is discarded as a result of either single use of vials or for other reasons?".* The average of responses was 15%, with a median of 10%. The highest response was 60% (one respondent) and the lowest was 1% (one respondent).

Details of all responses, and the cancer network in which the oncology pharmacists work, are given at Table 11.

Table 11. Oncology pharmacists' estimates of the proportion of trastuzumab for the treatment of MBC discarded as a result of either single use of vials or for other reasons

Pharmacist's Oncology Network	Proportion of trastuzumab for the treatment of MBC discarded as a result of either single use of vials or for other reasons?
Anglian Cancer Network	10%
Avon, Somerset & Wiltshire Cancer Network	15%
Central South Coast Cancer Network	20%
Central South Coast Cancer Network	15%
Central South Coast Cancer Network	5%
Essex Cancer Network	10%
Greater Manchester & Cheshire Cancer Network	25%
Kent & Medway Cancer Network	1%
Kent & Medway Cancer Network	20%
Merseyside & Cheshire Cancer Network	4%
North East London Cancer Network	5%
North East London Cancer Network	5%
North London Cancer Network	50%
North Trent Cancer Network	15%
Pan Birmingham Cancer Network	10%
Pan Birmingham Cancer Network	6%
South West Wales Cancer Network	60%
Surrey, West Sussex & Hampshire Cancer Network	20%
Sussex Cancer Network	5%
Sussex Cancer Network	10%
Sussex Cancer Network	20%
Thames Valley Cancer Network	10%
West London Cancer Network	10%
West of Scotland Cancer Network	10%

Appendix 2

A2.1. Updated Systematic Review

A2.1.1 Background to the systematic review

Database searches were rerun on 28th February 2007 and on 10th March 2008 for both prospective and retrospective studies with the restricted comparator list (as in our original submission), and the review was updated. Full details of the databases searched and search strategies employed (together with their findings) are provided in sections below.

A2.1.2 Databases searched and date span of searches

The following databases were examined from 1985 up to 10th March 2008:
Medline
Medline in process
Embase
Central (CCTR) CINAHL

The searches were run on: 24 November 2006; 28 February 2007; 10 March 2008.

A2.1.3 Search strategies

The complete search strategies together with the numbers of citations retrieved for the updated search are shown below for each database that was searched.

Medline and Medline in Process

#	Searches	Results
1	(trastuzumab or Herceptin).mp.	2508
2	(lapatinib or Tykerb).mp.	174
3	(capecitabine or Xeloda).mp.	1442
4	(vinorelbine or Navelbine).mp.	2231
5	(gemcitabine or Gemzar).mp.	5103
6	(docetaxel or Taxotere).mp.	4842
7	(paclitaxel or Taxol).mp.	16138
8	or/1-7	26285
9	Breast Neoplasms/	148631
10	9 and (advanced or metastat$ or refract$ or recurren$ or salva$ or (late adj stage) or resistan$).mp.	34293
11	((advanced or metastat$ or refract$ or recurren$ or salva$ or (late adj stage) or resistan$) and breast).mp.	43977
12	((stage IIIB or stage IIIc or stage IV) and breast).mp.	984
13	Neoplasm Metastasis/ or Neoplasm Recurrence, Local/	116816
14	13 and breast.mp.	17357
15	10 or 11 or 12 or 14	48826
16	8 and 15	388
17	Neoplasm Proteins/ or Antibodies, Monoclonal/ or Antineoplastic Agents/	286662
18	(trastuzumab or Herceptin).mp.	2508

19	Receptor, erbB-2/ or Genes, erbB-2/ or receptor, epidermal growth factor/	23912
20	erb?B.mp.	11448
21	neu.mp.	5356
22	(her-2 or her2).mp.	6407
23	or/17-22	309140
24	16 and 23	1788

Embase

#	Searches	Results
1	breast/	30125
2	1 and (advanced or metastat$ or refract$ or recurren$ or salva$ or (late adj stage) or resistan$).mp.	4393
3	exp breast tumor/	146057
4	3 and (advanced or metastat$ or refract$ or recurren$ or salva$ or (late adj stage) or resistan$).mp.	36083
5	((advanced or metastat$ or refract$ or recurren$ or salva$ or (late adj stage) or resistan$) and breast).mp.	42890
6	((stage IIIB or stage IIIc or T4 or stage IV) and breast).mp.	1338
7	metastasis/ and breast.mp.	11891
8	2 or 4 or 5 or 6 or 7	47795
9	(trastuzumab or Herceptin).mp.	7044
10	(lapatinib or Tykerb).mp.	999
11	(capecitabine or Xeloda).mp.	4372
12	(vinorelbine or Navelbine).mp.	6547
13	(gemcitabine or Gemzar).mp.	11511
14	(docetaxel or Taxotere).mp.	11936
15	(paclitaxel or Taxol).mp.	29113
16	or/9-15	47659
17	8 and 16	6569
18	(trastuzumab or Herceptin).mp.	7044
19	trastuzumab/	6911
20	(erb2 or erb-b2 or erb b2).mp.	375
21	Antineoplastic Agent/ or Monoclonal Antibody/ or ONCOGENE C ERB/ or Protein Tyrosine Kinase Inhibitor/ or Oncogene Neu/ or Epidermal Growth Factor Receptor 2/	200837
22	(her2 or her-2 or neu).mp.	9879
23	or/18-22	206761
24	17 and 23	3671

CINAHL

#	Searches	Results
1	(trastuzumab or Herceptin).mp.	375
2	(lapatinib or Tykerb).mp.	32
3	(capecitabine or Xeloda).mp.	204
4	(vinorelbine or Navelbine).mp.	126
5	(gemcitabine or Gemzar).mp.	266
6	(docetaxel or Taxotere).mp.	411
7	(paclitaxel or Taxol).mp.	898
8	or/1-7	1921
9	Breast Neoplasms/	17010
10	9 and (advanced or metastat$ or refract$ or salva$ or (late adj stage) or resistan$).mp.	1210
11	((advanced or metastat$ or refract$ or salva$ or (late adj stage) or resistan$) and breast).mp.	1543
12	((stage IIIB or stage IIIc or stage IV) and breast).mp.	37
13	metastasis/ and breast.mp.	1212
14	or/10-13	2232
15	8 and 14	357
16	Neoplasm Proteins/ or Antibodies, Monoclonal/ or Antineoplastic Agents/	8252
17	(trastuzumab or Herceptin).mp.	375
18	Receptor, erbB-2/ or Genes, erbB-2/ or receptor, epidermal growth factor/ or "HER-2/neu Oncogene"/	88
19	(erb2 or erb-b2 or erb b2).mp.	5
20	neu.mp.	2212
21	(her2 or her-2).mp.	364
22	or/16-21	8618
23	15 and 22	228

CENTRAL (Cochrane)

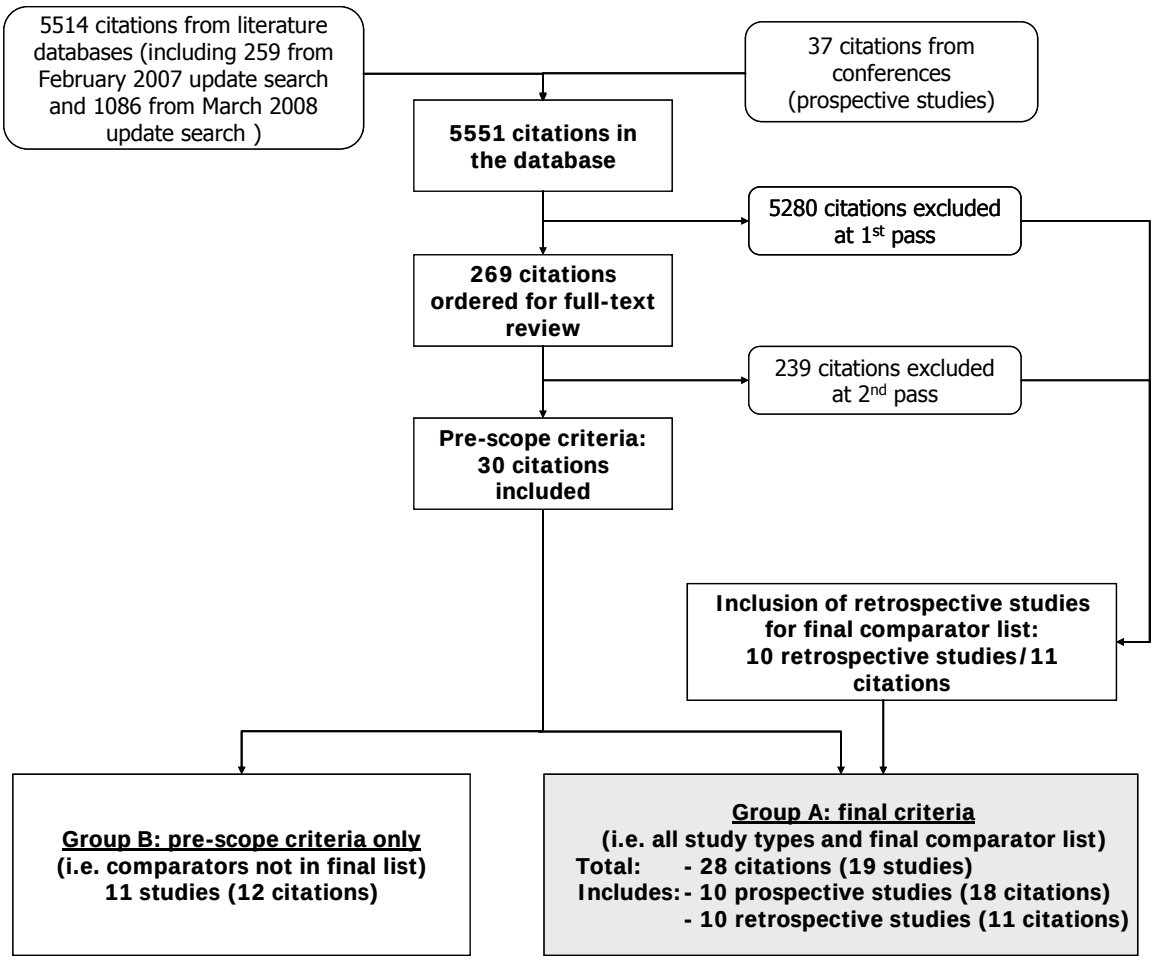
ID	Search	Hits
#1	MeSH descriptor Breast Neoplasms, this term only	5742
#2	(#1 AND (advanced OR metastat* OR refract* OR salva* OR (late AND adj AND stage) OR resistan* OR recurren*))	2396
#3	breast and (advanced or metastat* or refract* or salva* or (late adj stage) or resistan* or recurren*) in Clinical Trials	3354
#4	breast and (stage IIIB or stage IIIc or stage IV) in Clinical Trials	284
#5	(#2 OR #3 OR #4)	3682
#6	trastuzumab or Herceptin in Clinical Trials	150
#7	lapatinib or Tykerb in Clinical Trials	9
#8	capecitabine or Xeloda in Clinical Trials	194

#9	vinorelbine or Navelbine in Clinical Trials	439
#10	gemcitabine or Gemzar in Clinical Trials	602
#11	docetaxel or Taxotere in Clinical Trials	733
#12	paclitaxel or Taxol in Clinical Trials	1426
#13	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)	2718
#14	trastuzumab or Herceptin in Clinical Trials	150
#15	her-2 or her2	240
#16	erb2 or erb-b2 or erb b2	16
#17	neu	239
#18	(#14 OR #15 OR #16 OR #17)	449
#19	MeSH descriptor Neoplasm Metastasis, this term only	1417
#20	MeSH descriptor Neoplasm Recurrence, Local, this term only	2332
#21	((#19 OR #20) AND breast)	1030
#22	(#5 OR #21)	3742
#23	(#22 AND #13 AND #18)	86
#24	(#23) Limited to RCT	49

A2.1.4 Flow diagram

Studies were included/excluded on the basis of explicit criteria described in and the results of each stage of the inclusion/exclusion process are summarised below in figure A1. There was a very large number of excluded trials, the details of which are available upon request.

Figure 1: Flow diagram of included/excluded studies.



Note: The number of included citations reflects multiple publications from the same trial

A2.1.5 Additional searches

In addition to the searches of the electronic databases, the details of which are shown in Section 1.1.1, a number of other sources were utilised. These included sources likely to contain information on ongoing trials with a view to highlighting any data that may emerge (NCI clinical trial database; ClinicalTrials.gov; EORTC UK; National Register of Cancer Trials; GSK internal clinical trial and publication databases). Hand-searching of recent conference proceedings (years 2004-2007) that may have contained relevant data was also undertaken. The conferences included were as follows:

- ASCO (American Society of Clinical Oncology)
- ECCO (European Cancer Conference)
- ESMO (European Society for Medical Oncology)
- EORTC-NCI-AACR European Breast Cancer Conference
- SABCS (San Antonio Breast Cancer Symposium)

- St Gallen Breast Cancer Meeting

ASCO, ECCO, ESMO and SABCS conference proceedings were also hand searched for..

In addition, four study protocols were identified (i) Piccart-Gebhart 2004; Pusztai 2005 [SWOG S0347, NCT00103233]; (ii) NCT00444587; (iii) NCT00448279 (THOR) and (iv) NCT00130507 [GEICAM 2004-06] but no publications containing data from these studies were identified. Two additional protocols were identified but some data have been reported from these studies: (i) NCT00148876 [German Breast Group study 26; von Minckwitz 2007] and (ii) NCT00301899 (Fumoleau 2007).

A2.1.6 Data abstraction strategy

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into a Reference Manager™ database. For the March 2008 update, citation details were downloaded into the Heron internet systematic review database (SRDB™).

A2.1.6.1 First pass of citations

Citations were first screened based on the abstract supplied with each citation. Those that did not match the eligibility criteria were excluded at this 'first pass'. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded in the first pass. In instances when it was not possible to include or exclude citations based on the abstract, full-text copies were ordered. Full-text copies of all references that could potentially meet the eligibility criteria were also ordered at this stage.

A2.1.6.2 Second pass of citations

The eligibility criteria were applied to the full-text citations. Each citation was screened twice by independent reviewers. Any discrepancies were resolved by discussion with a third party reviewer. For the March 2008 update, each citation was screened once. All included studies were extracted into Word extraction grids.

A2.1.7 Data extraction strategy

For the March 2008 update, each study was extracted once and then reviewed by an independent reviewer.

A2.1.8 Quality assessment

A concise critical appraisal was written for each study. In addition the studies were appraised using the Jadad scoring system where appropriate and graded according to concealment of allocation. This information is available to NICE on request.

A2.1.9 Qualitative assessment

A descriptive analysis of each extracted study was made during the data extraction process. The analysis assessed the study for quality by considering the following five features, which could introduce bias:

- Methods of generation of random allocation and concealment at randomisation
- Blinding of trial participants and investigators
- Baseline characteristics
- Completeness of treatment and follow-up
- Applicability of the study to clinical practices in the UK
- Statistical methods used to compensate for missing outcome data

A2.1.10 Relevant studies identified by the systematic review

Details of studies meeting the inclusion criteria for the systematic review are included in Tables 1-6.

Table 1: Relevant studies meeting the inclusion criteria for the systematic review (identified by update to systematic review conducted in March 2008)

Study	Study design	Country/centre status	Intervention	ITT popn. N (n[$])	Participants	Prior therapy (subgroup)	ErbB2+ popn.	Main study objectives / study description
Prospective Studies								
von Minckwitz 2007 /2008 (Conference abstract)	Phase III, Randomised controlled trial	Multicentre Europe	Arm X-Capecitabine 2500 mg/m² d1-14 q21d or Arm XH - Capecitabine 2500 mg/m²d1-14q21+ Trastuzumab 6mg/kg q3w	156 (of 482 patient target)	Patients with ErbB2+ metastatic breast cancer patients had previously been treated with either trastuzamab and taxane as adjuvant therapy, trastuzamab and taxanes as 1st line metastatic therapy or trastuzamab given alone or in combination with further chemotherapy as 1st line metastatic therapy	anthracycline Arm X 69.2%, Arm XH 75.6% taxane / trastuzumab (1st line) = 71% trastuzumab alone or with a non-taxane containing chemotherapy = 27% taxane plus trastuzumab + taxane as adjuvant therapy = 2%	100%	To compare the time to disease progression in patients with ErbB2+ metastatic breast cancer with progression following previous treatment with trastuzumab.
Bartsch 2007	Phase II, non-comparative, single-centre study	Single-centre • Austria	capecitabine 1250mg/m2 b.d. d1-14 q3w + trastuzumab 8mg/kg loading dose then 6mg/kg q3w	40 (21)	Patients with ErbB2-positive advanced breast cancer who had received treatment with an anthracycline and taxane or vinorelbine in either the adjuvant or metastatic settings and at least one line of trastuzumab for advanced disease	anthracycline = 100% taxane = 61% vinorelbine = 92.5% vinorelbine + taxane = 57.5% trastuzumab = 100%	100%	To evaluate the efficacy and tolerability of capecitabine plus trastuzumab after anthracycline and taxane/vinorelbine failure and prior trastuzumab exposure
Jackisch 2007 (Conference abstract)	Prospective, observational study	Multi-centre • Germany	trastuzumab alone; trastuzumab + chemotherapy +/- endocrine therapy; trastuzumab + endocrine therapy only	485	Patients with metastatic breast cancer who received trastuzumab between 2001 and 2006, some of whom continued to receive trastuzumab beyond first progression	45% of patients received 1-4 prior chemotherapy regimens anthracycline = 79% taxane = NR trastuzumab = NR	100%*	To review the use of trastuzumab in routine clinical practice
Chollet 2007 / Bachelot 2007 (Conference abstract)	Phase II, non-comparative study	Multi-centre • France	trastuzumab 8mg/kg loading dose then 6mg/kg q3w or 4mg/kg loading dose then 2mg/kg qw + vinorelbine 30mg/m2 d 1and 8 q3w	17 (interim data)	Patients with ErbB2+ metastatic breast cancer who had progressed following 1st line trastuzumab + taxane therapy	anthracyline = NR taxane =100% trastuzumab = 100%	100%	To assess the clinical benefit of trastuzumab + vinorelbine as treatment for women with erbB2+ metastatic breast cancer beyond disease progression

Study	Study design	Country/centre status	Intervention	ITT popn. N (n[$])	Participants	Prior therapy (subgroup)	ErbB2+ popn.	Main study objectives / study description
Retrospective studies								
Adamo 2007	Retrospective study	Two centre • Italy	trastuzumab ± chemotherapy	70 (26)	Women with ErbB2+ metastatic breast cancer who received trastuzumab-based therapy (alone or in combination) and some patients received second, third and further lines of trastuzumab treatment. Of those who received a second line, 14 received monotherapy and 12 combination therapy	trastuzumab = 100%* anthracyclines = 17 (24%) taxanes = 2 (3%)	100%	To evaluate the safety and activity of trastuzumab-containing regimens
Carabantes-Ocon 2007	Retrospective study	Single centre • Spain	trastuzumab ± chemotherapy +/or hormonal therapy	24	Patients with ErbB2+ metastatic breast cancer who received a first and second line of trastuzumab-containing therapy, of whom 17 patients went on to receive a third line and 7 patients a fourth line.	trastuzumab = 100% taxane = NR anthracycline + NR	100%	To study the clinical benefit of trastuzumab as monotherapy or in combination with chemotherapy/hormonal therapy in treatment of ErBb2+ metastatic breast cancer after progression on prior trastuzumab therapy
Hutka 2007 (Conference abstract)	Retrospective study	Single centre • Poland	trastuzumab ± chemotherapy	42 (12)	Patients with ErbB2+ metastatic breast cancer treated with trastuzumab (n=42), of whom 12 were treated with further trastuzumab on progression (8 patients in combination with chemotherapy and 4 patients as monotherapy)	trastuzumab = 100% anthracycline = NR taxane = NR	100%	To determine whether continuation of trastuzumab with further lines of chemotherapy after progression on a previous trastuzumab-containing regimen improves clinical outcomes
Metro 2007 (Conference abstract)	Retrospective study	Single centre • Italy	trastuzumab ± chemotherapy	59 (37)	Patients with ErbB2+ metastatic breast cancer treated with a first line trastuzumab regimen (n=59), of whom 37 received a second line regimen	trastuzumab = 100% anthracycline = NR taxane = NR	100% (IHC3+: 83%)	To determine the activity of trastuzumab administered beyond disease progression in patients who had received at least one trastuzumab-based regimen
Montemurro 2007 (Conference abstract)	Retrospective study	Multicentre • Italy	trastuzumab ± chemotherapy	286 (112)	Patients with ErbB2+ advanced breast cancer progressing during or after an initial trastuzumab-based regimen; trastuzumab was continued beyond progression in 112 patients	trastuzumab = 100% anthracycline = NR taxane = NR	100%*	To evaluate clinical outcomes in ErbB2+ advanced breast cancer patients progressing on trastuzumab-based therapy
Yanmaz 2006 (Conference	Retrospective study	Single centre • Turkey	trastuzumab + chemotherapy +/or	33 (60 lines of TBP	Patients with ErbB2+ metastatic breast cancer,	trastuzumab = 100% anthracycline = NR	100%	To determine the efficacy of trastuzumab when continued beyond

Study	Study design	Country/centre status	Intervention	ITT popn. N (n[$])	Participants	Prior therapy (subgroup)	ErbB2+ popn.	Main study objectives / study description
abstract)			hormonal therapy	given)	some of whom received trastuzumab beyond progression (TBP) combined with chemotherapy and/or hormonal therapy	taxane = NR		progression in women with metastatic breast cancer

Table 2: Baseline characteristics for additional trastuzumab beyond progression prospective studies

Study	Characteristic	Population
Von Minckwitz 2007	Age (median, years) KPS ≥ 80 ER- / PR- Grade 3/4 disease ≥ 1 metastatic sites	Arm X 59; Arm XH 53 Arm X 81%; Arm XH 86% Arm X 42%; Arm XH 41% Arm X 61%; Arm XH 56.2% NR
Bartsch 2007	Age (median, years) KPS > 70 ER- / PR- Stage IV disease ≥ 1 metastatic sites	58.5 100% 74% NR 97.5%
Jackisch 2007	Age (median, years) KPS > 70 ER- / PR- Stage IV disease ≥ 1 metastatic sites	57 NR 37% 91% NR
Chollet 2007/Bachelot 2007	Age (median, years) KPS > 70 ER- / PR- Stage IV disease ≥ 1 metastatic sites	54 NR 47% NR NR
Adamo 2007†	Age (median, years) KPS > 80 ER- / PR- Stage IV disease > 2 metastatic sites	57 97% NR NR NR
Carabantes-Ocon 2007	Age (median, years) KPS > 80 ER- / PR- Stage IV disease > 2 metastatic sites	NR NR 37.5% NR NR
Hutka 2007	Age (median, years) KPS > 90 ER- / PR- Stage IV disease > 2 metastatic sites	49 NR NR NR NR
Metro 2007	Age (median, years) KPS > 90 ER- / PR- Stage IV disease > 2 metastatic sites	51 NR 58% NR NR
Montemurro 2007	Age (median, years) KPS > 90 ER- / PR- Stage IV disease > 2 metastatic sites	NR NR NR NR NR
Tokajuk. 2006	Age (median, years) KPS > 90 ER- / PR- Stage IV disease > 2 metastatic sites	52 NR 33% NR 66%
Yanmaz 2006	Age (median, years) KPS > 80 ER- / PR- Stage IV disease > 2 metastatic sites	NR NR NR NR NR

Table 3: Summary of key findings from trastuzumab beyond progression studies

Study	Interventions	Median TTP	CR N (%)	PR N (%)	SD N (%)	Response Rate	Median OS	Median PFS (mths)
Prospective studies								
Von Minckwitz 2007 / 2008	trastuzumab + capecitabine (N=78) capecitabine (N=78)	8.2 mths 5.6 mths	7.7% 2.7%	40.3% 24.3%	27.3% 27.0%	48.0% 27.0%	25.5mths 20.4 mths	-
Bartsch 2007	trastuzumab + capecitabine (N=21*)	7 mths	-	4 (19%)	10 (48%)	-	-	-
Jackisch 2007	trastuzumab only trastuzumab + chemotherapy +/- endocrine therapy trastuzumab + endocrine therapy (N=485)	-	-	-	-	45% 56% 30%		
Chollet / Bachelot 2007	trastuzumab + vinorelbine (N=17*)	-	2 (12%)	3 (18%)	4 (23%)	30%	-	-
Retrospective studies								
Adamo 2007	trastuzumab ± chemotherapy (N=26)	9 mths	0	6 (23%)	16 (62%)	6 (23%)	-	-
Carabantes-Ocon 2007	trastuzumab + chemotherapy +/or hormonal therapy (N=24*)	-	-	-	15 (62%)	8 (33%)	-	-
Hutka 2007	trastuzumab ± chemotherapy (N=12*)	-	-	-	-	6 (50%)	160 wks	-
Metro 2007	trastuzumab ± chemotherapy (N=37*)	6.7 mths	-	-	-	29%	38 mths	-
Montemurro 2007	trastuzumab ± chemotherapy (N=112*)	7.8 mths	-	-	-	25%	24.2 mths	-
Tokajuk 2006	trastuzumab ± chemotherapy (N=27) 14*	5.1 mths	-	-	-	35.7% (PR)	-	-
Yanmaz 2006	trastuzumab + chemotherapy +/or hormonal therapy (N=33; 60 lines of TBP)	-	-	12 (20%)†	19 (32%)†	-	-	-

* Patients on second-line trastuzumab therapy; † evaluated on 60 lines of trastuzumab beyond progression (TBP)

Note: The efficacy data reported in Table iii above relate only to patients who received trastuzumab beyond progression (i.e. second line and beyond). Where data were available for separate lines, the tabulated data is for second-line therapy only. The results for the Bartsch 2007 study involving patients receiving trastuzumab plus capecitabine may represent a partial overlap of those for a sub-set of patients in the Bartsch 2006 publication included in GSK's original submission who received the same combination.

Table 4: Adverse events reported for patients treated with trastuzumab beyond disease progression in additional studies identified (n, (%))

Study	Treatment	All serious AEs	Nausea/ vomiting	Haematological events	Stomatitis / Mucositis	Diarrhoea	Hand-foot syndrome (PPE)	Head-ache	Pain	Fatigue / Asthenia	Infection	Peripheral neuro-pathy	Constip ation	Other
Prospective														
Von Minckwitz 2008	trastuzumab + capecitabine (N=78)		14.3%	Neutropenia 26.6% (G3/4 5.3%) Anaemia 64.0% Thrombocytopenia 9.7% Leucopenia 55.4 % (G3/4 8.1%)	27.3%	46.8% (G3/4 15.6%)	80.6% (G3/4 32.5%)			46.8% (G3/4 3.9%)		32.5% (G3/4 2.6%)		Nail changes 23.4% (G3/4 3.9%)
Bartsch 2007	trastuzumab + capecitabine (N=21)		-	Neutropenia 6 (29%) Thrombocytopenia 0% Anaemia 2 (9.5%)	2 (9.5%)	8 (38%)	10 (48%)			1 (9%)				
Bachelot/ Chollett 2007	trastuzumab + vinorelbine (N=17)			Neutropenia (G3/4) 23.5%										
Retrospective														
Adamo 2007	trastuzumab ± chemotherapy (N = 80)									5.7%				Rash 1.4% Fever 5.7% Increased bilirubin 1.4%

Note:
AEs were not reported except cardiotoxicity (see Table xx) in the following study: Jackisch 2007. No AEs were reported in the following studies: Hutka 2007, Metro 2007, Montemurro 2007, Carabantes-Ocon 2007; Yanmaz 2007

Table 5: Cardiac events reported for patients treated with trastuzumab beyond disease progression

Study	Treatment	All cardiac events	Serious cardiac events
Prospective			
Von Minckwitz 2008	trastuzumab + capecitabine (N=78)	13.0% (G3/4 5.2%)	NR
Bartsch 2007	trastuzumab + capecitabine (N=21)	0	NR
Jackisch 2007	trastuzumab ± chemotherapy, trastuzumab + hormonal therapy (N=485)	1.0%	1.0% (G3/4)
Bachelot/Chollet 2007	trastuzumab + vinorelbine (N=17[#])	2	
Retrospective studies			
Adamo 2007	trastuzumab ± chemotherapy (N = 70)	8 (11.4%)	1 (1.4%)

[#] Cardiac function data only available for 9 patients
No cardiac AEs were reported in the following studies: Montemurro 2007, Metro 2007, Hutka 2007, Carabantes-Ocon 2007; Yanmaz 2007

Table 6: Non-randomised studies meeting the inclusion criteria for the systematic review but with non-relevant interventions .

Study	Study design	Country / centre status	Intervention	ITT population N	Participants	Prior therapy (subgroup)	ErbB2 positive population	Main study objectives / study description	Reason for excluding
Link 2007	Retrospective	USA	albumin-bound paclitaxel (80-125mg/m^2 on d1, d8, d15 or 170-200mg/m^2 q2w of q4w cycle) + bevacizumab 10mg/kg q2w		Patients with metastatic breast cancer with $\geq$ 2 previous chemotherapy regimens for adjuvant/metastatic disease. 12 patients were ErbB2+. 20 patients were ER and/or PR positive. These patients had been treated with various hormonal therapies including tamoxifen, aromatase inhibitors, fulvestrant.	anthracycline = 85% taxanes = 87.5% trastuzumab = 30%	30%	To evaluate the combination of albumin-bound paclitaxel + bevacizumab in heavily pretreated patients with MBC	Not relevant intervention – albumin-bound paclitaxel + bevacizumab
Fumoleau 2007 (Conference abstract)	Phase II, non-comparative study	Multicentre • UK • France • Spain • Canada • Italy	trastuzumab 4mg/kg loading dose then 2mg/kg qw or 8mg/kg loading dose then 6mg/kg q3w + pertuzumab 840mg loading dose then 420 mg q3w	42 (interim data)	Patients with ErbB2+ metastatic breast cancer who had progressed during latest of $\leq$ 3 prior trastuzumab containing regimens	trastuzumab = 100% anthracycline = 64% taxane = NR	100%	To assess safety and efficacy of trastuzumab plus pertuzumab in ErbB2+ metastatic breast cancer patients who had progressed during trastuzmab therapy	Not relevant intervention – trastuzumab + pertuzumab, another targeted agent
Morabito 2004 (Conference abstract)	Phase II, non-comparative study in which recruitment is ongoing*	Not reported	vinorelbine 25mg/m2 d1, d8 q21d + gemcitabine 800 mg/m2 d1, d8 q21 + trastuzumab 2mg/kg/w q3w	26	Patients with ErbB2+ metastatic breast cancer. Prior treatment included anthracyclines and/or taxanes/ trastuzumab. Of the patients included in the study, 90% had prior first-line chemotherapy and 10% second line.	anthracycline = NR taxane = NR taxane & anthracycline = NR trastuzumab = 35%	100%*	To evaluate the efficacy of trastuzumab in combination with gemcitabine and vinorelbine in second/third line therapy in MBC.	Not relevant intervention – trastuzumab-based regimen beyond progression but with two (cf single) chemotherapy agents. Details of anthracycline and taxane prior treatment levels not reported
Andres 2005	Phase II, non-comparative trial	Single centre • Spain	gemcitabine 2000mg/m2 d1 q3w + capecitabine 2500 mg/m2 d1-14 q3w	39	Patients with metastatic breast cancer who had progressed after one or more anthracycline-containing regimens or had a medical contraindication to anthracyclines.	anthracycline = 85% taxane = 90% taxane & anthracycline = NR trastuzumab = 13%	NR	To evaluate the response rate of gemcitabine / cisplatin in patients previously treated with anthracyclines and taxanes.	Not relevant intervention – capecitabine + gemictabine. Also low level (13%) of trastuzumab pre-treatment

Study	Study design	Country / centre status	Intervention	ITT population N	Participants	Prior therapy (subgroup)	ErbB2 positive population	Main study objectives / study description	Reason for excluding
					Patients who had received anthracyclines only for adjuvant treatment must also have received at least one cycle of taxane-containing chemotherapy.				
Bari 2005	Phase II, non-comparative trial	Multicentre • Italy	capecitabine 1000mg/m2 bid d1-14 q3w + paclitaxel 60mg/m2 qw	33	Patients must have been exposed to anthracyclines in either the adjuvant or advanced setting. Those with ErbB2+ tumours must have been treated with a trastuzumab-containing regimen. Patients treated with high-dose chemotherapy followed by peripheral blood stem cell rescue were also eligible.	anthracycline = 91% taxane = 66.6% taxane & anthracycline = NR trastuzumab = 18%	18%	To evaluate the effect of salvage therapy with capecitabine plus weekly paclitaxel in patients with heavily pre-treated advanced breast cancer.	Not relevant intervention – capecitabine + paclitaxel Also low level (18%) of trastuzumab pre-treatment
Bayo 2005 (Conference abstract)	Phase II, non-comparative trial*	Not reported	cisplatin 25mg/m2 d1, d8 q3w + gemcitabine 1000 mg/m2 d1, d8 q3w	31	Patients with ErbB2+ metastatic breast cancer. Prior treatment included anthracyclines and/or taxanes. 26% of patients had received a second line of chemotherapy; none had received a third line. 29% had received trastuzumab.	anthracycline = 97% taxane = 90% taxane & anthracycline = NR trastuzumab = 29%	NR	To evaluate the activity and toxicity profile of cisplatin and gemcitabine in combination for the treatment of metastatic breast cancer in 2nd - 3rd line treatment of metastatic breast cancer.	Not relevant intervention - capecitabine + gemcitabine
Stemmler 2005b	Phase II, non-comparative, multi-centre	Multicentre • Germany	gemcitabine 750mg/m2 d1, d8 q3w + cisplatin 30mg/m2 d1, d8, q3w +trastuzumab 2mg/kg/w	20	Patients with ErbB2+ metastatic breast cancer. Prior treatment included anthracyclines and/or taxanes.	anthracycline = 90% taxane = NR taxane & anthracycline = 55% trastuzumab = 35%	100%	To evaluate the efficacy and tolerability or gemcitabine and cisplatin plus trastuzumab in previously treated patients with metastatic breast cancer by determining the	Not relevant intervention – trastuzumab-based regimen beyond progression but with two (cf single) chemotherapy agents.

Study	Study design	Country / centre status	Intervention	ITT population N	Participants	Prior therapy (subgroup)	ErbB2 positive population	Main study objectives / study description	Reason for excluding
								objective response rate. A median of six cycles were delivered.	
Donadio 2005	Phase II, non-comparative	Multicentre • Italy	capecitabine 1,000mg/m2 bid d1-14 q3w + cisplatin 20mg/m2 d1, d8, d15, d22, d29 q6w	39	Patients were required to have metastatic adenocarcinoma of the breast pre-treated with both anthracyclines and taxanes in at least 2 prior lines of chemotherapy. A sub-group of patients had also received trastuzumab.	anthracycline = 100% taxane = 100% taxane & anthracycline = NR trastuzumab = 12.8%	NR	To evaluate the effect of weekly cisplatin plus capecitabine in metastatic breast cancer patients heavily pre-treated with both anthracyclines and taxanes.	Not relevant intervention - capecitabine + cisplatin
Morabito 2006	Phase II study non-randomised, non-comparative,	Not reported	vinorelbine 25mg/m2 d1, d8 q21d + gemcitabine 800 mg/m2 d1, d8 q21 + trastuzumab 2mg/kg/w q3w	30	Women with metastatic breast cancer, expressing ErbB2+ who had progressed following first-line chemotherapy, which included treatment with, anthracyclines and/or taxanes, and trastuzumab. Patients were excluded if they had previously been treated with vinorelbine or gemcitabine. ECOG status was = 2.	anthracycline = 16.7% adjuvant anthracycline = 36.7% taxane = 56.7% taxane & anthracycline= 26.7% trastuzumab = 23.3%	100%	To evaluate the safety and efficacy of combined treatment with trastuzumab, gemcitabine and vinorelbine as second-line therapy for HER-2 over expressing metastatic breast cancer patients.	Not relevant intervention – trastuzumab-based regimen beyond progression but with two (cf single) chemotherapy agents.
Mrozek 2006	Phase II study of weekly docetaxel and capecitabine in patients with metastatic breast cancer.	Multicentre • US	docetaxel 30mg/m2 d1, d8, d15 q28d + capecitabine 800mg/m2 bid d1-21 q28d	39	A maximum of 2 previous chemotherapy regimens for metastatic breast cancer were permitted, previous treatment with capecitabine or docetaxel were permitted as long as treatment ceased > 6 months previous to the study	anthracycline = 51% taxane = 36% taxane & anthracycline = NR trastuzumab = 16%	13%	To evaluate the toxicity, overall response rate and TTP of weekly docetaxel and capecitabine in patients with metastatic breast cancer.	Not relevant intervention – docetaxel + capecitabine
Orlando 2006	Phase II, non-comparative	Single centre • Italy	trastuzumab 6mg/kg q3w +	22	Patients with metastatic breast cancer previously	chemotherapy = 100%	100%	To test the activity and tolerability of	Not relevant intervention – trastuzumab-based regimen

Study	Study design	Country / centre status	Intervention	ITT population N	Participants	Prior therapy (subgroup)	ErbB2 positive population	Main study objectives / study description	Reason for excluding
			methotrexate 2.5 bid d1, d4 qw + cyclophosphamide 50mg qd		treated with trastuzumab for metastatic disease and with an ECOG performance status of <3.	anthracycline = NR taxane = NR taxane & anthracycline = NR trastuzumab = 100%		the combination of trastuzumab with metronomic, low dose chemotherapy with cyclophosphamide (CYC) and methotrexate (MET) in metastatic breast cancer pretreated with trastuzumab for metastatic disease.	beyond progression but with two (cf single) chemotherapy agents.
Massacesi 2005	Phase II, non-comparative study	Not reported	capecitabine 1000mg/m^2 bid d1-14 q4w + mitomycin C 6mg/m^2 d1 q4w	53	Patients with metastatic breast cancer previously treated with anthracyclines and taxanes. An ECOG performance status <3 and a life expectancy of at least 3 months were also required.	anthracycline = 96.2% taxane = 90.6% taxane & anthracycline = 86.8% trastuzumab = 13.2% trastuzumab and taxane = 11.3% trastuzumab and taxane and/or vinorelbine = 7.5%	20.5%	To evaluate the efficacy of capecitabine and mitomycin C in metastatic breast cancer pre-treated with anthracyclines and taxanes.	Not relevant intervention – capecitabine + mitomycin

q3w = every 3 weeks; * inferred value; NR = Not recorded; NA = Not applicable

A 2.2 Pooling of TTP data from studies investigating trastuzumab beyond progression

TTP was the most commonly reported time-to-event endpoint in the studies identified of trastuzumab use beyond progression. In order to provide a supportive indirect comparison with lapatinib plus capecitabine, a pooled median TTP for trastuzumab beyond progression was estimated, first converting months TTP to weeks TTP for each study using the relationship [weeks=months x (52/12)]. Owing to the absence of data on the variance of the median TTP estimates, each study (or arm within study) was weighted by the number of subjects within the pooling process. A weighted standard deviation of the pooled estimate was calculated by taking the weighted sum of the squared differences from the pooled estimates. Given the pooled estimate of the median TTP (27.0 wks) and its corresponding standard deviation (2.0), a 95% CI was calculated for this pooled estimate (23.3 to 31.1 wks)) assuming that median TTP would follow a lognormal distribution (Table vi). Given the inconsistent reporting of results for individual regimens it was not feasible to differentiate between the efficacy of continued trastuzumab when given alone, or when given in combination with chemotherapy.

Table 7. Pooling estimates of median TTP in studies of trastuzumab in HER2+ MBC patients who progressed on prior T therapy

Author (year)	Treatment	N	TTP reported (1=y, 0=n)	Median TTP (wks)
Continued trastuzumab				
Tripathy (2004)	T+CT	93	0	0.0
Stemmler (2005)	T+CT	23	0	0.0
Extra (2006)	T+CT	107	0	0.0
Hutka (2007)	T+CT	12	0	0.0
Bangemann (2000)	T+V	10	1	13.0
Bangemann (2000)	T+C	17	1	13.0
Bangemann (2000)	T+D	9	1	15.2
Suzuki (2003)	T+V	24	1	13.1
Gelmon (2004)	T+V	33	1	26.0
Gelmon (2004)	T+P	20	1	24.0
Gelmon (2004)	T-only	10	1	30.5
Fountzilas (2005)	T+CT	80	1	22.6
Garcia-Saenz (2005)	T+CT	31	1	13.0
Bartsch (2006)	T+CT	54	1	26.1
Tokajuk (2006)	T+CT	14	1	22.2
Adamo (2007)	T+/-CT	26	1	39.1
Bartsch (2007)	T+C	21	1	34.8
Metro (2007)	T+/-CT	37	1	29.0
Montemurro (2007)	T+/-CT	112	1	33.9
Von Minckwitz (2007)	T+C	77	1	35.6
Minimum				13.0
Maximum				39.1
Weighted mean				
Mean				27.0
SD				7.9

SE				2.0
Derivation of HRs and SEs of HRs based on median TTPs				
Median TTP				
	Est	**SE**	**95%CI**	**95%CI**
Method			**Lower**	**Higher**
Weighted	27.0	2.0	23.3	31.1

Unweighed mean and SD=simple average and stdev of median TTPs (X_is).
Unweighed SE=Unweighed SD/sqrt(N studies).
Weighted mean calculated with X_i weighted by N_i. Weighted SD calculated with $(X_i-\mu)^2$ weighted by N_i. Weighted SE=Weighed SD/sqrt(N studies)
SD_i for median TTP $_i$s not available. Fixed and random effects estimates therefore computed assuming either by assuming $SD_i = 1.1 \times X_i$ based on data on ratio of SD:Mean (1/coefficient of variation [CV]) of KM estimated PFS for C-only (1.1) and C+L (1.1) in EGF100151.

Table 8. Derivation of hazard ratios and standard errors based on median TTP: updated sample

	Median TTP				**Implied HR vs C+L**			
			95%CI				**95%CI**	
Method	**Est**	**SE**	**Lower**	**Upper**	**Est**	**SE**	**Lower**	**Upper**
Unweighted	24.4	2.2	20.3	29.1	0.77160	0.07118	0.64742	0.92736
Weighted	**27.0**	**2.0**	**23.3**	**31.1**	**0.69814**	**0.05136**	**0.60637**	**0.80812**
Fixed Effects	20.8	1.1	18.8	23.0	0.90549	0.04586	0.82112	1.00108
Random Effects	20.8	1.1	18.8	23.0	0.90549	0.04586	0.82112	1.00108

95%CI for median TTP calculated assuming lognormal distribution. Implied HR vs C-only (and associated 95CIs) obtained by solving for value in PH weibull function that yields median TTP. SE of implied HRs obtained by taking natural log of HRs and associated 95%CI and calculating implied SE (equal to [Est-95%CI-L]/normsinv(0.975).

C-Only PFS gamma:	1.392
C-Only PFS lambda:	0.006

Appendix 3

Details of minor corrections to the economic model

A3.1 – Discounting of (Post progression Survival) PPS with trastuzumab – based therapy under assumption that PPS with trastuzumab – based therapy is equal to that for lapatinib plus capecitabine

In the base-case, we assumed that PPS with trastuzumab -based therapies would be equal to that of lapatinib plus capecitabine. However, in the original model, we failed to account for the difference in discounting of PPS due to the differences in TTP with trastuzumab -based therapy vs. lapatinib plus capecitabine. Because progression occurs earlier with trastuzumab than with lapatinib plus capecitabine, expected PPS with trastuzumab should be slightly less discounted than that with lapatinib plus capecitabine. In essence discounted PPS with trastuzumab should be slightly greater than that with lapatinib plus capecitabine.

Accordingly, in the updated model, under the assumption that PPS with trastuzumab -based therapy is equal to that for lapatinib plus capecitabine, the discounted expected PPS with trastuzumab -based therapy is equal to the discounted expected PPS with lapatinib plus capecitabine multiplied by the ratio of the discount factor (i.e., $(1+\text{discount rate})^{-t}$) at the mean time to progression for trastuzumab -based therapy to the discount factor at the mean time to progression for lapatinib plus capecitabine.

A3.2 Disutility for disease progression.

The original submission used a value of 31.9%. The current model uses a value of 32.0%. This difference appears to be due to rounding. The exact value calculated from the Lloyd study (to 5 decimals) is 31.95245%. Therefore, 32.0% is marginally more accurate.

A3.3 Hazard ratio for PFS with trastuzumab-based regimens.

The original submission used a value of 0.870. The current model uses a value of 0.86396 (to 5 decimals). This difference is due to rounding. The original pooled median TTP with trastuzumab-based therapy was estimated to be 21.83491 weeks (to 5 decimals). The corresponding estimate of the HR for trastuzumab vs. capecitabine-only is 0.86396 (to 5 decimal places). Using a value of 21.80_ weeks (as reported in the submission), the corresponding estimate for the HR for trastuzumab vs. capecitabine-only is 0.86535 (to 5 decimals), which rounds to 0.870. Therefore, the current estimate of 0.86396 (to 5 decimals) is more accurate.

A3.4 Costs of wastage of capecitabine in T+C strategy.

In the original submission, the cost of wastage for capecitabine in the trastuzumab plus capecitabine strategy was calculated incorrectly, with wastage for capecitabine calculated using the vials calculation instead of assuming a proportion of the final prescription. The new model results are correct.

Appendix 4

Methods for estimation of hazard ratios from study GBG 26 for trastuzumab plus capecitabine versus capecitabine only, for economic modelling

Please note that shaded text and figures 1-4 should be treated as academic 'in confidence'

Background

In the evaluation of the cost-effectiveness of lapatinib in the treatment of women with HER2+ MBC who had received prior treatment with an anthracycline, a taxane and trastuzumab, submitted as part of GSK's original submission to NICE in April 2007, we compared the cost-effectiveness of lapatinib plus capecitabine (L+C) versus C-only based on effectiveness data from the EGF100151 trial. To obtain estimates of effectiveness for L+C and C-only, we fit PH Weibull survival functions to patient-level failure-time data on PFS and OS from the EGF100151 trial.

We also conducted an indirect comparison of the cost-effectiveness of L+C versus TZ as monotherapy (TZ-only), or in combination with capecitabine (TZ+C) or vinorebline (TZ+V). Lacking data from head-to-head studies, we estimated the clinical effectiveness of TZ-based therapies based on a pooled estimate of median TTP / PFS with continued TZ in prospective and retrospective cohort studies of this treatment strategy (TTP and PFS were assumed to be similar in this population). While the use of effectiveness data from non-comparative studies may be necessary in the absence of head-to-head trials, results of the GBG 26 / BIG 3-05 trial, a head-to-head comparison of TZ+C versus C-only in HER2+ trastuzumab-refractory patients, have recently become available (1,2). Accordingly, the purpose of this analysis was to estimate HRs for TZ+C versus C-only for PFS/TTP and OS using data from the GBG 26 /BIG 3-05 trial and methods similar to those employed to estimate the PFS and OS for L+C versus C-only from the EGF100151 data (i.e., PH Weibull survival models) for use in an updated evaluation of the cost-effectiveness of lapatinib.

The GBG 26 / BIG 3-05 study

The GBG 26 / BIG 3-05 study was a randomized controlled trial of TZ+C vs. C-only in women with HER2+ MBC who had received at least one prior course of TZ and no more than one prior course of palliative chemotherapy (CT). In both groups, capecitabine (C) was administered 2500 mg/m² on days 1-14, q21 days. Patients randomized to TZ+C also received TZ 6 mg/kg q3 weeks. The study was planned to recruit 241 pts per arm to show an improvement from 4 to 5.1 months (hazard ratio 0.8) from continuing TZ. However, the trial was closed end of May 2007 on advice of the Independent Data Monitoring Committee after having recruited only 156 patients because of slow accrual. Preliminary results of the GBG 26 / BIG 3-05 study based on a median of 11.8 months of follow-up were presented at the 2007 San Antonio Breast Cancer Symposium (SABCS) (1). Results based on 15.6 months of follow-up were subsequently presented at the 2008 American Society of Clinical Oncology (ASCO) Annual Meeting (2). Results for PFS, TTP, and OS reported at SABCS 2007 and ASCO 2008 are summarized in Table1 below.

Table 1. Summary of results from GBG 36 / BIG 3-05

		SABCS 2007				ASCO 2008			
Outcome	**Treatment**	**Median**	**p**	**HR[1]**	**p**	**Median**	**p**	**HR[1]**	**P**
PFS	T+C	8.5	nr	0.71	nr	Nr	nr	nr	Nr
	C-only	5.6				Nr			
TTP	T+C	Nr	nr	Nr	nr	8.2	0.0338	0.69	0.034
	C-only	Nr				5.6			
OS	T+C	20.3	nr	0.79	nr	25.5	0.257	0.76	0.26
	C-only	19.9				20.4			

nr=not reported

[1]From Cox proportional hazard regression model.

It should be noted that PFS and OS were reported at SABCS 2007 whereas TTP and OS were reported at ASCO 2008. No statistical testing was reported for results in the SABC 2007 poster.

Methods

We estimated the three parameters of PH Weibull models for T+C and C-only for TTP (λ^{TTP}, γ^{TTP}, $HR^{TTP}_{T+C\ vs\ C\text{-}only}$) and OS ($\lambda^{OS}$, γ^{OS}, $HR^{OS}_{T+C\ vs\ C\text{-}only}$) in GBG 26 / BIG 3-05 using Accelerated Failure Time (AFT) regression (SAS PROC LIFEREG) and product-limit survival estimates for TTP and OS reported at ASCO 2008.[1] We used data from the ASCO 2008 poster because these data were based on complete follow-up (median 15.6 months). Although the ASCO 2008 poster reported only TTP and not PFS, it was reasonable to approximate PFS with TTP, because in patients with MBC, deaths from causes other than breast cancer are rare. Also, as shown in Table 1 above, the effect of T+C versus C-only on TTP reported at ASCO 2008 (HR=0.69) was similar to that reported for PFS at SABC 2007 (HR=0.71). Product limit survival estimates for TTP and OS in GBG 36 / BIG 3-05, reproduced from Figures 5 and 6 of the ASCO 2008 poster, are shown in Figures 1 and 2 below.

[1] It should be noted that the HR obtained from the PH Weibull AFT regression model does not necessarily equal that obtained from Cox PH regression model.

Figure 1. TTP in GBG 26/ BIG 3-05 trial: Figure 5 in ASCO 2008 poster

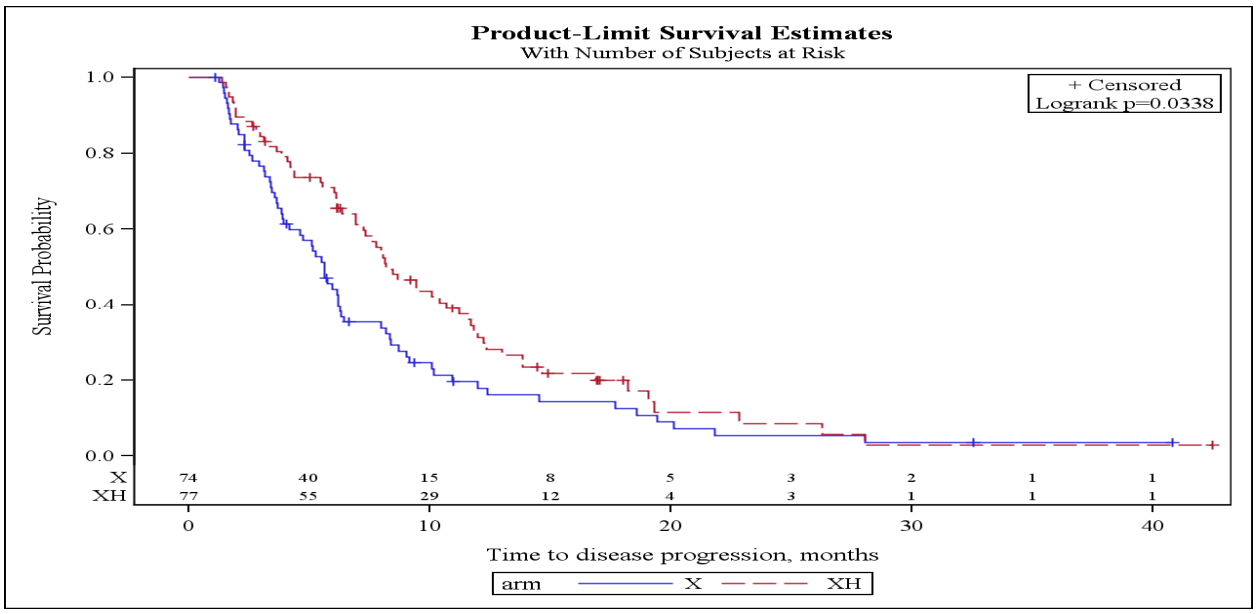
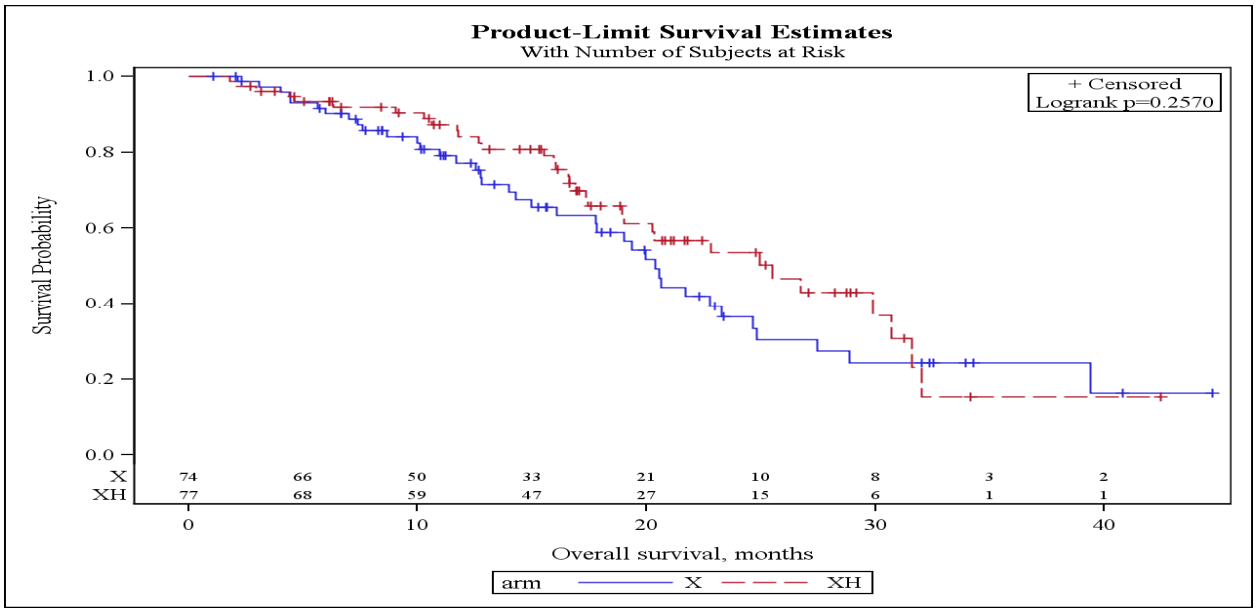


Figure 2. OS in GBG 26/ BIG 3-05 trial: Figure 5 in ASCO 2008 poster



Patient-level failure time data for TTP and OS were obtained by first digitizing the survival proportions and censoring times for TTP and OS reported in Figures 5 and 6 of the GBG 26 / BIG 3-05 2008 ASCO poster using digitizing software (XY extract). These data were then combined with information on numbers of subjects at risk at five month intervals of follow-up (as reported in each figure) to approximate the analytic data sets that were used to generate the figures (i.e., for each patient in the trial, a failure time and censoring variable were created). Ambiguity in censoring times was resolved using the Microsoft Excel Solver assuming that censoring events

would be distributed uniformly across five month time intervals. Product-limit estimated TTP and OS obtained from these replicate datasets are shown in Figures 3 and 4 below. These figures closely match those reported in the 2008 ASCO poster (Figures 1 and 2 above [original Figures 5 and 6 in the poster]).

Figure 3. Product limit estimated TTP generated from replicated GBG 26/ BIG 3-05 dataset

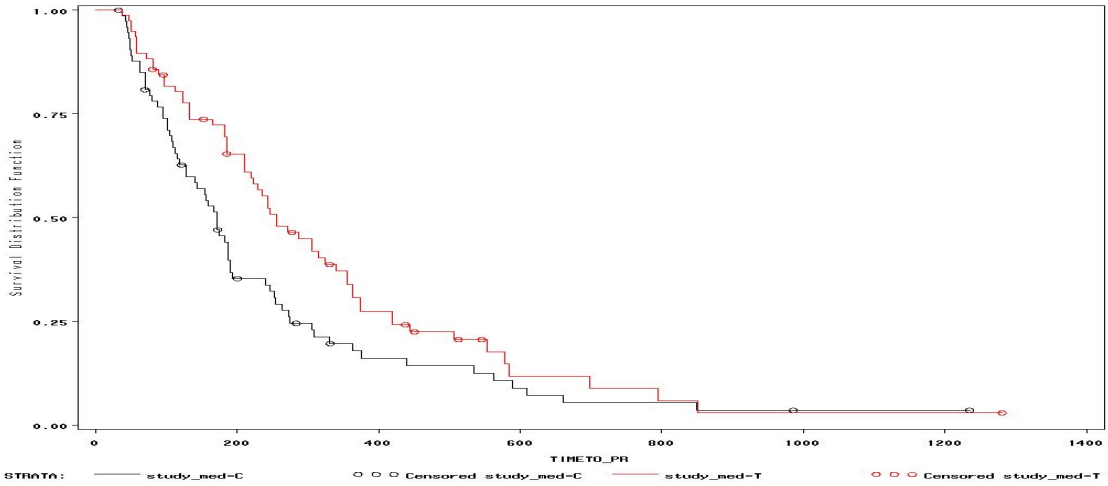
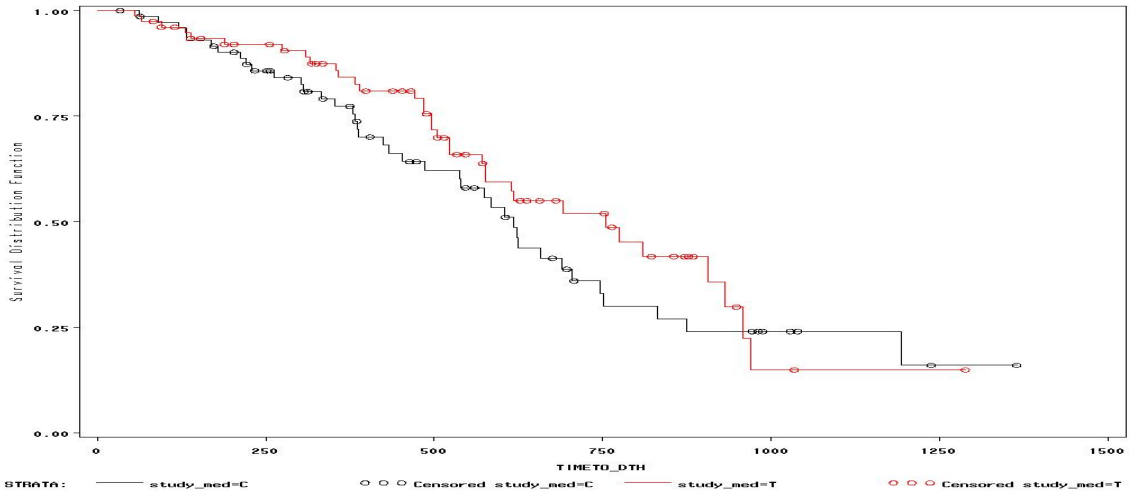


Figure 4. Product-limit estimated OS generated from replicated GBG 26/ BIG 3-05 dataset



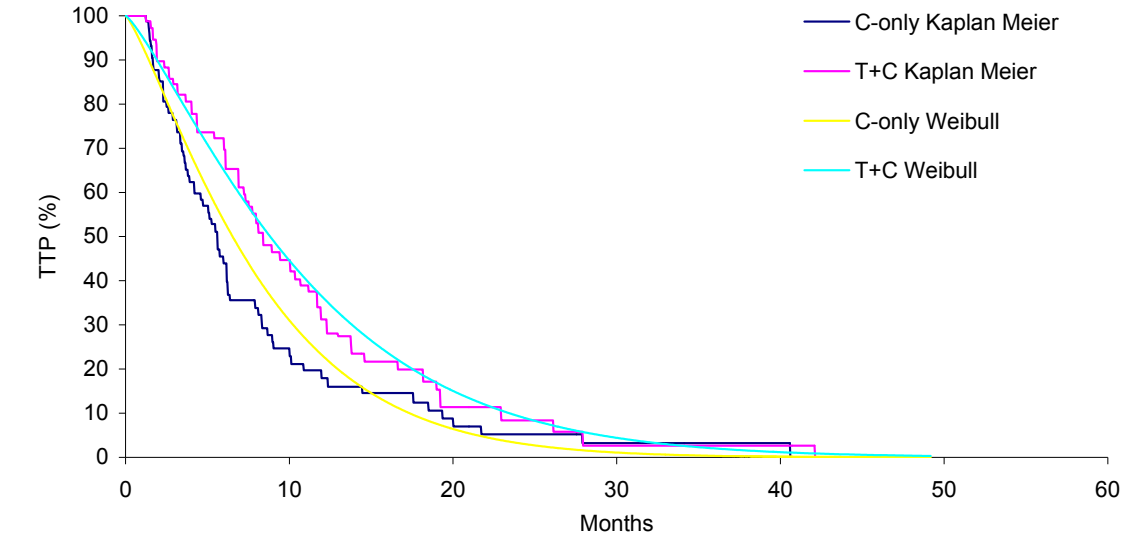
These replicate datasets were then analyzed using AFT regression (SAS PROC LIFEREG) to obtain parameters of the Weibull distributions for TTP and OS. These parameters are shown in Table 2 below.

Table 2. Parameters of Weibull Model from Von Minckwitz

	TTP		OS	
	Estimate	**SE**	**Estimate**	**SE**
AFT model output (from SAS)				
Intercept	5.8913	0.1043	6.8014	0.1027
Estimate $_{L+C \text{ vs. } C\text{-only}}$	0.3015	0.1457	0.1397	0.1368
Scale	0.8131	0.0536	0.5788	0.0539
Survival function parameters				
λ	0.003736	0.000390	0.001279	0.000131
γ	1.229861	0.081073	1.727713	0.160891
HR $_{L+C \text{ vs } C\text{-only}}$	0.739708	0.107775	0.869619	0.118964
γ =1/scale. λ =exp(Intercept + Estimate $_{L+C \text{ vs } C\text{-only}}$). HR=exp(Estimate$_{L+C \text{ vs. } C\text{-only}}$)				

Comparisons of the PH Weibull and Kaplan-Meier (Product Limit) estimated TTP and OS from GBG 26 /BIG 3-05 are shown in Figures 5 and 6 below. The fitted models match the empirical survival distributions well. Measured in terms of the "area under the curve", expected TTP is 35.6 weeks for TZ+C and 47.3 weeks for C-only based on the Kaplan-Meier estimates (difference=11.7 weeks). Based on the the PH Weibull model, expected TTP is 35.8 weeks for TZ+C and 48.4 weeks for C-only (difference=12.6 weeks). Measured out to 42.3 months (maximum follow-up in GBG 26/BIG 3-05) expected OS is 106 weeks for TZ+C and 97 weeks for C-only based on the Kaplan-Meier estimates (difference=9 weeks). Based on the Weibull model, expected OS is 96 weeks for TZ+C and 107 weeks for C-only (difference=11 weeks).

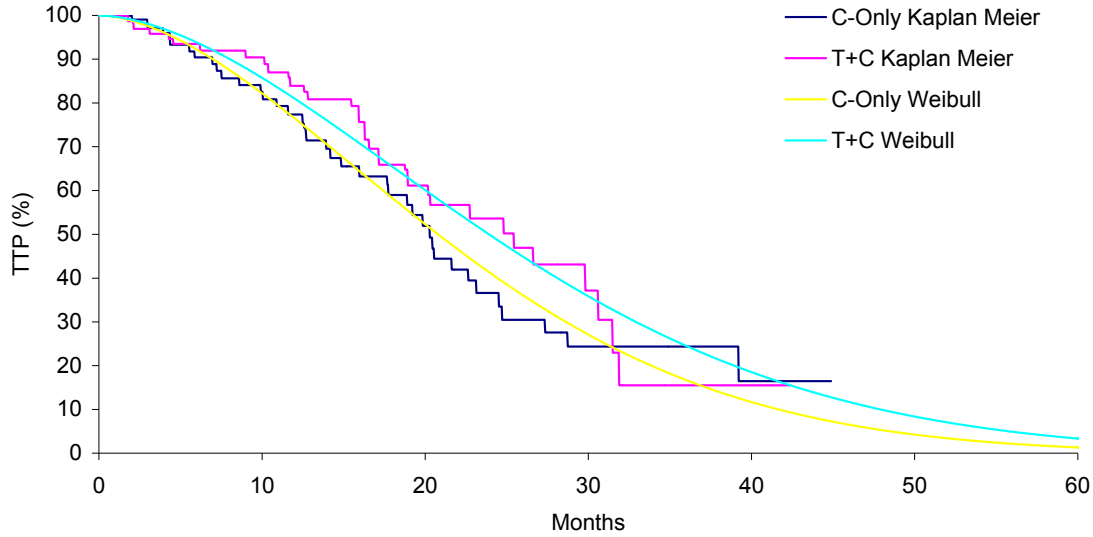
Figure 5. Kaplan-Meier and PH Weibull estimated TTP from GBG 26 /BIG 3-05



No. at Risk

T+C	74	15	5	2	1	0
C-only	77	29	4	1	1	0

Figure 6. Kaplan-Meier and PH Weibull estimated OS from GBG 26 /BIG 3-05



No. at Risk						
T+C	74	50	21	8	2	0
C-only	77	59	27	6	1	0

DISCUSSION

Using data from GBG 26 / BIG 3-05 and AFT regression, we estimated the PH Weibull HR for T+C versus C-only for TTP to be 0.740; the corresponding figure for OS was 0.870. This compares with estimates of 0.608 for PFS and 0.834 for OS for L+C vs C-only using similar methods and data from EGF100151.

In the hierarchy of research designs, the results of randomized, controlled trials are considered to be evidence of the highest grade (3). According to NICE, data from head-to-head trials should be presented in the reference-case analysis, if available (4). Glenny and colleagues describe an approach recommended by NICE for conducting indirect comparisons which involves approximating a direct comparison by comparing HRs with a respect to common control group (5). The use of data from GBG 26 /BIG 3-05 are consistent with this approach as this trial compared T+C to a control arm similar to that with which L+C was compared in EGF100151 (i.e., C-only).

The use of HRs for T+C vs C-only estimated from GBG 26/BIG 3-05 in an indirect comparison with L+C is not without limitations, however. Specifically, patients in the EGF100151 study were more advanced/refractory than those in the GBG 26/BIG 3-05 study as evidenced by the fact that 98% of patients in the GBG 26/BIG 3-05 study were receiving 2nd line CT whereas 50% of those in the EGF100151 trial had received ≥4 prior lines of CT. This difference in patient populations is reflected in the study outcomes. In the EGF 100151 trial, median PFS with C-only was 17.6 wks (4.1 months) whereas in the GBG 26 / BIG 3-05 trial, median PFS C-only was 24.3 wks (5.6 months). Similarly, median OS for C-only in the EGF100151 trial (Sep2007 data) was 64.7 wks (14.9 months) whereas median OS in the GBG 26/BIG 3-05 trial was 88.6 wks (20.4 months).

While it is clear therefore that the population in the EGF100151 study was more refractory than that in the GBG 26/BIG 3-05 trial, and that an indirect comparison of survival times for PFS or OS with L+C from EGF100151 with that for TZ+C from GBG 26/BIG 3-05 may be biased, only the HRs for TZ+C vs. C-only for TTP and OS from the GBG 26/BIG 3-05 trial are to be used in the economic comparison,

consistent with the approach recommended by Glenny and colleagues (5). So the key question is whether the effect of HER2-targeted treatment, expressed in terms of a relative hazard (i.e., HR) for progression or death compared with C-only, is affected by the "refractoriness" of disease. While the possibility of such an interaction must be recognized, we know of no data to support such a hypothesis for either TZ or lapatinib.

Another issue concerning the GBG 26 / BIG 3-05 data relates to the fact that since the enrolment was terminated early, there are some differences across treatment groups in the baseline characteristics of the enrolled subjects. In particular, age was a mean of 59 years in those receiving C-only and a mean of 52.5 years in those receiving TZ+C. Although no p-value was provided, assuming an SD of age of 10 years, similar to that in EGF100151 and consistent with the age-range reported for GBG 26 / BIG 3-05, this difference of 6.5 years in mean age is likely to be statistically significant (mean age was 2.1 years greater with L+C vs. C-only in EGF100151; this difference was not statistically significant). While there is a possibility of bias due to differences in age between treatment groups in the GBG 26/BIG 3-05 study, we know of no data to support the hypothesis of worsening outcomes by age among women with HER2+ MBC. In the Cox proportional hazards regression models on TTP and OS conducted for EGF100151, age was not a significant predictor of either TTP or OS.

Finally, it should be noted that we used data from GBG 26/BIG 3-05 on TTP and propose that the HR for T+C vs C-only for TTP be used to approximate the HR for T+C vs. C-only for PFS. We used data on TTP for T+C vs. C-only because data on PFS were not reported in the final analysis of data from the GBG 26/BIG 3-05 study. We believe this is reasonable, as the effect of T+C versus C-only on TTP based on final analysis of 15.6 months follow-up (HR=0.69) was similar to that reported for PFS based on preliminary analysis of 11.8 months follow-up (HR=0.71). In EGF100151 the HR for L+C vs C-only for independently-assessed TTP (HR=0.57) was similar to that for independently assessed PFS (HR=0.55).

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4. National Institute for Health and Clinical Excellence, Guide to the methods of technology appraisal. June 2008.
5. Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, Bradburn M, Eastwood AJ; International Stroke Trial Collaborative Group. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv.

Appendix 5.

Probabilistic sensitivity analyses for Scenarios 6 and 9

Scenario 6
- new lapatinib price £11.49**;**
- Sep2007 OS from EGF100151;
- HRs for trastuzumab regimens for PFS and OS from GBG 26/BIG 3-05;
- trastuzumab dosage 2 mg/kg/d q1w;
- wastage included as in original model)

Scenario 9 - as per Scenario 6 but:
- assuming 88.4% patients receive trastuzumab 6 mg/kg/d q3w and 11.6% trastuzumab receive it 2 mg/kg/d q1w;
- 15% trastuzumab wastage calculated by inflating trastuzumab costs by 100/85

A5.1. Summary results

Table 1. Summary of PSA results: Scenarios 6 and 9 - Capecitabine monotherapy

	Scenario 6	Scenario 9
ΔCost, £	14,015	14,015
95%CI	(9,710, 18,449)	(9,710, 18,449)
ΔQALY	0.1494	0.1494
95%CI	(-0.031, 0.339)	(-0.031, 0.339)
ΔCost/ΔQALY, £	93,825	93,825
95%CI	(37,138, Dominated)	(37,138, Dominated)
Quadrant of cost-effectiveness plane		
NE (Cost>0, QALYs>0)	94.4%	94.4%
SE (Cost<0, QALYs≥0, or Costs=0, QALYs>0; dominant)	0.0%	0.0%
SW (Cost<0, QALYs<0)	0.0%	0.0%
NW (Cost>0, QALYs≤0 or Cost=0, QALYs<0 ; dominated)	5.6%	5.6%
Probability Lapatinib preferred | WTP (£) for QALY, %		
5,000	0%	0%
10,000	0%	0%
15,000	0%	0%
20,000	0%	0%
25,000	0%	0%
30,000	2%	2%

Table 2. Summary of PSA results: Scenarios 6 and 9 - Vinorelbine monotherapy

	Scenario 6	Scenario 9
ΔCost, £	11,726	11,726
95%CI	(7,571, 16,296)	(7,571, 16,296)
ΔQALY	0.1494	0.1494
95%CI	(-0.015, 0.356)	(-0.015, 0.356)
ΔCost/ΔQALY, £	78,503	78,503
95%CI	(31,314, Dominated)	(31,314, Dominated)
Quadrant of cost-effectiveness plane		
NE (Cost>0, QALYs>0)	95.9%	95.9%
SE (Cost<0, QALYs≥0, or Costs=0, QALYs>0; dominant)	0.0%	0.0%
SW (Cost<0, QALYs<0)	0.0%	0.0%
NW (Cost>0, QALYs≤0 or Cost=0, QALYs<0 ; dominated)	4.1%	4.1%

Probability Lapatinib preferred | WTP (£) for QALY, %		
5,000	0%	0%
10,000	0%	0%
15,000	0%	0%
20,000	0%	0%
25,000	1%	1%
30,000	6%	6%

Table 3. Summary of PSA results: Scenarios 6 and 9 - Trastuzumab plus vinorelbine

	Scenario 6	**Scenario 9**
ΔCost, £	-8,958	-3,583
95%CI	(-19,890, -42)	(-13,258, 3,802)
ΔQALY	0.0263	0.0263
95%CI	(-0.292, 0.257)	(-0.272, 0.269)
ΔCost/ΔQALY, £	dominant	dominant
95%CI	Undefined	Undefined
Quadrant of cost-effectiveness plane		
NE (Cost>0, QALYs>0)	1.8%	9.9%
SE (Cost<0, QALYs≥0, or Costs=0, QALYs>0; dominant)	55.3%	47.1%
SW (Cost<0, QALYs<0)	42.2%	36.4%
NW (Cost>0, QALYs≤0 or Cost=0, QALYs<0 ; dominated)	0.7%	6.6%
Probability Lapatinib preferred | WTP (£) for QALY, %		
5,000	97%	84%
10,000	97%	84%
15,000	97%	83%
20,000	96%	82%
25,000	95%	80%
30,000	93%	78%

Table 4. Summary of PSA results: Scenarios 6 and 9 - Trastuzumab plus capecitabine

	Scenario 6	**Scenario 9**
ΔCost, £	-6,450	-1,075
95%CI	(-17,689, 1,039)	(-9,523, 5,439)
ΔQALY	0.0263	0.0263
95%CI	(-0.278, 0.292)	(-0.291, 0.282)
ΔCost/ΔQALY, £	dominant	dominant
95%CI	Undefined	Undefined
Quadrant of cost-effectiveness plane		
NE (Cost>0, QALYs>0)	3.5%	21.3%
SE (Cost<0, QALYs≥0, or Costs=0, QALYs>0; dominant)	55.1%	32.6%
SW (Cost<0, QALYs<0)	39.6%	30.7%
NW (Cost>0, QALYs≤0 or Cost=0, QALYs<0 ; dominated)	1.8%	15.4%
Probability Lapatinib preferred | WTP (£) for QALY, %		
5,000	95%	64%
10,000	94%	63%
15,000	94%	63%
20,000	93%	62%
25,000	92%	63%
30,000	89%	61%

Table 5. Summary of PSA results: Scenarios 6 and 9 - Trastuzumab monotherapy

	Scenario 6	**Scenario 9**
ΔCost, £	-4,993	638

95%CI	(-15,290, 2,454)	(-7,608, 8,476)
ΔQALY	0.0263	0.0263
95%CI	(-0.273, 0.293)	(-0.274, 0.257)
ΔCost/ΔQALY, £	dominant	24,227
95%CI	Undefined	Undefined
Quadrant of cost-effectiveness plane		
NE (Cost>0, QALYs>0)	5.5%	31.2%
SE (Cost<0, QALYs≥0, or Costs=0, QALYs>0; dominant)	52.7%	26.1%
SW (Cost<0, QALYs<0)	39.1%	18.1%
NW (Cost>0, QALYs≤0 or Cost=0, QALYs<0 ; dominated)	2.7%	24.6%
Probability Lapatinib preferred | WTP (£) for QALY, %		
5,000	92%	46%
10,000	91%	46%
15,000	90%	48%
20,000	90%	49%
25,000	88%	50%
30,000	85%	52%

A5.2 Detailed probabilistic sensitivity analysis results for individual comparisons – Scenario 6

A5.2.1. Lapatinib plus capecitabine versus capecitabine monotherapy

Figure 1. Cost-effectiveness plane for lapatinib plus capecitabine versus capecitabine monotherapy

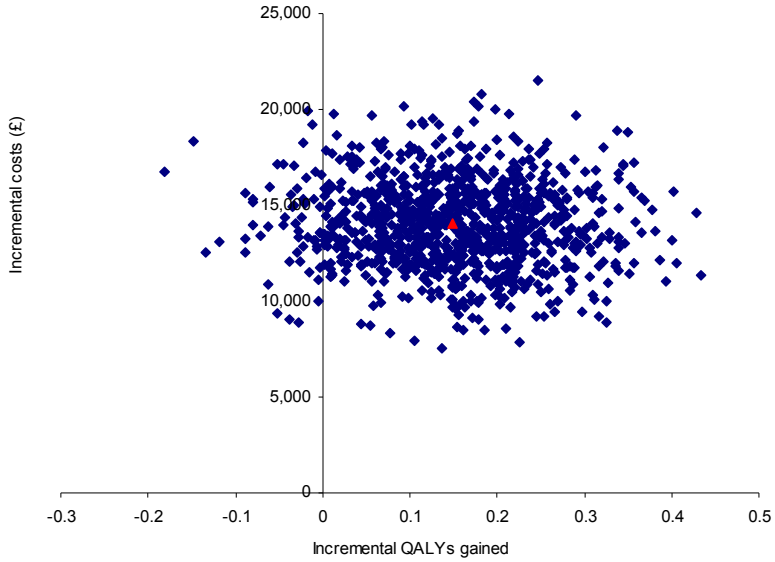
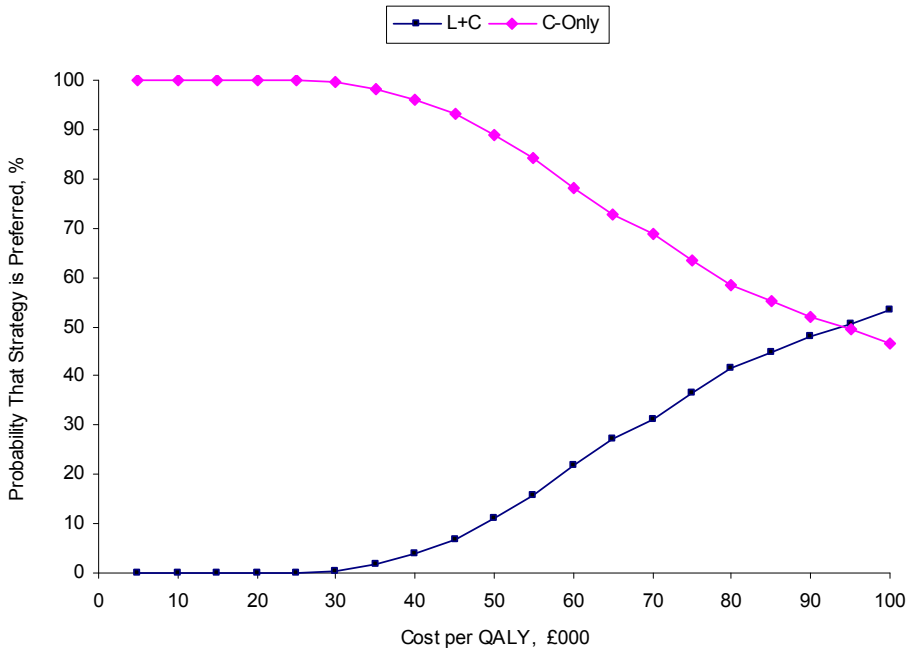


Figure 2. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus capecitabine monotherapy



A5.2.2: Lapatinib plus capecitabine versus vinorelbine monotherapy

Figure 3. Cost-effectiveness plane for lapatinib plus capecitabine versus vinorelbine monotherapy

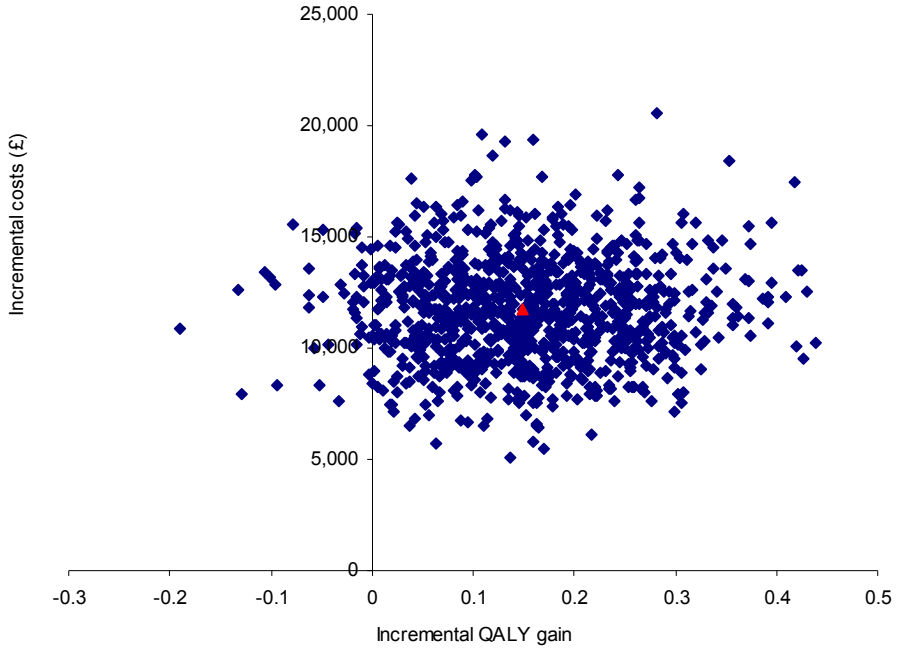
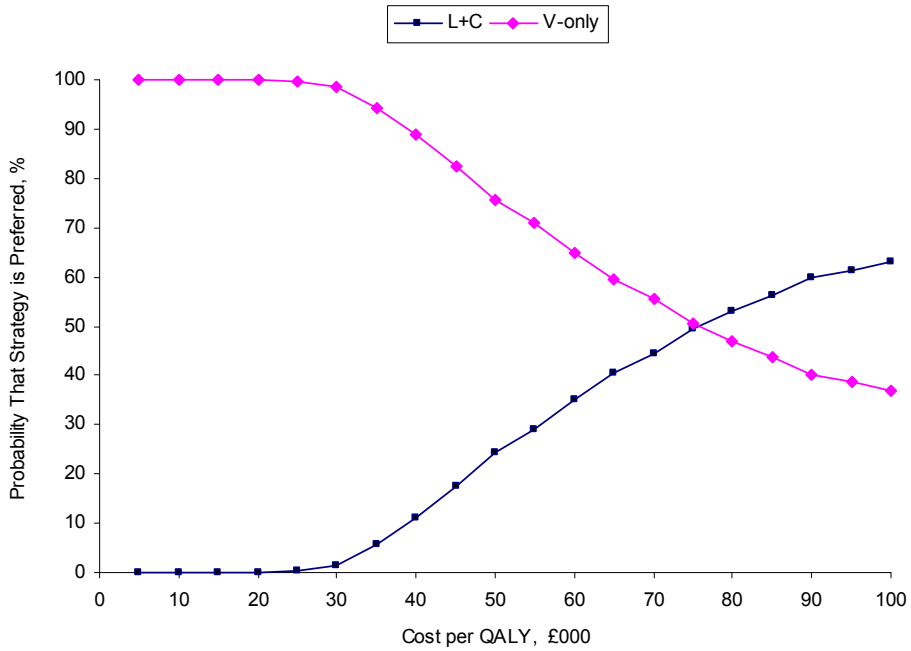


Figure 4. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus vinorelbine monotherapy



A5.2.3: Lapatinib plus capecitabine versus trastuzumab plus vinorelbine

Figure 5. Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus vinorelbine

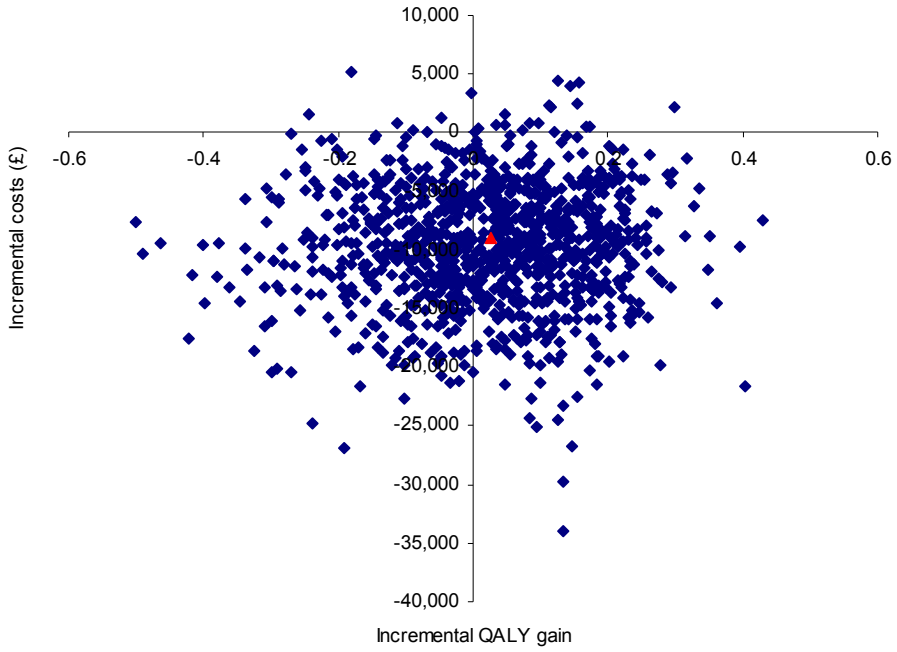
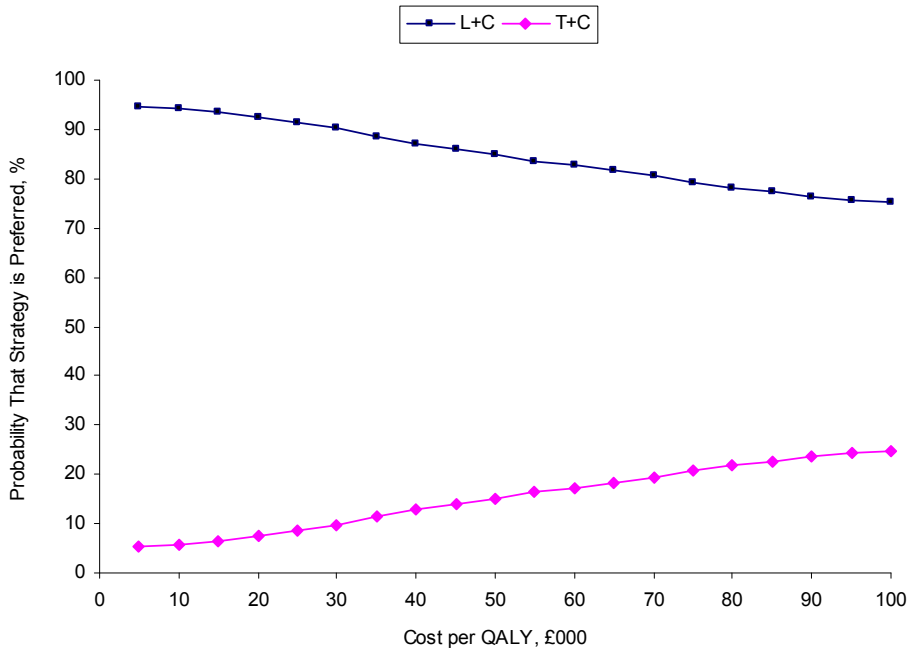


Figure 6. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus vinorelbine



A5.2.4: Lapatinib plus capecitabine versus trastuzumab plus capecitabine

Figure 7 Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus capecitabine

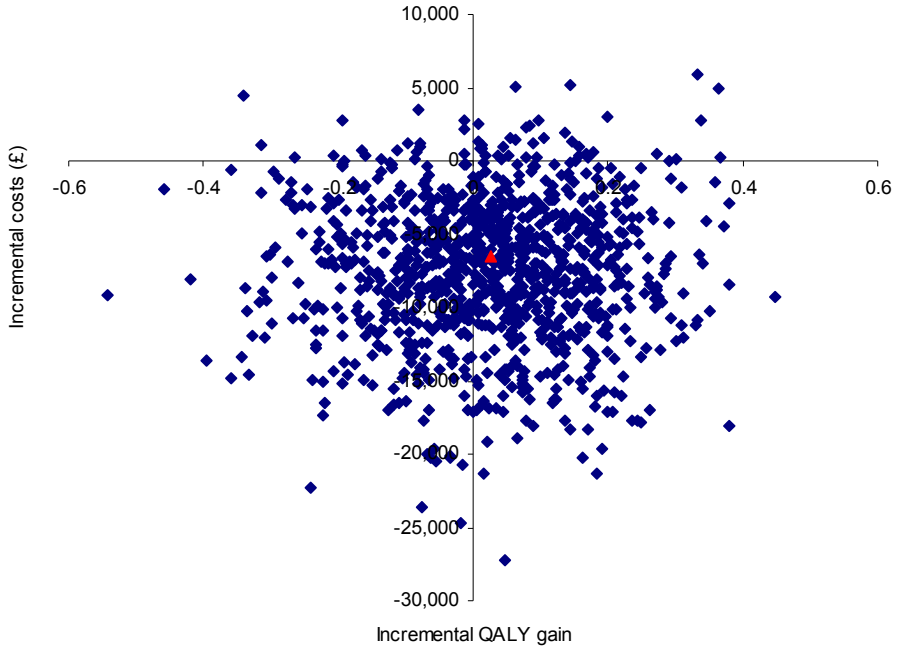
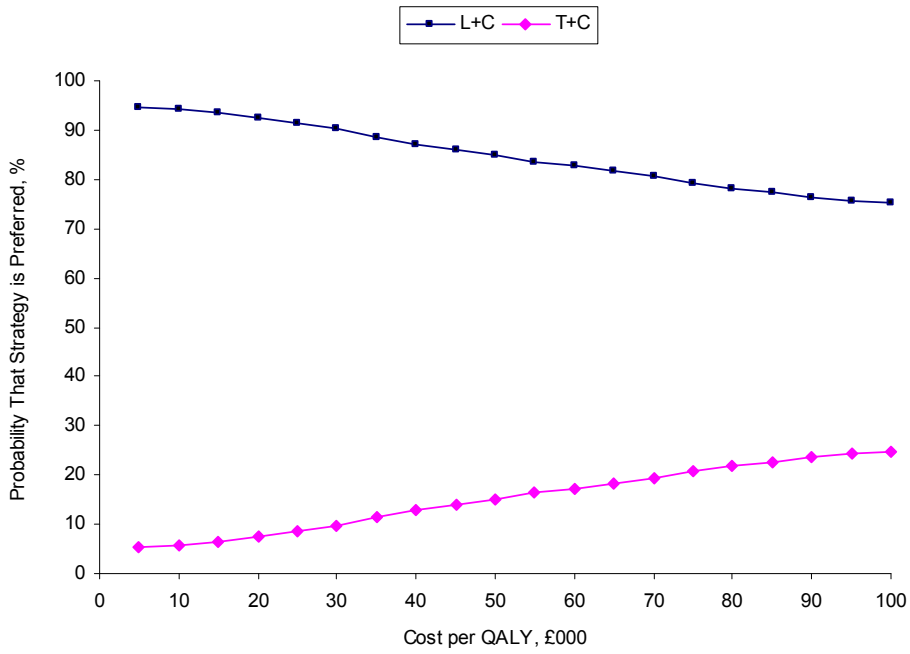


Figure 8 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus capecitabine



A5.2.5 Lapatinib plus capecitabine versus trastuzumab monotherapy

Figure 9. Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab monotherapy

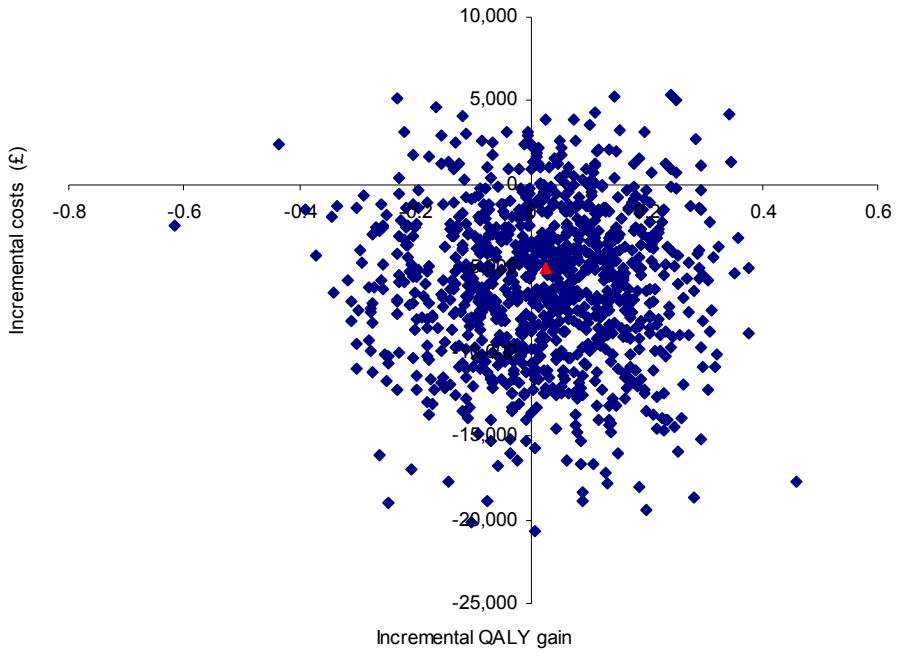
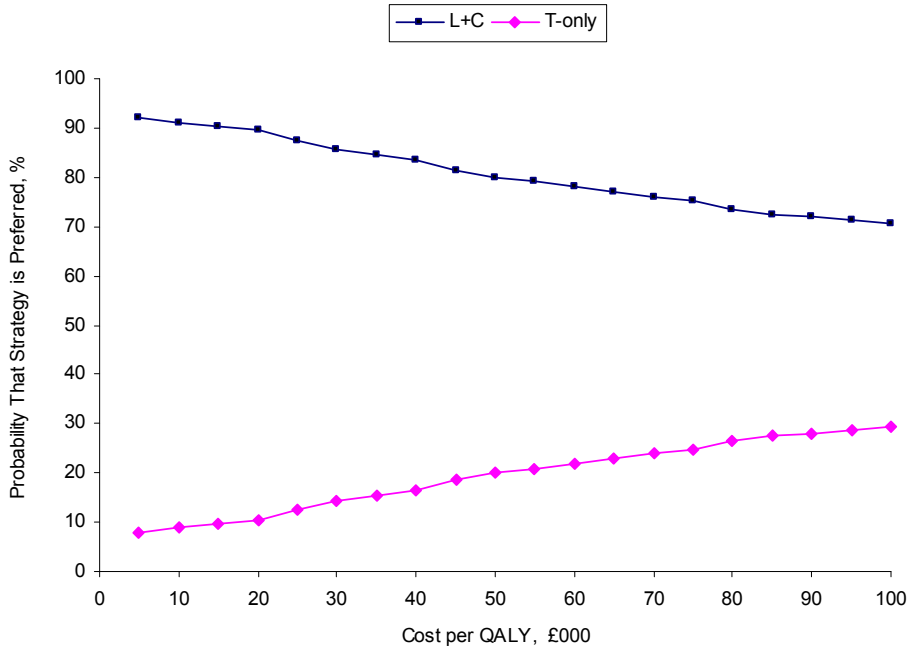


Figure 10. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab monotherapy



A5.3 Detailed probabilistic sensitivity analysis results for individual comparisons – Scenario 9

A5.2.1. Lapatinib plus capecitabine versus capecitabine monotherapy

Figure 1. Cost-effectiveness plane for lapatinib plus capecitabine versus capecitabine monotherapy

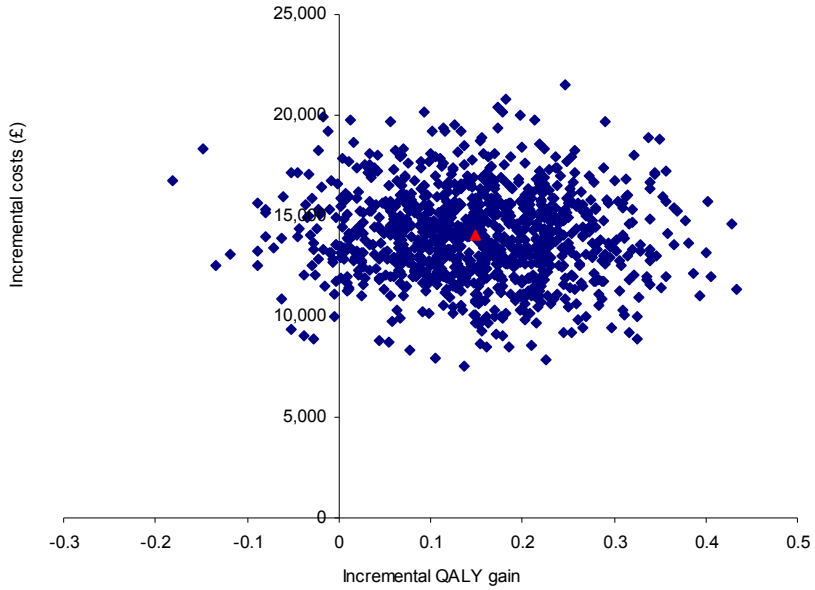
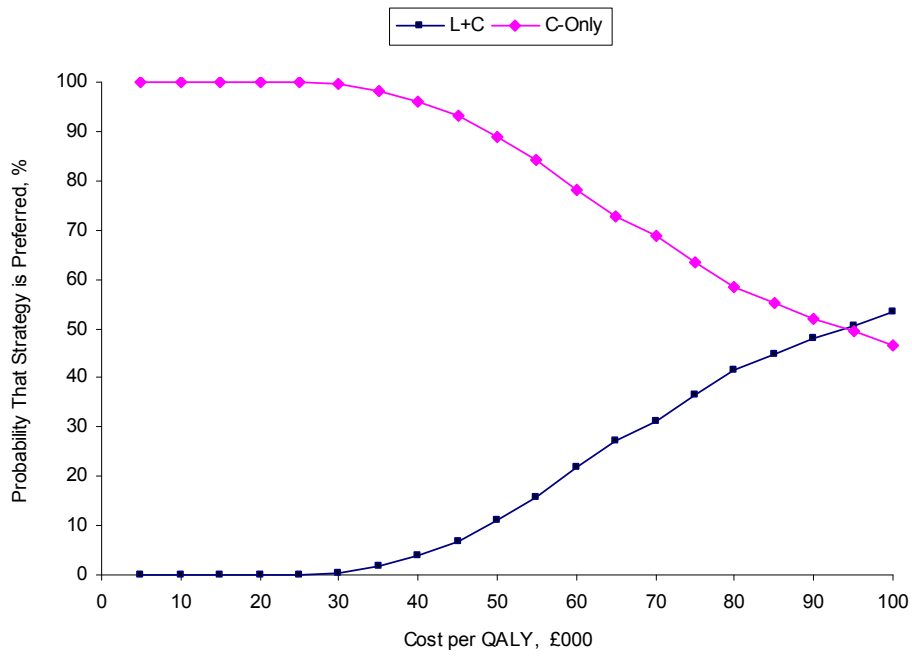


Figure 2. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus capecitabine monotherapy



A5.2.2: Lapatinib plus capecitabine versus vinorelbine monotherapy

Figure 3. Cost-effectiveness plane for lapatinib plus capecitabine versus vinorelbine monotherapy

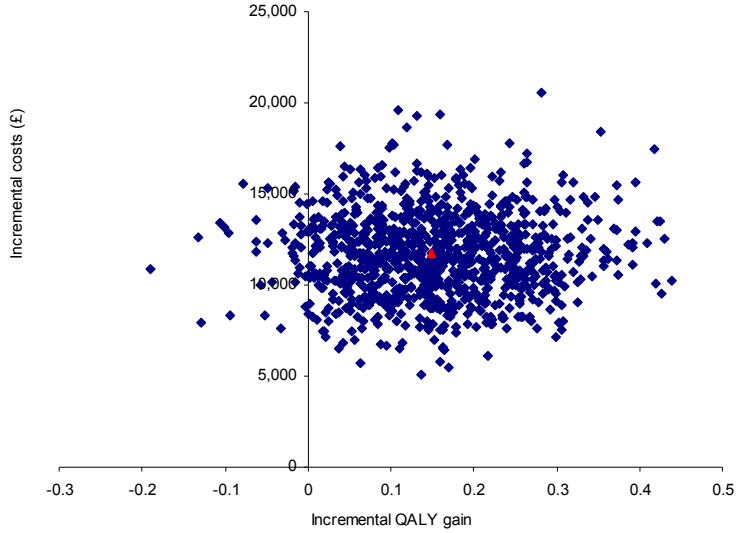
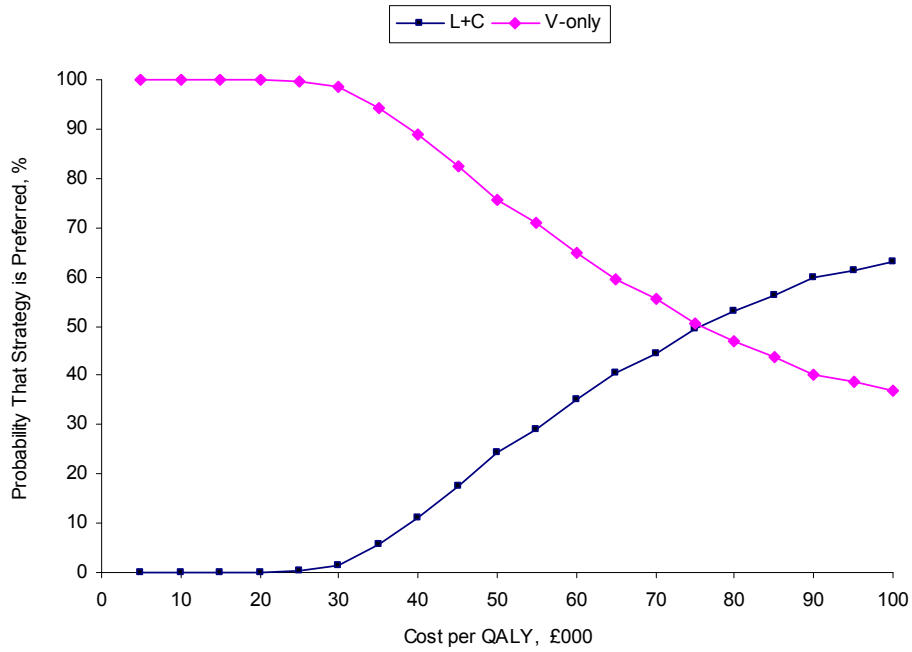


Figure 4. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus vinorelbine monotherapy



A5.2.3: Lapatinib plus capecitabine versus trastuzumab plus vinorelbine

Figure 5. Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus vinorelbine

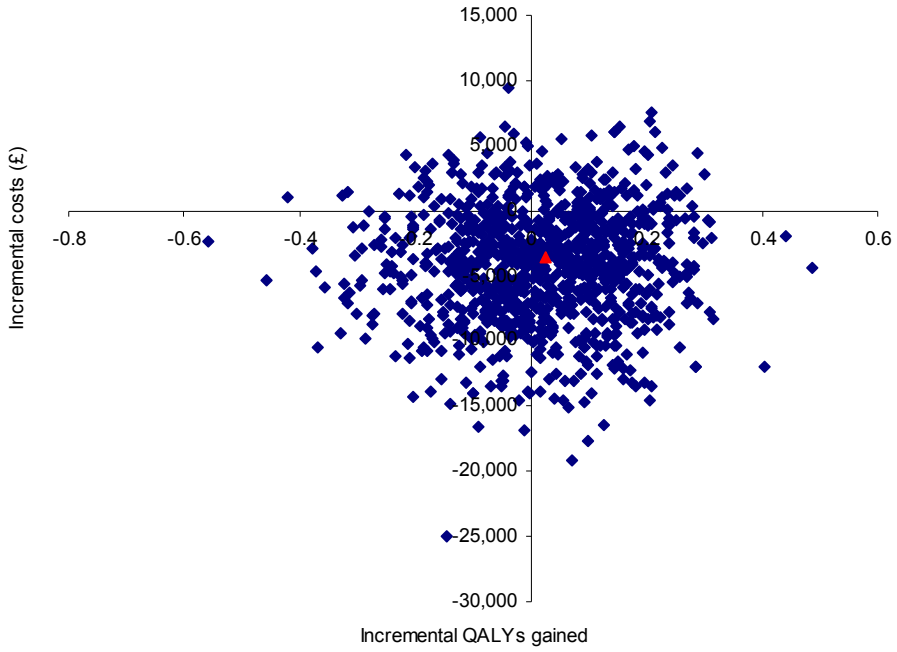
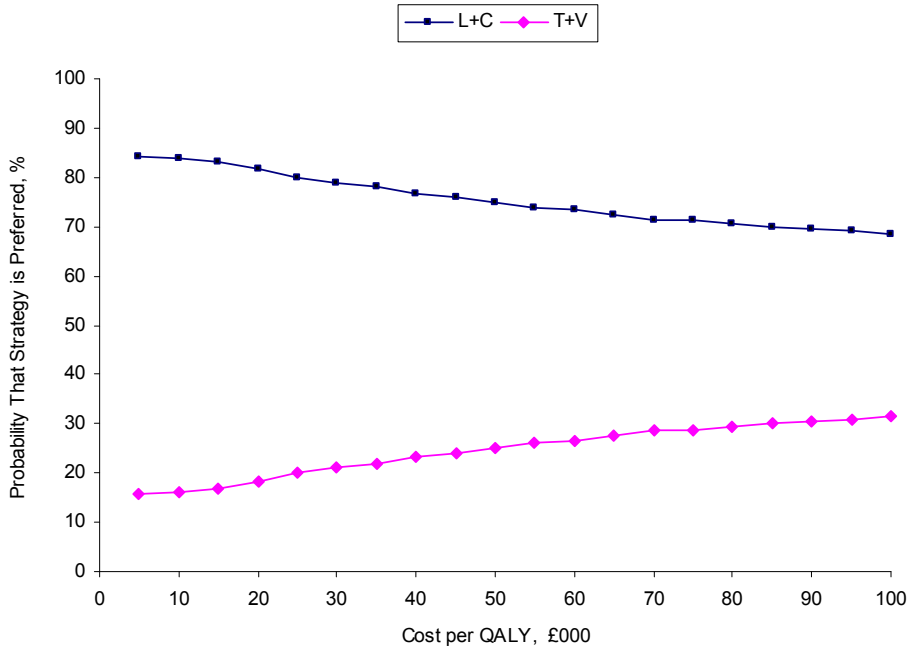


Figure 6. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus vinorelbine



A5.2.4: Lapatinib plus capecitabine versus trastuzumab plus capecitabine

Figure 7 Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus capecitabine

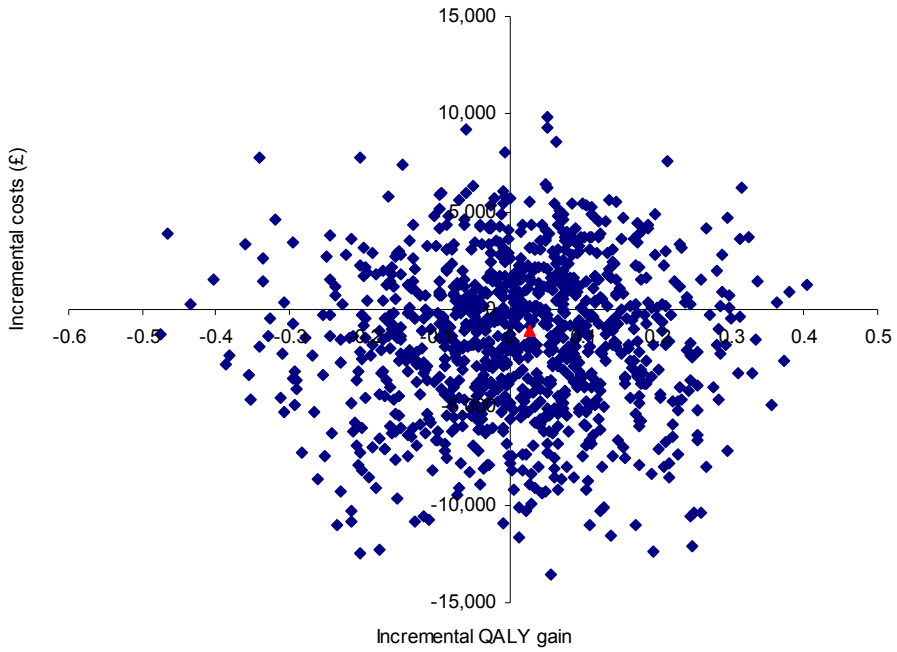
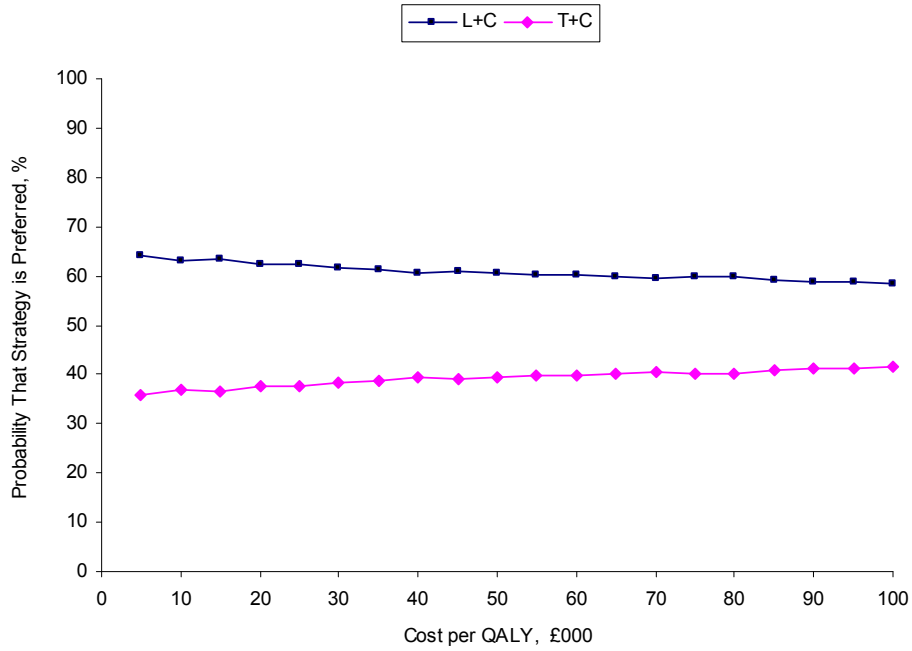


Figure 8 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus capecitabine



A5.2.5 Lapatinib plus capecitabine versus trastuzumab monotherapy

Figure 9. Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab monotherapy

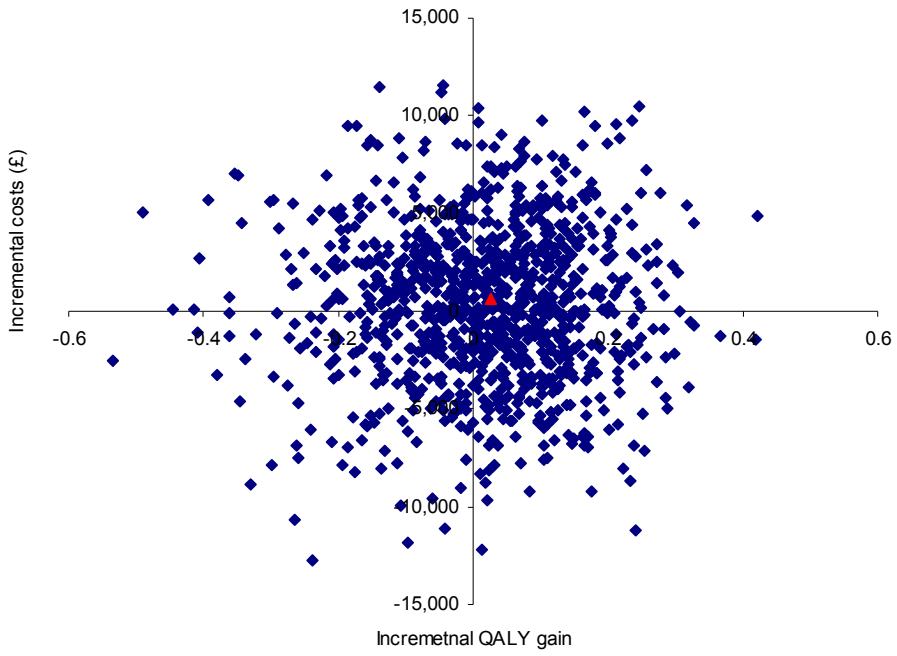


Figure 10. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab monotherapy