NHS
National Institute for Health and Clinical Excellence

Single Technology Appraisal

Eribulin for the treatment of locally advanced or metastatic breast cancer

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Eribulin for the treatment of locally advanced or metastatic breast cancer

Contents:

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Eribulin for the treatment of locally advanced or metastatic breast cancer

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

- provide a copy of the statistical analysis plan for the EMBRACE trial
- provide patient details (demographics, baseline characteristics and prior chemotherapy regimens) by each geographical region included in the EMBRACE trial
- provide tables of patient details from the EMBRACE trial (demographics, baseline characteristics and prior chemotherapy regimens [as requested above]) by treatment of physician's choice (TPC) (that is, capecitabine, vinorelbine and gemcitabine)
- clarify whether the European Medicines Agency (EMA) stipulated the use of TPC as the comparator or whether the EMA agreed that TPC was the most useful comparator
- provide information on protocol violations in the EMBRACE trial, and the number and type of violations for each arm of the trial for the whole trial population
- provide information on the post-progression treatments given to patients in both arms of the EMBRACE trial, and the number of patients who received each treatment
- provide clarification of the numbers of human epidermal growth factor receptor 2 (HER2) positive patients in each arm of the EMBRACE trial who

received pre-treatment with trastuzumab (that is, before entering the trial)

- provide further information about adverse events for the EMBRACE trial population, including a summary of treatment-emergent adverse events in the eribulin group by Common Terminology Criteria for Adverse Events (CTCAE) grade with an incidence of at least 1% in either treatment group
- update all analyses and tables in the original submission to incorporate the discounted price of eribulin (as in the Department of Health-approved patient access scheme)
- provide a revised copy of the raw trial data matrix in the submitted model (range B1221:S1985 of the 'Data trial' worksheet) with four additional columns as follows:
  - Progression-free survival days, based on investigator assessment.
  - Progression-free survival days, censored, based on investigator assessment.
  - Days on treatment.
  - Days until response occurs (for responders (complete response/ partial response) only.)

    This was to allow the ERG to be able to examine the sensitivity of model results to different assumptions about the definition of disease progression, the duration of treatment and the timing of treatment response.

Licensed indication

Eribulin (Halaven, Eisai) monotherapy was licensed by the EMA in March 2011 for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

Key issues for consideration

- Overall survival gain from region 1 clinical data is greater than the overall survival gain shown in the overall intention to treat (ITT) population analyses. Does the Committee consider the results of the subgroup analyses of region 1 or the ITT population to be most appropriate to a UK clinical setting?
- Does the Committee agree that TPC is an appropriate comparator? Are the comparisons of eribulin versus individual comparators (vinorelbine, capecitabine and gemcitabine) reliable given the small numbers of patients in each comparison and the fact that these were post-hoc exploratory analyses?
- Does the Committee consider that the trial was conducted appropriately, given the ERG's comments that there were a large number of protocol violations?
- Does the Committee consider the investigator review of progression-free survival results to be reliable given the ERG's comments that a considerable number of patients did not receive scans?
- Instead of projecting expected lifetime experience of those individuals still alive at the time of data cut-off, the manufacturer's model assumed that all such patients died at the time of censoring. Does the Committee consider that projection of overall survival data would have been more appropriate?
- Is it appropriate that the manufacturer used a single average body surface area value for all patients and did not take account of any differences between individual patients?
- Were the costs of administration and costs of best supportive care estimated appropriately?
- Does the Committee consider the manufacturer's approach to generate utility values for the economic model from the Lloyd et al. mixed model analysis results to be appropriate, particularly the method for extending the range of adverse events to be included in the analysis?

- The manufacturer populated the economic model with results of the independent review of disease progression, supplemented as necessary by investigator data to supply missing values. Does the Committee agree with this approach or consider that the investigator data should have been used instead?
- Does the Committee consider that eribulin meets the end-of-life criteria and does this depend on whether data from region 1 or the ITT population are used?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients whose locally advanced or metastatic breast cancer has progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless these treatments were not suitable for these patients.
Intervention	Eribulin monotherapy
Comparators	Treatment of physicians choice (TPC) Vinorelbine Capecitabine Gemcitabine
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life (HRQL)
Economic evaluation	Cost per quality-adjusted life year (QALY) Lifetime time horizon for estimating clinical and cost effectiveness Costs will be considered from the perspectives of the NHS and Personal Social Services

1.2 Evidence Review Group comments

1.2.1 Population

The ERG noted that the patients included in the key trial (EMBRACE) reported in the manufacturer's submission are those with locally advanced breast cancer or metastatic breast cancer (defined in the trial as locally recurrent or metastatic breast cancer) who have received between two and five prior chemotherapy treatments. Patients could have been treated with hormone therapy and patients with HER2-positive tumours could also have been treated with trastuzumab. The ERG concluded that the patient

population in the key trial was consistent with the scope issued by NICE and the eligible UK population.

The ERG noted that, in the clinical section of the submission, the manufacturer presents evidence that relates to the overall ITT trial population as well as a subgroup of the overall trial population described as region 1. Region 1 patients were those recruited in centres based in North America, Western Europe or Australia.

1.2.2 Intervention

The ERG commented that eribulin is a first-in-class anti-neoplastic agent belonging to the halichondrin class of drugs. It noted that eribulin is administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle.

1.2.3 Comparators

The ERG noted that the comparator in the manufacturer's submission is TPC, defined as any available single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care. The ERG noted the manufacturer's justification of including TPC as a comparator rather than individual anti-cancer treatments (see page 33 of the manufacturer's submission) and agreed that the TPC approach was pragmatic, in accordance with the NICE 'Guide to the methods of technology appraisal' and reflective of patient experience in England and Wales.

However, the ERG cautions that averaging the effects of a range of diverse treatments (as with TPC) will obscure patient responses to individual treatments. The ERG noted the manufacturer's subgroup analyses that compare TPC patient outcomes with the outcomes of the chemotherapy comparators (vinorelbine, capecitabine and gemcitabine) which form the basis of the manufacturer's economic case. However, the ERG noted that these subgroups are very small and the trial was not powered to detect differences

between individual treatment subgroups; therefore the ERG considers that the reliability of the results of any such analyses is questionable.

1.2.4 Outcomes

The ERG noted that the manufacturer has addressed all the outcomes stated in the scope, including overall survival, progression-free survival, objective response rate, adverse events of treatment and health-related quality of life. The ERG highlighted that the primary endpoint of the EMBRACE trial was overall survival, noting that overall survival is considered to be the most robust outcome in trials of anti-cancer treatments and that very few trials of treatments for metastatic breast cancer employ overall survival as the primary endpoint.

1.2.5 Time frame

The ERG noted that patients in the EMBRACE trial were followed up until death or study closure. At the time of the submission, 589 (77%) patients had died and the maximum duration of censored overall survival was 34.66 months (2.89 years). In the eribulin arm, the last observation was a death (uncensored) at 34.66 months. In the TPC arm, the last observation was censored (still alive) at 31.80 months; the last death (uncensored) was at 31.05 months. The ERG noted that in the manufacturer's economic model all the patients in the trial are assumed to have died at the time of the last observation (censored or uncensored).

1.3 Statements from professional/patient groups and nominated experts

Professional groups agreed that the choice of TPC as the comparator arm in the key EMBRACE trial reflects clinical practice in the UK, and that the drugs chosen by the treating physicians in this group compare well with the options used in practice. They acknowledged that it would make any direct clinical and economic comparisons difficult but highlighted that it was very unusual for a chemotherapy trial in advanced breast cancer to show an overall survival

benefit and therefore these results were a positive step forward. The professional groups also noted that the most important outcomes, overall survival and toxicity, were measured in the EMBRACE trial.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

2.1.1 Eribulin compared with TPC − the EMBRACE trial

The manufacturer's submission presented clinical-effectiveness data from one randomised controlled trial. EMBRACE was a multi-centre, phase III, open-label, randomised parallel two-arm study that evaluated the efficacy and safety of eribulin with TPC. The study included 762 patients (508 eribulin, 254 TPC) and was conducted at 135 centres in 19 countries, with 51 patients across 10 UK centres. The patients in the trial had locally advanced breast cancer or metastatic breast cancer and had previously been treated with between two and five chemotherapy regimens, including a taxane and an anthracycline; at least two regimens had to have been given for locally advanced breast cancer or metastatic breast cancer. The median age of patients was 55 years, 75.9% patients were post-menopausal and 92.3% were white. Eribulin was administered as an intravenous infusion of 1.4 mg/m^2 over 2–5 minutes on days 1 and 8 of a 21-day cycle. The primary outcome measured by the trial was overall survival and the manufacturer noted that this was particularly important in the pre-treated population because they have a short life expectancy, results are expected in a reasonable timeframe and there are very few effective next line therapies. Secondary outcome measures included progression-free survival, objective response rate (the number of patients with a confirmed complete response or confirmed partial response divided by the number of patients in the analysis population), clinical benefit rate (the number of patients with a confirmed complete response, a confirmed partial response or stable disease of at least 6 months, divided by the number

of patients in the analysis population) and duration of response (time from first documented complete response or partial response until disease progression or death from any cause).

2.1.2 Subgroup analysis in the EMBRACE trial

Patients in the EMBRACE trial were pre-stratified according to geographical region, HER2 status and prior treatment with capecitabine, and then randomised in a 2:1 ratio to receive either eribulin or TPC. Pre-planned subgroup analyses explored the effect of these strata, as well as other characteristics commonly assessed in cancer studies. Overall survival results for patients from region 1 (approximately 64% of the total population in both treatment arms) were presented separately, alongside results for the overall ITT population.

Additional post-hoc subgroup analyses were conducted to investigate the comparison of eribulin with the individual treatments within the TPC group that were defined as comparators in the NICE scope (that is, capecitabine, vinorelbine and gemcitabine). The manufacturer stated that since the TPC that patients randomised to eribulin would have received was recorded, it was possible to make comparisons between eribulin patients who would have received that TPC (if they had been randomised to that group) against those who did receive it, hence maintaining randomisation for these individual comparisons.

2.1.3 EMBRACE study results – overall EMBRACE population

The primary analysis was conducted when 55% of the patients had died and an updated analysis was conducted, as requested by the regulatory authorities, when 77% of the patients had died. The manufacturer reported that the median overall survival was significantly longer with eribulin (13.1 months) versus TPC (10.6 months). The hazard ratio for overall survival was 0.809 (95% confidence interval [CI] 0.66, 0.991; p = 0.041). This suggested that the use of eribulin reduced the hazard or risk of death by 19% compared

with TPC. The manufacturer highlighted that eribulin was the first monotherapy to provide statistically significant improvements in overall survival in pre-treated patients with metastatic breast cancer. Sensitivity analysis adjusting for the number of prior chemotherapy regimens and oestrogen receptor status was consistent with the primary analyses, with the hazard ratio favouring treatment with eribulin compared with TPC. These results were reinforced with the updated analysis, conducted when 77% of patients had died, because the median overall survival remained significantly longer with eribulin (13.2 months) versus TPC (10.5 months) with a hazard ratio of 0.805 (95% CI 0.667, 0.958; p = 0.014).

The results of all secondary endpoints were reported from the time of the primary analysis (when 55% of the patients had died). The analysis of progression-free survival indicated that median progression-free survival was significantly longer with eribulin (3.6 months) than with TPC (2.2 months), when assessed by investigator review (p = 0.002). However, the difference was not statistically significant when assessed by independent review (3.7 months with eribulin and 2.2 months with TPC; p = 0.137). The manufacturer stated that this difference arose from the censoring of almost twice as many patients in the independent review than in the investigator review. Sensitivity analyses, whereby different censoring rules were applied, reported similar results to the primary analysis.

The objective response rate was significantly different in favour of eribulin compared with TPC for the independent assessment (12.2% [95% CI: 9.4, 15.5] versus 4.7% [95% CI: 2.3, 8.4], p = 0.002) as well as for the investigator-based assessments (13.2% [95% CI: 10.3, 16.7] versus 7.5% [95% CI: 4.3, 11.9], p = 0.028). The clinical benefit rate was non-statistically significantly different in favour of eribulin compared with TPC (22.6% [95% CI: 18.9, 26.7] versus 16.8% [95% CI: 12.1, 22.5]), although the manufacturer noted that this reflects the similar proportions of patients with stable disease in the eribulin and TPC arms. The manufacturer highlighted the higher rates of complete and

partial responses in the eribulin group and contended that these suggest a clinically significant benefit of eribulin therapy. The results are presented in table 1.

Table 1 Objective response rate and clinical benefit rate (see page 65 of the manufacturer's submission)

Response category	Treatment group			
	Independent review		Investigator review	
	Eribulin (n = 468) n (%)	TPC (n = 214) n (%)	Eribulin (n = 468) n (%)	TPC (n = 214) n (%)
Complete response	3 (0.6%)	0	1 (0.2%)	0
Partial response	54 (11.5%)	10 (4.7%)	61 (13.0%)	16 (7.5%)
Stable disease	208 (44.4%)	96 (44.9%)	219 (46.8%)	96 (44.9%)
Progressive disease	190 (40.6%)	105 (49.1%)	176 (37.6%)	97 (45.3%)
Not evaluable	12 (2.6%)	3 (1.4%)	11 (2.4%)	5 (2.3%)
Unknown	1 (0.2%)	0	0	0
ORR (complete or partial response)	57 (12.2%)	10 (4.7%)	62 (13.2%)	16 (7.5%)
95% CI	(9.4 to 15.5)	(2.3 to 8.4)	(10.3 to 16.7)	(4.3 to 11.9)
p value	0.002		0.028	
Clinical benefit rate (complete or partial response, or stable disease ≥ 6 months)	106 (22.6%)	36 (16.8%)	130 (27.8%)	43 (20.1%)
95% CI	(18.9 to 26.7)	(12.1 to 22.5)	(23.8 to 32.1)	(14.9 to 26.1)

CI, confidence interval; TPC, treatment of physician's choice; ORR, objective response rate

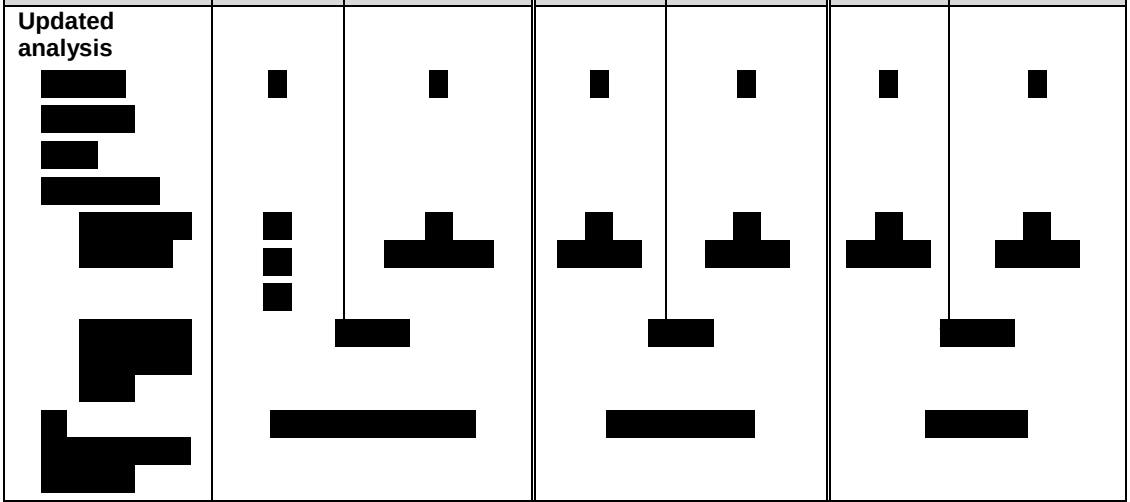
An independent assessment of the duration of response indicated that the median duration of response with eribulin (4.2 months) was not significantly different in patients treated with TPC (6.7 months). The manufacturer stated that given the small numbers of responders in the TPC group (n = 10, three of whom experienced disease progression during the study), comparison of duration of response between the two groups was not meaningful. Similar trends were observed for the investigator assessment of duration of response.

2.1.4 EMBRACE study results − subgroup analyses

Overall survival was analysed according to geographical region, both at the time of the primary analysis and the updated analysis. In both analyses, a significantly longer overall survival difference of 3.1 months was observed for patients from region 1 who were randomised to eribulin (13.1 months in the primary analysis; 13.2 months in the updated analysis) compared with patients who received TPC (10 months in the primary analysis; 10.1 months in the updated analysis). Secondary outcome data for patients in region 1 were not presented in the manufacturer's submission.

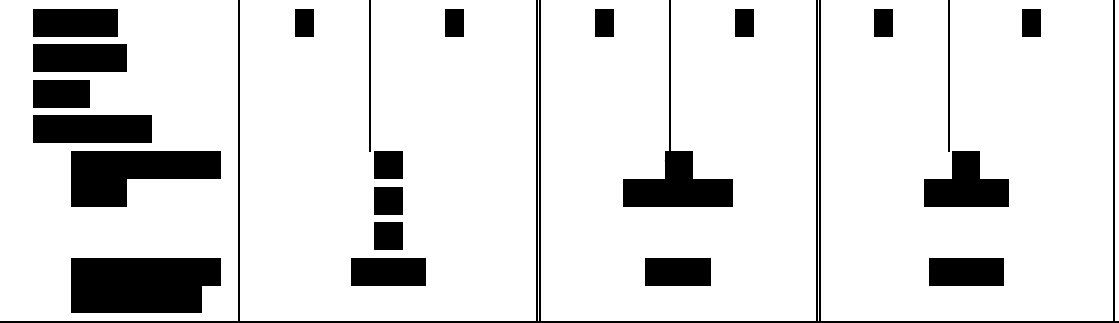
The manufacturer also presented confidential results of post-hoc subgroup analyses which were conducted to investigate the comparison of eribulin with individual treatments of the TPC group (capecitabine, vinorelbine and gemcitabine), for the overall ITT population as well as the region 1 population. Results were presented for the updated analysis when 77% of the total study patients had died, because these represented the most mature data, and are outlined in tables 2 and 3 respectively.

Table 2 Post hoc analyses – overall survival by TPC group; overall EMBRACE population; updated analysis when 77% of patients had died (please see page 67 of the manufacturer's submission)

Parameter	Treatment group					
	Eribulin	Capecitabine	Eribulin	Vinorelbine	Eribulin	Gemcitabine
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated analysis						

CI, confidence interval; HR, hazard ratio; TPC, treatment of physician's choice

Table 3 Post hoc analyses – overall survival by TPC group; Region 1 population; updated analysis when 77% of patients had died (please see page 68 of the manufacturer's submission)

Parameter	Treatment group					
	Eribulin	Capecitabine	Eribulin	Vinorelbine	Eribulin	Gemcitabine
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated analysis						

CI, confidence interval; HR, hazard ratio; NE, not estimable due to insufficient events; TPC, treatment of physician's choice

2.1.5 Non-RCT evidence

In support of the results of the EMBRACE trial, the manufacturer presented evidence from three phase II, multi-centred, single arm, open-label trials (Study 201, Study 211 and Study 221). The primary outcome of objective response rate in each study was 14.3%, 9.3% and 21.3% respectively. Median overall survival in each study was 9 months, 10.4 months and 10.9 months respectively, whilst median progression free survival was 2.6 months in Studies 201 and 211 and 3.7 months in Study 221. Duration of disease in each of the three studies was 5.6 months, 4.1 months and 3.9 months respectively. For further information please see pages 70-82 of the manufacturer's submission and page 39 of the ERG report for a tabulated summary.

2.1.6 Health-related quality of life

No HRQL data were collected during the EMBRACE trial and the manufacturer presented data from two of the phase II studies instead (Study 201 and Study 211).

Study 201 utilised the FACT-B tumour-specific quality of life questionnaire and the manufacturer noted that the mean change from baseline in the Trial Outcomes Index was similar for responders and non-responders to eribulin therapy. However, 57% of eribulin responders showed an increased quality of life compared with 45% of eribulin non-responders. None of the eribulin responders reported deterioration in quality of life, although 11% of the overall study population did report deterioration. Based on the responses to the FACT-B questionnaire, the manufacturer concluded that quality of life may be improved in patients whose tumour responds to eribulin treatment. The manufacturer was unable to interpret data for the assessment of tumour-related symptoms because of the level of non-response.

Study 211 utilised the EORTC Quality of Life QLQ-C30 with the breast cancer-specific module. The manufacturer reported that the quality of life data

were difficult to interpret because of the level of non-response but that exploratory analyses indicated no symptomatic change among patients with tumour response, whereas symptomatic deterioration was experienced by patients whose disease had progressed by the end of treatment cycle two.

The manufacturer did not use data from Studies 201 and 211 in any further analyses of HRQL.

2.1.7 Adverse events

The manufacturer stated that the clinical trial data demonstrated that eribulin is associated with a predictable safety profile and is generally well tolerated for a chemotherapeutic agent being used in pre-treated patients with advanced or metastatic breast cancer. In the EMBRACE study, the majority of adverse events experienced were mild or moderate (CTCAE grade 1 or 2) and treatment discontinuations overall as a result of adverse events were lower for eribulin patients compared with the TPC arm of the EMBRACE study (13.3% versus 15.4%).

Haematological toxicity (for example, neutropenia) with eribulin was evident, although not dissimilar in frequency to some of the other chemotherapeutic drugs and manageable with dose delays or reductions and the use of growth factors. Development of CTCAE grade 3 or 4 adverse events of neutropenia occurred in 21.1% and 24.1% of patients, respectively, in the EMBRACE study. However, it led to discontinuation in 0.6% of patients, and febrile neutropenia (4.6%) and thrombocytopenia (2.6%) were infrequent.

Common non-haematological adverse events experienced during eribulin treatment in the EMBRACE study included asthenia/fatigue, alopecia, nausea and peripheral neuropathy; the manufacturer considered that these were usually manageable with dose delays or reductions, or supportive therapies. grade 3 and 4 non-haematological adverse events were infrequent and only observed in more than 5% of patients for asthenia/fatigue (around 9%) and peripheral neuropathy (around 8%).

2.2 Evidence Review Group comments

The ERG considered that the manufacturer's search strategy was appropriate and found no relevant studies additional to those presented in the manufacturer's submission.

The ERG noted that a single phase III randomised control trial (EMBRACE) forms the majority of the clinical effectiveness evidence in the manufacturer's submission. However, the ERG noted that the design of the EMBRACE trial was robust and the baseline characteristics were well balanced across treatment arms as well as across regions. In addition, the post-progression treatments appeared to be similar in number and type across both arms of the trial, thereby minimising the likelihood of affecting the overall survival results.

The ERG raised concerns that there were a large number of protocol violations of major inclusion and exclusion criteria, but stated that because the protocol violations were relatively evenly distributed across the two treatment arms, it was unlikely that these protocol violations had an impact on the overall study results. The ERG stated that the findings were generalisable to UK clinical practice because there were enough patients in the trial from European Union countries with care pathways similar to those in the UK. The ERG noted that the patients in the overall EMBRACE trial and in the region 1 subgroup were younger (median age of 55 years and 56.5 years respectively) than patients typically seen in UK clinical practice who are likely to have a median age of between 60 and 65 years, although the ERG was aware that patients in clinical trials do tend to be younger than those seen in clinical practice. The ERG was also satisfied that TPC treatments given in the EMBRACE trial reflected UK clinical practice.

The ERG considered the statistical approach employed in the EMBRACE trial to be generally appropriate, but raised concerns about post-hoc analyses conducted by the manufacturer by splitting the TPC treatment arm into seven groups (capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines,

hormonal therapy and other drugs) without appropriate adjustment for multiple testing, thus increasing the risk of chance findings. The ERG highlighted that the results from these post-hoc analyses should be interpreted with caution. It was also noted that the definition for patient censoring differed between the primary and updated analyses (when 55% and 77% of patients respectively had died). In the updated analysis, those lost to follow-up were censored at the data cut-off date, whereas in the primary analysis they were censored at the last known visit date.

With respect to the results in the overall population, the ERG noted that the difference in progression-free survival was not statistically significant when assessed by independent review, rather than by investigator review. It noted the manufacturer's justification that this difference arose from the censoring of almost twice as many patients in the independent review than in the investigator review but added that a considerable number of patients did not receive scans at all, thus further reducing the quantity of verifiable evidence as well as raising concerns about the quality of the trial.

The ERG noted that the relative improvement in median overall survival in the region 1 population was 3.1 months in both primary and updated analyses, while in the overall trial population the relative improvement was 2.5 months (primary analysis) and 2.7 months (updated analysis). In order to explore whether or not differences in prognosis exist between patients from region 1 and the remaining trial population (that is, patients from region 2 [Eastern Europe] and region 3 [Latin America/South Africa]), the ERG compared the mean overall survival for region 1 with the mean overall survival for regions 2 and 3 combined. No significant differences were noted, which suggested that patients in region 1 do not differ in terms of prognosis from the patients in the remainder of the trial population. Therefore, the ERG did not consider the results of the subgroup analyses of region 1 to be more appropriate than those of the overall ITT population. The ERG also highlighted that the

European marketing authorisation for eribulin was based on the results of the overall EMBRACE population.

The ERG noted the manufacturer's comparison of eribulin versus individual TPCs (vinorelbine, capecitabine and gemcitabine) and highlighted that the analyses were exploratory post-hoc analyses and that the numbers of patients within each comparison were small and did not always seem to reflect the 2:1 randomisation ratio.

The ERG also highlighted that the HRQL evidence was weak because it was based on data from a small number of patients and derived from phase II trials in which there was no comparator arm.

2.3 Statements from professional/patient groups and nominated experts

Professional groups noted that the EMBRACE trial reflected UK clinical practice because the majority of the trial patients (64%) were recruited from North America, Western Europe and Australia. They highlighted the importance of the statistically significant increase in overall survival in the eribulin treated group, emphasising that overall survival was not a surrogate marker. Patient experts also highlighted that eribulin would offer an additional option for patients for whom previous chemotherapy regimens had failed. This was considered important because metastatic breast cancer is not curable and many of the treatments available for advanced or metastatic breast cancer are increasingly available for use in the primary setting, rather than in the metastatic setting, and these patients also have an increased risk of drug resistance. Patient experts noted that the short 2−5 minute duration of infusion has advantages over other chemotherapy agents which can extend to up to 90 minutes. Patient experts also commented that treatment with eribulin may result in increased fatigue, neutropaenia and peripheral neuropathy, but that the side effect profile of eribulin is likely to be manageable for patients in this setting.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

No publications evaluating the cost effectiveness of eribulin for the treatment of locally advanced or metastatic breast cancer from a UK perspective were identified, although seven economic evaluations were considered relevant to inform the structure, assumptions and model inputs of the new economic model that the manufacturer developed for this submission.

The model was a semi-Markov state transition model that compared eribulin monotherapy with TPC as well as individual chemotherapeutic agents (capecitabine, gemcitabine and vinorelbine). Only data from patients in region 1 of the EMBRACE trial were included in the economic evaluation because this population was considered most relevant to clinical practice in England and Wales.

The model had three main health states: treated, progressive and dead. All patients in the model were initially assigned to the 'treated' health state which comprised both stable and responsive patients, therefore assuming that treatment response was not a significant predictor for disease progression or death. Patients in the 'treated' health state incurred the costs of drug acquisition and administration, as well as grade 3 and grade 4 treatment-related toxicities. Different utilities for stable and responsive disease were used and weighted by the proportion of patients responding. The 'progressive' health state captured the clinical outcomes and resource use for patients whose disease progressed following previous treatment. Cycles continued until all patients were in the 'dead' state and for the purposes of resource use and quality of life estimations, patients were assumed to enter a 'terminal' state for one cycle prior to entering the 'dead' state. The probabilities of disease progression and death were derived from survival functions based on time-to-event patient-level data from the EMBRACE trial.

A trial duration time horizon was employed in the model. This means that no extrapolation of trial outcomes was undertaken, and when the trial ended (after 2.89 years) all patients who were alive were transitioned into a 'terminal' state. The manufacturer stated that this was a conservative assumption because no further potential additive benefits of eribulin on survival were taken into consideration.

The perspective adopted in the economic evaluation was that of the NHS and Personal Social Services and costs and benefits were discounted at 3.5% per annum. The emergence of grade 3 and grade 4 treatment-related toxicities in EMBRACE was modelled to estimate the associated costs and utility decrements. Because EQ-5D data were not collected during the EMBRACE trial, QALYs were estimated using utility values from published literature. The manufacturer identified five studies of interest and focused on the study by Lloyd et al. 2006; this study assessed UK-based societal preferences for different stages of metastatic breast cancer and toxicities. The manufacturer's model assumes that patient HRQL is a function of current disease state and the presence of grade 3 or grade 4 treatment-related toxicities (those affecting 10% or more patients were included in the model). To estimate QALYs, time spent in each health state was multiplied by a corresponding utility composed of the underlying state utility and the mean toxicity-related decrement. The manufacturer used the following utility values from the Lloyd et al. study for the treated health state (0.715 for patients with stable disease and 0.790 for patients with responsive disease) and the progressive health state (0.443). The value used for the terminal health state (0.160) was derived from the economic study by Hutton et al., using values obtained from oncology nurses using standard gamble methodology, because this was not reported in the Lloyd et al. study. The quality of life values for each health state and utility decrements for each adverse event are summarised on pages 124 and 125 of the manufacturer's submission and in table 4 below.

The manufacturer included drug-related costs, including administration costs, health state costs as well as costs related to adverse events. Categories and components of resource use were defined for each of the three states based on a literature review and clinical opinion solicited by the manufacturer. To elicit clinical opinion the manufacturer conducted an advisory board meeting with five leading oncologists in the field of breast cancer; in addition, seven oncologists were interviewed face to face using a pre-specified proforma to identify resource use during each state. Unit drugs costs (including co-medications) were based on the prices listed in the 'British national formulary' edition 60. Drug administration costs were based on the NHS Reference Cost Schedule 08−09. It was assumed that any drug left over from a treatment was wasted. For vinorelbine, the base case considered capsules and intravenous infusion as part of the sensitivity analysis. The average cost of the treatment in the TPC arm was calculated from a weighted average of the cost of drugs according to the usage of drugs in the EMBRACE trial. Resources consumed in all three health states included chemotherapy support medication, special interventions, scans and laboratory tests, hospitalisations and outpatient visits. In the stable health state, additional resources were also included when considered as 'follow-up' care and included chemotherapy support medication, special interventions, scans and laboratory tests.

An average body surface area of 1.74 m^2 was assumed, based on the mean value reported in a study of UK women receiving chemotherapy. Each drug's dose per m^2 was multiplied by the mean body surface area to determine the dose in milligrams.

In addition, the Department of Health has approved a patient access scheme for eribulin and these discounted costs were incorporated in the manufacturer's analysis. Please see pages 128−139 of the manufacturer's submission for the detailed cost analysis.

A summary of the parameters used in the model is presented in table 4.

Table 4 Parameters and values used by the manufacturer in the economic model (please see page 49 of the ERG report)

Model variable	Costs per vial	Costs per cycle		
Drug costs	**Unit costs (£)**	**Drug acquisition (£)**	**Administration (£)**	**Total (£)**
Eribulin	[redacted] (1 mg / 2 ml)	[redacted]	420	1738
TPC*	N/A	930	296	1335
Vinorelbine	61.25 (30 mg X 1)	919	681	1599
Gemcitabine	162.57 (1000 mg)	974	454	1428
Capecitabine	265.55 (500 mg X 120)	531	210	740
Progression-free survival (region 1, K-M); value (95% CI) [distribution]				**Source**
Eribulin vs TPC HR	0.8930 (0.6960 to 1.1450) (normal)			Independent review
Eribulin vs capecitabine HR	0.6195 (0.2962 to 1.2957) (normal)			Independent review
Eribulin vs gemcitabine HR	0.8141 (0.4245 to 1.5613) (normal)			Independent review
Eribulin vs vinorelbine HR	0.6906 (0.4353 to 1.0956) (normal)			Independent review
Overall survival (region 1, K-M); value (95% CI) [distribution]				**Source**
Eribulin vs TPC HR	0.7910 (0.6390 to 0.9810) (normal)			Independent review
Eribulin vs capecitabine HR	0.3539 (0.1543 to 0.8078) (normal)			Independent review
Eribulin vs gemcitabine HR	0.6790 (0.3605 to 1.2787) (normal)			Independent review
Eribulin vs vinorelbine HR	0.5805 (0.3651 to 0.9229) (normal)			Independent review
Utility values; value (range)				**Source**
Treated/stable	0.715 (0.620 to 0.810)			QoL searches
Treated/responsive	0.790 (0.790 to 0.840)			QoL searches
Progressive	0.443 (0.33 to 0.650)			QoL searches
Terminal	0.160 (0.130 to 0.250)			QoL searches
Anaemia, anorexia, dyspnoea, oedema, heart failure, hyperbilirubimaemia, hypertension, hypokalemia, neuropathy, neutropenia, pain, peripheral neuropathy, pulmonary embolism, thrombocytopenia, urinary tract infection	-0.124 (-0.16 to -0.09)			QoL searches – mean of 5 utilities reported by Lloyd et al.
Diarrhoea, vomiting	-0.103 (-0.13 to -0.08)			QoL searches
Fatigue	-0.115 (-0.14 to -0.09)			QoL searches

Febrile neutropenia	-0.150 (-0.19 to -0.11)	QoL searches
Stomatitis	-0.151 (-0.19 to -0.11)	QoL searches
CI, confidence interval; HR, hazard ratio; QOL, quality of life; TPC, treatment of physician's choice; K-M, Kaplan Meier		

The manufacturer presented four scenarios as the base-case analysis. These were eribulin versus TPC as reported in the EMBRACE trial and eribulin versus the three individual comparisons outlined in the NICE scope: capecitabine, vinorelbine and gemcitabine.

The base-case results for each of the comparisons are presented in tables 5, 6, 7 and 8 and indicate an incremental cost-effectiveness ratio (ICER) of £46,050 per QALY gained versus TPC; £27,183 versus gemcitabine; £35,602 versus vinorelbine and £47,631 versus capecitabine.

Table 5 Base-case results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£36,035	0.6887	£5,586	0.1213	£46,050
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TPC, treatment of physician's choice					

Table 6 Base-case results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.6885	£5,177	0.1904	£27,183
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Table 7 Base-case results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.6291	£4,041	0.1136	£35,602
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Table 8 Base-case results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.7853	£12,779	0.2683	£47,631
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

3.1.1 Sensitivity analysis

The manufacturer carried out one-way deterministic sensitivity analysis on all model parameters except overall survival and progression-free survival (for which one-way deterministic sensitivity analysis was not considered appropriate) and tornado diagrams depicting these are presented on page 153 of the manufacturer's submission. The results were most sensitive to the cost and dose of eribulin, mean body surface area and utilities for the progressive stable and responsive states). A probabilistic analysis was carried out for each of the four base-case analyses and it demonstrated a low level of uncertainty around the base-case results (see pages 156−159 of the manufacturer's submission).

Several scenario analyses were carried out in order to demonstrate the cost effectiveness of eribulin in alternative settings. First, the manufacturer conducted a scenario analysis on the assumption that eribulin qualifies for consideration under the end-of-life guidance. In this analysis, the manufacturer assigned a utility value equal to that of healthy members of the population of the same age and sex (0.83) for the period of survival beyond that achieved under the standard of care. This reduced the ICER to £26,589 per QALY gained compared with TPC and to £15,019, £20,875 and £27,356 per QALY gained when compared with gemcitabine, vinorelbine and capecitabine respectively.

Second, sensitivity analysis was carried out to determine the cost effectiveness of eribulin when drug costs were calculated using per-milligram pricing rather than per vial and therefore assuming no wastage. This reduced the ICER to £42,672 per QALY gained compared with TPC and to £26,330, £22,473 and £45,085 per QALY gained when compared with gemcitabine, vinorelbine and capecitabine respectively.

Third, the manufacturer stated that the cost of vinorelbine was uncertain in the model because some centres use the intravenous formulation and others use the oral formulation. These formulations have substantially different prices so an analysis was carried out using the intravenous cost of vinorelbine. Results indicated that the ICER would increase from that demonstrated in the base case to £52,407 per QALY gained compared with TPC and to £54,817 per QALY gained compared with vinorelbine.

Fourth, a scenario analysis was carried out to examine the cost effectiveness of eribulin versus TPC when using data for all regions in the clinical trial. This resulted in ICERs of £50,059, £26,242, £41,276 and £92,084 per QALY gained in the comparisons versus TPC, gemcitabine, vinorelbine and capecitabine respectively.

Lastly, the manufacturer carried out a structural sensitivity analysis by using hazard ratios calculated from the clinical trial to estimate the survival of patients in each of the treatment arms instead of using Kaplan Meier curves. This resulted in ICERs of £48,110, £37,292, £22,996 and £35,493 per QALY gained in the comparisons versus TPC, gemcitabine, vinorelbine and capecitabine respectively.

The manufacturer concluded that sensitivity analysis showed the results of the model to be sensitive to a range of parameters and that general trends showed that drug cost, utility of the health states and cost of the health states consistently appeared in the top ten most influential variables for the comparisons presented.

3.2 Evidence Review Group comments

The ERG noted that the manufacturer's model was generally well constructed and in accordance with the scope issued by NICE. However, the ERG highlighted several issues around the identification, measurement and valuation of costs and consequences.

The ERG noted that the chemotherapy treatments were dosed on the basis of the body surface area of the individual patient, and that the model used a fixed average value for all patients (1.74 m^2) sourced from a UK survey of chemotherapy patients, rather than taking account of body surface area differences between patients. The ERG re-estimated the costs of chemotherapy drugs per cycle by using body surface area values from the Sacco et al. study in the population of patients receiving palliative chemotherapy. The ERG's estimated costs, including wastage, were lower than those used in the manufacturer's model for all regimens except nab-paclitaxel, as indicated on page 62 of the ERG report.

The ERG also noted that the cost of administration of chemotherapy estimated in the manufacturer's submission may not be accurate because unit costs of administration relating to the NHS Reference Cost Schedule 08−09

were used, rather than the most recent figures; all chemotherapy administration was allocated to an out-patient department, but clinical advice to the ERG indicated that such therapy would normally be administered in a designated chemotherapy day-case unit; the manufacturer had ignored the different healthcare resource group costs appropriate to the first administration of a course of therapy (using the 'subsequent cycles' costs instead). Adjusting for these discrepancies resulted in higher costs of administration in both arms of the model, except for cycle 8 of the TPC arm. These are presented on page 63 of the ERG report.

The ERG also expressed concerns around the cost of supportive care estimated in the manufacturer's submission. The ERG noted that in the progression-free survival health state costs for a quarterly bone scan, together with a set of pathology tests twice per treatment cycle, were included in the manufacturer's model. However, the ERG noted that regular bone scans for monitoring patient condition were specifically not recommended in the NICE Clinical Guideline No. 81, and for costing purposes the ERG considered that routine pre-infusion pathology testing is included within the health resource group costs for chemotherapy delivery. In addition, the ERG highlighted that the manufacturer's model included no provision for the cost of primary and community-based services received before disease progression. The ERG estimated the annual cost of monitoring and supportive care in the progression-free survival state to be £2,915.34 using the NHS Reference Cost Schedule 09−10 and PSSRU Unit Costs of Health & Social Care 2010 in contrast to £2,836.24 in the manufacturer's base case.

In the post-progression survival state, the ERG considered that the most appropriate basis for cost estimation was that used in the NICE guideline, based on a package of care from community nurses (including specialist nurses), therapist and GP home visits. Using the latest PSSRU unit costs, this package resulted in an annual cost of £5,720.79 per patient. By contrast, the manufacturer's model appeared to be based on a more hospital-centric

pattern of care with out-patient visits to a specialist oncologist every 3 weeks, and to an oncology nurse every 6 weeks. A battery of pathology tests was included every 3 weeks, along with regular bone scans and CT scans. In addition, approximately 10% of patients received radiotherapy in each 3-week model period. The total estimated annual cost per patient in the manufacturer's base case was £4,059.82.

The ERG noted that the cost per patient in the terminal state in the manufacturer's model was large (£19,711.85) and dominated by hospice care. Moreover, in the absence of available cost information for hospice services, the hospital critical care daily costs were used as a proxy. The ERG considered that a more appropriate approach to estimating the cost of terminal care in the UK setting is to use the method described in the NICE Clinical Guideline No. 81, based on a Marie Curie report (which assumed 40% of patients died in hospital, 10% in a hospice and 50% at home), updating the cost estimates to current prices. This yielded a lower estimate of £4,003.05 per patient.

The ERG raised several concerns around the manufacturer's approach to utility estimation. The ERG noted that the manufacturer employed the Lloyd et al. mixed model analysis results to generate utility values for the economic model. However, the ERG noted that the age parameter in the published paper refers to the age of 100 participants in the valuation exercise, and not to the age of patients. For consistency with the standard UK EQ-5D tariff scores, the ERG considered that the mean age should be set to 47 – the mean age of the original York study − and recalculated the expected utility values for patients in the stable, responder and progression states (without adverse events) on this basis. The revised utility estimates were consistently higher than those in the submitted model (0.756 instead of 0.715 for stable; 0.823 instead of 0.790 for responder; 0.496 instead of 0.443 for progression).

The ERG also noted that the utility model by Lloyd et al. included only six specific adverse events and that the manufacturer's model had extended the

range of adverse events which may be included in the analysis by calculating an average disutility for four of the six adverse events estimated by Lloyd et al. and then applying this average value to all other adverse events. The ERG highlighted that this method was prone to distortion because some of the adverse events in the EMBRACE trial have been found in other studies to have larger disutility values than the average used in the manufacturer's model (-0.124). In addition, the ERG highlighted that the manufacturer's base-case model limits consideration only to those grade 3 or 4 adverse events that feature in 10% or more of patients, with an option to use a 5% threshold instead. The ERG considered that these restrictions were arbitrary and risked excluding small events of great importance in terms of disutility and cost because they had too few events recorded, even though the difference between trial arms may be significant. The ERG cited the example of grade 3/4 febrile neutropenia, which occurred in 4.6% of eribulin patients but only 1.6% of TPC patients and was therefore excluded from the model, despite being one of the most serious and potentially life-threatening consequences of chemotherapy. The ERG also outlined some concerns around the methods used to calculate costs and loss of patient utility that could lead to both over- and under-estimation of the impact of adverse event-related incremental differences in the manufacturer's model, and these are presented on page 66 of the ERG report.

The ERG noted that in the manufacturer's submission investigators assessed disease progression through scans and patient examinations while the independent reviewers assessed disease progression via imaging data only. The investigator records were complete for all patients, whereas those from the independent assessors were only available where sufficient scan results were available for the patient. The ERG was aware that although the manufacturer had cited several limitations associated with the independent review, the economic model was populated with results from the independent review, supplemented as necessary by investigator data to supply missing values, stating that these should be considered more objective. The ERG

considered that, because the independent assessors were only able to verify a reduced number of patient outcomes, the investigator results should have been used in the economic evaluation, noting that this would also have been more reflective of clinical practice. In addition, the ERG noted that the objective response rate in the clinical study report was not the same as that used in the manufacturer's economic model. The model used a lower rate as it divided 'response' by the whole population whereas the clinical study report divided 'response' by the evaluable population. The ERG suggested that this approach may be conservative but noted that there was insufficient information to comment on this approach.

The ERG noted that the manufacturer calculated the Kaplan-Meier product-limit estimates of progression-free survival and overall survival from the patient records for the selected population and comparators up to the time of death or censoring. Instead of projecting expected life-time experience of those individuals still alive at the time of data cut-off, it was assumed that all such patients died at the time of censoring. The ERG highlighted that although this method of dealing with censored individual records seems straightforward, there is potential for bias to be introduced, which can have a significant impact on the incremental survival (survival gain). The ERG also noted that the NICE reference case requires decision analysis to take account of costs and outcomes that are likely to be affected by the choice of treatment at any subsequent time, and in the case of advanced or metastatic cancers this is generally interpreted as the whole of the remaining lifetime of patients.

The ERG noted that the behaviour of a Kaplan-Meier plot can become unstable and erratic when only small numbers of cases remain alive and uncensored, because a single event can give rise to very large changes in the survival estimate towards the tail of the distribution. This long tail could contribute disproportionately to the estimated mean survival that is equivalent to the total area under the Kaplan-Meier plotted curve (AUC), and because it may occur in either arm of a trial it could, in some cases, completely reverse a

small but consistent treatment benefit seen in the bulk of the trial population. The ERG noted that the manufacturer's model did not make any adjustments to ameliorate this risk, and therefore it was likely that in some model scenarios overall survival may be either over- or under-estimated by using the Kaplan-Meier analyses without amendment. The ERG undertook a revised survival analysis to compare with unadjusted survival estimates. This involved truncating the accumulation of survival time (AUC) at a common time in both trial arms, to eliminate the effect of residual 'tails' of different sizes and durations. To preserve as much of the original data as possible, this time was set by comparing the times at which the last recorded trial event (that is, death in the case of overall survival) occurred in the two trial arms, and truncating the analysis at the earlier of these values. In both populations, the estimated mean gain in overall survival from use of eribulin was reduced by 10−14 days (14−15%), which alone may increase the size of the estimated ICER by approximately 18−19%.

In addition, the ERG explored the potential impact on cost-effectiveness results of projecting survival trends to the end of life. The ERG examined the cumulative mortality hazard plots for the EMBRACE trial arms, which revealed consistent long-term linear trends for both eribulin and TPC beyond the first 3− 4 months of the trial, indicating that exponential survival functions would be appropriate for projecting overall survival beyond the available data. Maximum likelihood exponential parameter values were estimated from the post-100 days' trial evidence. The lifetime estimated overall survival was then obtained as the sum of the observed survival time (AUC) up to 750 days from randomisation, and the exponential projected survival time from 750 days until the death of all patients. It was not possible for the ERG to amend the submitted model directly to incorporate the effects of using projected overall survival estimates. However, an approximation was achieved by increasing the aggregated post-progression survival, and adjusting post-progression costs and post-progression utility values in parallel.

Table 6 summarises all the estimates of overall survival including the ERG projected values.

Table 6 Estimates of overall survival summarised (page 76 of the ERG report)

		Eribulin	TPC	OS gain
ITT population				
Manufacturer's model	days (months)	473 (15.53)	402 (13.20)	71 (2.33)
K-M no truncation / no projection	days (months)	474 (15.56)	403 (13.23)	71 (2.32)
K-M with truncation / no projection	days (months)	463 (15.20)	403 (13.23)	60 (1.97)
K-M to 750 days / projection >750 days	days (months)	523 (17.19)	441 (14.50)	82 (2.69)
Region 1 population				
Manufacturer's model	days (months)	474 (15.58)	389 (12.78)	85 (2.80)
K-M no truncation / no projection	days (months)	475 (15.62)	391 (12.83)	85 (2.79)
K-M with truncation / no projection	days (months)	462 (15.18)	391 (12.83)	71 (2.35)
K-M to 750 days / projection >750 days	days (months)	528 (17.37)	430 (14.12)	99 (3.25)

ITT, intention to treat; OS, overall survival; TPC, treatment of physician's choice; K-M, Kaplan Meier

The ICERs obtained by the ERG from making modifications to the manufacturer's model are shown in Table 7 for the region 1 population and Table 8 for the ITT population. Detailed results are available on page 75 of the ERG report.

Table 7 ERG revisions to cost-effectiveness model results for region 1 population

	Incremental		
	Costs	QALYs	ICER
Manufacturer's model with PAS	**£5,472**	**0.1213**	**£45,106**
+Discounting logic	£5,559	0.1235	£45,009
+Terminal period logic	£5,471	0.1215	£45,031
+Mid-cycle correction	£5,354	0.1214	£44,123
+Amend drug & admin costs	£8,240	0.1213	£67,928
+Amend state based costs	£5,836	0.1213	£48,108
+Amend utility values	£5,472	0.1320	£41,452
+Investigator PFS data	£5,583	0.1237	£45,115
+Febrile neutropenia	£5,513	0.1212	£45,486
ERG revised estimate	**£8,454**	**0.1368**	**£61,804**
Additional sensitivity analyses based on ERG revised estimate			
+ IV vinorelbine	£8,538	0.1368	£62,418
+ projected OS estimation	**£8,454**	**0.1548**	**£55,905**

ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year.

Table 8 ERG revisions to cost-effectiveness model results for ITT population

	Incremental		
	Costs	QALYs	ICER
Manufacturer's model with PAS	**£4,436**	**0.0914**	**£48,536**
+Discounting logic	£4,524	0.0930	£48,645
+Terminal period logic	£4,436	0.0916	£48,447
+Mid-cycle correction	£4,318	0.0914	£47,251
+Amend drug & admin costs	£7,798	0.0914	£85,323
+Amend state based costs	£4,793	0.0914	£52,446
+Amend utility values	£4,436	0.1006	£44,076
+Investigator PFS data	£4,898	0.0978	£50,074
+Febrile neutropenia	£4,480	0.0913	£49,081
ERG revised estimate	**£8,269**	**0.1086**	**£76,110**
Additional sensitivity analyses based on ERG revised estimate			
+ IV vinorelbine	£8,362	0.1086	£76,970
+ projected OS estimation	**£8,269**	**0.1229**	**£68,590**

ICER, incremental cost-effectiveness ratio; ITT, intention to treat; IV, intravenous; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year.

The ERG highlighted that the single dominant contribution to the large change in ICERs in the ERG revised estimates is from the revised costs of TPC drug acquisition and administration. The other changes are minimal or, taken together, mildly beneficial to the case for eribulin.

The ERG concluded that if the whole population of the EMBRACE trial is considered sufficiently representative of UK patients and clinical practice, then the best estimated ICER for eribulin exceeds £76,000 per QALY gained but may fall to about £68,000 if projected lifetime estimates of overall survival are preferred to truncated estimates. If region 1 patients are deemed representative of the UK NHS context, then the ERG estimated ICER exceeds

£61,000 per QALY gained, but reduces to almost £56,000 if survival projections are preferred.

The ERG agreed that the three key elements of the NICE end-of-life criteria appear to be met when the clinical data from region 1 are used to estimate mean overall survival gain, stating that the life expectancy of patients with locally advanced or metastatic breast cancer was likely to be less than 24 months; that the ERG had projected a mean overall survival gain of 3.25 months for the region 1 population; and finally that eribulin was licensed for a small patient population. However, a mean overall survival gain of 2.69 months was estimated for the overall (ITT) population indicating that the end-of-life criteria would not be met for the overall population. The ERG highlighted that the manufacturer's method of adjusting the ICER, given that eribulin appeared to meet the NICE end-of-life criteria, was not the most commonly used procedure, although it was an alternative to applying a higher threshold of acceptability. The ERG particularly highlighted that the results of such an analysis should only be considered as relevant to the normal NICE range of acceptability (£20,00−£30,000 per QALY gained), rather than the normal practice used in most appraisals of applying a higher threshold value, because using both together would amount to double counting.

4 Equalities issues

No equalities issues were raised during the development of the scope or in any of the submissions.

5 Authors

Raisa Sidhu, Zoe Charles, with input from the Lead Team (Martin Duerden, Susan Griffin and Alison Hawdale).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Bagust A, Boland A, Davis H et al. (2011) Eribulin for the treatment of locally advanced or metastatic breast cancer

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Eisai Ltd.

II Professional/specialist, patient/carer and other groups:

- Royal College of Pathologists
- Royal College of Physicians (also on behalf of NCRI /RCR/ACP/JCCO)
- Breast Cancer Care
- Breakthrough Breast Cancer
- Breast Cancer Campaign
- NHS Camden

C Additional references used:

Lloyd A, Nafees B, Narewska J. et al. (2006) Health state utilities for metastatic breast cancer. British Journal of Cancer 95: 683−90

Sacco JJ, MacBeth F, Bagust A. et al. (2010) The average body surface area of adult cancer patients in the UK: A multicentre retrospective study PLoS ONE 5(1)

Hutton J, Brown R, Borowitz M. et al. (1996) A new decision model for cost utility comparisons of chemotherapy in recurrent metastatic breast cancer. PharmacoEconomics 9 (Suppl 2 (Conference paper)):8-22

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Eribulin for the treatment of locally advanced or metastatic breast cancer

Final Scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of eribulin within its licensed indication for the treatment of people with breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease.

Background

Breast cancer is the most common malignancy affecting women in the UK accounting for 1 in 3 of all cancers in women. Over 40,000 women and almost 300 men were newly diagnosed with breast cancer in England and Wales during 2007. Furthermore, over 12,000 deaths due to breast cancer occurred in the UK in 2007, with an average rate of 38.6 deaths per 100,000 women and 0.2 deaths per 100 000 men. Approximately 5% of women presenting with breast cancer have advanced disease with distant metastases (where cancer cells have spread to other parts of the body), and it is estimated that around 35% of those presenting with early or localised breast cancer will eventually develop metastatic breast cancer.

The role of current treatments for advanced and metastatic breast cancer is to palliate symptoms, prolong survival and maintain a good quality of life with minimal adverse events. The NICE clinical guideline for advanced breast cancer (CG81) recommends first-line treatment with an anthracycline-based chemotherapy regimen. Where an anthracycline is unsuitable (for example if the person has previously received anthracycline-based adjuvant therapy or has a contraindication to anthracyclines), or where the disease relapses following an anthracycline-based regimen, the clinical guideline recommends docetaxel monotherapy. The guideline states that combination chemotherapy may be considered to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. NICE technology appraisal guidance No. 116 recommends gemcitabine in combination with paclitaxel, within its licensed indication, for the treatment of metastatic breast cancer that has relapsed following adjuvant/neoadjuvant chemotherapy, only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. Vinorelbine or capecitabine should be considered for subsequent lines of therapy. Gemcitabine monotherapy is also used in clinical practice in the UK.

The technology

Eribulin (E7389, Eisai) is a synthetic analogue of halichondrin.B, which inhibits tubulin polymerisation. The destabilisation of tubulin polymers disrupts the assembly and formation of microtubules, which in turn arrests cancer cell division. Eribulin is administered intravenously.

Eribulin does not currently have a UK marketing authorisation for the treatment of locally advanced or metastatic breast cancer. It has been studied in clinical trials as monotherapy for the treatment of women with locally advanced or metastatic breast cancer whose disease has relapsed after at least two chemotherapy treatments (which must have included an anthracycline and a taxane). In one study eribulin has been compared with capecitabine and in another with a 'treatment of physician's choice'. Eribulin has also been studied in a non-randomised trial after the failure of an anthracycline, a taxane and capecitabine.

Intervention(s)	Eribulin monotherapy
Population(s)	People with breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease and whose disease has progressed.
Comparators	• vinorelbine • capecitabine • gemcitabine
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 116, Jan 2007, 'Gemcitabine for the treatment of metastatic breast cancer'.Transferred to static list May 2010. Technology Appraisal No.62, May 2003, 'Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer '. Updated in clinical guideline 81. Technology Appraisal No.54, December 2002, 'Guidance on the use of vinorelbine for the treatment of advanced breast cancer '. Updated in clinical guideline 81. Technology Appraisal No. 34, Mar 2002, 'Guidance on the use of trastuzumab for the treatment of advanced breast cancer'. Currently subject to review. Publication date tbc. Technology Appraisal No. 30, September 2001, 'Taxanes for the treatment of breast cancer'. Updated in clinical guideline 81. Technology Appraisal in Preparation, 'Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer)'. Publication date tbc. Technology Appraisal in Preparation, 'Sunitinib in combination with capecitabine for the treatment of advanced and/or metastatic breast cancer'. Publication date tbc. Related Clinical Guidelines Clinical Guideline No. 81, Feb 2009, 'Advanced breast cancer: diagnosis and treatment'. This guideline updates and replaces technology appraisal guidance 62 (capecitabine), 54 (vinorelbine) and 30 (taxanes). Clinical Guideline No. 80, Feb 2009, 'Breast cancer (early and locally advanced): diagnosis and treatment'.

Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Eribulin for the treatment of locally advanced and metastatic breast cancer

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Manufacturers/sponsors • Eisai (eribulin) Patient/carer groups • Afiya Trust • Black Health Agency • Breakthrough Breast Cancer • Breast Cancer Campaign • Breast Cancer Care • Breast Cancer Haven • Breast Cancer UK • CANCERactive • Cancer Black Care • Cancer Equality • Chinese National Healthy Living Centre • Counsel and Care • Equalities National Council • Helen Rollason Heal Cancer Charity • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Muslim Health Network • South Asian Health Foundation • Specialised Healthcare Alliance • Sue Ryder Care • Tenovus • Women's Health Concern Professional groups • Association of Cancer Physicians • British Association for Services to the Elderly	General • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Medicines and Healthcare products Regulatory Agency • National Association for Primary Care • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • NHS Quality Improvement Scotland • Public Health Wales NHS Trust • Scottish Medicines Consortium Comparator manufacturers • Actavis (vinorelbine) • Hospira (vinorelbine) • Medac UK (vinorelbine) • Pierre Fabre (vinorelbine) • Roche Products (capecitabine) • Wockhardt (vinorelbine) Relevant research groups • Against Breast Cancer • Breast Cancer Hope • Breast Cancer Research Trust • Cochrane Collaboration – Cochrane Breast Cancer Group • Institute of Cancer Research

Consultees	**Commentators (no right to submit or appeal)**
• British Geriatrics Society • British Institute of Radiology • British Oncological Association • British Oncology Pharmacy Association • British Psychosocial Oncology Society • Cancer Networks Pharmacists Forum • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Society of Medicine • Royal Pharmaceutical Society • Society and College of Radiographers • United Kingdom Clinical Pharmacy Association • United Kingdom Oncology Nursing Society <u>Others</u> • Aneurin Bevan Health Board • Department of Health • NHS Camden • Welsh Assembly Government	• MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Policy Research Institute on Ageing and Ethnicity • Pro-Cancer Research Fund • Research Institute for the Care of Older People <u>Evidence Review Group</u> • Liverpool Reviews & Implementation Group, University of Liverpool • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • None

NICE is committed to promoting equality and eliminating unlawful discrimination. Please let us know if we have missed any important organisations from the lists contained within the matrix and which organisations we should include who have a particular focus on relevant equality issues

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees
Organisations that accept an invitation to participate in the appraisal; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England.

The manufacturer/sponsor of the technology is invited to make an evidence submission, respond to consultations and has the right to appeal against the Final Appraisal Determination (FAD).

All non-manufacturer/sponsor consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators
Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; NHS Quality Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*.

All non-manufacturers/sponsors commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)
An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the manufacturer/sponsor evidence submission to the Institute.

[1] Non manufacturer consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Eribulin for the treatment of locally advanced breast cancer or metastatic breast cancer

Eisai Ltd.

Single technology appraisal (STA)

Version: FINAL

Submission date: 11th March 2011

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Abbreviations

AE	Adverse event
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
CBR	Clinical benefit rate
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EM(E)A	European Medicines Agency
EMBRACE	Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389
EORTC-QOL	European Organisation for Research and Treatment of Cancer Quality of Life
ER	Oestrogen receptor
FACT-B	Functional Assessment of Cancer Therapy-Breast
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IV	Intravenous
LABC	Locally advanced breast cancer
LD	Longest diameter
LY	Life year
MBC	Metastatic breast cancer
MRI	Magnetic resonance imaging
N/A	Not applicable
NE	Not estimable
NHS	National Health Service
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease

PFS	Progression free survival
PP	Per protocol
PR	Progesterone receptor
PaR	Partial response
QALY(s)	Quality-adjusted life year(s)
RCT	Randomised, controlled trial
RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse event
SD	Stable disease
SPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
TNM	Tumour, Nodes, Metastasis
TOI	Trial outcome index
TPC	Treatment of Physician's Choice
VAS	Visual analogue scale

Executive summary

Background and unmet medical need in metastatic breast cancer

Breast cancer is the most common malignancy among women in the UK and metastatic breast cancer (MBC), is the most advanced form of the disease

There is currently no cure for MBC and the long-term prognosis is poor. The aim of treatment in this setting therefore is to prolong life. The average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving chemotherapy. At the point in therapy where eribulin will be used (following at least two chemotherapeutic regimens for advanced disease), the length of survival is expected to be less

A great unmet need exists for treatments that improve overall survival for women with MBC, particularly those that do not respond or become refractory to agents such as anthracyclines and taxanes and in many cases capecitabine. There is no proven single agent that prolongs survival for such women; indeed, until now there have been few, if any, data to guide oncologists in selecting subsequent therapy and their relative clinical effectiveness

Eribulin and EMBRACE trial

Eribulin is a first-in-class chemotherapy treatment belonging to the halichondrin class of drugs. It is a non-taxane inhibitor of microtubule dynamics, and has a novel mode of action that is distinct from those of other tubulin targeting agents currently in clinical use, including taxanes (e.g. docetaxel) and vinca alkaloids (e.g. vinorelbine)

For the first time, eribulin as a single agent chemotherapy has shown a significant improvement in median overall survival in women with heavily pretreated metastatic breast cancer. This finding comes from the pivotal phase III EMBRACE trial.

Overall survival is recognised as the most definitive cancer outcome and is of most importance to patients and clinicians when making decisions regarding treatment options

There is no standard of care for these pre-treated patients in the advanced stages of breast cancer. The choice of treatment will depend on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient’s quality of life

In the absence of a single standard of care for women with pre-treated breast cancer, the EMBRACE trial randomly allocated 762 women in a 2:1 ratio either to eribulin (508) or treatment of the physician's choice (TPC; 254); TPC arm included currently available monotherapies, including capecitabine, gemcitabine and vinorelbine, used in MBC treatment . This represents "a real-life situation” because there are no guidelines on which chemotherapy to use at this stage of the disease and reflects choices made by the oncologist and their patients.

- Median overall survival was significantly improved in women assigned to eribulin (13.1 months) compared with TPC (10.6 months), an increase in duration of survival of 23% (2.5 months) (P = .041).

- The updated analysis performed after 77% of patients had died and on request of the regulatory authorities, confirmed these results; median OS (eribulin 13.2 months vs. TPC 10.5 months) was improved by 2.7 months (p=0.014)

- The planned analysis of patients from geographical region 1 (North America/Western Europe/Australia) showed a significant OS benefit of eribulin over TPC of 3.1 months (p=0.031).

- The 1 year survival rates were 53.9% in the eribulin group and 43.7% in the TPC group.

[redacted]

Eribulin had a manageable profile of toxic effects, which is similar to those of other chemotherapeutic agents used in this setting.

People with advanced breast cancer will generally suffer from a gradual reduction in HRQL as the disease progresses. People achieving disease control on treatment may benefit from HRQL improvements or a reduction in the detrimental effects of the disease of quality of life. Phase II eribulin trial data suggests that HRQL does not deteriorate and in many patients improves in patients who have objective positive tumour response to eribulin treatment, whereas patients who progress may suffer deterioration in their HRQL

Eribulin is licensed as monotherapy for the treatment for patients with LABC or MBC who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

Eribulin is provided as a ready to use solution in a vial, avoiding the need for time consuming reconstitution or dilution associated with many IV chemotherapeutic agents. It is administered as a quick and convenient 2-5 minute IV infusion with no special handling or tubing required. As such, the use of eribulin may be associated with healthcare resource savings.

The recommended dose of the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 of eribulin mesylate). Each cycle of treatment (21 days) with eribulin consists of only two doses, administered on Days 1 and 8. Each vial contains 1.0 mg of eribulin mesylate, equivalent to 0.88 mg eribulin . It is anticipated that if tolerated, patients will continue on eribulin treatment until disease progression.

<u>Economic evaluation</u>

A semi-Markov state transition model was developed in Microsoft Excel to model the lifetime clinical and economic outcomes for a hypothetical cohort of patients with LABC/MBC. The model structure was informed by and adapted from published economic evaluations of breast cancer treatments as reviewed in Section 6.1.2 in particular Brown et al, Cooper et al, Hutton et al and Takeda et al (Section 6).

The patient population in the model matches the pivotal Phase III RCT for eribulin (EMBRACE) and therefore included patients with LABC/MBC whose disease had progressed after at least two prior chemotherapy regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane in line with the licensed indication for eribulin.

Transitions between the three health states of “Treated, “Progressive” and “Dead” were governed by probabilities of disease progression and death derived from survival functions based on time-to-event patient-level data from the EMBRACE trial:

- Progression-free survival data from EMBRACE governed transitions from the “Treated” to “Progressive” health states at the conclusion of each model cycle.
- Overall survival data from EMBRACE governed transitions to the “Terminal” state at the conclusion of each model cycle.

The proportion of patients in the “Treated” health state whose tumour(s) exhibited a complete response (CR) or partial response (PaR) were defined using the objective response rate (ORR) as per the EMBRACE trial (34).

A trial duration horizon is employed in the model. At the end of the duration of trial all patient s that are alive are transitioned into a “Terminal” state; this avoids any need for extrapolation of trial outcomes. This is a conservative assumption since no further potential additive benefits of eribulin on survival are taken into consideration.

The emergence of Grade 3 and Grade 4 treatment-related toxicities in EMBRACE was modelled to estimate the associated costs and utility decrements (34).

Four scenarios are presented as the base case analysis. These were eribulin versus TPC as reported in the clinical trial and eribulin versus the three individual comparisons outlined in the scope; capecitabine, vinorelbine and gemcitabine. In addition, the analysis focused on patients from region 1 (as detailed in section 6.3.1.) as this was the most appropriate patient group to consider.

Base-case results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£36,035	0.6887	£5,586	0.1213	£46,050

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Base-case results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.6885	£5,177	0.1904	£27,183

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Base-case results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.6291	£4,041	0.1136	£35,602

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Base-case results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.7853	£12,779	0.2683	£47,631

Based on NICE's supplementary advice on end-of-life treatment, eribulin appears to meet these criteria. That is, it is indicated for a relatively small number of patients who have LABC/MBC and have had a previous anthracycline and a taxane, the medicine is indicated for the treatment of patients with a diagnosis of a terminal illness and who are not, on average, expected to live for more than 24 months, and eribulin provides an additional extension of 3.1 months compared to current NHS treatment (See Section 5.10.3). A scenario analysis was conducted on the assumption that eribulin qualifies for consideration under the end-of-life guidance, using the full utility value of 0.83 for eribulin patients surviving beyond a certain number of days (the cumulative survival in the comparator arm).

End of life analysis results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£36,035	0.7775	£5,586	0.2101	£26,589

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

End of life analysis results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.8427	£5,177	0.3447	£15,019

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

End of life analysis results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.7092	£4,042	0.1937	£20,875

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

End of life analysis results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.9841	£12,779	0.4671	£27,356

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Eribulin is the first and only single agent chemotherapy to demonstrate a significant overall survival benefit in patients with late stage LABC/MBC, a patient population with few treatment options and an unmet medical need. At this stage of treatment there is no clear standard of care as none of the current treatments have demonstrated a survival benefit over any other. Therefore, many people with LABC/MBC see their disease progress after receiving multiple therapies. Now with eribulin patients can be offered a new option that has been shown to improve overall survival for metastatic disease.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class.

Brand name: HALAVEN® (subject to European Medicines Agency [EMA] approval).

Approved name: Eribulin mesylate; E7389.

Therapeutic class: Eribulin is a first-in-class anti-neoplastic agent belonging to the halichondrin class of drugs. The Anatomical Therapeutic Chemical Classification System code is L01XX41.

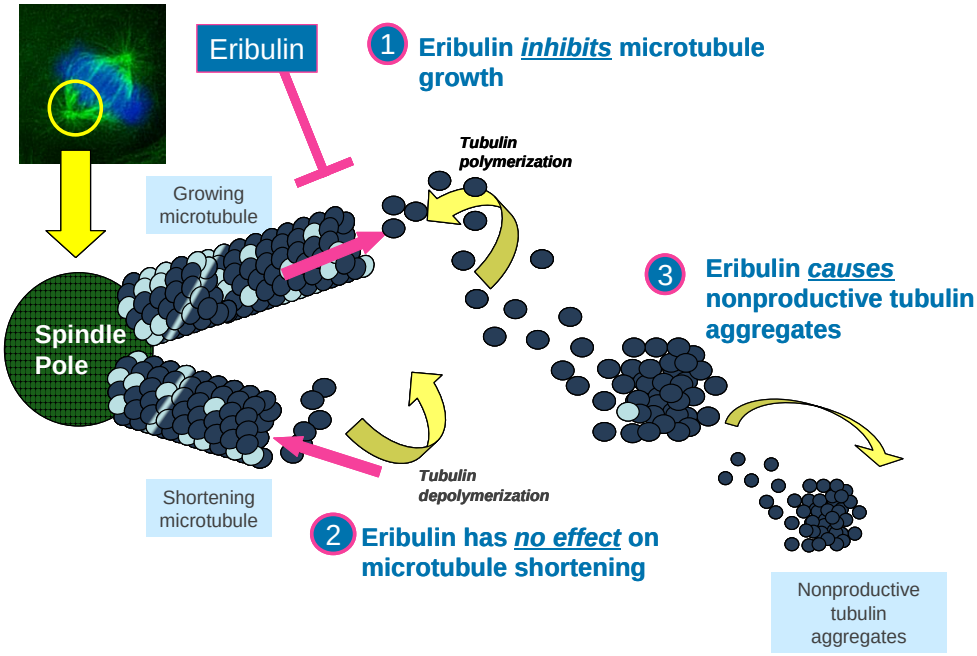
1.2 What is the principal mechanism of action of the technology?

Eribulin is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai* and the most potent member of the halichondrin family of polyether macrolides.

It is an innovative chemotherapy treatment which is a non-taxane inhibitor of microtubule dynamics, with a unique mechanism of action. Eribulin exerts its anticancer effects via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles, and ultimately, apoptotic cell death following prolonged mitotic blockage (1, 2). It does this by inhibiting the growth phase of microtubule dynamics, without affecting the shortening phase, and sequesters tubulin into non-productive aggregates (Figure 1) (1). This pattern is distinct from that of members of tubulin-targeting classes currently in clinical use, including taxanes (e.g. docetaxel) and vinca alkaloids (e.g. vinorelbine).

Taxanes which affect microtubule shortening show higher neuropathy characteristics, compared with eribulin which does not affect the microtubule shortening phase (3). Furthermore, the ability to sequester tubulin into non-productive aggregates, further distinguishes eribulin from other tubulin-targeting classes and, as a result, eribulin retains activity against drug-resistant cells that harbour β-tubulin mutations associated with taxane resistance. 16

Figure 1: Eribulin mechanism of action
(based on Jordan et al and Okouneva et al (1, 2))



1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

CHMP positive opinion was granted on January 21st 2011 and marketing authorisation from EMA is expected end of March or early April 2011.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

There are currently no major issues identified by the regulatory organisation that will delay marketing authorisation. There were no special conditions attached to the marketing authorisation.

1.5 What are the (anticipated) indication(s) in the UK?

Eribulin monotherapy is indicated for the treatment of patients with LABC or MBC who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Study 209, a randomised, controlled Phase II study to compare eribulin and ixabepilone for the occurrence or exacerbation of neuropathy in 98 patients (planned enrolment) with

advanced breast cancer. Study completion and final results are expected in September 2011.

Study 224, a single-arm, open-label Phase II continuation study to evaluate the safety of patients who continue to receive E7389 after completing the Phase II Study 221. Study completion and final results are expected in March 2012.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated date of availability in the UK is April 2011.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Eisai Ltd. has applied for European marketing authorisation with the EMA, under the centralised procedure; Eribulin is expected to be marketed across Europe. In the US, eribulin was approved by the FDA in November 2010. Eribulin has also been approved for use in Singapore.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Scottish Medicines Consortium: planned submission in 2011.

The All Wales Medicines Strategy Group has been informed by Eisai Ltd. that eribulin is undergoing the NICE Single Technology Appraisal process.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1: Details of technology being appraised

Pharmaceutical formulation	HALAVEN 0.44 mg/ml solution for injection. It is supplied as a clear, colourless aqueous solution, ready for injection. Each vial contains 1.0 mg of eribulin mesylate, equivalent to 0.88 mg eribulin.
Acquisition cost (excluding VAT)	[redacted] per vial
Method of administration	Intravenous.
Doses	The recommended dose of the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 of eribulin mesylate). If desired, the dose may be diluted in up to 100 ml of normal saline for injection (an aqueous solution of 0.9% w/v of sodium chloride).
Dosing frequency	Each dose should be administered intravenously over 2–5 minutes on Days 1 and 8 of a 21-day cycle.
Average length of a course of treatment	Each treatment cycle, comprising two doses (Days 1 and 8), every 21 days.
Average cost of a course of treatment	[redacted] per cycle depending on body weight and dose adjustment
Anticipated average interval between courses of treatments	Patients will move from cycle to cycle immediately unless specific Grade 3/4 toxicities necessitate a dose delay.
Anticipated number of repeat courses of treatments	In the EMBRACE study, patients received an average of 5 cycles of eribulin treatment.
Dose adjustments	Patients should be clinically evaluated during treatment by physical examination and laboratory testing including complete blood counts. If Grade 3 or 4 toxicities are present, then treatment should be delayed to allow recovery. Patients should only be retreated when ANC is ≥1 x 10^9/L and platelets are ≥75 x 10^9/L and all other toxicity from a previous cycle has recovered to Grade 2 or less. A dose reduction to 0.97 mg/m^2 is recommended for the retreatment of patients with specific Grade 3/4 toxicities in the previous cycle (See Section 4.2 of SPC for details [Appendix Section 9.1]). If toxicities reoccur, an additional dose reduction to 0.62 mg/m^2 is recommended. Further reoccurrence may warrant treatment discontinuation. Impaired liver function due to metastases: The recommended dose in patients with mild hepatic impairment (Child-Pugh A) is 0.97 mg/m^2 and for patients with moderate hepatic impairment (Child-Pugh B) is 0.62 mg/m^2. Severe hepatic impairment has not been studied but it is expected that a more marked dose reduction is needed. Impaired liver function due to cirrhosis: This patient group has not been studies. The doses above may be used in mild and moderate impairment but close monitoring is advised as the doses may need readjustment. Patients with severely impaired renal function (creatinine clearance <40 ml/min) may need a reduction of the dose. The optimal dose for this patient group remains to be established.

Abbreviations: ANC, absolute neutrophil count; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; RCT, randomised, controlled trial.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Eribulin is provided as a ready to use solution, avoiding the need for reconstitution or dilution associated with many IV chemotherapeutic agents. As with any IV treatment, good peripheral venous access, or a patent central line, should be ensured prior to administration. However, eribulin may be administered as a quick and convenient 2-5 minute IV infusion with no special handling or tubing required, and may therefore realise savings, compared with some chemotherapeutic agents, in associated healthcare resources, e.g. nursing time.

Pre-medication (antihistamine or steroids) to prevent hypersensitivity reactions is not routinely required prior to injection with eribulin, unlike many IV chemotherapeutic agents.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

There is no requirement to monitor patients receiving eribulin over and above usual clinical practice.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There is no stated requirement for routine pre-medication in the product SPC.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Disease incidence

Breast cancer is the most common malignancy in women in the UK; it accounts for around 1 in 3 cases of cancer in women (4) and the lifetime risk of developing breast cancer for a woman is 1 in 8 (4). The incidence has almost doubled over the last three decades (4), with around 42,300 women (> 99% of cases) and 300 men (< 1%) newly diagnosed with breast cancer in England and Wales during 2008 (4). The risk of developing breast cancer is strongly correlated with age; 81% of cases in the UK occur in women aged 50 years and over (4).

Breast cancer severity and prognosis

Breast cancer is classified according to its type, grade (how abnormal the cancer cells are), and stage (extent or severity of the cancer). Other important factors used to classify breast cancer are the presence of oestrogen and/or progesterone receptors (ER-positive and PR-positive) and an increased level of human epidermal growth factor receptor 2 (HER2) compared to normal breast cells (HER2-positive). All of these aspects impact upon the prognosis for the patient and guide the selection of the most appropriate treatment.

The extent or severity of the cancer can be determined by the Tumour, Nodes, Metastasis (TNM) staging system. The TNM staging system takes into account the size of the tumour, whether the lymph nodes are affected, and whether cancer has spread to other parts of the body (metastasised) (5, 6). LABC/MBC, is the most advanced form of breast cancer, where the cancer is no longer localised to the breast and has spread to other parts of the body, commonly the lungs, liver, brain and bone (5). Although few patients are diagnosed with MBC (around 5% (7)), the risk of recurrence persists for many years following remission of non-metastatic disease. It is estimated that 30%, 46%, and 71% of patients initially diagnosed with stages I, II, and III disease, respectively, will eventually progress to metastatic disease (7). Symptoms can be severe including cancer-related fatigue and uncontrolled local disease, along with further complications relating to the organ(s) to which the cancer has spread (8). LABC/MBC has a significant impact on quality of life (9-11), and patients commonly suffer psychological and psychiatric disturbances (12).

There is currently no cure for LABC/MBC and the long-term prognosis is poor. Whereas 5-year survival rates of 92% have been reported for tumours diagnosed at the earliest stage, 5-year survival in those diagnosed with metastatic disease is low, around 13% (13). As reported in the recent NICE assessment report for lapatinib and trastuzumab, the average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving chemotherapy (14). At the point in therapy where eribulin will be used – following at least two chemotherapeutic regimens for advanced disease – the length of survival would be expected to be even less.

Current management and goals of treatment

Overall, the current management of LABC/MBC is complex and diverse, with treatment options combined in a multi-disciplinary approach; treatment choice for physicians and patients will depend upon a number of factors, including:

- exposure and response to therapy at earlier stages of treatment
- menopausal status
- ER/PR and HER2 status
- tolerability
- patient preference
- availability of drugs
- patient's quality of life.
- performance status
- age
- site of disease
- treatment goals

Systemic therapy, in the form of hormonal therapies, chemotherapeutic agents, and targeted/biologic agents, are current treatment options for LABC/MBC. There are a variety of single and combination therapies that can be used in a sequential regimen approach; therefore, when disease progression occurs during first-line treatment a second is tried, and so on.

Pre-treated patients (e.g. patients who have already received treatment with anthracyclines and taxanes), however are a particularly challenging subgroup to manage effectively since by this stage patients will have progressed despite treatment, and further treatment options will have limited effectiveness. Treatment for this advanced stage of the disease is focused on prolonging survival, while controlling the symptoms experienced and improving the patient's quality of life (8). Overall survival is recognised as the most definitive cancer outcome (15, 16) and is of most importance to patients when making decisions regarding treatment options (17). Although many patients gain significant benefit from continuing treatment through several lines of chemotherapy – 40% of patients with metastatic disease have been shown to achieve disease control of at least 6 months with third-line chemotherapy (18) – there is minimal high-quality evidence about the relative clinical effectiveness of current treatments (8) and none have demonstrated a survival benefit over any other (8, 19).

2.2 How many patients are assumed to be eligible? How is this figure derived?

There is very limited data in the UK describing the number of patients at different lines of treatment in the metastatic setting

Our best estimates predict there are around 1,100-1,700 patients. This includes patients who are HER2+ve. There is no experience of using eribulin in combination with anti-HER2 therapy. According to Synovate data[a] from Q3 2010 there are 1,100 patients with metastatic breast cancer who have received at least 2 previous chemotherapeutic treatments in the metastatic setting (20).

Using a combination of epidemiological data and Synovate date the following patient numbers can be derived:

- Around 42,600 people were newly diagnosed with breast cancer in England and Wales during 2007 (4).
- It is estimated that 5% (n=2,130) of patients initially presenting with breast cancer will be diagnosed with LABC/MBC (8).
- In addition, around 35% (n=14,165) of those with a primary diagnosis of breast cancer at an earlier stage will develop metastases in the future (8), equating to a total of 16,295 patients with LABC/MBC.
- Based on the indication, eribulin monotherapy will be given to patients with LABC or MBC who have progressed after at least two chemotherapeutic regimens for advanced disease. Assuming that all patients receive active treatment (e.g. chemotherapy, biologic therapy, hormonal therapy), it is estimated that 61.8% (n=10,070) of these will receive first-line chemotherapy for LABC/MABC (20).
- Of those treated with chemotherapy at first-line, around 16.8% will go on to receive chemotherapy at third-line or later (20), equating to 1,692 patients who would be eligible for treatment with eribulin.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE have published two clinical guidelines for the diagnosis and treatment of breast cancer, along with cancer service guidance on improving outcomes in breast cancer. A number of technology appraisals have also been published which are of relevance to the treatment of patients with LABC/MBC, the details of all of which are provided below.

NICE Clinical Guideline No. 81, Feb 2009, 'Advanced breast cancer: diagnosis and treatment' (21).

NICE Clinical Guideline No. 80, Feb 2009, 'Breast cancer (early and locally advanced): diagnosis and treatment' (22).

NICE Guidance on Cancer Services, Aug 2002, 'Improving outcomes in breast cancer' (23). This guidance provides recommendations on the provision of services for

[a] Synovate track the usage of anti-cancer drugs, through a representative panel of cancer specialists completing forms directly from patient medical records in each country, including the UK.

the treatment, management and care of patients with breast cancer, to ensure that all breast cancer patients across England and Wales receive high-quality healthcare.

Technology Appraisal No. 116, Jan 2007, 'Gemcitabine for the treatment of metastatic breast cancer' (24). The guidance states that "Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate."

Technology Appraisal No. 34, Mar 2002, 'Guidance on the use of trastuzumab for the treatment of advanced breast cancer' (25). The guidance states that "Trastuzumab in combination with paclitaxel (combination trastuzumab is currently only licensed for use with paclitaxel) is recommended as an option for people with tumours expressing human epidermal growth factor receptor 2 (HER2) scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate. Trastuzumab monotherapy is recommended as an option for people with tumours expressing HER2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen receptor positive patients."

The following Technology Appraisals have been updated and replaced by NICE clinical guideline 81.

Technology Appraisal No. 62, May 2003, 'Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer' (26).

Technology Appraisal No. 54, Dec 2002, 'Guidance on the use of vinorelbine for the treatment of advanced breast cancer' (27).

Technology Appraisal No. 30, Sep 2001, 'Guidance on the use of taxanes for the treatment of breast cancer' (28).

In addition, three further technology appraisals are currently described as 'in process' for: lapatinib (previously treated advanced/MBC); bevacizumab (in combination with non-taxane chemotherapy for the first-line treatment of MBC); bevacizumab (in combination with a taxane for the first-line treatment of HER2 negative MBC); fulvestrant (LABC/MBC).

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The population considered suitable for eribulin treatment within this submission consists of patients with LABC/MBC, whose disease has progressed after at least two prior chemotherapy regimens in the advanced setting.

In line with the pivotal Phase III randomised, controlled trial (RCT) – EMBRACE – prior treatment must have included an anthracycline and a taxane. This population and the advanced stage of treatment at which these patients find themselves reflects the indication for eribulin, the population for which evidence is presented herein, and the anticipated place for eribulin in the clinical management pathway.

The patient population considered are a particularly difficult group to manage effectively. By this stage patients will have progressed despite treatment with anthracyclines and taxanes, and further treatment options will be of limited effectiveness. As recognised by NICE guidelines, one of the key priorities for treating this advanced stage of breast cancer is to prolong survival, while controlling the symptoms experienced and improving the patient's quality of life (8). However, none of the available treatment options have demonstrated a survival benefit over any other (8, 19) and the motivation for a patient to continue treatment may be compromised as a result.

NICE Clinical Guideline 81

Based on the NICE clinical guideline for advanced breast cancer (Clinical Guideline 81 (8, 21)), it is recommended that chemotherapy treatment in the advanced setting commences with an anthracycline-based regimen. If disease progresses following anthracycline treatment or in cases where an anthracycline is unsuitable (if the person has previously received anthracycline-based adjuvant therapy or has a contraindication to anthracyclines), systemic chemotherapy should be offered in the following sequence:

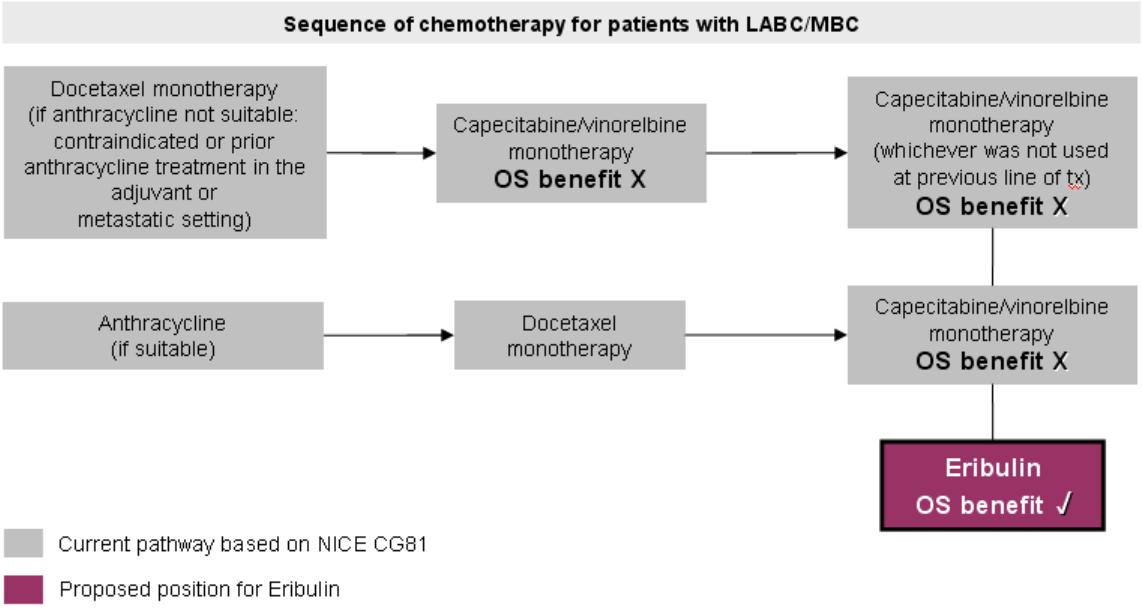
- First-line: single-agent docetaxel
- Second-line: single-agent vinorelbine or capecitabine
- Third-line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).

Gemcitabine combination therapy with paclitaxel appears to have a first-line positioning alongside docetaxel monotherapy (NICE guidance 116 (24)), however gemcitabine-based therapy is also used at second/third-line. Therefore, there may be more interventions used in clinical practice at third-line or later than those outlined in NICE clinical guideline 81.

The population considered suitable for eribulin treatment within this submission consists of patients with LABC/MBC, whose disease has progressed after at least two prior chemotherapy regimens in the advanced setting. It is therefore anticipated that eribulin will be used as a third-line chemotherapy (as an alternative to capecitabine and vinorelbine).

Therefore, the introduction of eribulin will not change the clinical pathway outlined in the NICE guideline. The current pathway below is based on NICE Clinical Guideline 81 and the proposed position of eribulin in this pathway is depicted in Figure 2.

Figure 2: Treatment pathway for advanced breast cancer



Abbreviations: CG, Clinical Guideline; LABC, Locally advanced breast cancer; MBC, metastatic breast cancer; **OS**, Overall survival.

Current clinical practice

Whilst the NICE clinical guidelines clearly defines vinorelbine monotherapy and capecitabine monotherapy as options for second-line treatment and beyond, in clinical practice, it is apparent that for patients with LABC/MBC, particularly at this advanced point in their treatment, numerous types of treatment may be used. The choice of treatment will depend on factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient's quality of life. Combination chemotherapy may be considered where a greater probability of response is important and when the patient understands and are likely to tolerate the additional toxicity associated with the treatment (8, 21).

Therefore, there may be more interventions used in clinical practice at third-line or later than those outlined in the NICE clinical guideline. However, as acknowledged by NICE (8), there is minimal high-quality evidence about the relative clinical effectiveness of current treatments, survival benefit has not been demonstrated for one treatment over another (8, 19) and overall, no optimal option is available to these patients.

It is clear that eribulin will provide a much needed treatment option for patients whose disease has progressed after at least two prior chemotherapy regimens in the advanced setting (third-line and later). Eribulin represents the first major advance in chemotherapy treatment in this setting in almost a decade. It is the first monotherapy to demonstrate statistically significant improvements in OS in LABC/MBC patients previously treated with an anthracycline and a taxane, while offering a safety and tolerability profile that is acceptable for a follow-on chemotherapeutic agent.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Pre-treated breast cancer patients, such as those considered by this submission, have very limited treatment options. The chemotherapeutic agents with the best efficacy in breast cancer, the anthracyclines and taxanes, are typically used at earlier stages of the disease, leaving many LABC/MBC patients anthracycline and taxane-resistant, and thereby limiting the number of treatment options at this stage of disease (29). The proportion of patients responding to chemotherapy declines through successive lines of treatment (18), while no RCTs of the currently available monotherapies have demonstrated a survival advantage over any other single agent in the treatment of anthracycline and taxane-resistant metastatic disease (19). This is a weakness in the clinical evidence acknowledged by NICE (8), particularly as the majority of patients believe that the primary goal of treatment is to prolong their life (17).

The tolerability of current LABC/MBC treatment varies; chemotherapy agents can be particularly toxic and are recognised to be the most burdensome aspect of cancer management for patients (30). Side effects commonly include peripheral neuropathy, alopecia, mucositis, nausea, vomiting, increased infection, and fatigue. These can adversely affect a patients' quality of life (30), be costly to manage (31), and lead to discontinuation of a particular therapy (32) in a significant number of patients, thereby impacting on overall treatment outcomes.

As such, management of patients with LABC/MBC is a trade-off between the risk of unpleasant side effects (toxicity) and the potential benefits (clinical efficacy, e.g. OS) (8); treatment choices are thus strongly influenced by physician and patient preference in terms of side effect profiles and outcomes such as OS.

Other issues relating to current practice include the inconvenience to the patient and the treating healthcare professional, and the level of resource use required for administration.

- The majority of chemotherapy regimens require IV administration and vary in their infusion times (e.g. paclitaxel is administered over 3 hours). Patients may experience difficulties with venous access as a result of multiple prior therapies, while long infusion times can be inconvenient and increase the burden to the patients' lives.
- Variability exists in frequency of dosing schedules (e.g. vinorelbine requires weekly administration). The lack of consistency and the impact that missing doses may have on clinical outcomes mean that patient outcomes may also be inconsistent.
- Many IV chemotherapy regimens require reconstitution or dilution before administration (e.g. gemcitabine, vinorelbine), increasing the burden on healthcare resources, and potentially leading to dosing errors. Vinorelbine is also a vesicant.
- Premedication with steroids and/or antihistamines to prevent hypersensitivity reactions during administration is necessary with many chemotherapeutic agents (e.g. paclitaxel). This increases the overall cost of treatment and adds to the potential drug-related adverse effects that the patient may experience.

Overall, there is a clear unmet need for new therapeutic agents that extend overall survival in LABC/MBC patients (including those that have been heavily pre-treated)

without an intolerable side effect profile, and thus maintain patients' quality of life and reduce the need for dose reductions, delays, or discontinuations.

Eribulin, a non-taxane inhibitor of microtubule dynamics, is an innovative chemotherapy treatment with a unique mechanism of action that sets it apart from members of tubulin-targeting classes currently in clinical use, including taxanes (e.g. docetaxel) and vinca alkaloids (e.g. vinorelbine). Eribulin exerts its anticancer effects by inhibiting the growth phase of microtubule dynamics, without affecting the shortening phase, and sequesters tubulin into non-productive aggregates (1).

Eribulin represents the first major advance in chemotherapy treatment in this setting in almost a decade. It is the first monotherapy to demonstrate statistically significant improvements in overall survival in LABC/MBC patients previously treated with an anthracycline and a taxane, while offering a safety and tolerability profile that is acceptable for a follow-on chemotherapeutic agent. Eribulin is generally well tolerated, with fewer discontinuations and dose interruptions due to adverse events.

Furthermore, eribulin is provided as a ready to use solution, avoiding the need for time consuming reconstitution or dilution associated with many IV chemotherapeutic agents. It is administered as a quick and convenient 2-5 minute IV infusion with no special handling or tubing required. As such, the use of eribulin may be associated with healthcare resource savings. Each cycle of treatment with eribulin consists of only two doses, administered on Days 1 and 8 of the 21-day cycle. Pre-medication (antihistamine or steroids) to prevent hypersensitivity reactions is not routinely required prior to injection.

2.6 Please identify the main comparator(s) and justify their selection.

As described in Section 2.4 there is currently no single pattern of treatment in the UK for patients in the advanced stages of breast cancer, who have already been treated with an anthracycline and a taxane. An approach for the comparator arm of any clinical study in this setting can be one of physician choice (i.e. TPC), and it is this approach that Eisai Ltd. agreed upon to use for the comparator arm of the pivotal Phase III EMBRACE study with the EMEA (as was). It can be argued that practically speaking it would not be feasible to conduct large scale trials to compare eribulin with individual therapies due to the diversity of treatment used at this stage of the disease. Using TPC as a comparator allows treatment selection to be based on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient's quality of life, representing the choices regularly taken in clinical practice. Offering patients a choice of treatment and taking their preferences into account is crucial to this approach, as recognised by the NICE cancer services guidance (23).

By using TPC as a comparator in clinical trials and in this submission, a pragmatic approach is employed to compare eribulin to the current treatment landscape, consisting of a variety of therapeutic options instituted by practicing physicians on a day-to-day basis. EMBRACE is the first trial of this kind to effectively compare an investigational agent to such real-life choices in the pre-treated LABC/MBC patient population, and by doing so it is believed to provide the best assessment of the value of eribulin for this

population. This approach is directly relevant to the UK, given that 10 UK centres were included in the EMBRACE study.

NICE guidance to manufacturers on the technology appraisal process (33) recognises that comparators should be selected based on current standard of care, and that standard of care will vary across the NHS. The mixture of therapies currently used in clinical practice in the UK, and those chosen by physicians within the EMBRACE trial validate the TPC approach agreed with the EMEA and the approach taken within this submission.

As such, the approach taken reflects that of the primary analysis of the EMBRACE study; eribulin compared with TPC. In line with the final scope, comparisons with specific chemotherapeutic agents (gemcitabine, vinorelbine and capecitabine) have also been included. The emphasis given to such individual treatment comparisons should be balanced by an understanding of the diversity of options currently employed in clinical practice, as outlined above.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The safety profile of eribulin is acceptable for a chemotherapeutic agent in the follow-on setting and the drug is generally well tolerated. Anticipated Grade 3 or 4 (severe or life-threatening) toxicities with an incidence of ≥ 1% include neutropenia, leucopoenia, fatigue/asthenia, peripheral neuropathy and febrile neutropenia (summary of product characteristics [SPC], Appendix Section 9.1). Such toxicities are expected to be managed either in an outpatient or inpatient setting as with other chemotherapy regimens.

Anti-emetics are commonly used as supportive treatment in line with local hospital protocols. Eribulin treatment would not be associated with the need for any specific additional supportive treatment, over and above current chemotherapeutic options.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

LABC/MBC is generally managed by a multi-disciplinary healthcare team in tertiary, secondary and primary care. The location of care, along with staff usage, and the cost of administration, monitoring and tests would be similar to IV chemotherapeutic agents currently used in clinical practice. As such, the introduction of eribulin is not anticipated to require additional resource over and above the current provision of IV chemotherapeutic agents within the NHS.

On the contrary, compared with many current chemotherapeutic agents, eribulin may reduce the resource burden, while providing a more convenient method of dosing and administration for the patient and the healthcare professional, as described in Section 2.5.

2.9 Does the technology require additional infrastructure to be put in place?

No, the infrastructure for the administration of chemotherapeutic agents for the treatment of breast cancer is already in position within the NHS.

2.10 Appraising the value of innovation

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Eribulin is the first and only single agent therapy to demonstrate a significant overall survival benefit in patients with late stage LABC/MBC, a patient population with few treatment options and an unmet medical need. At this stage of treatment there is no clear standard of care as none of the current treatments have demonstrated a survival benefit over any other.

Many people with LABC/MBC see their disease progress after receiving multiple therapies. Now with eribulin people can be offered a new option that has been show to improve survival with metastatic disease.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Eribulin is administered as a quick and convenient 2-5 minute IV infusion with no special handling or tubing required, thereby reducing the inconvenience and burden to the patient associated with longer infusion times. The potential impact of this is has not been captured in the health economic evaluation, but the potential savings in associated healthcare resources, e.g. nursing time, should be realised.

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

Clinical data to support the overall survival benefit with eribulin is taken from the pivotal Phase III EMBRACE study and is described in detail in Section 5.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

No specific equity and equality issues.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No specific equity and equality issues.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

N/A – no equity or equality issues.

4 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease and whose disease has progressed.	As defined by scope	As per licensed indication: Treatment of patients with locally advanced or metastatic breast cancer that have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.
Intervention	Eribulin monotherapy	As defined by scope	N/A
Comparator(s)	Vinorelbine Capecitabine Gemcitabine	TPC Vinorelbine Capecitabine Gemcitabine	The selection of TPC as a comparator reflects the real life choices for LABC/MBC patients who have already been treated with an anthracycline and a taxane. There is currently no single pattern of treatment in the UK for patients at this stage of the disease. An approach for the comparator arm of any clinical study in this setting can be one of physician choice (i.e. TPC), and it is this approach that Eisai Ltd. agreed upon to use for the comparator arm of the pivotal Phase III EMBRACE study with the EMEA (as was). Treatment in this setting is based on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient's quality of life, representing the choices regularly taken in clinical practice. This is reflected in the Treatment of Physician's Choice. Offering patients a choice of treatment and taking their preferences into account is crucial to this approach, as recognised by the NICE cancer services guidance (23). By using TPC as a comparator in clinical trials and in this submission, a pragmatic approach is employed to compare eribulin to the current treatment landscape, consisting of a variety of therapeutic options instituted by practicing physicians on a day-to-day basis. EMBRACE is the first trial of this kind to effectively compare an investigational agent to such real-life choices in the pre-treated LABC/MBC patient population, and by doing so it is believed to provide

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			the best assessment of the value of eribulin for this population. NICE guidance to manufacturers on the technology appraisal process (33) recognises that comparators should be selected based on current standard of care, and that standard of care will vary across the NHS. The mixture of therapies currently used in clinical practice at this stage of the disease in the UK, validate the TPC approach. This reflects the primary analysis of the EMBRACE study; eribulin compared with TPC. In line with the final scope, comparisons with specific chemotherapeutic agents have also been included. The emphasis given to such individual treatment comparisons should be balanced by an understanding of the diversity of options currently employed in clinical practice, as outlined above.
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment HRQL	As defined by scope	N/A
Economic analysis	Cost per QALY. Time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services	As defined by scope. Time horizon for estimating clinical and cost effectiveness will be patients' lifetime (base case), and as such will be sufficient to capture differences in costs and outcomes between the interventions compared.	N/A

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	perspective.		
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	The decision problem addressed by this submission reflects the indication for eribulin (see Section 1.5).	N/A

Abbreviations: EMEA, European Medicines Agency; FDA, Food and Drug Administration; HRQL, health-related quality of life; LY, life year; MBC, metastatic breast cancer; NHS, National Health Service; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

Section B – Clinical and cost effectiveness

5 Clinical evidence

Summary of efficacy and safety

- The efficacy, safety and tolerability of eribulin for the treatment of patients with late-stage breast cancer has been demonstrated in a pivotal Phase III, randomised, controlled open-label trial (EMBRACE) (34-36), and in three supporting Phase II, single-arm studies (37-42).

- EMBRACE study compared eribulin with Treatment of Physician's Choice (TPC). The TPC arm included currently available monotherapies, including capecitabine, gemcitabine and vinorelbine, used in LABC/MBC† treatment. At least two regimens had to have been given for LABC/MBC and prior therapy had to include an anthracycline and a taxane. It is the first and only study of LABC/MBC treatment designed to reflect real-world clinical experience in this specific patient population.
  - The average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving chemotherapy (14)
  - The absence of a proven regime to extend overall survival (OS) in this patient population (8, 19) has led to wide variability in the treatments selected for use. In light of this, there is no specific standard of care but rather a range of therapies that may be selected based upon patient and physician preference.
  - The TPC approach was supported by the EMEA, and allows treatment selection to be based on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient's quality of life. This reflects both typical clinical practice, and individual physician and patient preference for treatment.
  - By comparing to current clinical practice rather than a specific agent, the EMBRACE trial provides the best assessment of the value of eribulin for this patient population. Sub-group analyses do allow comparison of eribulin with capecitabine, vinorelbine and gemcitabine, as identified in the NICE scope.
  - For all patients enrolled in the EMBRACE study a TPC agent was discussed between the physician and the patients in order to ensure the most appropriate treatment was selected for them before being randomised in the study.
  - Despite the option of best supportive care and radiotherapy, all treated patients in the TPC arm received pharmacotherapy; 93.7% of patients (ITT population) received chemotherapy, including vinorelbine (24.0%), gemcitabine (18.1%), capecitabine (17.3%), taxanes (15.0%), and anthracyclines (9.4%). Hormonal treatment was given to 3.5% of patients. Although biologic therapy was a treatment option, no patients received this treatment.
  - Eribulin was administered at 1.23 mg/m^2 IV (equivalent to 1.4 mg/m^2 eribulin mesylate) over 2–5 minutes on Days 1 and 8 of a 21-day cycle, with no requirement for pre-medication (antihistamine or steroids) to prevent hypersensitivity reactions, unlike many IV chemotherapeutic agents.

- There is minimal high-quality evidence for the relative clinical effectiveness of current therapies in this specific patient population (8), and although OS is recognised as the most reliable cancer outcome (15, 16) and is of most importance to patients (17), no single agent has demonstrated a survival benefit over any other (8, 19).
- In contrast, eribulin is the first monotherapy to demonstrate a statistically significant improvement in OS in comparison to another treatment, for this specific population with pre-treated LABC/MBC.
    - In the EMBRACE trial, the primary outcome of median OS with eribulin was 13.1 months (n=508) compared with 10.6 months (n=254) for TPC (p = 0.041), an increase in duration of survival of 23% (2.5 months) that reflects a 19% reduction in the risk of death (primary analysis after 55% of patients had died).
    - The benefit of eribulin was apparent within one year; for patients in the eribulin group, the one-year survival rate estimate was 53.9% compared with 43.7% for patients in the TPC group.
    - Updated analysis as requested by regulatory authorities, performed after 77% of patients had died, confirmed these results; median OS (eribulin 13.2 months vs. TPC 10.5 months) was improved by 2.7 months (p=0.014).
    - Planned sub-group analysis of patients from geographical region 1 (North America/Western Europe/Australia) showed a significant OS benefit of eribulin over TPC of 3.1 months in the primary analysis (p=0.009) and the updated analysis (p=0.031).
    - The clinical benefit of eribulin was maintained versus capecitabine, vinorelbine and gemcitabine, as identified in the NICE scope.

      [redacted]

      These analyses included only eribulin patients who would have received that specific drug had they been randomised to the TPC arm, and hence maintains randomisation for these individual comparisons.
- Eribulin also demonstrates superior efficacy for patients with pre-treated LABC/MBC when compared with TPC in a number of secondary outcomes.
    - Median progression free survival (PFS) was 3.6 months for eribulin and 2.2 months for TPC, when assessed by investigator review (p = 0.002), and 3.7 months and 2.2 months, respectively, when assessed by independent review (p = 0.137).
    - Outcomes of objective response rate (ORR; a complete response or a partial response) and clinical benefit rate (CBR; a complete response or partial response or stable disease for at least 6 months) were also positive for eribulin, compared with TPC.
- Three single-arm Phase II studies provide further evidence for the efficacy and safety of eribulin, and support the results demonstrated in the Phase III EMBRACE study.
- Phase II data suggests that HRQL does not deteriorate and in many patients

improves in patients who have objective positive tumour response to eribulin treatment, whereas patients who progress may suffer deterioration in their HRQL.

- Eribulin is associated with a predictable and well-characterised safety profile and is generally well-tolerated, for a chemotherapeutic agent being used in pre-treated LABC/MBC patients
  - In the EMBRACE study, overall rates of adverse events (AEs) experienced with eribulin are acceptable for a chemotherapeutic agent in the follow-on LABC/MBC setting, with the majority of AEs experienced being mild or moderate (Grade 1 or 2).
  - The most frequently reported AEs (of any grade) with eribulin therapy were asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy (32%)and nausea (both 34.6%) (Consistent with the pooled safety analysis presented in the SPC [See Appendix, Section 9.1]).
  - Grade 3/4 AEs of neutropenia occurred in 21.1% and 24.1% of patients, respectively. However, neutropenia led to discontinuation in only 0.6% of patients, while febrile neutropenia (4.6%) and thrombocytopenia (2.6%) were infrequent. Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the study (unless defined by local practice protocols).
  - Peripheral neuropathy, a common chemotherapy side effect, was generally mild/ moderate (Grade 1/2), with Grade 3/4 peripheral neuropathy being infrequent (~8%); of those patients with Grade 3/4 peripheral neuropathy, 63% were able to continue treatment. There is no evidence that patients who were enrolled in the study with pre-existing neuropathy were more likely to develop new or worsening symptoms than those who entered the study without the condition.
  - Eribulin is generally well tolerated, with fewer discontinuations and dose interruptions due to AEs than TPC in the EMBRACE study.
  - As a result, the duration of therapy in EMBRACE was longer in the eribulin arm than the TPC arm, reflecting the promising efficacy and safety profile of this agent for the follow-on treatment of LABC/MBC.

- Based on NICE's supplementary advice on end-of-life treatment, eribulin would appear to meet the key criteria for life extending, end-of life treatments.
  - Average survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving chemotherapy (14).
  - The EMBRACE study shows that eribulin can provide at least 3 months of additional survival, compared with TPC, capecitabine, vinorelbine and gemcitabine.
  - A small cohort of around 1,100-1,700 patients would be eligible to be considered for eribulin therapy.
- For pre-treated patients with LABC/MBC, for which there is minimal high-quality evidence and no monotherapy has demonstrated a survival benefit over any other, there is clear evidence that eribulin provides statistically significant and clinically meaningful improvements in survival compared with current treatment options, combined with an acceptable safety and tolerability profile.

†Defined in the EMBRACE study as locally recurrent or MBC.

5.1 Identification of studies

A systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of eribulin. Ovid Medline(R) In-Process & Other Non-Indexed Citations and Ovid Medline(R), Embase (Ovid) and The Cochrane Library (incorporating the Central Register of Controlled Trials, CENTRAL) were searched with no restrictions on date or language of publication. This was supplemented by additional searching of www.clinicaltrials.gov and conference proceedings from ASCO. The manufacturer's clinical trial database was also searched for all completed studies from the eribulin clinical trial programme and these were also assessed for inclusion, including unpublished studies.

Using Boolean operators, the searches used terms (including MeSH headings as appropriate) for eribulin, including any alternative names (e.g. Halaven, E7389). Since the searches returned very few results from the three electronic databases (n=146) no additional search terms for disease or study design were included.

The search strategy is provided in Section 9.2.

5.2 Study selection

5.2.1 Eligibility criteria

Studies identified (i1) were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded (e1), and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage (i2) were then assessed based on the full text; further papers were excluded (e2), yielding the final data set for inclusion (i3). The final included data set consisted of clinical studies for eribulin.

Inclusion and exclusion selection criteria are shown in Table 2.

Table 2: Eligibility criteria used in search strategy

	Description	Justification
Inclusion criteria		
Population	Patients with locally advanced or metastatic breast cancer	As specified by the NICE scope
Interventions	Eribulin (or various names thereof, e.g. E7389)	Technology under appraisal
Outcomes	Overall survival, progression-free survival, response rate, adverse effects of treatment, HR-QL	As specified by the NICE scope
Study design	RCTs, observational studies, Phase II-III	RCTs prioritised as per STA guidance. Non-randomised evidence (e.g. observational data, open label clinical trials) were also identified by the search for possible inclusion.

	Description	Justification
Language restrictions	None	
Exclusion criteria		
Population	Patients with any other disease, including earlier stages of breast cancer	As specified by the NICE scope
Interventions	Other interventions used for the treatment of locally advanced or metastatic breast cancer	No further evidence for comparator treatments was sought, due to the availability of head to head data from the pivotal Phase III RCT for eribulin
Outcomes	Pharmacokinetic, pharmacodynamic outcomes (bioavailability, dose ranging)	Not relevant to the decision problem
Study design	Letters, Reviews	These types of records represent lower levels of evidence and were excluded to minimise potential sources of bias.
Language restrictions	None	

Abbreviations: RCT, randomised, controlled trial; STA, Single Technology Appraisal; NICE, National Institute for Health and Clinical Excellence.

5.2.2 Flow diagram of included and excluded studies

Following assessment and exclusion of studies based on title, abstract and full text, 15 records, including clinical study reports (CSRs) were identified in total covering four eribulin studies (EMBRACE [Study 305], Study 201, Study 211, Study 221) (34-48).

Four records were conference abstracts for studies that have been subsequently published as full manuscripts.

- Blum et al (43) and Blum et al (44) are both conference abstracts of Study 201, subsequently published by Vahdat et al (38).
- Vahdat et al (45) is a conference abstract of Study 211, subsequently published by Cortes et al (40).
- Cortes et al from 2008 (46) is a conference abstract presenting data for both Study 201 and 211.

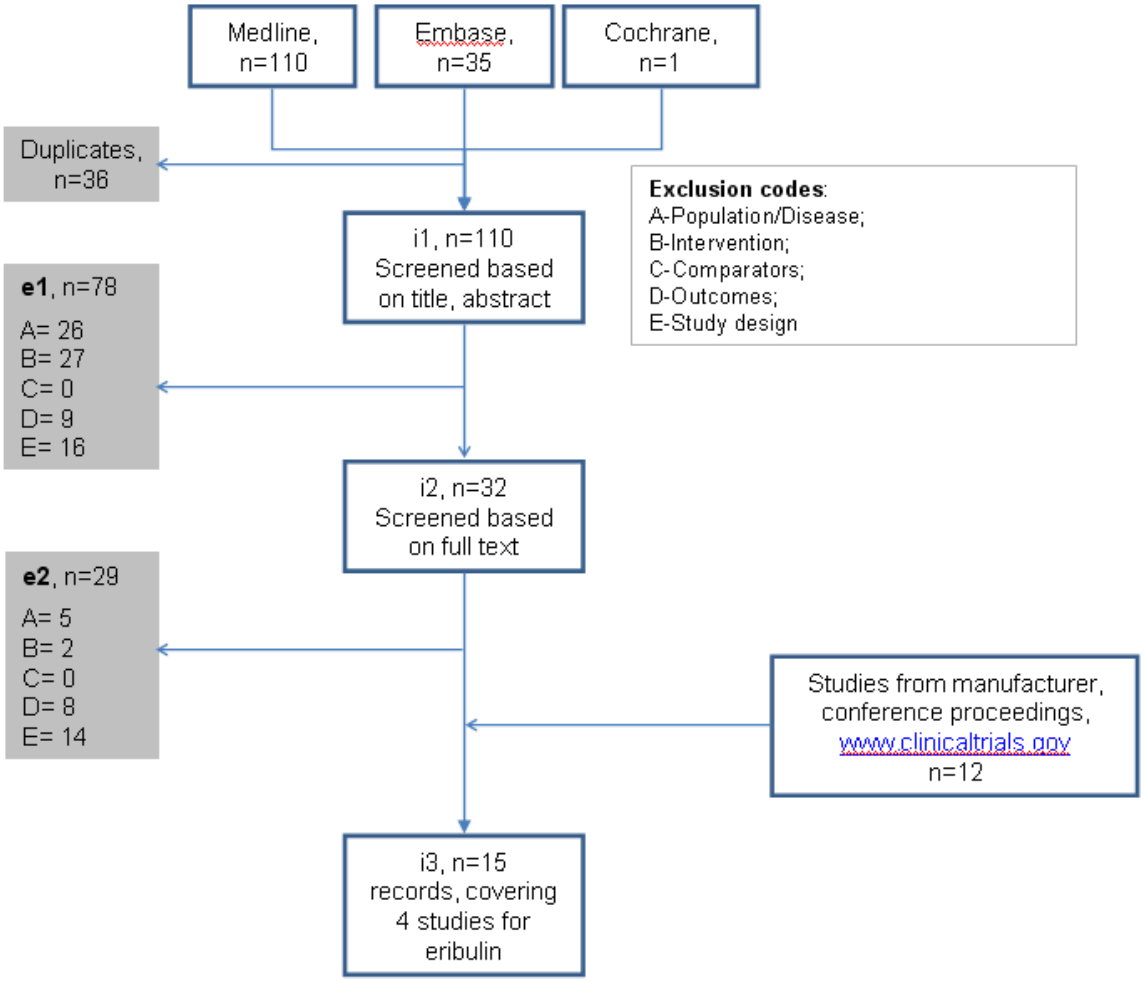
In addition, Twelves et al (36) report on the pivotal Phase III eribulin EMBRACE study (Study 305) in conference abstract form. One manuscript by Twelves et al (35) only reports on the methodology for the EMBRACE study, however this has been included for completeness. An additional clinical study report (47) and a conference poster (48), both detailing additional analyses of overall survival for the EMBRACE study are also included. The study was recently published online (85).

There are no sources in the current document.

A list of excluded studies is provided in Section 9.2.

The flow diagram for the systematic review is shown in Figure 3.

Figure 3: Flow diagram for the systematic review of clinical evidence



5.2.3 Data sources of identified studies

One RCT for eribulin (EMBRACE) was identified in the searches and is described further in this submission. The main sources of information for this trial are listed below.

Pivotal Phase III EMBRACE (Study 305)

- Twelves et al (35) and Twelves et al (36).
- Additional information was drawn from the CSR for the EMBRACE study (E7389-G000-305) (34), as well an additional study report (47) and a conference poster (48), both detailing additional analyses of overall survival from the EMBRACE study.

In addition, three Phase II non-randomised, open-label studies are described further in this submission, providing supporting evidence. The main sources of information for these trials are listed below.

Phase II Study 201

- Vahdat et al (38)
- Additional information was drawn from the CSR (37).

Phase II Study 211

- Cortes et al (40)
- Additional information was drawn from the CSR (39).

Phase II Study 221

- Iwata et al (42)
- Additional information was drawn from the CSR (41).

5.2.4 Complete list of relevant RCTs

The systematic review of clinical evidence identified one RCT of eribulin in the population of interest to this submission (Table 3).

Table 3: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Objective	Primary study ref.
EMBRACE (Study 305); Phase III, randomised, open-label, randomised parallel two-arm, multi-centre study	Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen). (Equivalent to 1.23 mg/m^2 of eribulin, as stated in the SPC)	TPC which could consist of any monotherapy (chemotherapy, hormonal, biologic) or supportive care only.	Patients with LABC/MBC† that had received two to five prior chemotherapy regimens (≥ two for advanced disease), including an anthracycline and a taxane, unless contraindicated.	Primary objective: to evaluate the OS of patients treated with eribulin versus TPC. Secondary objectives: to evaluate PFS, ORR, duration of response and safety.	CSR (34). Supporting references: Twelves et al (35); Twelves et al (36); Twelves et al (48); Additional study report of overall survival (47).

Abbreviations: CSR, clinical study report; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; LABC, Locally advanced breast cancer; MBC, metastatic breast cancer; TPC, Treatment of Physician's Choice. †Defined in the EMBRACE study as locally recurrent or MBC.

5.2.5 Studies comparing the intervention directly with the appropriate comparator(s) stated in the decision problem

The pivotal Phase III eribulin EMBRACE study compares eribulin with treatment in the form of Treatment of Physician's Choice (TPC), comprising any monotherapy for the treatment of breast cancer available to the study investigators. TPC is described in more detail in Section 5.3.1. However, TPC did include the three chemotherapy agents identified in the NICE scope – capecitabine, gemcitabine and vinorelbine. Analyses of eribulin versus TPC and versus these three individual agents are presented within the clinical sections.

5.2.6 Studies excluded from further discussion

None of the identified studies were excluded from further discussion.

5.2.7 List of relevant non-RCTs

The non-RCTs relevant to this submission are summarised in Table 4.

Table 4: List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
Study 201; Phase II, single-arm, open-label, multi-centre study.	Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1, 8 and 15 of a 28-day cycle (n=70). Because of neutropenia (at Day 15), a further cohort of patients (n=33) was added to explore an alternative regimen of eribulin; 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen).	Patients with advanced/ metastatic breast cancer who had previously received treatment with at least an anthracycline and a taxane.	Primary objective: to assess the response rate (ORR) to eribulin. Secondary objectives: to evaluate duration of response, PFS, OS, and safety.	CSR (37); Vahdat et al (38)	Provides supporting efficacy and safety evidence for eribulin in the population of relevance to the decision problem.
Study 211; Phase II, single-arm, open-label, multi-centre study.	Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen).	Patients with LABC/MBC, previously treated with an anthracycline, a taxane and capecitabine.	Primary objective: to assess the response rate (ORR) to eribulin. Secondary objectives: to evaluate duration of response, PFS, OS, and safety.	CSR (39); Cortes et al (40)	Provides supporting efficacy and safety evidence for eribulin in the population of relevance to the decision problem.
Study 221; Phase II, single arm, open-label, multi-centre study.	Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen).	Japanese patients with LABC/MBC, previously treated with an anthracycline, a taxane.	Primary objective: to assess the response rate (ORR) to eribulin, and safety. Secondary objectives: to evaluate duration of response, PFS and OS.	CSR (41); Iwata et al (42)	Provides supporting efficacy and safety evidence for eribulin in the population of relevance to the decision problem.

Abbreviations: CSR, Clinical study report; LABC, locally advanced breast cancer; MBC, Metastatic breast cancer; ORR, objective response rate; OS, Overall survival PFS, Progression-free survival.

5.3 Summary of methodology of relevant RCTs

5.3.1 Methods: EMBRACE (Study 305)

Context: Treatment comparator (TPC)

EMBRACE, the pivotal Phase III eribulin RCT, compared the efficacy and safety of eribulin with Treatment of Physician's Choice (TPC). The selection of TPC as a comparator reflects the real life choices for MBC patients who have already been treated with an anthracycline and a taxane.

There is currently no single pattern of treatment in the UK for patients at this stage of the disease, as described in Section 2.4. An approach for the comparator arm of any clinical study in this setting can be one of physician choice (i.e. TPC), and it is this approach that Eisai Ltd. agreed upon to use for the comparator arm of the EMBRACE study with the EMEA (as was). Using TPC as a comparator allows treatment selection to be based on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient's quality of life, representing how treatment decisions are made in clinical practice. Offering patients a choice of treatment and taking their preferences into account is crucial to this approach, as recognised by the NICE cancer services guidance (23), and reflects current practice.

In the EMBRACE study TPC was defined as any available single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care. For all patients enrolled in the EMBRACE study a TPC agent was first defined by the physician and this choice could be discussed with the patient to ensure the most appropriate treatment was selected for them.

By using TPC as a comparator in clinical trials and in this submission, a pragmatic approach is employed to compare eribulin to the current treatment landscape, consisting of a variety of therapeutic options instituted by practicing physicians on a day-to-day basis. EMBRACE is the first trial of this kind to effectively compare an investigational agent to such real-life choices in the pre-treated MBC patient population, and by doing so it is believed to provide the best assessment of the value of eribulin for this population. This approach is directly relevant to the UK, given that 51 patients at 10 UK centres were treated in the EMBRACE study; UK based patients in the TPC arm (n=13) were given a variety of monotherapies including capecitabine, vinorelbine, gemcitabine, carboplatin and paclitaxel.

NICE guidance to manufacturers on the technology appraisal process (33) recognises that comparators for technology appraisals should be selected based on current standard of care, and that standard of care will vary across the NHS. The mixture of therapies currently used in clinical practice in the UK, and those chosen by physicians within the EMBRACE trial would appear to validate the TPC approach supported by regulators for the EMBRACE study.

Methodology

The methodology of the EMBRACE study is summarised in Table 5.

Table 5: Methodology: EMBRACE study

	Details
Objective	Primary objective: To evaluate the overall survival of patients treated with eribulin versus TPC in patients with LABC/MBC[†], who had received two to five prior chemotherapy regimens. Secondary objectives: To evaluate PFS, ORR, duration of response and safety.
Location	Conducted in 135 centres in 19 countries (Argentina, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and the United States). Fifty-one patients at 10 centres in the United Kingdom

	Details
	were treated.
Design	A multi-centre, Phase III, open-label, randomised parallel two-arm study, conducted in 762 patients (508 eribulin, 254 TPC) with LABC/MBC†. Patients had previously been treated with between two and five chemotherapy regimens, including a taxane and an anthracycline; at least two regimens had to have been given for LABC/MBC.
Duration of study	The primary analysis of OS was carried out when 55% (422) of patients had died. At this point the median OS was 13.1 months and 10.6 months in the eribulin and TPC arms, respectively. The study is however, still in active follow up.
Method of randomisation	Patients were pre-stratified according to geographical region, HER2 status, and prior treatment with capecitabine, and then randomised in a 2:1 ratio to receive either eribulin or TPC. For all patients in the study a TPC agent was first defined; physicians could discuss the TPC option with the patient to ensure the most appropriate treatment was selected for them. The agent of the patient's and physician's choice was then confirmed by the investigator using an interactive voice response system. Patients were then stratified and randomised to one of the two treatment arms according to a randomisation schedule. Centres were required to enter patient identification and information on stratification factors. Treatment allocation and a randomisation number were given for each patient. This process ensured that each agent of the physician's choice was independently randomised against eribulin to support subgroup analyses.
Method of blinding	Investigators and patients were not blinded to study treatment as this was an open-label study. However, the Eisai study team was blinded to data for the primary outcome (OS) until database lock to avoid potential bias. Independent statisticians conducted an interim analysis – after 50% of the planned deaths had been observed – and assisted with queries surrounding all death events.
Intervention and comparator	Eribulin (n=508, randomised) • Eribulin mesylate administered as an IV infusion of 1.4 mg/m^2 over 2–5 minutes on Days 1 and 8 of a 21 day cycle. • There was no requirement for pre-medication (antihistamine/ steroids) to prevent hypersensitivity reactions, unlike many IV chemotherapy agents. TPC (n=254, randomised) • Defined as any available single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; radiotherapy; or best supportive care, administered according to local practice. The use of other investigational drugs, or products not registered for cancer treatment was not permitted. Although best supportive care and radiotherapy were treatment options, all patients in the TPC group received pharmacotherapy. Patients could have received biologic therapy (trastuzumab) in centres where this was available; however, no patients actually received this therapy (see Section 5.3.7). • Combination therapies were not allowed, reflecting the higher toxicity generally associated with these treatments (8), and their relatively low use in clinical practice in later lines of therapy.
Permitted and disallowed concomitant medications	Medications allowed during the study included: any medication considered necessary for the patient's welfare that was not expected to interfere with the evaluation of the study, at the discretion of the investigator. Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the study (unless defined by local practice protocols). Medications disallowed in the eribulin group during the study included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone

	Details
	therapy, radiation therapy, gene therapy, biologics, or immunotherapy. Medications disallowed in the TPC group included: any other anti-tumour therapy not identified as the TPC; any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert.
Discontinuation of study therapy	Patients continued on study treatment until unacceptable toxicity, progression of disease, or until in the opinion of the investigator, discontinuation of therapy was in the best interest of the patient. Patients who demonstrated clinical benefit continued treatment for as long as this was sustained.
Assessments	Survival was recorded during the study and following treatment discontinuation for any reasons other than consent withdrawal. Follow-up for survival was assessed at three-monthly intervals until death. Tumour assessment was performed according to the RECIST methodology (49). Baseline tumour assessments were performed within 4 weeks of the start of treatment, consisting of: CT or MRI scans of the chest, abdomen, pelvis, and any other areas of suspected disease; photographs of skin lesions (if present); and bone scans. Tumour assessments were performed in all patients at eight-weekly intervals (± 1 week), or sooner if there was suspicion of disease progression. Scans and photography were performed in those areas where disease was found at baseline, and in any new areas of suspected disease. Bone scans were only repeated during the study if clinically indicated. Tumour responses were confirmed by a second assessment ≥ 4 weeks later. Patients with CR/PaR or SD (See Section 5.3.4), who withdrew from treatment before disease progression, continued to have tumour assessments every 3 months until progressive disease or the start of a new anticancer treatment. Tumour assessments were made by investigators via imaging data and clinical examinations. Imaging data was independently reviewed (CT, MRI, bone scans, x-rays, and photographs) in a blinded fashion at a central facility. Efficacy outcomes of tumour response were presented for both investigator and independent reviews.
Primary outcomes	OS (described in further detail in Section 5.3.4).
Secondary outcomes	• PFS • ORR • Duration of response • Safety (Efficacy outcomes described in further detail in Section 5.3.4).
Duration of follow-up	Follow-up for the primary outcome (OS) was assessed at three-monthly intervals until death.

Abbreviations: CR, Complete response; CT, Computed tomography; HER2, Human epidermal growth factor receptor 2; ITT, Intent-to-treat; LD, Longest diameter; MBC, Metastatic breast cancer; MRI, Magnetic resonance imaging; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PP, Per protocol; PaR, Partial response; RECIST, Response evaluation criteria in solid tumours; SD, Stable disease; TPC, Treatment of Physician's Choice. †Defined in the EMBRACE study as locally recurrent or MBC.

5.3.2 Participants: EMBRACE (Study 305)

The inclusion and exclusion criteria for the relevant RCTs are summarised in Table 6.

Table 6: Eligibility criteria of the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
EMBRACE (Study 305)	Patients eligible for the study had to meet the following criteria: • Female patients aged ≥ 18 years with confirmed carcinoma of the breast. • Patients with LABC/MBC† who had received between two and five prior chemotherapeutic regimens: ○ Regimens had to include an anthracycline and a taxane in any combination or order. ○ One or two of these regimens could have been administered as adjuvant and/or neoadjuvant therapy, but at least two had to be given for relapsed or metastatic disease. ○ Patients had proved refractory to the most recent chemotherapy, documented by progression on or within 6 months of therapy. ○ Patients with HER2 positive tumours could have additionally been treated with trastuzumab. ○ Patient could additionally have been treated with hormone therapy. • Resolution of all chemotherapy or radiation-related toxicities to Grade 1 severity or lower, except for stable sensory neuropathy to ≤ Grade 2 and alopecia. • ECOG performance status of zero to two. • Life expectancy of ≥ 3 months. • Adequate renal, bone marrow and liver function, as determined by laboratory tests, based on pre-specified values. • Patients willing and able to comply with the study protocol and gave written consent.	Patients were excluded from the study for any of the following: • Patients who had received chemotherapy, trastuzumab or hormonal therapy within 3 weeks, or any investigational drug within 4 weeks of commencing treatment. • Radiation therapy encompassing > 30% of marrow. • Prior treatment with mitomycin C or nitrosourea. • Pulmonary lymphangitic involvement that resulted in pulmonary dysfunction requiring active treatment. • Patients with brain or subdural metastases, unless they had completed local therapy and had discontinued use of corticosteroids for this indication for ≥ 4 weeks before starting study treatment. • Patients with meningeal carcinomatosis. • Patients who were receiving anti-coagulant therapy (warfarin or related compounds), other than for line patency, and could not have been changed to heparin-based therapy if randomised to eribulin. If a patient was to continue on mini-dose warfarin, then they were to be closely monitored. • Severe/uncontrolled intercurrent illness/infection, significant cardiovascular impairment or known positive HIV status. • Patients with organ allografts requiring immunosuppression. • Patients with pre-existing neuropathy > Grade 2 (≤ Grade 2 neuropathy did not preclude a patient from being enrolled). • Patients with a hypersensitivity to Halichondrin B and/or a chemical derivative. • Patients with a prior malignancy (other than previous breast cancer, carcinoma in situ of the cervix, or non-melanoma skin cancer), unless

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		diagnosed and definitively treated ≥ 5 years previously with no evidence of recurrence. • Women who were pregnant/ breast-feeding; women of childbearing potential with a positive pregnancy test at screening/ no pregnancy test/ surgically sterile/ using adequate contraception measures.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; HER2, Human epidermal growth factor receptor 2; HIV, Human Immunodeficiency Virus; LABC, Locally advanced breast cancer; MBC, Metastatic breast cancer.
†Defined in the EMBRACE study as locally recurrent or MBC.

5.3.3 Baseline characteristics: EMBRACE (Study 305)

Demographic data for all patients included in the EMBRACE study are shown in Table 7. The median age of patients was 55 years, 92.3% of patients were white, and most (75.9%) patients were post-menopausal. The two treatment groups were well balanced in terms of demographic characteristics.

Table 7: Patient demographics: EMBRACE study (ITT population)

Characteristic	Eribulin (N=508)	TPC (N=254)	Total (N=762)
Median Age (range)	55.0 years (28–85)	55.0 years (27–81)	55.0 years (27–85)
Age distribution, n (%)			
< 40 yrs	34 (6.7%)	17 (6.7%)	51 (6.7%)
≥ 40 – < 65 yrs	380 (74.8%)	180 (70.9%)	560 (73.5%)
≥ 65 yrs	94 (18.5%)	57 (22.4%)	151 (19.8%)
Race, n (%)			
Caucasian	470 (92.5%)	233 (91.7%)	703 (92.3%)
Black	20 (3.9%)	14 (5.5%)	34 (4.5%)
Asian/Pacific Islander	3 (0.6%)	2 (0.8%)	5 (0.7%)
Other	15 (3.0%)	5 (2.0%)	20 (2.6%)
Geographic region, n (%)			
North America, Western Europe, Australia	325 (64.0%)	163 (64.2%)	488 (64.0%)
Eastern Europe	129 (25.4%)	64 (25.2%)	193 (25.3%)
Latin America, South Africa	54 (10.6%)	27 (10.6%)	81 (10.6%)
Reproductive status, n (%)			
Fertile	46 (9.1%)	20 (7.9%)	66 (8.7%)
Post-menopausal	379 (74.6%)	199 (78.3%)	578 (75.9%)
Surgically sterile	78 (15.4%)	35 (13.8%)	113 (14.8%)
Infertile	5 (1.0%)	0	5 (0.7%)

Abbreviations: TPC, Treatment of Physician's Choice.

The eribulin and TPC groups were also well-matched in terms of prior chemotherapy regimens received by the patients, and baseline disease and tumour characteristics (e.g. HER2 status, ER/PR status, and site of disease) (Table 8). Overall, 42.0% of patients had an ECOG performance status of 0; 48.6% and 8% of patients had an ECOG performance status of 1 and 2, respectively. The median duration of disease was 5.2 years in all patients and the most common tumour site involved in disease at baseline was bone, reported in 464 (60.9%) patients.

Table 8: Baseline characteristics: EMBRACE study (ITT population)

Characteristic	Eribulin (N=508)	TPC (N=254)	Total (N=762)
Median time since original diagnosis (range)	5.4 years (0.1, 37.4)	5.1 years (0.6, 22.9)	5.2 years (0.1, 37.4)
ER Status, n (%)†			
+	336 (70.0%)	171 (70.4%)	507 (70.1%)
–	143 (29.8%)	72 (29.6%)	215 (29.7%)
Unknown	1 (0.2%)	0	1 (0.1%)
PR Status, n (%)†			
+	254 (56.2%)	123 (54.7%)	377 (55.7%)
–	197 (43.6%)	102 (45.3%)	299 (44.2%)
Unknown	1 (0.2%)	0	1 (0.1%)
HER2 status, n (%)†			
+	83 (18.0%)	40 (17.2%)	123 (17.8%)
–	373 (81.1%)	192 (82.8%)	565 (81.6%)
Unknown	4 (0.9%)	0	4 (0.6%)
Triple negative (ER/PR/HER2-negative), n (%)†	93 (18.3%)	51 (20.9%)	144 (19.8%)
No. of organs involved‡, n (%)			
1	85 (16.7%)	35 (13.8%)	120 (15.7%)
2	172 (33.9%)	82 (32.3%)	254 (33.3%)
3	145 (28.5%)	77 (30.3%)	222 (29.1%)
4	71 (14.0%)	37 (14.6%)	108 (14.2%)
5	24 (4.7%)	16 (6.3%)	40 (5.2%)
≥ 6	9 (1.8%)	7 (2.8%)	16 (2.1%)
Tumour sites in > 10% patients overall, n (%)			
Bone	306 (60.2%)	158 (62.2%)	464 (60.9%)
Liver	296 (58.3%)	159 (62.6%)	455 (59.7%)
Lymph nodes	220 (43.3%)	118 (46.5%)	338 (44.4%)
Lung	197 (38.8%)	95 (37.4%)	292 (38.3%)
Pleura	87 (17.1%)	42 (16.5%)	129 (16.9)
Breast	54 (10.6%)	24 (9.4%)	78 (10.2%)
ECOG performance status, n (%)			
0	217 (42.7%)	103 (40.6%)	320 (42.0%)
1	244 (48.0%)	126 (49.6%)	370 (48.6%)
2	39 (7.7%)	22 (8.7%)	61 (8.0%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; ITT, Intent-to-treat; PR, progesterone receptor; TPC, Treatment of Physician's Choice. †For the ER, PR, HER2 and triple negative status, the percentages are calculated from the total number of patients tested; ‡The number of organs involved was based on the investigator review data.

Most patients had received several prior chemotherapies in the adjuvant and/or LABC/MBC setting, with a median duration of the last chemotherapy of 3.53 months and a range of 0 to 32.0 months. Ninety-nine percent of patients had previously received a taxane, 98.7% had received an anthracycline, and 73.4% had received capecitabine (Table 9). To be eligible for this study, patients had to be refractory to their most recent chemotherapy, documented by progression on or within six months of therapy; overall 80.6%, 57.7% and 67.7% of patients were refractory to taxanes, anthracyclines and capecitabine, respectively, highlighting the limited options and the need for new therapies in this patient population.

In general, the eribulin group and TPC group were well balanced in terms of prior anti-cancer therapies.

Table 9: Prior chemotherapy regimens: EMBRACE study (ITT population)

	Eribulin (N=508)	TPC (N=254)	Total (N=762)
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)			
1	1 (0.2%)	0	1 (0.1%)
2	65 (12.8%)	31 (12.2%)	96 (12.6%)
3	176 (34.6%)	83 (32.7%)	259 (34.0%)
4	166 (32.7%)	79 (31.1%)	245 (32.2%)
5	85 (16.7%)	51 (20.1%)	136 (17.8%)
≥ 6	13 (2.6%)	9 (3.5%)	22 (2.9%)
Duration of last chemotherapy (months)			
Median (min, max)†	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)
No. of patients who previously (adjuvant and LABC/MBC setting) received: n (%)			
Taxanes	503 (99.0%)	251 (98.8%)	754 (99.0%)
Anthracyclines	502 (98.8%)	250 (98.4%)	752 (98.7%)
Capecitabine	370 (72.8%)	189 (74.4%)	559 (73.4%)
No. of patients refractory‡ to: n (%)			
Taxane	410 (80.7%)	204 (80.3%)	614 (80.6%)
Anthracycline	284 (55.9%)	156 (61.4%)	440 (57.7%)
Capecitabine	342 (67.3%)	174 (68.5%)	516 (67.7%)

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice. †patients with zero duration of last chemotherapy were patients who received only a single dose of the last chemotherapy agent that they were receiving prior to starting on study; ‡refractory was defined as progressed within 6 months of receiving the therapy.

5.3.4 Outcomes: EMBRACE (Study 305)

Context

As recognised by NICE guidelines, one of the key priorities for treating this advanced stage of breast cancer is to prolong survival, while controlling the symptoms experienced and improving the patient's quality of life (8). The EMBRACE study employed primary and secondary efficacy outcomes, including OS, PFS, ORR and duration of response,

that are all commonly used measures of efficacy for breast cancer drugs and clinically relevant.

The primary outcome of OS is considered the most reliable cancer outcome, particularly in the pre-treated population considered here (i.e. short life expectancy, where results are expected in a reasonable timeframe and there are very limited effective next line therapies) (15, 16). It is precise and easy to measure, documented by the date of death and thus is not subject to assessment bias. However, no RCTs of the currently available monotherapies have demonstrated a survival advantage over any other single agent in the treatment of anthracycline and taxane-resistant MBC (19).

Primary outcome – Overall Survival

- Defined as the time from the date of randomisation until death from any cause.

Secondary outcome – Progression-free survival

- Defined as the time from randomisation until disease progression or death due to any cause in the absence of disease progression.
- Analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data.

Secondary outcome – Objective response rate and clinical benefit rate

Tumour response was evaluated according to RECIST criteria (49). Target and non-target lesions were assigned to response assessment categories (Table 10), and the overall tumour response determined for all possible combinations of target and non-target lesions, with or without the occurrence of new lesions (Table 11).

Table 10: Tumour response assessment categories

Category	Definition
Complete response (CR)	Target lesions: the disappearance of all target lesions. Non-target lesions: the disappearance of non-target lesions lesions and normalisation of tumour marker levels.
Partial response (PaR)	Minimum of a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline summed LD.
Progressive disease (PD)	Target lesions: a minimum of a 20% increase in the sum of the LD of target lesions, taking as reference the smallest summed LD recorded since the treatment started or the appearance of one or more new lesions. Non-target lesions: the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
Stable disease (SD)	Target lesions: neither sufficient shrinkage to qualify for PaR nor sufficient increase to qualify for PD, taking as reference the smallest summed LD since the treatment started.
Incomplete response/SD	Non-target lesions: persistence of one or more non-target lesions or/and maintenance of tumour marker level above the normal limits.

Abbreviations: CR, Complete response; LD, Longest diameter; PD, Progressive disease; PaR, Partial response; SD, Stable disease.

Table 11: Objective response criteria

Overall response	New lesions	Target lesions	Non-target lesions
CR	No	CR	CR
PaR	No	CR	Incomplete response/SD
	No	PaR	No PD
SD	No	SD	No PD
PD	Yes or No	PD	Any
	Yes or No	Any	PD
	Yes	Any	Any

Abbreviations: CR, Complete response; PD, Progressive disease; PaR, Partial response; SD, Stable disease.

The best overall tumour response was the best response achieved from the start of treatment until disease progression or recurrence, and was calculated as the ORR and the CBR, defined below.

ORR

- defined as the number of patients with a confirmed complete response (CR) or confirmed partial response (PaR) divided by the number of patients in the analysis population.

CBR

- defined as the number of patients with a confirmed CR, a confirmed PaR or stable disease (SD) of at least 6 months, divided by the number of patients in the analysis population.

ORR and CBR analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data.

Secondary outcome – Duration of response

- Defined as the time from first documented CR or PaR (time that measurement criteria were met for whichever status is recorded first) until disease progression or death from any cause.
- Analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data.

5.3.5 Statistical analysis and definition of study groups: EMBRACE (Study 305)

Population datasets analysed

Intent-to-treat (ITT) population: all patients who were randomised, irrespective of whether or not they actually received study treatment or whether they received the medication they were randomised to.

Per protocol (PP) population: all patients in the ITT population who met the major inclusion criteria for the study, and who did not have any other major protocol violation. Major violations included patients who were treated on the opposite treatment group than the one to which they were randomised.

Response evaluable population: all patients with measurable disease, defined as the presence of at least one measurable lesion, using RECIST criteria (49). This was identified by independent review.

Safety population: all patients who were randomised and who received at least a partial dose of study treatment. The population was based on the actual treatment received.

Primary hypothesis under investigation and power calculation

The study was designed to provide evidence to either:

- support the null hypothesis, that the survival distributions in the eribulin and TPC groups were equal, or;
- to reject this hypothesis in favour of the alternative hypothesis, that the survival distributions between groups are not equal.

The primary analysis was planned to occur when 411 deaths had been recorded; it was estimated that 630 patients in total (420 in eribulin and 210 in TPC) needed to be enrolled, leading to an initial estimated maximum study duration of 26.5 months. As pre-specified in the protocol, the overall event rate was evaluated 15 months after the first patient was recruited. Since the number of deaths was smaller than expected at this

point, the sample size was increased to allow up to a maximum of 1,000 patients. Sample size re-assessment was done on an ongoing basis in a blinded fashion. As soon as it became apparent that 411 deaths would be reached within a reasonable timeframe, study recruitment was stopped at 762 randomised patients. The primary analysis was actually performed when 422 (55%) patients had died.

A further updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up. This data is present in the eribulin SPC (see Appendix Section 9.1 and Refs (47, 48)). Results for this updated analysis are presented.

Population included in primary analysis of primary outcome and methods for handling missing data

The primary analysis of the primary outcome (OS) was compared between the eribulin and TPC groups in the ITT population. These analyses were also performed on the PP population. For patients for whom a date of death was not recorded, i.e., those who were lost to follow-up or who were alive at the date of data cut-off, time to death was censored at the time of last contact.

Statistical tests in primary analysis of primary outcome

The primary outcome (OS) was compared between the randomised treatment groups in the ITT population, using a two-sided stratified log-rank test at a significance level of 0.049. The test was stratified by HER2 status, prior capecitabine treatment, and geographical region.

Kaplan-Meier survival curves were used to summarise the OS, using 95% limits at selected time points. The Kaplan-Meier estimate of the median survival time, and first and third quartiles was presented with 95% CIs.

The HR was presented based on fitting a Cox regression model and was stratified according to the type of treatment received, HER2 status, prior capecitabine treatment and geographical region. An additional Cox regression model was fitted in which the HR was also adjusted for the number of prior chemotherapy regimens and ER status (covariates).

Secondary outcomes: Population datasets included, methods for handling missing data and statistical tests

Analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data.

PFS was assessed in both the ITT and PP populations, while the response evaluable population was considered the primary population for the analysis of ORR and duration of response.

For the analysis of PFS, patients who had not progressed on the data cut-off date or who were lost to follow-up, were censored at that date. For the analysis of duration of response, patients were censored at the last date of tumour assessment if treatment was

discontinued for a reason other than PD or death, if the patient started a new cancer treatment, or if the patient was still on treatment without PD as of the data cut-off date.

Kaplan-Meier plots and the Kaplan-Meier estimates of the medians, and first and third quartiles were presented with the 95% CI for PFS and duration of response. PFS was compared between the treatment groups using a two-sided stratified log-rank test at the 5% significance level. Duration of response was compared between treatment groups using a two-sided log-rank test. ORR was analyzed using exact Pearson Clopper 2-sided 95% confidence limits for the tumour response rates in each treatment group, and was statistically compared between the two treatment groups using a Fisher's Exact Test. Sensitivity analyses of these assessments were also performed.

5.3.6 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-planned subgroup analyses: EMBRACE (Study 305)

Since EMBRACE was a global study, and recognising differences in clinical practice and drug availability, patients were pre-stratified by geographical region, HER2 status and prior capecitabine treatment. Pre-planned subgroup analyses explored the effect of these strata, as well as other characteristics commonly assessed in cancer studies. Pre-planned subgroup analyses included were as follows:

- Strata: Geographic region, HER2 status, and prior capecitabine treatment.
- Demographic characteristics: Age group, race.
- Receptor expression: hormonal receptor status (ER and PR), triple negative status (ER negative, PR negative and HER2 negative).
- Disease characteristics: Visceral/non-visceral disease, number of organs involved.
- Prior chemotherapy: Number of prior chemotherapy regimens, number of prior chemotherapy regimens for advanced or metastatic disease, patients who progressed while on treatment with a taxane or other tubulin-inhibiting agent.

Post-hoc subgroup analyses: EMBRACE (Study 305)

Additional post-hoc subgroup analyses were conducted to investigate the comparison of eribulin with individual treatments of the TPC group in the ITT population. Since the TPC that the patient would have received was recorded, it was possible to compare data between TPC groups for patients who were selected for eribulin and the individual TPC groups. Therefore, comparisons between the eribulin and TPC arm were conducted in two ways:

- Analysis 1) eribulin patients who would have received that TPC if they had been randomised to that group against those that did, and
- Analysis 2) all patients who received eribulin versus the individual TPC group.

5.3.7 Participant flow: EMBRACE (Study 305)

A total of 762 patients were randomised in this study (Table 12 and Figure 4); 508 to eribulin and 254 to TPC (2:1 randomisation; ITT population). Twelve patients were discontinued before the start of treatment (six in each arm), and one patient received a

different treatment (eribulin) to the one allocated (TPC). In total, 503 patients received eribulin and 247 patients received TPC (safety population).

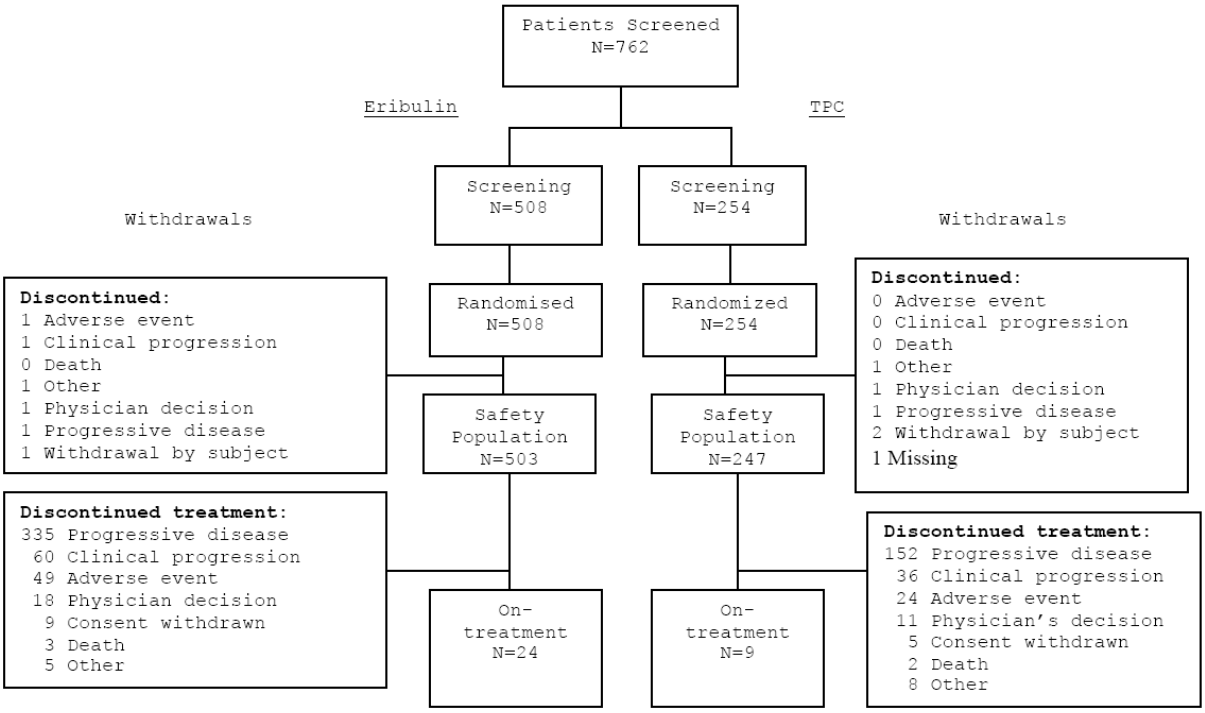
A total of 484 (95.3%) patients in the eribulin group and 244 (96.1%) patients in the TPC group had discontinued study treatment at the time of data cut-off for the primary analysis (when 55% of patients had died; See Section 5.3.5). The main reason for discontinuation in both treatment groups was progressive disease (assessed by RECIST, Table 12).

Table 12: Patient disposition: EMBRACE study

	Treatment Group		Total
	Eribulin (N = 508) n (%)†	**TPC (N = 254) n (%)†**	**(N = 762) n (%)†**
Randomised	508	254	762
ITT Population‡	508 (100.0%)	254 (100.0%)	762 (100.0%)
Safety Population§	503 (99.0%)	247 (97.2%)	750 (98.4%)
Response Evaluable Population¶	468 (92.1%)	214 (84.3%)	682 (89.5%)
PP Population††	459 (90.4%)	216 (85.0%)	675 (88.6%)
Discontinued from study treatment	484 (95.3%)	244 (96.1%)	728 (95.5%)
Reason for discontinuation from study treatment‡‡			
Adverse Events (including toxicity)	50 (9.8%)	24 (9.4%)	74 (9.7%)
Withdrew Consent	10 (2.0%)	7 (2.8%)	17 (2.2%)
Progressive Disease according to RECIST criteria	336 (66.1%)	153 (60.2%)	489 (64.2%)
Clinical progression	61 (12.0%)	36 (14.2%)	97 (12.7%)
Physician's decision	18 (3.5%)	13 (5.1%)	31 (4.1%)
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)
Death	3 (0.6%)	2 (0.8%)	5 (0.7%)
Other	6 (1.2%)	9 (3.5%)	15 (2.0%)
Survival Status at data cut-off for the primary analysis§§			
Alive	230 (45.3%)	104 (40.9%)	334 (43.8%)
Died	274 (53.9%)	148 (58.3%)	422 (55.4%)
Lost to Follow-up	4 (0.8%)	2 (0.8%)	6 (0.8%)

Abbreviations: ITT, Intent-to-treat; PP, Per protocol; RECIST, Response evaluation criteria in solid tumours; TPC, Treatment of Physician's Choice. †Percentages are based on all randomised patients; ‡ITT Population: All patients who were randomised irrespective of whether or not they actually received medication; §Safety Population: All patients who were randomised and who received at least a partial dose of study treatment; ¶Response Evaluable Population: All patients with measurable disease, defined as the presence of at least one measurable lesion, as per RECIST by independent review; ††PP Population: All patients in the ITT Population who met the major inclusion criteria for the study, and who did not have any other major protocol violation; ‡‡Reasons for discontinuation are based on the planned treatment in the ITT Population; §§performed when 55% of people had died.

Figure 4: EMBRACE study flow chart



Abbreviations: TPC, Treatment of Physician's Choice.

Although best supportive care and radiotherapy were treatment options in the TPC arm, all treated patients in the TPC group received pharmacotherapy, and are summarised in Table 13. Chemotherapy was the most common treatment in the TPC group (n=238, 93.7%, ITT population) followed by hormonal treatment (n=9, 3.5%, ITT population). Although patients could have been treated with biologic therapy (trastuzumab) in centres where this treatment was available, no patients actually received this therapy. The remaining seven patients in the TPC arm (ITT population) were discontinued prior to treatment initiation (n=6) or received eribulin instead of the planned TPC (n=1).

Table 13: Treatment of Physician's Choice: EMBRACE study (ITT population)

TPC therapy	TPC (N = 254) n (%)
Chemotherapy	238 (93.7%)
Vinorelbine	61 (24.0%)
Gemcitabine	46 (18.1%)
Capecitabine	44 (17.3%)
Taxanes†	38 (15.0%)
Anthracyclines‡	24 (9.4%)
Others§	25 (9.8%)
Hormonal therapy	9 (3.5%)
Fulvestrant	4 (1.6%)
Letrozole	3 (1.2%)
Exemestane	1 (0.4%)
Tamoxifen	1 (0.4%)

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice. †Taxanes included paclitaxel (21 patients), docetaxel (10 patients), nab-paclitaxel (five patients) and ixabepilone (three patients) (one patient received paclitaxel in combination with gemcitabine and was included in the gemcitabine group); ‡Anthracyclines included doxorubicin (19 patients), liposomal doxorubicin (four patients) and mitoxantrone (one patient); §Other chemotherapeutic agents were cisplatin, carboplatin, cyclophosphamide, etoposide, mitomycin, fluorouracil and methotrexate (one patient received cyclophosphamide and methotrexate). ¶The remaining seven patients in the ITT population were discontinued prior to treatment initiation or received eribulin instead of the planned TPC.

5.3.8 Treatment duration: EMBRACE (Study 305)

Overall exposure to study treatment was longer in the eribulin group compared with the TPC group (118 days vs. 64 days [chemotherapy] and 30 days [hormonal], respectively; Table 14). More than half of patients (58.6%) received five or more cycles of eribulin treatment, with 22.7% (n=114) and 2.4% (n=12) of patients on treatment for > 6 months and > 1 year, respectively. The longer duration of therapy with eribulin demonstrates the superior efficacy of eribulin compared with TPC, since therapy was discontinued on disease progression and PFS was longer with eribulin treatment than TPC. Furthermore, there is a positive safety and tolerability profile demonstrated by eribulin within this trial; specifically, the percentage of patients with dose discontinuation or dose interruption due to AEs experienced was lower in the eribulin group compared with the TPC group (The safety and tolerability of eribulin is discussed further in Section 5.9).

Table 14: Exposure to eribulin: EMBRACE study (Safety population)

	Eribulin (N=503)	TPC (Chemotherapy) (N=238)	TPC (Hormonal) (N=9)
Duration of exposure, median days (min, max)	118 (21–497)	64.0 (1–644)	30.0 (25–188)
Number of cycles completed on study, n (%) 1–2 3–4 5–6 > 6 Range	 81 (16.1%) 127 (25.2%) 110 (21.9%) 185 (36.8%) 1–23 cycles	 NA	 NA
Dose intensity, median mg/m^2/week (min, max)	0.85 (0.2, 1.0)	NA	NA
Relative dose intensity, % (min, max)	91% (30, 110)	NA	NA
Patients with dose interruption, n (%)	28 (5.6%)	21 (8.8%)	2 (22.2%)
Patients with dose delay, n (%)	248 (49.3%)	98 (41.2%)	0 (0.0%)
Patients with dose reduction, n (%)	145 (28.8%)	63 (26.5%)	0 (0.0%)

Abbreviations: NA, Not applicable; TPC; treatment of Physician's Choice.

5.4 Critical appraisal of relevant RCTs

A critical appraisal of the EMBRACE study is presented in Section 9.3.

5.5 Results of the relevant RCTs

5.5.1 Results: EMBRACE (Study 305)

Primary efficacy outcome: Overall survival

Primary analysis

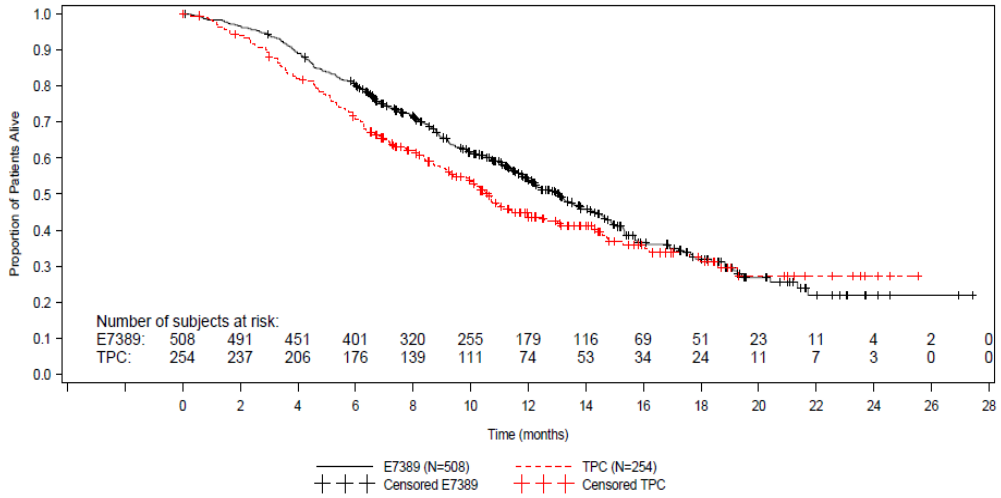
The EMBRACE trial met its primary endpoint based: in the primary analysis of OS in the ITT population performed when 55% (422) of patients had died, median OS was significantly longer with eribulin versus TPC (13.1 months/399 days vs. 10.6 months/324 days, p = 0.041), representing a 23% increase (2.5 months/75 days) in the duration of survival (Table 15). The use of eribulin reduced the hazard or risk of death by 19% compared with TPC (HR 0.809, 95% CI: 0.660, 0.991). This increase in OS is clinically relevant for patients at this stage of disease and makes eribulin the first and only monotherapy to provide statistically significant improvements in OS in pre-treated patients with MBC.

Kaplan-Meier analysis of OS in the ITT population is shown in Figure 5 (primary analysis); differences in OS appeared within 2 months of the start of treatment, and the benefit of eribulin was apparent within one year. Patients receiving eribulin treatment had a one-year survival rate estimate of 53.9%, compared with 43.7% for patients in the TPC group.

Sensitivity analyses

Sensitivity analysis also adjusting for the number of prior chemotherapy regimens and ER status was consistent with the primary analyses, with the HR in favour of eribulin compared with TPC (Table 15).

Figure 5: Kaplan-Meier analysis of overall survival (primary analysis): EMBRACE study (ITT population)



Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice. E7389 is the code name for eribulin.

Table 15: Kaplan-Meier analysis of overall survival (primary analysis): EMBRACE study (ITT population)

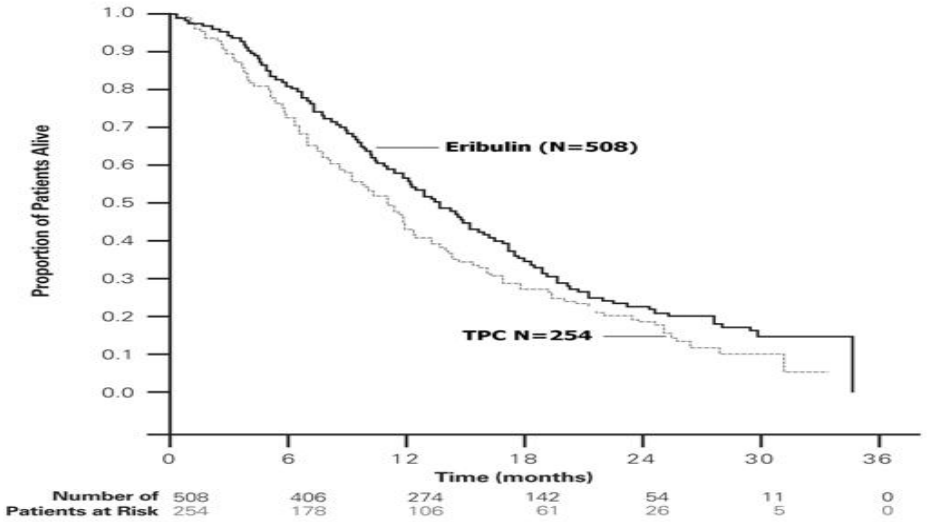
Parameter	Treatment Group	
	Eribulin (N = 508)	TPC (N = 254)
Number of patients who died†, n (%)‡	274 (53.9%)	148 (58.3%)
Overall Survival, days		
Median (95% CI)	399 (360, 434)	324 (282, 380)
3rd Quartile (95% CI)	650 (573, NE)	NE (547, NE)
Diff in Medians (95% CI)	75.0 (21.4, 128.6)	
Stratified log-rank test:	p = 0.041	
One-year survival rate, proportion (95% CI)	0.539 (0.492, 0.586)	0.437 (0.371, 0.502)
Two-year survival rate, proportion (95% CI)	0.219 (0.148, 0.290)	0.272 (0.188, 0.355)
HR, (eribulin/TPC): main analysis§		
Estimate (95% CI)	0.809 (0.660, 0.991)	
HR (eribulin/TPC): sensitivity analysis¶		
Estimate (95% CI)	0.810 (0.660, 0.994)	

Abbreviations: CI, Confidence interval; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, Hazard ratio; ITT, Intent-to-treat; NE, Not estimable due to insufficient events; TPC, Treatment of Physician's Choice. †The primary analysis was carried out when 55% of total study patients had died. ‡The remaining patients were censored; §HR based on a Cox model including HER2 status, prior capecitabine treatment, and geographical region as strata; ¶HR based on a Cox model including HER2 status, prior capecitabine treatment, geographical region as strata, and number of prior chemotherapy regimens, and ER status as covariates.

Updated analysis (as requested by the regulatory authorities)

This result was confirmed with an updated OS analysis carried out when 77% of patients had died, with the median OS of the eribulin group (13.2 months/403 days) compared with the TPC group (10.5 months/321 days) improved by 2.7 months (82 days; HR 0.805, 95% CI: 0.667, 0.958, p=0.014) (Table 16 and Figure 6). The updated analysis demonstrates that the survival curves remain separated for the duration of the analysis (See SPC [Appendix Section 9.1] and Refs (47, 48) for updated analysis).

Figure 6: Kaplan-Meier analysis of overall survival (updated analysis): EMBRACE study (ITT population)



Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice. Source: See SPC (Appendix Section 9.1) and Refs (47, 48).

Table 16: Kaplan-Meier analysis of overall survival (updated analysis): EMBRACE study (ITT population)

Parameter	Treatment Group	
	Eribulin (N = 508)	TPC (N = 254)
Number of patients who died†, n (%)‡	386 (76.0%)	203 (79.9%)
Overall Survival, days		
Median (95% CI)	403 (367, 438)	321 (281, 365)
3rd Quartile (95% CI)	677 (605, 752)	636 (533, 730)
Diff in Medians (95% CI)	82.0 (29.9, 134.1)	
Stratified log-rank test :	p = 0.014	
One-year survival rate, proportion	0.545 (0.501, 0.588)	0.428 (0.367, 0.490)
Two-year survival rate, proportion	0.219 (0.179, 0.260)	0.192 (0.138, 0.246)
HR, (eribulin/TPC): main analysis§		
Estimate (95% CI)	0.805 (0.667, 0.958)	
HR (eribulin/TPC): sensitivity analysis¶		
Estimate (95% CI)	0.809 (0.680, 0.963)	

Abbreviations: CI, Confidence interval; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, Hazard ratio; ITT, Intent-to-treat; NE, Not estimable due to insufficient events; TPC, Treatment of Physician's Choice. †Updated analysis was carried out when 77% of total study patients had died; ‡The remaining patients were censored; §HR based on a Cox model including HER2 status, prior capecitabine treatment, and geographical region as strata; ¶HR based on a Cox model including HER2 status, prior capecitabine treatment, geographical region as strata, and number of prior chemotherapy regimens, and ER status as covariates. Source: See SPC (Appendix Section 9.1) and Refs (47, 48).

Secondary efficacy outcomes: Progression-free survival

Tumour response was assessed by both the investigator (Investigator review) and through a blinded, independent review. Whereas investigators could assess progression through imaging scans and patient examinations, representing more closely what would happen in clinical practice, the independent reviewers only had access to the imaging data. Although independent review of progression is designed to avoid bias, it is associated with limitations that may explain any differences observed in the results achieved by these two methods:

- Patients were no longer scanned when the investigator deemed that they had PD, leading to informative censoring. Even if the independent reviewers did not find PD, they could no longer follow the patients' tumour responses since scans were not available to review. A consequence of this is that some progressions in the investigator's review become censored in the independent review.
- Progression of patients with non measureable disease could only be assessed by independent review if non-target lesions progressed or if new lesions appeared.
- Patients who progressed clinically without radiologic findings could not be assessed by the independent reviewers.

The PFS results were consistent with the OS results, with a longer duration of PFS observed in the eribulin group compared with the TPC group. Overall, treatment with

eribulin reduces the risk of progression by 24% (investigator review) and 14% (independent review), compared with TPC (Table 17). In the ITT population, median PFS was 3.6 months/110 days for eribulin and 2.2 months/66 days for TPC, when assessed by investigator review ($p = 0.002$), and 3.7 months/113 days and 2.2 months/68 days, respectively, when assessed by independent review ($p = 0.137$). This apparent difference arose from the censoring of almost twice as many patients in the independent review than in the investigator review. Study scans stopped once the investigator had declared disease progression, leading to many censored patients in the independent review, who could only assess nonmeasurable disease for progression if non-target lesions progressed or new lesions appeared. For the PP population, the difference was statistically significant for both investigator and independent analyses ($p < 0.05$). The maximum effect was observed within the first 6 months; however the difference was apparent from the first radiographic assessment, performed as per protocol at Week 8 (Figure 7).

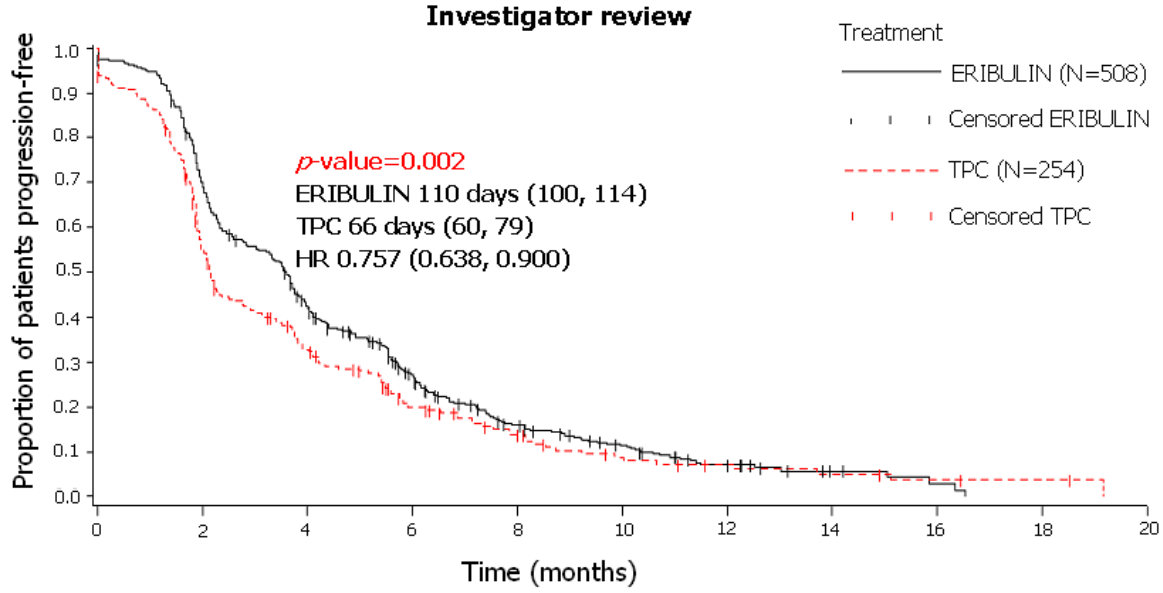
Sensitivity analyses, whereby different censoring rules were applied, reported similar results to the primary analysis. Censoring rules applied included: the start of a new anti-cancer treatment was considered as a progression event and not censored; censoring data when death or progressive disease occurred after one or more missed tumour assessments; and after two or more missed tumour assessments.

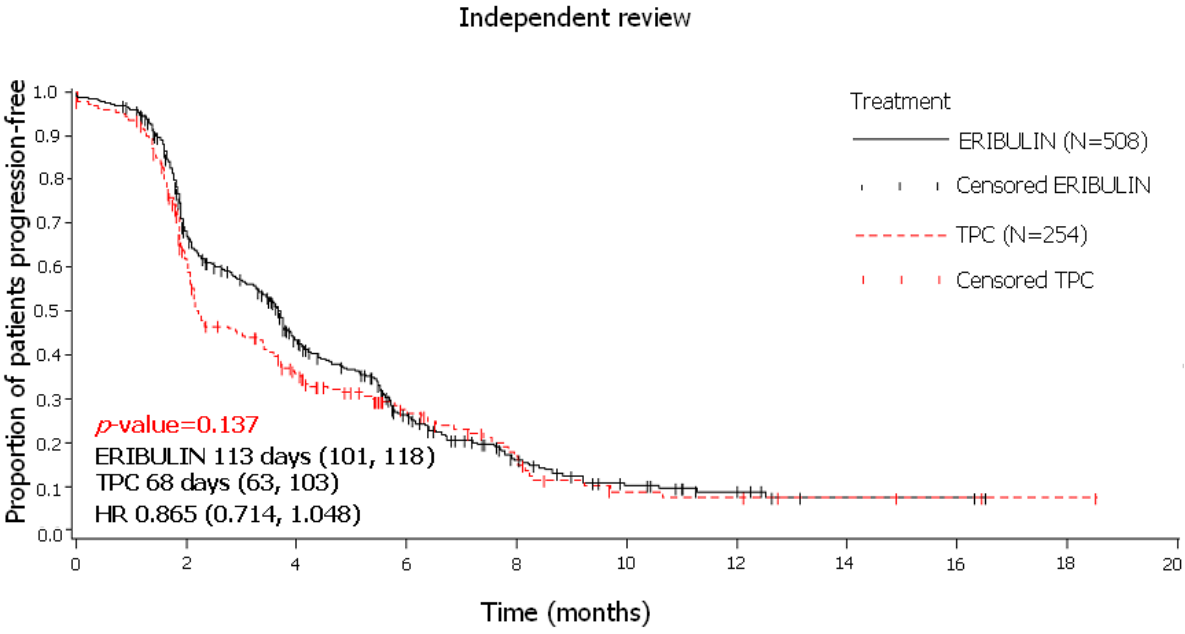
Table 17: Kaplan-Meier analysis of progression-free survival: EMBRACE study (ITT population)

Parameter	Treatment group			
	Independent review		Investigator review	
	Eribulin (N = 508)	TPC (N = 254)	Eribulin (N = 508)	TPC (N = 254)
Number of patients who progressed or died, n (%)†	357 (70.3%)	164 (64.6%)	429 (84.4%)	206 (81.1%)
Progression-free survival, days				
Median	113	68	110	66
(95% CI for median)	(101, 118)	(63, 103)	(100, 114)	(60, 79)
p-value	0.137		0.002	
HR (eribulin/TPC)‡				
Estimate (95% CI)	0.865 (0.714, 1.048)		0.757 (0.638, 0.900)	
Progression-free survival rate, proportion (95% CI)				
3 months	0.571 (0.526, 0.617)	0.449 (0.381, 0.517)	0.558 (0.514, 0.601)	0.414 (0.351, 0.477)
6 months	0.263 (0.219, 0.307)	0.276 (0.210, 0.342)	0.272 (0.231, 0.312)	0.198 (0.145, 0.252)
9 months	0.123 (0.085, 0.161)	0.113 (0.054, 0.172)	0.137 (0.103, 0.170)	0.103 (0.058, 0.148)
12 months	0.088 (0.051, 0.125)	0.073 (0.020, 0.126)	0.071 (0.043, 0.099)	0.072 (0.031, 0.112)

Abbreviations: CI, Confidence interval; HR, Hazard ratio; TPC, Treatment of Physician's Choice. †The remaining patients were censored; ‡HR based on a Cox model including HER2 status, prior capecitabine treatment and geographical region as strata.

Figure 7: Kaplan-Meier analysis of progression-free survival: EMBRACE study (ITT population)
Investigator review (top) and independent review (bottom)





Abbreviations: HR, Hazard ratio; TPC, Treatment of Physician's Choice.

Secondary efficacy outcomes: Objective response rate and clinical benefit rate

Based on the independent review of patients with measurable disease at baseline (Response evaluable population; n=682), the ORR (patients with a CR or a PaR) was statistically significantly greater for eribulin compared with TPC (12.2% [95% CI: 9.4, 15.5] vs. 4.7% [95% CI: 2.3, 8.4], p = 0.002) (Table 18). Results from the investigator review were similar, with 13.2% (95% CI: 10.3%, 16.7%) of patients receiving eribulin achieving an objective response compared to 7.5% (4.3%, 11.9%) of patients in the TPC group (p = 0.028). The magnitude of the ORR should be considered in the context of the

population enrolled in this study, which had been pre-treated in the advanced setting with at least 2 previous chemotherapies.

Based on independent review, the CBR – patients with a CR, a PaR or SD of at least 6 months duration – was higher in the eribulin group compared with the TPC group (22.6% [95% CI: 18.9, 26.7] vs. 16.8% [95% CI: 12.1, 22.5]). The overlapping confidence intervals between the two treatment arms suggest that the differences observed were not statistically significant, but this is a reflection of the similar proportions of SD ≥ 6 months in both arms. However, the CR and PaR rates were higher for the eribulin group compared to the TPC group, suggesting a clinically significant benefit of eribulin therapy. Results were similar for the investigator review.

Table 18: Objective response rate and clinical benefit rate: EMBRACE study (Response evaluable population)

Response Category	Treatment Group			
	Independent Review		Investigator Review	
	Eribulin (N = 468) n (%)	TPC (N = 214) n (%)	Eribulin (N = 468) n (%)	TPC (N = 214) n (%)
CR	3 (0.6%)	0	1 (0.2%)	0
PaR	54 (11.5%)	10 (4.7%)	61 (13.0%)	16 (7.5%)
SD	208 (44.4%)	96 (44.9%)	219 (46.8%)	96 (44.9%)
PD	190 (40.6%)	105 (49.1%)	176 (37.6%)	97 (45.3%)
Not Evaluable	12 (2.6%)	3 (1.4%)	11 (2.4%)	5 (2.3%)
Unknown	1 (0.2%)	0	0	0
ORR (CR or PaR)	57 (12.2%)	10 (4.7%)	62 (13.2%)	16 (7.5%)
95% CI†	(9.4, 15.5)	(2.3, 8.4)	(10.3, 16.7)	(4.3, 11.9)
p-value‡	0.002		0.028	
CBR (CR or PaR, or SD ≥ 6 months)	106 (22.6%)	36 (16.8%)	130 (27.8%)	43 (20.1%)
95% CI†	(18.9, 26.7)	(12.1, 22.5)	(23.8, 32.1)	(14.9, 26.1)

Abbreviations: CBR, Clinical benefit rate; CI, Confidence interval; CR, Complete response; PD, Progressive disease; ORR, Objective response rate; PaR, Partial response; SD, Stable disease; TPC, Treatment of Physician's Choice. †Exact Pearson-Clopper 2-sided CI; ‡Fisher's Exact Test.

Secondary efficacy outcomes: Duration of response

Amongst the patients who responded (CR or PaR, n=57), the median duration of response with eribulin was clinically relevant, calculated at 4.2 months/128 days (95% CI: 116.0, 152.0) by independent review. This was not significantly different from patients treated with TPC (6.7 months/205 days [95% CI: 205.0, 212.0], p = 0.159; independent review); however, given the small numbers of responders in the TPC group (n=10, three of whom experienced disease progression during the study), comparison of duration of response between the two groups is not meaningful. Similar trends were observed for the investigator assessment of duration of response.

Pre-planned subgroup analyses – overall survival

OS was analysed according to geographical region, a significantly longer OS was observed for patients from Region 1 (North America/Western Europe/Australia) who were randomised to eribulin compared with patients who received TPC (Primary analysis, p=0.009; Updated analysis p=0.031) (Table 19); OS observed was 3.1 months longer for eribulin for both the primary analysis and the updated analysis (13.1 months vs. 10.0 months in the primary analysis; 13.2 months vs. 10.1 months in the updated analysis).

Table 19: Kaplan-Meier analysis of overall survival for geographical region 1 (North America, Western Europe, Australia): EMBRACE study (ITT population)

Parameter	Treatment Group	
	Eribulin (N = 325)	TPC (N = 163)
Primary analysis		
Number of patients who died†, n (%)‡	182 (56.0%)	104 (63.8%)
Overall Survival, days		
Median (95% CI)	399 (359, 452)	306 (255, 332)
Stratified log-rank test:	p = 0.009	
HR, (eribulin/TPC)§, estimate (95% CI)	0.724 (0.568, 0.924)	
Updated analysis		
Number of patients who died†, n (%)‡	252 (77.5%)	132 (81.0%)
Overall Survival, days		
Median (95% CI)	402 (359, 451)	308 (255, 332)
Stratified log-rank test:	p = 0.031	
HR, (eribulin/TPC) §, estimate (95% CI)	0.791 (0.639, 0.980)	

Abbreviations: CI, Confidence interval; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, Hazard ratio; ITT, Intent-to-treat; NE, Not estimable due to insufficient events; TPC, Treatment of Physician's Choice. †Primary analysis was carried out when 55% of total study patients had died, whereas the updated analysis was carried out when 77% of total study patients had died; ‡The remaining patients were censored; §HR based on a Cox model including HER2 status and prior capecitabine treatment as strata. Updated OS analysis taken from Ref (47).

Post-hoc subgroup analyses – overall survival by TPC group

Additional post-hoc analyses were conducted to investigate the comparison of eribulin with each individual TPC group in the ITT Population. For all patients enrolled in the EMBRACE study a TPC agent was first defined by the physician and this choice could be discussed with the patient to ensure the most appropriate treatment was selected for them. Patients were then stratified and randomised to one of the two treatment arms (eribulin or TPC) according to a randomisation schedule. This process ensured that each agent of the physician's choice was independently randomised against eribulin to support subgroup analyses. As such these sub-group analyses compared those eribulin patients who would have received that specific TPC agent if they had been randomised to that group, against those that did receive that specific TPC agent. Results are presented for the updated analysis only as this represents the more mature data set (as

requested by the regulatory authorities, conducted when 77% of total study patients had died).

[redacted]

Table 20: Post hoc analyses – overall survival by TPC group: EMBRACE study, updated analyses based on eribulin patients who would have received that TPC if they had been randomised to that group

Parameter	Treatment group					
	Eribulin (N [redacted])	Capecitabine (N [redacted])	Eribulin (N = [redacted])	Vinorelbine (N = [redacted])	Eribulin (N = [redacted]	Gemcitabine (N [redacted])
Updated analysis						
xxxxxxxxxx xxxxxxxxxxx	xx	xx	xx	xx	xx	xx
xxxxxxxxxxxxxxxxxx xxx						
xxxxxxxxx	xxx xxxxxx	xx xxxxxxx	xxx xxxxxx	xxx xxxxxx	xxxxx xxxxxxx	xxx xxxxxx
xxxxxxxxxxxxxxx xx	xxxxxxxxxx		xxxxxxxxx		xxxxxxxxx	
xxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxx		xxxxxxxxxxxxxxx		xxxxxxxxxxxx	

[redacted]

[redacted]

Table 21: Post hoc analyses – overall survival by TPC group for geographical region 1 (North America, Western Europe, Australia): EMBRACE study, updated analyses based on eribulin patients who would have received that TPC if they had been randomised to that group

Parameter	Treatment group					
	Eribulin (N [redacted])	Capecitabine (N [redacted])	Eribulin (N [redacted])	Vinorelbine (N = [redacted])	Eribulin (N = [redacted])	Gemcitabine (N [redacted])
Updated analysis						
xxxxxxxxxxxx xxxxx						
xxxxxxxxxxxxx	xxx xxxxxxx	xxx xxxxxxx	xxx xxxxxx	xxx xxxxxxx	xxx xxxxxxx	xxx xxxxxx
xxxxxxxxxxxxxxx xxxxxx	xxxxxx		xxxxxx		xxxxxx	
xxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx		xxxxxxxxxxxxxx		xxxxxxxxxxxxxx	
[redacted]						

5.6 Meta-analysis

5.6.1 Meta-analysis methods and results

A meta-analysis was inappropriate because only one RCT for eribulin in the population relevant to the decision problem is currently available.

5.6.2 Qualitative overview if meta-analysis inappropriate

N/A.

5.6.3 Trials excluded from analysis

N/A.

5.7 Indirect and mixed treatment comparisons

5.7.1 Identification of studies

An indirect/mixed treatment comparison was not conducted because the pivotal Phase III eribulin RCT (EMBRACE) provided direct head to head evidence versus a range of treatments reflecting typical clinical practice.

5.7.2 Study selection, and methodology, quality assessment and results of relevant RCTs

N/A.

5.7.3 Summary of trials used to inform the comparison

N/A.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

N/A.

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

N/A.

5.7.6 Please present the results of the analysis.

N/A.

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

N/A.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

N/A.

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

N/A.

5.8 Non-RCT evidence

Summary of efficacy, Phase II studies (Study 201, Study 211, Study 221)

- Three Phase II, open-label single-arm studies have been conducted to assess the efficacy and safety of eribulin in patients with LABC or MBC; Study 201, Study 211 and Study 221 (37-42).
- Study 201 and Study 211 were conducted predominantly in US and European populations as per EMBRACE; Study 221 was conducted solely in Japan.
- Study 201 reported on 2 eribulin dosing regimens; a 21-day cycle comprising two doses and a 28-day cycle comprising three doses. The 21-day cycle was better tolerated and no differences in efficacy were seen between the two regimens; therefore, eribulin was subsequently administered at 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle in Studies 211, 221 and 305, providing the basis for the licensed dosing regimen.
- Efficacy results from these three Phase II studies are consistent with the pivotal Phase III EMBRACE study. For Study 201, Study 211 and Study 221:
  - the primary outcome of ORR was 14.3%, 9.3% and 21.3%, respectively.
  - median OS was 9.0 months, 10.4 months and 10.9 months, respectively.
  - median PFS was 2.6 months, 2.6 months and 3.7 months, respectively.
  - duration of response was 5.6 months, 4.1 months and 3.9 months, respectively.
- HRQL does not deteriorate and in many patients improves in patients who have objective positive tumour response to eribulin treatment, whereas patients who progress may suffer deterioration in their HRQL.
- In conclusion, these studies provide further evidence for the efficacy of eribulin, and support the results demonstrated in the pivotal Phase III EMBRACE study.

The identification of non-RCT evidence is described in Sections 5.1 and 5.2. Non-RCTs relevant to this submission are listed in Table 4 in Section 5.2.7. The methodology and results of Study 201, Study 211 and Study 221 are presented below.

Critical appraisal of relevant non-RCTs

A critical appraisal of the single-arm non-RCT studies included can be found in Section 9.7. In brief, adequate methods of recruitment were used in the included studies (e.g. prospective design, inclusion/exclusion criteria adequately reported). All studies reported outcomes consistent with the EMBRACE study, including OS, PFS and ORR. Patients were generally representative of those seen in clinical practice. During the follow-up period more than 90% of participants in each study were reported to have been followed-up and were included in the analyses reported.

Study 201

Methodology: Study 201

The methodology of Study 201 (37, 38) is summarised in Table 22.

Table 22: Methodology: Study 201

	Details
Objective	Primary objective: to assess the response rate (ORR) to eribulin in pre-treated patients with MBC. Secondary objectives: to evaluate duration of response, PFS, OS, quality of life and safety.
Location	23 centres in the United States.
Design	Phase II, open-label, single-arm study conducted in 103 patients with advanced/MBC, previously treated with at least an anthracycline and a taxane.
Duration of study	12th November 2004 – 1st November 2006. Patients continued on treatment as long as there was clinical benefit (as per EMBRACE).
Main inclusion criteria	• Female patients aged ≥ 18 years with histologically or cytologically confirmed MBC not amenable to curative therapy (surgery or radiation); • Prior anthracycline / taxane therapy given sequentially or in combination (patients may have had prior treatment with other agents as well); • Measurable disease (defined by RECIST); • Progression on or within 6 months of last chemotherapy; • ECOG performance status of 0 to 1 ; • Life expectancy of ≥ 3 months; • Adequate renal, bone marrow, and liver function. Any pre-existing sensory neuropathy had to be of Grade 2 or less.
Main exclusion criteria	• Chemotherapy, radiation, hormonal therapy, or trastuzumab within 2 weeks of commencing study treatment; • Radiation therapy that encompassed greater than 10% of marrow; • Active symptomatic brain metastases; • Anticoagulation therapy with warfarin.
Intervention and comparator	Eribulin (n=103) • Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1, 8 and 15 of a 28-day cycle (n=70). • Because of neutropenia (at Day 15), the protocol was amended and a second cohort of patients (n=33) was added to explore an alternative regimen of eribulin; 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen).
Permitted and disallowed concomitant medications	Permitted medications included any medication considered necessary for the patient's welfare not expected to interfere with the evaluation of the study, at the discretion of the investigator. Palliative radiotherapy was permitted to control bone pain as long as the irradiated area did not involve > 10% of the bone marrow; the irradiated area was not used to assess tumour response. Medications disallowed included: other investigational drugs; anti-tumour therapies, drugs metabolised by CYP3A4, potent inhibitors or inducers of CYP3A4 (eribulin is a CYP3A4 substrate), and anticoagulant therapy (warfarin).
Discontinuation of study	Patients continued on study treatment until they experienced progression of

	Details
therapy	disease, no longer had clinical benefit or experienced unacceptable toxicity.
Assessments	Tumours were assessed using RECIST methodology as per the EMBRACE study (See Table 5). Assessments were carried out every two cycles. Tumour response was confirmed by a second examination 4–8 weeks later. Independent review of tumour assessments was performed for all patients, except for those patients (n = 37) determined by investigators to have disease progression on or before their cycle two scan.
Primary outcomes	ORR (definition as per EMBRACE, Section 5.3.4)
Secondary outcomes	Duration of response; PFS; OS (definitions as per EMBRACE, Section 5.3.4, except for PFS and OS where the outcome was measured for the start of study medication, not randomisation); Quality of life; Safety. Quality of life was measured using: 1. FACT-B questionnaire: a validated, tumour-specific questionnaire containing 36 questions about the patient's emotional, functional, physical and social well-being. The scores from the 36 items are given equal weight and then summed to create a total FACT-B score from 0 to 144, with a higher number correlating to a more favourable quality of life. The TOI is the sum of the subscores for the physical well-being, functional well-being and breast cancer subscale domains. The FACT-B was completed prior to the first treatment, prior to each new treatment cycle and at the end of study treatment. 2. Tumour-related symptoms assessment using ECOG performance status, pain (VAS), analgesic consumption, weight changes.
Analysis populations	Primary analyses were conducted on the PP population (n= 87; patients who received at least one dose of study drug, and who met key inclusion criteria of having breast cancer which had progressed within 6 months of their last prior cytotoxic chemotherapy, and having measurable disease at baseline). Secondary efficacy analyses (and safety analyses) were performed on the ITT/Safety population (n=103; patients who had received at least one dose of eribulin).
Statistical methods	ORR and two-sided 95% CIs were calculated for the PP and ITT populations by using the binomial distribution. Secondary efficacy outcomes were assessed by using Kaplan-Meier estimates, and the medians and 95% CIs were determined. Summary statistics were presented for quality of life outcomes. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the data cut-off date were censored at that date.
Duration of follow up	Patients followed up every 3 months for OS (until all patients deceased), as per EMBRACE.

Abbreviations: CI, Confidence interval; CYP, Cytochrome P-450 system; ECOG, Eastern Cooperative Oncology Group; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; FACT-B, Functional Assessment of Cancer Therapy-Breast; ITT, Intent-to-treat; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PP, Per protocol; RECIST, Response evaluation criteria in solid tumours; TOI, Trial outcome index; VAS, Visual analogue scale.

Baseline characteristics, patient disposition and duration of treatment: Study 201

Of 104 patients enrolled onto Study 201, 103 received eribulin (ITT/Safety population); 70 patients on the 28-day dosing cycle and 33 on the 21-day dosing cycle. Eighty-seven

patients met the key inclusion criteria (PP population). The majority of patients discontinued treatment due to progressive disease. Patient disposition is summarised in Table 23.

The median age of patients in the ITT population was 55 years, and more than half of patients (54%) had an ECOG performance status of one at baseline. The frequency of ER/PR expression and HER2 over-expression is typical of breast cancer patients; 61% and 47% of patients were positive for ER and PR expression, respectively, and 14% over-expressed HER2. Patients were pre-treated, having received a median of four prior chemotherapy regimens (range, 1–11 regimens). Both the 28-day (n=70) and 21-day (n=33) treatment arms were well balanced with respect to baseline demographic and disease characteristics.

Table 23: Patient disposition: Study 201

	28-day schedule (N = 71) n (%)†	**21-day schedule (N = 33) n (%)†**	**Total (N = 104) n (%)**
Enrolled	71	33	104
ITT/Safety population‡	70 (99%)	33 (100%)	103 (99%)
PP population§	59 (83%)	28 (85%)	87 (84%)
Discontinued from study treatment	71 (100%)	33 (100%)	104 (100%)
Reason for discontinuation from study treatment			
Adverse Events	8 (11%)	1 (3%)	9 (9%)
Withdrew Consent	6 (9%)	1 (3%)	7 (7%)
Progressive Disease	55 (78%)	27 (82%)	82 (79%)
Physician's decision	1 (1%)	3 (9%)	4 (4%)
Lost to Follow-up	0	0	0
Other	1 (1%)	1 (3%)	2 (2%)
Death during treatment or ≤ 30 days of last treatment	5 (7%)	2 (6%)	7 (7%)

Abbreviations: ITT, Intent-to-treat; PP, Per protocol; RECIST, Response evaluation criteria in solid tumours; TPC, Treatment of Physician's Choice. †Percentages are based on enrolled patients; ‡ITT population: All patients who received at least one dose of eribulin; §PP population: all patients who received at least one dose of eribulin, and who met key inclusion criteria.

Patients in the 21-day cohort (licensed dosing regimen) received a median of four cycles of therapy, compared with a median of 2.5 cycles in the 28-day cohort, demonstrating the greater tolerability of the 21-day cycle. In line with this, 44 (63%) of 70 patients on the 28-day regimen experienced dose interruptions, delays, reductions, or omissions in cycle one, and 38 (54%) experienced these in cycle two. However, for the 21-day regimen (licensed dosing regimen), only six (18%) of 33 patients experienced these dose related issues during cycle one. This decreased to three patients (9%) during cycle two. These dose interruptions, delays, reductions, or omissions were primarily due to neutropenia in both groups.

Results: Study 201

- Primary efficacy outcome: ORR

In the PP population, the independently reviewed ORR observed in the 28-day and 21-day (licensed dosing regimen) cohorts were 10.2% (95% CI: 3.8, 20.8) and 14.3% (95% CI: 4.0, 32.7), respectively. This yielded an ORR of 11.5% (95% CI: 5.7, 20.1; all responses were PRs). Results were similar in the ITT population, yielding an ORR of 13.6% (95% CI: 7.6, 21.8; all responses were PRs) by independent review and 16.5% (95% CI: 9.9, 25.1; one CR) by investigator assessment. CBRs for the 28-and 21-day cohorts were 11.9% (95% CI: 4.9, 22.9) and 28.6% (95% CI: 13.2, 48.7), respectively, providing a CBR for the entire PP population of 17.2% (95% CI, 10.0, 26.8).

- Secondary efficacy outcomes

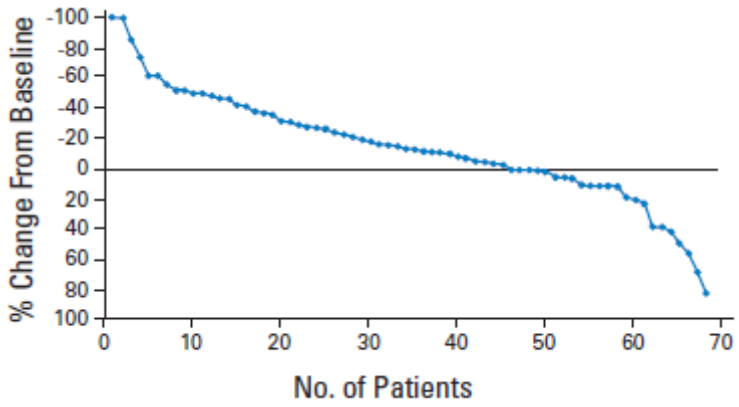
The median duration of response for the 10 patients who responded was 5.6 months (171 days; range, 44–363 days; PP population, independent review).

The median PFS by independent review was 2.6 months (79 days; 95% CI: 54, 107) and the six-month PFS rate was 25.9% (95% CI: 15.5, 36.3). The median OS was 9 months (275 days; 95% CI: 216, 481). Six-month and one-year survival rates were 67.8% (95% CI: 58.0, 77.6), and 45.7% (95% CI: 35.2, 56.2), respectively. Considering just those 10 patients in the PP population who responded to treatment, median PFS and OS was 8.7 months (264 days; range, 79–413 days) and 18.4 months (560 days; range, 372–785 days), respectively.

Since the 21-day cycle dosing regimen was better tolerated and no differences in efficacy were seen between this and the 28-day cycle, eribulin was subsequently administered at 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle in Studies 211, 221 and 305, providing the basis for the target dose regimen.

The change in tumour size (sum of longest single dimension for measurable lesions) from baseline to maximal tumour shrinkage is shown in Figure 9.

Figure 8: Change in tumour size from baseline to nadir



Each point represents a patient (Per-protocol population n=68; 19 patients did not have assessable tumour after the baseline.

- Quality of life outcomes

Based on the FACT-B tumour specific quality of life questionnaire, the mean change from baseline in Trial Outcomes Index (TOI; the sum of the subscores for the physical well-being, functional well-being and breast cancer subscale domains) was similar for responders and non-responders to eribulin therapy. However, 57% of eribulin responders showed an increased quality of life, as measured by an increase in TOI of 5 points or more, compared with 45% of eribulin non-responders. No patients in the responder subset showed deterioration of quality of life (decrease of 5 points or more), while 11% of the study population overall showed a deterioration of quality of life. This suggests that quality of life may be improved in patients who have objective positive tumour response to eribulin treatment. Data for the assessment of tumour-related symptoms were sparse and hence difficult to interpret.

Study 211

Methodology: Study 211

The methodology of Study 211 (39, 40) is summarised in Table 24.

Table 24: Methodology: Study 211

	Details
Objective	Primary: to evaluate the ORR to eribulin in pre-treated patients with LABC or MBC. Secondary: to evaluate duration of response, PFS, OS, pharmacokinetic/ pharmacodynamic and safety.
Location	78 centres in the United States and Western Europe.
Design	Phase II, open-label, single-arm, multi-centre study conducted in 291 patients with LABC or MBC, previously treated with at least an anthracycline and a taxane.
Duration of study	25th October 2005 – 1st September 2007. Patients continued on treatment as long as there was clinical benefit (as per EMBRACE).
Main inclusion criteria	• Female patients aged ≥ 18 years with histologically or cytologically confirmed LABC or MBC; • Measurable disease (defined by RECIST) and confirmation of breast carcinoma if a single lesion; • Two to five prior chemotherapeutic regimens including an anthracycline, a taxane, and capecitabine in any combination or order (≥ one administered for advanced/metastatic disease); • Progression on or within 6 months of completing the last chemotherapy treatment; • ECOG performance status of 0 to 2 ; • Life expectancy ≥ 3 months; • Adequate renal, bone marrow and liver function. Any pre-existing sensory neuropathy had to be of Grade 2 or less.
Main exclusion criteria	• Chemotherapy, biologic therapy or radiation therapy within 2 weeks of treatment, or hormonal therapy within 1 week of starting therapy; • Radiation therapy that encompassed more than 30% of bone marrow;

	Details
	• Prior treatment with eribulin, mitomycin, or nitrosourea; • Anticoagulant therapy with warfarin or related compounds; • Progression of known brain metastases
Intervention and comparator	Eribulin (n=291) • Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle.
Permitted and disallowed concomitant medications	Permitted medications included any medication considered necessary for the patient's welfare not expected to interfere with the evaluation of eribulin, at the discretion of the investigator. Palliative radiotherapy was permitted if the total irradiated area did not increase to > 30% of the bone marrow and if the area was not used to assess tumour response. Medications disallowed included: other investigational drugs; anti-tumour therapies, potent inhibitors or inducers of CYP3A4, and anticoagulant therapy
Discontinuation of study therapy	Patients continued therapy until they experienced progression of disease, unacceptable toxicity or until the investigator determined that discontinuation of therapy was in the best interest of the patient. Patients who demonstrated clinical benefit were allowed to continue treatment for as long as clinical benefit was sustained.
Assessments	Tumours were assessed using RECIST methodology as per the EMBRACE study (see Table 5). Assessments were carried out every two treatment cycles. Tumour response was confirmed by a second examination at least 4 weeks after response criteria were met. Independent review of tumour assessments was performed for all patients, except for those patients (n=91, eligible population) determined by investigators to have disease progression before or at the end of treatment cycle two.
Primary outcomes	ORR (definitions as per EMBRACE, Section 5.3.4)
Secondary outcomes	Duration of response; PFS; OS (definitions as per EMBRACE, Section 5.3.4, except for PFS and OS where the outcome was measured for the start of study medication, not randomisation); Quality of life; Safety. Quality of life was measured using: 1. EORTC-QOL Questionnaire C30 (version 3.0) with the breast cancer specific module BR23 (version 1.0), comprising a total of 53 questions and 23 functional or symptoms subscales. The latter are transformed via a linear transformation to standardize the raw scores so that scores range from 0 to 100. A higher score represents a better level of functioning or a worse level of symptoms. Questionnaires were completed on day 1 of each cycle and at study termination. 2. Tumour-related symptoms assessment using ECOG performance status, pain (VAS), analgesic consumption.
Analysis populations	Primary efficacy analyses were conducted on the eligible population (n=269; patients who received at least one dose of eribulin and met the key eligibility criteria). Secondary efficacy analyses (and safety analyses) were conducted using the ITT/Safety population (n=291; patients who had received at least one dose of eribulin).
Statistical methods	A maximum of 300 patients were planned for enrolment to provide a sample size of 250 eligible patients. This sample size would be sufficient to detect a difference in response rate of 8% to test the null hypothesis ORR of ≤ 15% and the alternate hypothesis ORR of 23%, with 88% power, based on a

	Details
	binomial test with a nominal $p < 0.025$ one-sided significance level. ORR and two-sided 95% CIs were calculated for the eligible and ITT populations using the binomial distribution. Secondary efficacy outcomes were assessed using Kaplan-Meier estimates, as were the corresponding medians and 95% CIs. Exploratory analyses were conducted for quality of life outcomes. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the data cut-off date were censored at that date.
Duration of follow up	Patients followed up every 3 months for OS (until all patients deceased), as per EMBRACE.

Abbreviations: CI, Confidence interval; CR, Complete response; CYP, Cytochrome P-450 system; ECOG, Eastern Cooperative Oncology Group; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; EORTC-QOL, European Organisation for Research and Treatment of Cancer Quality of Life; ITT, Intent-to-treat; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PaR, Partial response; RECIST, Response evaluation criteria in solid tumours; VAS, Visual analogue scale.

Patient disposition, baseline characteristics, and duration of treatment: Study 211

Of 299 patients enrolled onto Study 211, 291 received eribulin (ITT/Safety population), 269 of whom met the key inclusion criteria (eligible population). The majority of patients discontinued treatment due to progressive disease. Patient disposition is summarised in Table 25.

The median age of patients in the ITT/Safety population was 56 years, and nearly two thirds of patients had an ECOG performance status of 1 or more at baseline (63%). The frequency of HER2 over-expression was 11%, while 67% and 49% of patients were positive for ER and PR expression, respectively. Patients were pre-treated with a median of four prior chemotherapy regimens (range 1-6 regimens).

Table 25: Patient disposition: Study 211

	Eribulin (N = 299) n (%)†
Enrolled	299
ITT/Safety population‡	291 (97.3%)
Eligible population§	269 (90.0%)
Discontinued from study treatment	295 (98.7%)
Reason for discontinuation from study treatment	
Adverse Events	25 (8.4%)
Withdrew Consent	7 (2.3%)
Progressive Disease	212 (71.1%)
Clinical progression	30 (10.1%)
Physician's decision	11 (3.7%)
Lost to Follow-up	0
Other	10 (3.4%)
Death during treatment or ≤ 30 days of last treatment	12 (4%)

Abbreviations: ITT, Intent-to-treat; RECIST, Response evaluation criteria in solid tumours; TPC, Treatment of Physician's Choice. †Percentages are based on enrolled patients with available data (n=298). An additional patient was enrolled into the study, but her medical records were lost at the site; ‡ITT population: All patients who received at least one dose of eribulin; §Eligible population: all patients who received at least one dose of eribulin, and who met key eligibility criteria.

Patients received a median of four cycles of eribulin therapy. Of the 291 patients treated with eribulin, 61 patients (21.0%) experienced treatment delays, while 25 (8.6%) experienced dose omissions and 10 (3.4%) has dose reductions in cycle one. Dose delays or reductions were primarily due to neutropenia. There was no need to stop eribulin administration during the infusion for an acute reaction in any patient.

Results: Study 211

- Primary efficacy outcome: ORR

In the eligible population, the independently reviewed ORR was 9.3% (95% CI: 6.1, 13.4; all responses were PRs), and the CBR was 17.1% (95% CI: 12.8, 22.1). The investigator determined ORR was 14.1% (95% CI: 10.2, 18.9), and the CBR was 19.7% (95% CI: 15.1, 25.0). Results were very similar in the ITT population with an ORR and CBR of 9.3% (95% CI: 6.2, 13.2) and 17.2% (95% CI: 13.0, 22.0), respectively in the independent review, and 14.1% (95% CI: 10.3, 18.6) and 20.3% (95% CI: 15.8, 25.4), in the investigator review.

- Secondary efficacy outcomes

The median duration of response for the 25 patients who responded was 4.1 months (126 days; 95% CI: 89, 177; range 42–258 days, eligible population, independent review).

The median PFS by independent review was 2.6 months (79 days, 95% CI: 64, 92), and the six-month PFS rate was 15.6% (95% CI, 10.7, 20.5). Median OS was 10.4 months (315 days; range: 19–604 days), and the six-month OS rate was 72.3% (95% CI, 66.9, 77.6).

The change in tumour size (sum of longest single dimension for measurable lesions) from baseline to maximal tumour shrinkage is shown in Figure 9.

Figure 9: Change in tumour size from baseline to nadir

Each bar represents a patient (Eligible population n=250; 19 patients did not have assessable tumour measurements after the baseline assessment). Response assessed by independent review.

- Quality of life outcomes

Data for the assessment of quality of life outcomes were sparse, since often patients did not complete the forms and hence results are difficult to interpret. However, exploratory analysis indicated no symptomatic change among patients with tumour response, whereas symptomatic deterioration was experienced by patients who experienced disease progression by the end of treatment cycle two. For example, the mean disease effects score (EORTC-QOL subscale) increased from 43 at baseline to 50 in cycle two among patients with a best response of PD (showing deterioration), whereas the score decreased from 33 (baseline) to 31 (cycle four) among responders (all PaR). The mean pain VAS score increased from 28 (baseline) to 30 (cycle two) among patients with a best response of PD (showing increase in pain), whereas pain VAS score decreased from 18 (baseline) to 15 (cycle four) among responders (all PaR).

Study 221

Methodology: Study 221

The methodology of Study 221 (41, 42) is summarised in Table 26.

Table 26: Methodology: Study 221

	Details
Objective	Primary objective: to assess the ORR and safety of eribulin in Japanese patients with LABC or MBC. Secondary objectives: to evaluate duration of response, PFS and OS.
Location	22 centres in Japan

	Details
Design	Phase II, open-label single arm study conducted in 81 patients with LABC or MBC who have been previously treated with an anthracycline and a taxane.
Duration of study	21st January 2008 – 11th September 2009. Patients continued on treatment as long as there was clinical benefit (as per EMBRACE), but were transferred to continue treatment in an extension protocol (Study 224, ongoing) after the analysis for Study 221
Main inclusion criteria	• Female patients aged ≥ 20 and < 75 years with histologically or cytologically confirmed breast cancer; • Prior chemotherapy with anthracycline and taxane therapy, limited to 3 regimens in total; • Measurable disease; • Progression on or within 6 months of completing the last chemotherapy treatment; • ECOG performance status of zero to two; • Life expectancy ≥ 3 months; • Adequate renal, bone marrow, liver and lung function. Any pre-existing sensory neuropathy had to be of Grade 1; • Patients on previous chemotherapy (excluding 5-FU and molecular targeting drugs) or antibody targeting drugs (e.g. trastuzumab) had to have a washout of ≥ 4 weeks before commencing study treatment; • Patients on previous radiotherapy, hormonal therapy, 5-FU or molecular targeting drugs had to have a washout of ≥ 2 weeks before commencing study treatment.
Main exclusion criteria	• Active symptomatic brain metastases; • Radiation therapy encompassing ≥ 30% of bone marrow.
Intervention and comparator	Eribulin (n=81) • Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle.
Permitted and disallowed concomitant medications	Permitted medications included those considered necessary for the patient's welfare not expected to interfere with the evaluation of the study, at the discretion of the investigator. This included symptomatic treatment with G-CSF for neutropenia. Medications disallowed included: other investigational drugs; anti-tumour therapies; potent inhibitors or inducers of CYP3A4, and anticoagulant therapy
Discontinuation of study therapy	Patients continued on study treatment until they experienced progression of disease, no longer had clinical benefit, or experienced unacceptable toxicity
Assessments	Tumours were assessed using RECIST methodology as per the EMBRACE study (see Table 5). Assessments were carried out every 6 weeks (± 2 weeks) after initial administration. Independent review of tumour assessments was also performed.
Primary outcomes	ORR (definition as per EMBRACE, Section 5.3.4)
Secondary outcomes	Duration of response, PFS, OS and safety (definitions as per EMBRACE, Section 5.3.4, except for PFS and OS where the outcome was measured from registration in the study, not randomisation).
Analysis populations	Primary efficacy analyses were conducted in the FAS population (n=80; treated patients with evaluable efficacy data). Analyses were also conducted in the PP population (n=79; patients in the FAS who had to meet key

	Details
	eligibility criteria). Safety analyses were conducted in the safety population (n=81).
Statistical methods	ORR and two-sided 90 and 95% CIs were calculated for the FAS and PP populations using the binomial distribution. Secondary outcomes were assessed using Kaplan-Meier estimates, as were the corresponding medians and 95% CIs.
Duration of follow up	Patients followed up every 3 months for OS but were censored at analysis date and transferred to Study 224 (ongoing).

Abbreviations: CI, Confidence interval; CYP, Cytochrome P-450 system; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; FAS, Full analysis set; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PP, Per protocol; RECIST, Response evaluation criteria in solid tumours.

Patient disposition, baseline characteristics and duration of treatment: Study 221

Of 84 patients enrolled onto Study 221, 81 received eribulin (safety population), of which 80 comprised the FAS population and 79 the PP population. The majority of patients discontinued treatment due to progressive disease. Patient disposition is summarised in Table 27.

The median age of patients in the FAS population was 54, and 72.5% (n=58) of patients had an ECOG status of zero at baseline. HER2 over-expression was seen in 9 patients (11.3%), while 61% (n=49) and 46% (n=37) of patients were positive for ER and PR expression, respectively. Patients were pre-treated with a median of three prior chemotherapy regimens (range 1-5 regimens).

Table 27: Patient disposition: Study 221

	Eribulin (N = 84) n (%)†
Enrolled	84 (100%)
FAS‡	80 (95.2%)
PP population§	79 (94.0%)
Safety population	81 (96.4%)
Discontinued from study treatment	81 (96.4%)
Reason for discontinuation from study treatment (Treated patients)¶	
Aggravation of disease	5 (6.0%)
Withdrew Consent	2 (2.4%)
Progressive Disease	66 (78.6%)
Physician's decision	6 (7.1%)
Subjects were transferred to continuous treatment study (Study 224, ongoing)	6 (7.1%)
Other	3 (3.6%)
Death, during treatment or ≤ 30 days of last treatment	1 (1.2%)

Abbreviations: FAS, Full analysis set; Intent-to-treat; PP, Per protocol; RECIST, Response evaluation criteria in solid tumours; TPC, Treatment of Physician's Choice. †Percentages are based on enrolled patients; ‡FAS population: treated patients with evaluable efficacy data; §PP population: patients in the FAS who had to meet key eligibility criteria; ¶Subjects may have been assigned more than one reason for discontinuation.

The median number of treatment cycles with eribulin was five (range 1-20). Of the 81 patients treated with eribulin, 29 patients (35.8%) experienced treatment delays, while 54 (66.7%) experienced dose omissions and 27 (33.3%) has dose reductions in cycle one. No patients experienced dose interruptions during the infusion of eribulin.

Results: Study 221

- Primary efficacy outcome: ORR

In the FAS, the ORR was 21.3% (95% CI: 12.9, 31.8; all responses were PRs), for both independent and investigator assessments. CBRs for the FAS population were 27.5% (95% CI: 18.1, 38.6) and 28.8% (95% CI: 19.2, 40.0) for independent and investigator assessments. Results were very similar in the PP population.

- Secondary efficacy outcomes

The median duration of response (in the 17 patients who responded) was 3.9 months (119 days; 95% CI: 85, 148 days; FAS, independent review).

The median PFS was 3.7 months (112 days; 95% CI: 61, 133 days) and median OS was 10.9 months (331 days; 95% CI: 234, [upper CI not determined due to shortage of events]) (all FAS and independent review). Six-month PFS and OS rates were 20.1% (95% CI: 11.5, 30.5) and 72.3% (95% CI: 61.0, 80.8), respectively.

5.9 Adverse events

Summary of safety

- The pivotal Phase III RCT (EMBRACE) has demonstrated that eribulin is associated with a predictable and well-characterised safety profile and is generally well-tolerated, for a chemotherapeutic agent being used in pre-treated LABC/MBC patients. (34-36).
- Overall rates of AEs experienced with eribulin in the EMBRACE study are acceptable for a chemotherapeutic agent in the follow-on LABC/MBC setting.
  - The majority of AEs experienced with eribulin were mild or moderate (CTCAE Grade 1 or 2).
  - The most frequently reported AEs (all grades) with eribulin therapy were asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy and nausea (both 34.6%) (Consistent with the pooled safety analysis presented in the SPC [Appendix Section 9.1]). Febrile neutropenia (4.2%) and neutropenia (1.8%) the most frequently reported SAEs.
  - Development of Grade 3/4 AEs of neutropenia occurred in 21.1% and 24.1% of patients, respectively. However, neutropenia led to discontinuation in only 0.6% of patients, while febrile neutropenia (4.6%) and thrombocytopenia (2.6%) were infrequent. Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the study (unless defined by local practice protocols).
  - Peripheral neuropathy, a common side effect seen with some chemotherapies, was generally mild/ moderate (Grade 1/2) with the occurrence of Grade 3/4 peripheral neuropathy being low (~8%) ; of those patients with Grade 3/4 peripheral neuropathy, 63% were able to continue treatment. There is no evidence that patients who were enrolled in the study with pre-existing neuropathy were more likely to develop new or worsening symptoms than those who entered the study without the condition.
  - Palmar-plantar erythrodysaesthesia (hand-foot syndrome), commonly seen with certain chemotherapies, e.g. capecitabine (51), occurred in only 1.4% of patients at any severity grade with eribulin.
  - The incidence of GI events such as constipation, diarrhoea, and vomiting with eribulin was low (< 25%); where these GI AEs occurred they were generally mild (CTCAE Grade 1).
  - Deaths due to AEs were lower in the eribulin arm than the TPC arm (4.0% vs. 7.7%, respectively).
- Eribulin is generally well tolerated, with fewer discontinuations and dose interruptions due to AEs than TPC in the EMBRACE study.
  - Discontinuations due to AEs were lower in the eribulin group than in the TPC group (13.3% vs. 15.4%, respectively).
  - Dose interruptions were lower in the eribulin group than the TPC group (5.0% vs. 10.1%, respectively).
  - Dose reductions due to AEs were similar between the two treatment groups (16.9% vs. 15.8%, respectively).

- As a result, the duration of therapy in EMBRACE was longer in the eribulin arm than the TPC arm, reflecting the promising efficacy and safety profile of this agent for the follow-on treatment of MBC (See Section 5.3.8).
  - Median duration of exposure was 3.9 months (118 days) for eribulin, 2.1 months (64 days) for chemotherapy agents in the TPC arm, and 1.0 month (30 days) for hormonal agents in the TPC arm.

The identification of clinical evidence is described in Sections 5.1 and 5.2. All trials relevant to this submission are listed in Table 3 in Section 5.2.4 and Table 4 in Section 5.2.7. There were no relevant RCT studies designed primarily to assess the safety of eribulin. The main body of adverse event evidence is drawn from the pivotal Phase III eribulin RCT (EMBRACE, Study 305) and is presented in Section 5.9.2.

5.9.1 Trials designed to primarily assess safety

None.

5.9.2 Safety results from other relevant studies

EMBRACE (Study 305)

The methodology of this study has been described previously in Section 5.3. Treatment exposure has also been discussed previously in Section 5.3.8. Unless specified, AE refers to TEAE throughout.

Limited inference can be drawn from direct comparison of safety between patients treated with eribulin and those treated with TPC, as the TPC group comprises patients treated with a wide range of therapies. Further, as each of the therapies in the TPC group has a distinct safety profile, and the number of patients receiving each TPC was relatively small, conclusions cannot be drawn from the comparison of incidences of specific AEs between each TPC and eribulin. Therefore, although the AEs are presented for TPC overall and by specific agent, caution should be taken when making direct safety comparisons.

Brief overview

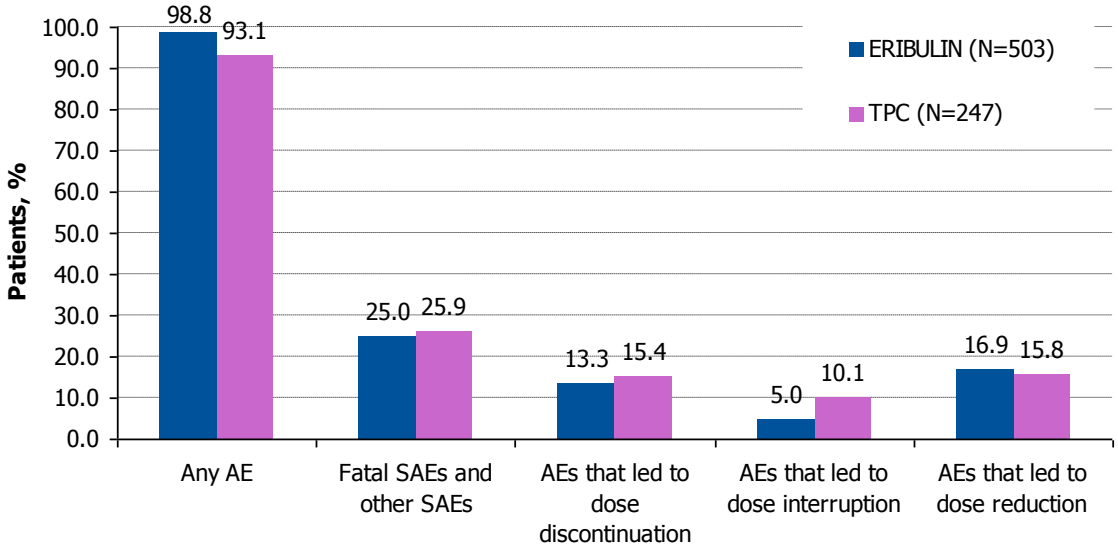
The EMBRACE study adequately characterised the safety profile of eribulin, demonstrating that eribulin is associated with a predictable and well-characterised safety profile and is generally well-tolerated. Almost all patients in the study (eribulin or TPC arms) experienced at least one AE, with SAEs reported for approximately 25% of patients (eribulin and TPC arms; Table 28 and Figure 10). The rates of AEs and SAEs in the eribulin group are acceptable for a chemotherapeutic agent in the follow-on MBC setting.

Table 28: Overall incidence of adverse events: EMBRACE study (Number of patients; Safety population)

	Treatment group				
AEs	**Eribulin N=503 n (%)**	**TPC N=247 n (%)**	**TPC group**		
			Vin. N=61 n (%)	**Gem. N=46 n (%)**	**Cape. N=44 n (%)**
Any AE	497 (98.8%)	230 (93.1%)	57 (93.4%)	44 (95.7%)	41 (93.2%)
Any treatment-related AE	474 (94.2%)	192 (77.7%)	49 (80.3%)	35 (76.1%)	35 (79.5%)
Any SAEs	126 (25.0%)	64 (25.9%)	16 (26.2%)	12 (26.1%)	13 (29.5%)
Fatal SAEs	20 (4.0%)	18 (7.3%)	3 (4.9%)	4 (8.7%)	4 (9.1%)
Other SAEs	114 (22.7%)	56 (22.7%)	14 (23.0%)	10 (21.7%)	11 (25.0%)
Any treatment-related SAEs	59 (11.7%)	17 (6.9%)	5 (8.2%)	2 (4.3%)	4 (9.1%)
AEs that led to discontinuation	67 (13.3%)	38 (15.4%)	7 (11.5%)	5 (10.9%)	5 (11.4%)
SAEs	20 (4.0%)	20 (8.1%)	5 (8.2%)	3 (6.5%)	2 (4.5%)
Non-serious AEs	53 (10.5%)	23 (9.3%)	3 (4.9%)	2 (4.3%)	3 (6.8%)
Other AEs of interest					
AE that led to dose delay	177 (35.2%)	80 (32.4%)	27 (44.3%)	18 (39.1%)	10 (22.7%)
AEs that led to dose interruption	25 (5.0%)	25 (10.1%)	7 (11.5%)	5 (10.9%)	10 (22.7%)
AEs that led to dose reduction	85 (16.9%)	39 (15.8%)	12 (19.7%)	7 (15.2%)	8 (18.2%)
AEs of CTCAE Grade 3	308 (61.2%)	114 (46.2%)	40 (65.6%)	22 (47.8%)	14 (31.8%)
AEs of CTCAE Grade 4	148 (29.4%)	33 (13.4%)	12 (19.7%)	7 (15.2%)	1 (2.3%)
Asthenia/ fatigue	270(53.7%)	98(39.7%)	-	-	-
Neutropenia	260(51.7%)	73(29.6%)	-	-	-
Alopecia	224(44.5%)	24(9.7%)	-	-	-
Peripheral neuropathy†	174(34.6%)	40(16.2%)	-	-	-
Arthralgia/ myalgia	109(21.7%)	29(11.7%)	-	-	-
Febrile neutropenia	23(4.6%)	4(1.6%)	-	-	-

Abbreviations: AE, Adverse event; Anthra., Anthracycline; Cap., Capecitabine; CTCAE, Common Terminology Criteria for Adverse Events; Gem., Gemcitabine; SAE, Serious adverse event; Tax., Taxane; TPC, Treatment of Physician's Choice; Vin., Vinorelbine. † Peripheral neuropathy includes peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia.

Figure 10: Overall incidence of AEs: EMBRACE study (Safety population)



Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, Serious adverse event; TPC, Treatment of Physician's Choice.

Adverse events

AEs occurring in at least 10% of patients in either arm of the EMBRACE study are shown in Table 29. The most common AEs were:

- asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy (34.6%) and nausea (34.6%) with eribulin.
- asthenia/fatigue (39.7%), neutropenia (29.6%), nausea (28.3%), anaemia (22.7%), and constipation (20.6%) with TPC.

Events that occurred at higher frequency with one TPC drug compared to the others in the TPC class included:

- neutropenia with vinorelbine (49.2%).
- neutropenia (37.0%) and nausea (39.1%) with gemcitabine.
- palmar-plantar erythrodysaesthesia syndrome (43.2%) with capecitabine.
- peripheral neuropathy (44.7%), neutropenia (39.5%), and alopecia (34.2%) with taxanes.
- mucosal inflammation (29.2%) and palmar-plantar erythrodysaesthesia syndrome (33.3%) with anthracyclines.

The majority of AEs experienced across both groups were CTCAE Grade 1 or 2, with the exception of neutropenia. Neutropenia, leucopoenia, peripheral neuropathy, and asthenia/fatigue were the most common AEs reported at more severe Grades 3/4 across both treatment arms. In the eribulin group, development of Grade 3 and Grade 4 AEs of neutropenia occurred in 21.1% and 24.1% of patients, respectively. Neutropenia rarely led to febrile neutropenia (4.6%).

AEs of peripheral neuropathy (34.6% of patients) were generally Grade 1/2 with the occurrence of Grade 3/4 peripheral neuropathy being low (7.8% and 0.4%, respectively). There is no evidence that patients who were enrolled in the study with pre-existing neuropathy were more likely to develop new or worsening symptoms than those who entered the study without the condition. Importantly, the incidence of all other Grade 3/4 non-haematologic toxicities, with the exception of asthenia/fatigue (8.8%) was ≤ 5% for eribulin. There was a low incidence of GI events such as constipation, diarrhoea, and vomiting in the eribulin group (< 25%); when these GI AEs occurred they were generally mild (CTCAE Grade 1).

Table 29: Most commonly reported adverse events by treatment group: EMBRACE study (Safety population; > 10% of patients in either study arm, all CTCAE grades)

System organ class AEs	Eribulin N=503 n (%)	TPC N=247 n (%)	Vin. N=61 n (%)	Gem. N=46 n (%)	Cape. N=44 n (%)
Any AE	497 (98.8 %)	230 (93.1)	57 (93.4%)	44 (95.7%)	41 (93.2%)
Blood and Lymphatic					
Neutropenia	260 (51.7%)	73 (29.6 %)	30 (49.2%)	17 (37.0%)	2 (4.5%)
Anaemia	94 (18.7%)	56 (22.7%)	13 (21.3%)	9 (19.6%)	10 (22.7%)
Leucopoenia	116 (23.1%)	28 (11.3%)	10 (16.4%)	8 (17.4%)	1 (2.3%)
Gastrointestinal					
Nausea	174 (34.6%)	70 (28.3%)	19 (31.1%)	18 (39.1%	9 (20.5%)
Constipation	124 (24.7%)	51 (20.6%)	24 (39.3%)	9 (19.6%)	6 (13.6%)
Diarrhoea	92 (18.3%)	45 (18.2%)	14 (23.0%)	9 (19.6%)	12 (27.3%)
Vomiting	91 (18.1%)	44 (17.8%)	13 (21.3%)	10 (21.7%)	10 (22.7%)
General disorders and administration site					
Asthenia/fatigue	270 (53.7%)	98 (39.7%)	31 (50.8%)	17 (37.0%)	17 (38.6%)
Pyrexia	105 (20.9%)	31 (12.6%)	6 (9.8%)	8 (17.4%)	6 (13.6%)
Mucosal inflammation	43 (8.5%)	25 (10.1%)	3 (4.9%)	3 (6.5%)	7 (15.9%)
Investigations					
Weight decreased	107 (21.3%)	35 (14.2%)	10 (16.4%)	5 (10.9%)	6 (13.6%)
Metabolism and nutrition					
Anorexia	98 (19.5%)	32 (13.0%)	11 (18.0%)	6 (13.0%)	6 (13.6%)
Musculoskeletal and connective tissue					
Arthralgia/ myalgia	109 (21.7%)	29 (11.7%)	7 (11.5%)	3 (6.5%)	8 (18.2%)
Back pain	79 (15.7%)	18 (7.3%)	7 (11.5%)	2 (4.3%)	4 (9.1%)
Bone pain	60 (11.9%)	23 (9.3%)	5 (8.2%)	4 (8.7%)	2 (4.5%)
Pain in extremity	57 (11.3%)	25 (10.1%)	11 (18.0%)	2 (4.3%)	8 (18.2%)
Nervous system					
Headache	97 (19.3%)	29 (11.7%)	9 (14.8%)	6 (13.0%)	8 (18.2%)

System organ class AEs	Eribulin N=503 n (%)	TPC N=247 n (%)	Vin. N=61 n (%)	Gem. N=46 n (%)	Cape. N=44 n (%)
Peripheral neuropathy†	174 (34.6%)	40 (16.2%)	12 (19.7%)	2 (4.3%)	5 (11.4%)
Respiratory, thoracic and mediastinal					
Dyspnoea	79 (15.7%)	31 (12.6%)	7 (11.5%)	6 (13.0%)	3 (6.8%)
Cough	72 (14.3%)	21 (8.5%)	4 (6.6%)	7 (15.2%)	3 (6.8%)
Skin and subcutaneous tissue					
Alopecia	224 (44.5%)	24 (9.7%)	2 (3.3%)	3 (6.5%)	3 (6.8%)
Palmar-plantar erythrodysaesthesia syndrome	7 (1.4%)	34 (13.8%)	0	0	19 (43.2%)

Abbreviations: AE, Adverse event; Anthra., Anthracycline; Cap., Capecitabine; CTCAE, Common Terminology Criteria for Adverse Events; Gem., Gemcitabine; Tax., Taxane; TPC, Treatment of Physician's Choice; Vin., Vinorelbine. †Peripheral neuropathy includes peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia.

SAEs

A similar percentage of patients experienced SAEs in both the eribulin and TPC group (25.0% vs. 25.9%, Table 28 and Figure 10). The most frequently reported SAEs in the eribulin group were febrile neutropenia (4.2%) and neutropenia (1.8%), while the most frequently reported SAEs in the TPC group were dyspnoea (3.6%) and asthenia (2.4%).

Deaths

At the end of the trial (data cut-off 12th May 2009) the rate of deaths in the eribulin group was comparable to that in the TPC group (53.9% [n=271] vs. 57.9% [n=143]); the primary reason for death in both groups was progressive disease (50.5% [n=254] vs. 54.7% [n=135]).

However, in terms of deaths related to toxicity, a lower proportion of patients had SAEs leading to death (only including SAEs that occurred during study treatment or within 30 days of the last study treatment) in the eribulin group compared with the TPC group (4.0% [n=20] vs. 7.3% [n=18], respectively). Similarly, the proportion of patients with AEs resulting in an outcome of death (only including deaths that occurred during study treatment, or within 30 days of their last study treatment) was also lower in the eribulin group than TPC group (4.0% [n=20] vs. 7.7% [n=19], respectively).

Treatment-related AEs

In total, 94.2% of patients reported AEs that were thought by the investigator to be treatment-related (Table 28) in the eribulin group compared to 77.7% of patients in the TPC group. The most commonly reported treatment-related AEs (eribulin vs. TPC) were:

- asthenia/fatigue (45.5% vs. 29.6)
- neutropenia (50.7% vs. 27.5%)
- alopecia (44.1% vs. 9.3%)
- peripheral neuropathy (31.6% vs. 13.8%)
- nausea (29.8% vs. 23.1%)
- leucopoenia (22.7% vs. 10.9%).

It should be noted that since the study was open-label, the assignment of events as treatment-related may be biased, possibly leading to more AEs reported as treatment-related for eribulin due to this being the novel therapy.

SAEs were reported as treatment-related for 11.7% of patients in the eribulin group and 6.9% of patients in the TPC group. The most common SAEs reported as treatment-related were febrile neutropenia and neutropenia in the eribulin group, and asthenia/fatigue and diarrhoea in the TPC group.

Discontinuation due to AEs

The percentage of patients experiencing AEs that led to either dose discontinuation or dose interruption was higher in the TPC group compared with the eribulin group (Table 28 and Figure 10). The proportion of patients who discontinued from the eribulin and TPC groups due to AEs were 13.3% and 15.4%, respectively; discontinuations due to

AEs thought to be treatment-related were 8.9% (n=45) and 6.9% (n=17), respectively. Dose interruptions due to AEs were required in 5.0% of patients in the eribulin arm compared with 10.1% of patients in the TPC group. The proportion of patients experiencing AEs that led to dose reduction was similar in the two groups (16.9% eribulin, 15.8% TPC).

While the most common AE leading to discontinuation of eribulin treatment was peripheral neuropathy (4.8% of patients), 63% (26/41) of the patients with Grade 3/4 peripheral neuropathy were able to continue treatment. Neutropenia led to eribulin discontinuation for only 0.6% patients.

Importantly, there is no evidence that eribulin is a vesicant or an irritant.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem

Please see summary box at the beginning of Section 5.9.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The clinical benefit of eribulin has been clearly demonstrated in the pivotal Phase III RCT EMBRACE. The results of this study provide clear evidence of a statistically significant and clinically meaningful improvement in OS compared with current treatment options, and is the first study to do so in this patient population. Pre-treated patients (such as those discussed here), are a particularly challenging subgroup to manage effectively since by this stage patients will have progressed despite treatment, and further treatment options will have limited effectiveness. This is highlighted by the eligibility criteria of the EMBRACE study in which patients had to be refractory to their most recent chemotherapy, documented by progression on or within six months of therapy; overall 80.6%, 57.7% and 67.7% of patients were refractory to taxanes, anthracyclines and capecitabine, respectively, highlighting the need for new therapies in this patient population.

Overall survival is recognised as the most reliable cancer outcome (15, 16) and is of most importance to patients when making decisions regarding treatment options (17). As identified by NICE, there is minimal high-quality evidence about the relative clinical effectiveness of current treatments (8) and none of the currently available monotherapies have demonstrated a survival benefit over any other (8, 19), including the specific agents identified in the NICE scope.

NICE identified that the level of evidence on the use of vinorelbine as a monotherapy is generally of very poor quality consisting mainly of low patient number, non-comparative phase II trials or small RCTs. None of the available data demonstrated an overall survival benefit over an alternative treatment (8). For capecitabine monotherapy, NICE concluded again that the level of evidence is generally of poor quality consisting mainly of low patient number, non-comparative phase II studies (8); although overall survival data for capecitabine is reported in these non-comparative studies, no comparative data

on overall survival is available (8). Recommendations from NICE for gemcitabine are based on its use in combination with paclitaxel only (24), and we are not aware of any comparative overall survival data available for gemcitabine monotherapy.

In contrast, in the Phase III, randomised, controlled EMBRACE trial, median OS with eribulin was 13.1 months compared with 10.6 months for TPC (p = 0.041), an increase in duration of survival of 2.5 months (23%) that reflects a 19% reduction in the risk of death. This analysis reflects the primary study analysis conducted when 55% of patients had died. An updated analysis, as requested by the regulatory authorities, reflecting a more mature dataset with longer follow up (77% of patient dead), confirmed these results; in this analysis median OS was improved by 2.7 months (eribulin 13.2 months vs. TPC 10.5 months, p=0.014). The extension of median survival is similar to that reported with docetaxel versus mitomycin plus vinblastine resulting in docetaxel becaming established in therapy.

Planned sub-group analysis of patients from geographical region 1 (North America/Western Europe/Australia), which is of direct relevance to the population that will be treated in England and Wales, showed a significant OS benefit of eribulin over TPC of 3.1 months in the primary analysis (13.1 months vs. 10.0 months, p=0.009) and the updated analysis (13.2 months vs. 10.1 months, p=0.031).

Eribulin also demonstrated relative improvements in overall survival, when compared with the specific chemotherapy agents identified in the NICE scope. The additional OS benefit for eribulin was 4.7 months, 4.2 months and 3.6 months in the updated analysis, compared with capecitabine, vinorelbine and gemcitabine, respectively. Similar results were obtained when the analyses were conducted using Region 1 patients only; the additional OS benefit for eribulin in the updated analysis was 5.7 months, 6.2 months and 3.7 months, compared with capecitabine, vinorelbine and gemcitabine, respectively. These analyses included only eribulin patients who would have received that specific drug had they been randomised to the TPC arm, and hence maintains randomisation for these individual comparisons.

The clinical benefit of eribulin is further demonstrated by a number of secondary outcomes from the EMBRACE study and supported by data from three single-arm Phase II trials. In the EMBRACE trial, median PFS was longer with eribulin compared with TPC (3.6 months versus 2.2 months, p = 0.002, investigator review; 3.7 months versus 2.2 months, p = 0.137, independent review); ORR (responding patients with either CR or PaR) and CBR (patients with CR or PaR or SD ≥ 6 months) were both improved (investigator and independent review); median duration of response with eribulin was clinically relevant at 4.2 months.

Eribulin exerts its anticancer effects by inhibiting the growth phase of microtubule dynamics, without affecting the shortening phase, and sequesters tubulin into non-productive aggregates (1). In this way eribulin represents an innovative chemotherapy treatment with a unique mechanism of action, that sets it apart from members of tubulin-targeting classes currently in clinical use, including taxanes (e.g. docetaxel) and vinca alkaloids (e.g. vinorelbine).

In terms of drug administration, eribulin is provided as a ready to use solution, avoiding the need for time consuming reconstitution or dilution associated with many IV chemotherapeutic agents, and the potential dosing errors that pre-mixing may lead to. Eribulin is administered as a quick and convenient 2-5 minute IV infusion with no special handling or tubing required, thereby reducing the inconvenience and burden to the patient associated with longer infusion times. Savings in associated healthcare resources, e.g. nursing time, may also be realised. Each cycle of treatment with eribulin consists of only two doses, administered on Days 1 and 8 of the 21-day cycle. Premedication with antihistamine or steroids to prevent hypersensitivity reactions is not routinely required prior to injection, unlike with some chemotherapeutic agents (e.g. paclitaxel); hence, the overall cost of treatment and the potential drug-related adverse effects that the patient may experience are potentially reduced.

Eribulin does not inhibit or induce CYP enzymes at relevant clinical concentrations, and no effect of CYP3A4 inhibitors or inducers on eribulin exposure is observed (See SPC [Appendix Section 9.1]). This lack of drug-drug interaction provides greater flexibility and less risk in this patient population who often receive concomitant medications to control the effects of their advanced disease or to manage concomitant diseases, which are common in this population.

The safety profile of eribulin has been well characterised in more than 900 patients at the licensed dosing regimen. The clinical trial data demonstrate that eribulin is associated with a predictable safety profile and is generally well-tolerated. In the pivotal Phase III EMBRACE study, overall rates of AEs experienced with eribulin are acceptable for a chemotherapeutic agent at this advanced stage of disease, with the majority of AEs experienced being mild or moderate (CTCAE Grade 1 or 2). Treatment discontinuations overall as a result of AEs were lower for eribulin patients compared with the TPC arm of the EMBRACE study (13.3% versus 15.4%).

Haematological toxicity (e.g. neutropenia) with eribulin is evident although not dissimilar in frequency to some of the other chemotherapeutic drugs. However, neutropenia experienced with eribulin in the EMBRACE study proved to be manageable with dose delays, dose reductions, and the use of growth factors. Primary prophylaxis with granulocyte colony stimulating factor (G-CSF) for the prevention of neutropenia was not a requirement of EMBRACE, unless defined by local practice protocols. In the UK, G-CSFs are infrequently used, and this was reflected in the study, in which only 1 UK patient received G-CSFs.

Myelosuppression, a common side effect of some cancer treatments, in which bone marrow activity is decreased, primarily manifests in eribulin-treated patients as neutropenia. Development of CTCAE Grade 3/4 AEs of neutropenia occurred in 21.1% and 24.1% of patients, respectively, in the EMBRACE study. However, neutropenia led to discontinuation in only 0.6% of patients, while febrile neutropenia (4.6%) and thrombocytopenia (2.6%) were infrequent. Patients experiencing Grade 3/4 haematological toxicity should only be retreated with eribulin once neutrophil levels recover to ≥ 1 x 10^9/L and platelets are ≥ 75 x 10^9/L. Patients experiencing febrile neutropenia, severe neutropenia, or severe thrombocytopenia require a reduction of the dose of eribulin (See SPC [Appendix Section 9.1]).

Common non-haematological AEs experienced during eribulin treatment in the EMBRACE study included asthenia/fatigue, alopecia, nausea and peripheral neuropathy; these were usually manageable with dose delays, dose reductions, or supportive therapies. Grade 3/4 non-haematological AEs were infrequent and only observed in more than 5% of patients for asthenia/fatigue (~9%) and peripheral neuropathy (~8%). Guidance for dose reductions in the event of any Grade 3/4 non-haematological AE is provided in the SPC (See Appendix Section 9.1). Events of peripheral neuropathy were generally manageable, with this AE leading to discontinuation of eribulin treatment in less than 5% of patients, while 63% of those with Grade 3/4 peripheral neuropathy were able to continue treatment. There is no evidence that patients who were enrolled in the EMBRACE study with pre-existing neuropathy were more likely to develop new or worsening symptoms than those who entered the study without the condition.

The AEs associated with chemotherapy treatment frequently negatively impact patients' quality of life but, during eribulin treatment, patients do not appear to experience worsening of their HRQL (Study 201 and Study 211, Section 5.8). In fact, patients whose tumours are controlled by eribulin may experience an improvement in HRQL parameters.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

There is minimal high-quality evidence about the relative clinical effectiveness of current treatments for patients at this advanced stage of the disease, as acknowledged by NICE (8). The pivotal eribulin study EMBRACE represents a high quality, large (> 750 patients), multi-centre, head to head RCT providing robust evidence for the statistically and clinically significant benefit of eribulin compared with current treatment options in pre-treated patients with LABC/MBC.

Treatment for this advanced stage of the disease is focused on prolonging survival, while controlling the symptoms experienced and improving the patient's quality of life (8). The EMBRACE study employed primary and secondary efficacy outcomes, including OS, PFS, ORR and duration of response, that are all commonly used measures of efficacy for breast cancer drugs and clinically relevant. The primary outcome of OS is considered the most reliable cancer outcome, particularly in the pre-treated population considered here (i.e. short life expectancy, where results are expected in a reasonable timeframe and there are very limited effective next line therapies) (15, 16). It is precise and easy to measure, documented by the date of death and thus is not subject to assessment bias. However, no RCTs of the currently available monotherapies have demonstrated a survival advantage over any other single agent in the treatment of anthracycline and taxane-resistant MBC (19). This is a clear weakness in the clinical evidence as acknowledged by NICE (8), particularly as the majority of patients believe that the primary goal of treatment is to prolong their life (17). Eribulin is now included in the AGO guidelines in Germany.

Eribulin, however is the first monotherapy to demonstrate statistically significant improvements in OS in pre-treated patients with LABC/MBC, while offering a safety and tolerability profile that is acceptable for a follow-on chemotherapeutic agent. As such this monotherapy represents the first major advance in chemotherapy treatment in this setting in almost a decade.

EMBRACE compared the efficacy and safety of eribulin with TPC, a comparator arm that reflects the real life choices faced by physicians and patients. Although an RCT has not been performed versus one specific comparator, by following the recommendations supported by the EMEA to use TPC, the EMBRACE trial reflects clinical practice and the reality that there is no single pattern of treatment for patients beyond 1st line in treatment in advanced breast cancer. It can be argued that practically speaking it would not be feasible to conduct large scale trials to compare eribulin with individual therapies due to the diversity of treatment used at this stage of the disease. Using TPC as a comparator allows treatment selection to be based on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient's quality of life, representing how treatment decisions are made in clinical practice. Offering patients a choice of treatment and taking their preferences into account is crucial to this approach, as recognised by the NICE cancer services guidance (23). NICE guidance to manufacturers on the technology appraisal process (33) recognises that comparators for technology appraisals should be selected based on current standard of care, and that standard of care will vary across the NHS. The mixture of therapies currently used in clinical practice, and those chosen by physicians within the EMBRACE trial would appear to validate the TPC approach for the EMBRACE study.

However, additional post-hoc analyses were conducted to investigate the comparison of eribulin with the individual agents, capecitabine, vinorelbine and gemcitabine, as defined within the NICE scope. Data were analysed using eribulin patients who would have received that specific drug had they been randomised to the TPC arm, and hence maintains randomisation for these individual comparisons (See Section 5.5.1. Consistent with the primary outcome versus TPC, the HR for survival benefit was in favour of eribulin for all comparisons with capecitabine, vinorelbine and gemcitabine. It should be noted that the interpretation of these subgroup analyses requires caution.

For secondary outcomes of tumour response in the EMBRACE study, such as PFS, patient assessments were made by investigators via imaging data and clinical examinations. Independent blinded review of imaging data alone was also performed. The PFS results achieved in this study support the primary outcome of OS but this was more robust when PFS was analysed according to the investigator's assessments rather than the independent review. The investigator review represents more closely what would happen in clinical practice, and although designed to avoid bias, the independent review is associated with some limitations as highlighted below.

- Patients were no longer scanned when the investigator deemed that they had PD, leading to informative censoring. Even if the independent reviewers did not find PD, they could no longer follow the patients' tumour responses since scans were not available to review. A consequence of this is that some progressions in the investigator's review become censored in the independent review.
- Progression of patients with non measureable disease could only be assessed by independent review if non-target lesions unequivocally progressed or if new lesions appeared.
- Patients who progressed clinically without radiologic findings could not be assessed by the independent reviewers.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The clinical data presented within this section provides a robust evidence base of direct relevance to the decision problem.

In line with the population defined by the decision problem, the pivotal EMBRACE study comprised patients with LABC/MBC[b] who had previously received at least two chemotherapy regimens for the advanced stage of the disease.

All the main outcomes defined by the decision problem are available within the evidence presented. As recognised by NICE guidelines, one of the key priorities for treating this advanced stage of breast cancer is to prolong survival, while controlling the symptoms experienced and improving the patient's quality of life (8).

By using primary and secondary efficacy outcomes of OS, PFS, ORR and duration of response, the pivotal EMBRACE study employed commonly used measures of efficacy for breast cancer drugs that are of clinical relevance. The importance of OS as a cancer trial outcome and the significance of the OS results from the EMBRACE study have been highlighted already in Section 5.10.2. However, given the reliability of OS as a primary trial outcome (15, 16), the lack of relative survival benefit demonstrated for existing treatments over one another (8, 19) and the importance of OS to patients in making treatment decisions (17), the significance of the results achieved with eribulin cannot be overstated. The EMBRACE study provides clear evidence of a statistically significant improvement in OS compared with current treatment options for pre-treated patients with LABC/MBC. For these patients with such advanced disease and few effective treatment options, this relative improvement in OS (~2.5 months, 23% improvement, 19% reduction in the risk of death) is clinically meaningful.

The EMBRACE trial provided evidence for the clinical benefit of eribulin compared with current treatment options used in clinical practice (TPC), and represents a valid approach to define the relative efficacy of eribulin in this setting. However, additional post-hoc analyses were conducted to investigate the comparison of eribulin with each individual TPC group, as defined within the NICE scope; compared with capecitabine, vinorelbine and gemcitabine, the HR for survival benefit was in favour of eribulin for all comparisons, consistent with the primary outcome comparison with TPC.

Based on NICE's supplementary advice on end-of-life treatment, eribulin would appear to meet the key criteria for life extending, end-of life treatments.

- "The treatment is indicated for patients with a short life expectancy, normally less than 24 months"

[b] Defined in the EMBRACE study as locally recurrent or MBC.

- The average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving chemotherapy (14). At the point in therapy where eribulin will be used – following at least two chemotherapeutic regimens for advanced disease – the length of survival would be expected to be even less.

- "There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment"
  - Eribulin provides an additional 3.1 months of life, compared with Treatment of Physician's Choice, based on a pre-planned analysis of patients in the EMBRACE study from geographic Region 1 (North America/Western Europe/Australia), which is of direct relevance to the population that will be treated in England and Wales.
  - Analyses (post-hoc) versus specific chemotherapy agents identified in the NICE scope also demonstrated relative improvements in overall survival. The additional OS benefit for eribulin was 4.7 months, 4.2 months and 3.6 months, compared with capecitabine, vinorelbine and gemcitabine, respectively. Using Region 1 patients only, the additional OS benefit for eribulin was 5.7 months, 6.2 months and 3.7 months, compared with capecitabine, vinorelbine and gemcitabine, respectively.
- "The treatment is licensed or otherwise indicated for small patient populations"
  - Based on calculations provided in Section 2.2, around 1,100-1,700 patients would be eligible to be considered for eribulin therapy.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Secondary outcomes relating to tumour response such as PFS, were assessed through both unblinded investigator assessment and blinded independent review in the EMBRACE study. The limitations associated with the independent review have been highlighted in Section 5.10.2, and with access to the patients themselves, the results of the investigator review would be more representative of the outcomes that would be achieved in clinical practice. It should be noted however that the PFS results support the primary outcome of OS regardless of the type of assessment carried out, although results were more robust when PFS was analysed according to the investigator's assessments rather than the independent review.

The majority of the evidence presented within this submission is for the licensed dosing regimen of 1.23 mg/m^2 of eribulin (equivalent to 1.4 mg/m^2 eribulin mesylate) administered intravenously over 2–5 minutes on Days 1 and 8 of a 21-day cycle, and is therefore directly relevant to the way in which eribulin will be administered in clinical practice. All patients (n=508) treated with eribulin in the EMBRACE study and the majority of patients in the supporting Phase II studies (n=405; Study 201, Study 211, Study 221) received eribulin at the licensed dosing regimen; for dose finding purposes

70 patients in Study 201 were also treated with the licensed dose but given on Days 1, 8 and 15 of a 28-day cycle.

Patient demographics and baseline disease characteristics were considered to be representative of pre-treated patients with advanced breast cancer that would be seen in clinical practice. The pivotal Phase III study EMBRACE was conducted predominantly in Western European and North American patients, including 51 patients treated in 10 UK centres. Patients had a median age of 55 years, 92.3% of patients were White, and most (75.9%) patients were post-menopausal. As demonstrated by figures from Cancer Research UK, breast cancer is strongly related to age and hormonal status; 81% of cases occur over the age of 50, with a rapid increase in incidence being linked to the menopause (4).

Overall, eribulin offers physicians and patients in England and Wales an innovative chemotherapy treatment to patients in England and Wales. At this stage of treatment there is minimal high-quality evidence about the relative clinical effectiveness of current treatments (8) and none of these treatments have demonstrated a survival benefit over any other (8, 19). In contrast, there is clear evidence that eribulin provides a statistically significant and clinically meaningful improvement in OS compared with current treatment options for pre-treated patients with LABC/MBC, a patient population with few treatment options and an unmet medical need.

6 Cost-effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

A systematic review was conducted to identify cost-effectiveness studies from the published literature relevant to the decision problem. Initially, the inclusion and exclusion criteria were chosen to identify all economic evaluations assessing treatments for locally advanced breast cancer (LABC)/metastatic breast cancer (MBC). The full review of papers was then restricted to those addressing the UK health care setting to ensure the inclusion and review of the most relevant analyses.

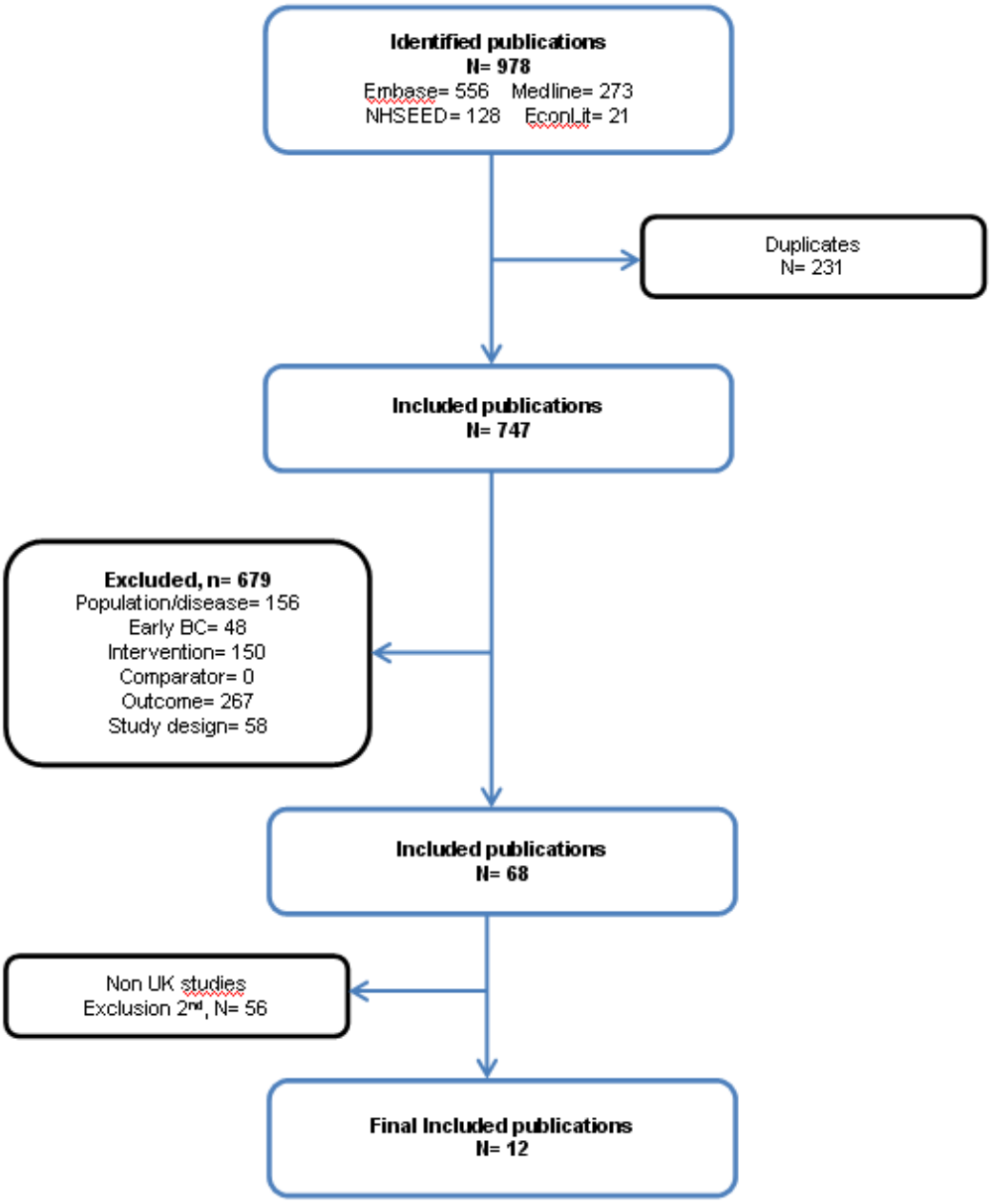
Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for LABC/MBC and were then combined with standard economic search terms. The search strategy is provided in the Appendix, Section 9.10.

This systematic review was supplemented by a search of the NICE website for relevant technology appraisals and clinical guidelines (see Section 9.10.5 for details).

The results of these searches are reported within this section. The flow diagram for the systematic review is shown in Figure 11.

Seven hundred and forty seven potentially relevant publications were identified for inclusion in the systematic review, of which 679 were excluded on the basis of title and abstract. After further review of the 68 identified studies, a further 56 were excluded. This was to focus the review on studies relevant to decision making in England and Wales. Twelve papers met the applied criteria.

Figure 11: Flow diagram for the systematic review of cost-effectiveness evaluations



6.1.2 Description of identified studies

One study was identified that assessed the cost effectiveness of treatment for third line MBC (52). Six studies were identified that assessed the cost effectiveness of chemotherapy for second line treatment of MBC, that is, where an anthracycline or alkylating agent had failed (53-58). The remaining five studies assessed the cost effectiveness of aromatase inhibitors e.g. letrozole, exemestane and/or oestrogen receptor antagonists (59-63).

In order that the review remained relevant to the decision problem, the seven studies assessing the cost effectiveness of therapies given at either second line (where

anthracyclines or an alkylating agent–containing agent had failed) or third line (following the failure of an anthracycline and a taxane) were the focus of the review. The remaining 5 studies were therefore excluded from further review (59-63).

Two of the studies identified (52, 57), reported the methods and results from manufacturer submissions to NICE for specific technology appraisals. An additional two relevant publications were identified from the search of the NICE website (the Evidence Review Group report for the gemcitabine technology appraisal, TA116 (64) and the NICE clinical guideline on advanced breast cancer, CG81 (8)). These publications also reported cost effectiveness analyses of chemotherapy for the second or third line treatment of MBC following the failure of an anthracycline in the UK and were therefore included in this review.

The identified studies assessed the cost effectiveness of a number of chemotherapies. These were, docetaxel, paclitaxel, vinorelbine, gemcitabine, doxorubicin (as second line after failure of a previous therapy), and combinations of these therapies. The majority of the studies (6 out of 7) reported that they used a Markov model to estimate the costs and benefits associated with the therapies included. Jones et al in 2004 (52) reported that they did not carry out an analysis but reported a model submitted by a manufacturer for the appraisal of capecitabine. The type of economic analysis carried out by the manufacturer was described as a simple cost effectiveness model with no further detail reported.

The majority of the models described used health states relating to recurrent MBC, response to treatment, stable disease, progressive disease and death. Clinical data was typically sourced from clinical trials reported in the published literature. All of the analyses report total costs and QALYs as outcome measures. The utility values and sources of the utility values were extracted and summarised in Section 6.4.6.

In general the studies were of good quality and were relevant to decision making in England and Wales. However, they did not address the cost effectiveness of eribulin. One study assessed the cost effectiveness of a treatment for third line, that is, capecitabine compared with vinorelbine following the failure of an anthracycline and a taxane (52). However, this analysis has since been updated in the form of a national clinical guideline (8). In addition, clinical evidence to support the intervention or comparator reported by Jones et al 2004 (52) appears to have been sparse, relying on non comparative clinical trials. NICE clinical guideline 81 (8), also addresses the cost-effectiveness of treatments following the failure of an anthracycline and a taxane. However, eribulin is not included in this analysis. In addition, the purpose of the model reported by the guideline focuses on optimal strategies of treatments rather than the cost effectiveness of one treatment at a specific line. A summary of all the reviewed studies has been included in Table 30.

To address the lack of published evidence for the cost effectiveness of eribulin, a de novo analysis has been carried out.

Table 30: Summary list of other cost-effectiveness evaluations

Study	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator) (£)	ICER (per QALY gained) (£)	Sensitivity analyses
Benedict et al, 2009 (53)	Cost utility analysis using Markov model; comparing taxanes in MBC patients. The primary source of clinical model inputs was clinical trial data.	MBC patients previously treated with an anthracycline	QALYs, discounted: Docetaxel= 1.18 paclitaxel 175mg/m2 every 21 days= 0.85 paclitaxel 90mg/m2 every 7 days= 0.89 nano albumin-bound paclitaxel 260,g/m2 every 21 days= 0.96 Incremental QALYs compared with docetaxel: paclitaxel 175mg/m2 every 21 days= 0.33 paclitaxel 90mg/m2 every 7 days= 0.29 nano albumin-bound paclitaxel 260,g/m2 every 21 days= 0.22	Discounted total costs: Docetaxel= 17,321 paclitaxel 175mg/m2 every 21 days=13,301 paclitaxel 90mg/m2 every 7 days= 15,973 nano albumin-bound paclitaxel 260,g/m2 every 21 days= 14,116 Incremental costs compared with docetaxel: paclitaxel 175mg/m2 every 21 days= 4,020 paclitaxel 90mg/m2 every 7 days= 1,348 nano albumin-bound paclitaxel 260,g/m2 every 21 days= 3,205	Cost/QALY all compared with docetaxel: paclitaxel 175mg/m2 every 21 days= 12,032 paclitaxel 90mg/m2 every 7 days= 4,583 nano albumin-bound paclitaxel 260,g/m2 every 21 days= 14,694 Net benefit (£20,000/QALY): Docetaxel= 6,340 paclitaxel 175mg/m2 every 21 days= 3,678 paclitaxel 90mg/m2 every 7 days= 1,805 nano albumin-bound paclitaxel 260,g/m2 every 21 days= 5,182	The one-way sensitivity analysis showed that survival parameters, paclitaxel costs and G-CSF costs were most influential variables in the model. In PSA, the probability of docetaxel being cost effective was 70% at a WTP threshold of £20,000/QALY.
Brown et al, 2001 (54)	Markov decision analysis model to simulate clinical course of patients with advanced BC during salvage chemotherapy from phase III clinical trial data for docetaxel, paclitaxel and vinorelbine	Women requiring chemotherapeutic treatment for anthracycline-resistant advanced breast cancer	Docetaxel versus paclitaxel, docetaxel = 0.7347 Paclitaxel = 0.6485 Incremental QALYs = 0.0862 Docetaxel versus vinorelbine Docetaxel = 0.7347 Vinorelbine = 0.4822 incremental QALYs = 0.2525	Docetaxel versus paclitaxel total costs docetaxel = 7,817 paclitaxel = 7,645 Incremental costs = 172 Docetaxel versus vinorelbine Total costs docetaxel = 7,817 with vinorelbine = 4,268 Incremental costs =	Cost per QALY for docetaxel compared with paclitaxel = 1,995 Cost per QALY for docetaxel compared with vinorelbine = 14,055.	One-way sensitivity analyses were carried out The effect of variations in the discount rates (both benefits and costs were discounted at 6%), utility values used to calculate the QALYs, costs applied to disease states and toxicities experienced, were investigated. The maximum cost/QALY for docetaxel versus paclitaxel was 6,055 (cost of progressive disease reduced to 100 per 3-week period). For docetaxel

Study	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator) (£)	ICER (per QALY gained) (£)	Sensitivity analyses
				3,549 over vinorelbine.		versus vinorelbine, the maximum cost/QALY was 15,095 (utility values for disease states pooled from 6 countries).
Cooper et al, 2003 (55)	Markov model (MCMC). The analysis was conducted to demonstrate the Bayesian approach to markov modelling. A practical application was presented for the cost effectiveness of docetaxel versus doxorubicin for the treatment of MBC. Results from three modelling methods were reported. Clinical inputs were mainly taken from a Bayesian meta-analysis of clinical trial data.	Women with MBC (second line treatment)	Mean incremental utilities for docetaxel versus doxorubicin were reported for three models: Classical Monte Carlo = 0.047 Bayesian (MCMC) = 0.040 Bayesian (MCMC) with informative prior distributions = 0.036	Mean incremental costs for docetaxel versus doxorubicin were reported for three models: Classical Monte Carlo = 5,250 Bayesian (MCMC) = 4,468 Bayesian (MCMC) with informative prior distributions = 4,438	The cost effectiveness acceptability curves show that at £100,000 per additional QALY, the probability that docetaxel is more cost effective than doxorubicin is 0.49.	When the cost of docetaxel was halved the probability that docetaxel is cost effective compared with standard treatment increased from 0.49 to 0.67 at £100,000 per additional QALY gained. Hence, the model results are reasonably sensitive to the cost of docetaxel.
Hutton et al, 1996 (56)	A Markov model was utilised to estimate benefits and costs of docetaxel versus paclitaxel. The main clinical outcomes in the model were taken from the published literature and expert opinion.	The study considered a hypothetical, but representative, female patient with MBC being treated following failure of an anthracycline containing regimen.	Total QALYs per patient: Paclitaxel= 0.5111 Docetaxel= 0.6016 Incremental QALYs= 0.0905	Total per-patient costs for the base-case: paclitaxel = 8,013 docetaxel = 8,233 Incremental costs = 220	docetaxel compared with paclitaxel = 2,431 per QALY	One-way sensitivity analyses were undertaken on efficacy and safety parameters and on drug costs. The results were sensitive to the efficacy of docetaxel: the ICER falls to 1,186 if docetaxel response rate increases from 47% to 56%.
Jones et al, 2004 (52) HTA	Simple cost effectiveness model of capecitabine compared with vinorelbine in	Patients with MBC previously treated with anthracyclines and a taxane.	Several base case QALY estimates were provided depending on the source of effectiveness data	Several base case cost estimates were provided depending on the source of effectiveness data	Based on the data available, the evaluation concluded that capecitabine monotherapy was more	Sensitivity analysis on the analysis of capecitabine versus vinorelbine were consistent with the base case estimate that

Study	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator) (£)	ICER (per QALY gained) (£)	Sensitivity analyses
Based on Roche data	patients previously treated with anthracyclines and a taxane. No further details of the model were reported. The main clinical outcomes were taken from published clinical trials.		Capecitabine: Blum, 1999= 0.56 Blum, 2001= 0.51 Reichardt, 2001= 0.45 Fumoleau, 2002= 0.66 Vinorelbine: Livingstone, 1997= 0.38 Udom, 2000= NA Zelek, 2001= 0.41	(drug costs only) Capecitabine: Blum, 1999 = 432 Blum, 2001= 466 Reichardt, 2001= 398 Fumoleau, 2002= 605 Vinorelbine: Livingstone, 1997= 689 Udom, 2000= 904 Zelek, 2001= 993	effective and less costly than vinorelbine. An additional analysis was carried out to assess the cost effectiveness of capecitabine in combination with docetaxel compared with docetaxel alone. The analysis considered an open label trial comparing the alternative and a mean utility value for stable and progressive disease from several literature sources.	capecitabine is dominant when compared with vinorelbine. PSA carried out for the analysis of capecitabine in combination with docetaxel compared with docetaxel alone showed that combination therapy is likely to be cost effective above a very modest willingness to pay threshold.
Jones et al, 2009 (57) HTA Further details included in the summary of NICE TA116.	Markov state transition model	Patients with MBC	Not reported	Not reported	The base-case cost-effectiveness estimate for gemcitabine/paclitaxel versus docetaxel is £17, 168 per QALY	Sensitivity analysis using a longer survival with docetaxel was conducted. The resulting incremental cost-effectiveness ratio was approximately £30,000 per QALY. PSA estimated a 70% probability of gemcitabine/paclitaxel being cost-effective relative to docetaxel at an arbitrary threshold willingness to pay of £35,000.
Takeda et al, 2007 (58) HTA	A markov model was developed to estimate the cost effectiveness of gemcitabine and paclitaxel in combination compared with paclitaxel alone for the treatment of MBC.	Patients with MBC	QALYs gained per patient GEM/PAC= 1.00 PAC= 0.83 Incremental QALYs gained with GEM/PAC versus PAC = 0.16	Cost per patient: GEM/PAC= 26,202 PAC= 16,653 Incremental costs for GEM/PAC versus PAC = 9,549	Cost per QALY gained = 58,876	A sensitivity analysis based on only 6 cycles of chemotherapy was carried out resulting in a cost per QALY of £38, 699 for GEM/PAC versus PAC. A sensitivity analysis based on only responsive and stable patients was carried out resulting in a cost per of PFS year gained of £91, 926 for

Study	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator) (£)	ICER (per QALY gained) (£)	Sensitivity analyses
						GEM/PAC versus PAC. PSA was carried out and demonstrated that that combination therapy is unlikely to be considered cost effective under £60,000 per QALY.
NICE TA116 – taken from the ERG report (64)/	The manufacturer model consisted of a markov state transition model to estimate the cost effectiveness of gemcitabine plus paclitaxel compared with docetaxel monotherapy, paclitaxel monotherapy and docetaxel plus capecitabine. Clinical data were taken from an indirect comparison carried out by the manufacturer.	Patients with MBC previously treated with anthracyclines	The incremental costs of gemcitabine combined with paclitaxel compared with docetaxel = 4,013	The incremental QALYs for gemcitabine combined with paclitaxel compared with docetaxel = 0.23	The estimated incremental cost/QALY reported as £17, 168 for gemcitabine in combination with paclitaxel (base-case analysis docetaxel as comparator). A comparison of gemcitabine plus paclitaxel with paclitaxel monotherapy resulted in an ICER of £30,100 per QALY. A comparison of gemcitabine plus paclitaxel with docetaxel plus capecitabine resulted in an ICER of £23,200 per QALY. In an illustrative analysis, the ERG found that using relative treatment effects to estimate overall survival for docetaxel monotherapy resulted in an ICER of £45,800 per QALY for a comparison of gemcitabine plus paclitaxel against docetaxel monotherapy	In sensitivity analyses, the incremental cost/QALYs for gemcitabine/paclitaxel combination compared with docetaxel were ranged from £13,000 to £21,000 per QALY gained. PSA estimated a 70% probability of gemcitabine/paclitaxel being cost-effective relative to docetaxel at an arbitrary threshold willingness to pay of £35,000.
NICE CG81 (8)	The guideline developers estimated the cost-utility of chemotherapy sequences for the treatment of patients	The model considering patients with MBC who have received prior anthracycline therapy.	QALYs are reported for 17 strategies. Gemcitabine plus docetaxel followed by capecitabine followed by vinorelbine yields the highest number of QALYs = 1.2	Total costs are reported for 17 strategies. Paclitaxel followed by no chemotherapy yields the lowest cost = £13,500 Gemcitabine plus	docetaxel followed by capecitabine followed by no chemotherapy was shown to be most cost-effective at a willingness to pay threshold of £20,000.	Three sources of uncertainty surrounding the analysis were investigated using one-way sensitivity analysis; the data used on the effectiveness of capecitabine monotherapy, the

Study	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator) (£)	ICER (per QALY gained) (£)	Sensitivity analyses
	with advanced breast cancer. A decision tree was used to represent all the possible consequences resulting from a sequence of treatments Clinical data were sourced from an indirect comparison and published clinical trials.		Paclitaxel followed by no chemotherapy yields the lowest number of QALYs = 0.36	docetaxel followed by capecitabine followed by vinorelbine yields the highest cost = £30,313	An incremental analysis was also reported.	effectiveness of third-line therapy and possible price discounts.

Abbreviations: ERG, Evidence review group; G-CSF, Granulocyte colony-stimulating factor; GEM, Gemcitabine; ICER, Incremental cost-effectiveness ratio; MBC, Metastatic breast cancer; MCMC, Markov chain Monte Carlo simulation; PAC, Paclitaxel; PSA, Probabilistic sensitivity analysis; QALY(s), quality-adjusted life year(s); WTP, willingness to pay.

6.1.3 Quality assessment

A quality assessment of each cost-effectiveness study is provided in the Appendix, Section 9.11.

6.2 De novo analysis

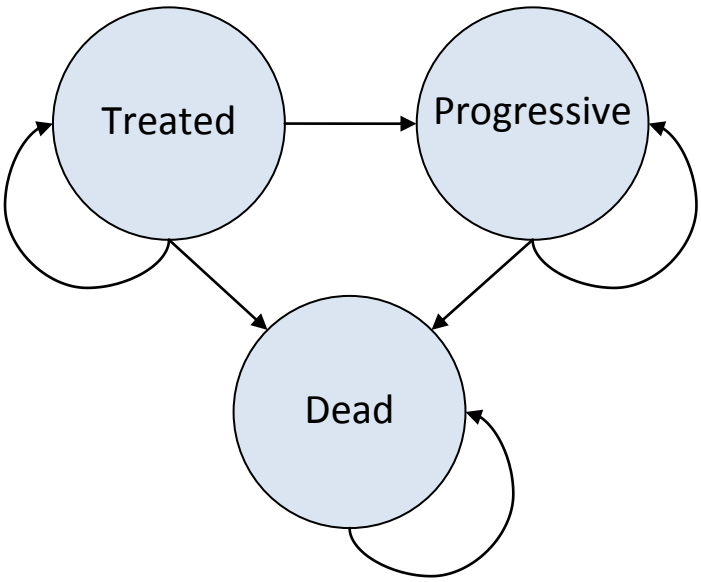
6.2.1 Patients

The patient population in the model matches the pivotal Phase III RCT for eribulin (EMBRACE) and therefore included female patients with LABC/MBC whose disease had progressed after at least two prior chemotherapy regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane. This is also in line with the licensed indication.

Model structure

6.2.2 Model schematic

Figure 12: Model schematic



6.2.3 Justification of model structure

A semi-Markov state transition model was developed in Microsoft Excel to model the lifetime clinical and economic outcomes for a hypothetical cohort of patients with LABC/MBC. The model structure was informed by and adapted from published economic evaluations of breast cancer treatments as reviewed in Section 6.1.2, in particular Brown et al, Cooper et al, Hutton et al and Takeda et al (54-56, 58).

All patients in the model were initially assigned to the “Treated” health state, comprising both stable and responsive patients. These patients matched those recruited into the clinical trial and would therefore be eligible for eribulin or the comparator treatment as outlined in Section 2.4. Patients remained on the assigned treatment drug until disease progression or death, as would be seen in clinical practice.

6.2.4 Definition of health states

Health states were defined for consistency with clinical outcomes reported in oncology clinical trials, including EMBRACE. The use of a single health state (“Treated”) to capture both stable and responsive patients comes with an implicit assumption that treatment response is not a significant predictor for disease progression or death. The validity of this assumption is tested by examination of patient-level data from the EMBRACE trial.

Patients remained on the assigned treatment drug until disease progression or death. The “Progressive” health state captures the clinical outcomes and resource use for patients whose disease progresses following previous treatment. Cycles continued until all patients were in the “Dead” state. For the purposes of resource use and quality of life estimations, patients were assumed to enter an “Terminal” state for one cycle prior to entering the “Dead” state.

Each health state was associated with health-care resource costs that were assigned in each model cycle. Patients in the “Treated” health state also incurred the costs of drug acquisition and administration, as well as grade 3 and grade 4 treatment-related toxicities. Each health state also had a corresponding utility that was assigned to estimate effectiveness. In the case of the “Treated” state, different utilities for stable and responsive disease were used and weighted by the proportion of patients responding.

6.2.5 Context

Although simplified, the model health states capture the relevant clinical outcomes and resource use for patients receiving eribulin or a comparator treatment; for example, the primary clinical outcome considered was OS as this is recognised as the most definitive cancer outcome and is of most importance to patients when making decisions regarding treatment options (see Section 2.1). Disease progression and death was captured using survival functions based on time-to-event patient-level data from the EMBRACE trial.

6.2.6 Key features of the economic evaluation

Table 31: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Current trial Follow-up – 2.89 Years	The model horizon represents the length of the clinical trial follow up and lack of long-term clinical data to inform further extrapolation.	EMBRACE clinical trial data (Section 5.3)
Cycle length	21 days	Eribulin treatment cycle	SPC

Factor	Chosen values	Justification	Reference
Half-cycle correction	No	As costs and benefits are applied over relatively short periods of time (21 days), no half cycle correction was added.	N/A
Were health effects measured in QALYs; if not, what was used?	Yes	As stated in the decision problem	NICE methods guide
Discount of 3.5% for utilities and costs	Yes	NICE methods guide	NICE methods guide
Perspective (NHS/PSS)	Yes	As stated in the decision problem	NICE methods guide

Abbreviations: N/A, Not applicable; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.

The base case economic analyses have been conducted using the end-of-life criteria, as defined by NICE. The suitability of applying end-of-life criteria has been described in Section 5.10.3. Scenario analysis is conducted without applying end-of-life criteria.

Technology

6.2.7 Intervention and comparator

The model compares eribulin monotherapy with a number of different comparators, as outlined below:

- Treatment of Physicians Choice (TPC);
  - As previously described in Section 2.6 and Section 5, this is the basis of the approach taken for the comparator arm of the pivotal Phase III eribulin clinical trial, and reflects a pragmatic approach to compare eribulin to the current treatment landscape, consisting of a variety of therapeutic options instituted by practicing physicians on a day-to-day basis.
- Individual chemotherapeutic agents, as defined by the NICE scope;
  - Capecitabine
  - Gemcitabine
  - Vinorelbine

All interventions are implemented in the model as per their marketing indications.

6.2.8 Treatment continuation rule

Treatment continuation rules were not considered in the economic model.

6.3 Clinical parameters and variables

6.3.1 How where clinical data implemented in the model?

Health state transitions

Transitions between the three health states of “Treated, “Progressive” and “Dead” were governed by probabilities of disease progression and death derived from survival functions based on time-to-event patient-level data from the pivotal Phase III eribulin trial (EMBRACE):

- **Progression-free survival** data from EMBRACE governed transitions from the “Treated” to “Progressive” health states at the conclusion of each model cycle. The model utilises independent review of progression to establish tranisiton.
- **Overall survival** data from EMBRACE governed transitions to the “Dead” state at the conclusion of each model cycle.

Response to treatment
The proportion of patients in the “Treated” health state whose tumour(s) exhibited a complete response (CR) or partial response (PaR) were defined using the **objective response rate** (ORR) as per the EMBRACE trial (34).

Treatment-related adverse events
The emergence of Grade 3 and Grade 4 treatment-related toxicities in EMBRACE was modelled to estimate the associated costs and utility decrements (34).Toxicities that occurred in at least 10% of patients in either trial arm (for any grade) were reported in the EMBRACE study report. Of these AEs, the rates of any grade 3 and 4 toxicities were included in the model.

The EMBRACE trial was a global study. The majority (64%) of participants were from Region 1 comprising North America, Western Europe, including the UK, and Australia. The remainder were from Region 2 (Eastern Europe) and Region 3 (Latin America/South Africa). In order that the economic analysis is as relevant to clinical practice in England and Wales as possible, only data from patients in Region 1 were considered in the economic evaluation.

6.3.2 Transition probabilities

Health-state transitions
Overall and progression-free survival functions were estimated independently for the eribulin and comparator arms using Kaplan-Meier estimates.

In general, a transition probability at day i was calculated as:

$$P = 1 - \frac{S(i)}{S(i-1)}$$

where:

- P is the transition probability (i.e., either to progressive disease in the case of PFS or death in the case of OS)
- S(t) is the modelled survival function.

Response to treatment
The ORRs were used to calculate the proportion of patients in the “Treated” state who were allocated a “responsive” (as opposed to “stable”) utility value (see Utilities, Section 6.4.9); this proportion was assumed constant over time.

ORRs as assessed by independent review were used (See Table 34). One-way sensitivity analyses considered the 95% confidence interval (CI) for each trial arm as calculated using the Pearson-Clopper normal approximation method. In probabilistic sensitivity analyses, a 95% CI and beta distribution were assumed.

Progression

The economic model used the probability of experiencing progression for the progression free survival data reported in the EMBRACE study. The model enabled the use of either the Kaplan meier curves of the Eribulin and of the comparator arm or the application of the relevant hazard ratio to the Kaplan meier curve of the comparator.
As mentioned previously, the data used to inform progression are the independent review of progression, which is a more conservative estinmate of the difference between the Eribulin and comparator. This is because a greater number of the patients in the independent review were censored. This censoring relates to the fact that when a patient progressed and this was established by the investigator, this patient discontinued treatment and was censored by the independent reviewer. However, when she was detected to have progressed by the independent reviewer, this patient was not censored by the investigator. The result is that fewer patients were assessed by the independent reviewer, lowering the power.

Overall Survival

Structural Uncertainty

The model uses two methods to estimate the difference in overall surviva (and, indeed progression-free survival)l. The first is the raw patient data, in the form of the Kaplan meier curves, are directly used to estimate cycle dependent probability of transition. Effectively, the model calculates the difference in the area under the curve. Due to the censoring of study data, the estimated difference calculated by the model is significantly less that that estimated by the median overall survival estimated by the clinical analysis. To attempt to overcome some of this uncertainty, the hazard ratio generated by the clinical analysis is applied to the Kaplan meier curve of the comparator arm. Generally speaking, this second approach increases the difference between the two trial arms, thus reducing the estimate of the ICER.

Region and Comparator define Eribulin and Comparator Group

When calculating the probability of progression and of death, in the Eribulin and individual drugs in the comparator arm, the Eribulin arm uses data cut down to those patient considered appropriate for and planned to get that comparator but who were then randomised to Eribulin. This analysis removes the potential for systematic heterogeneity in the Eribulin population linked to planned treatment choice.
It should also be noted that the reference case uses data from the EMBRACE study for Region 1, the geographical area of Western Europe, the North America and Australia. This choice was made because the results are more generalisable to UK patients.

Exptrapolation Beyond the Trial

The reference case does not extrapolate beyond the trial period. This assumption means that there will be no difference in total life years of the greater number of patients alive at

the end of the study who had taken Eribulin compared to the fewer alive who had not taken Eribulin This extremely conservative approach is presented to generate the 'worst-case scenario' for the cost effectiveness of Eribulin.

Treatment-related adverse events

Treatment-related toxicities reported in the EMBRACE study were mapped to a representative subset of toxicities according to clinical opinion. The mapping was performed to impose standardisation across myriad toxicities for simplicity and as a means of minimising the number of costs and utility values required as inputs in the modelling. The mappings are shown in Table 32.

Table 32: Adverse event mappings

Model toxicity	Included in mappings
Anaemia	Anaemia
Anorexia	Anorexia
Diarrhoea	Diarrhoea; dyspepsia
Dyspnoea	Dyspnoea
Oedema	Oedema; palmar-plantar erythrodysaesthesia syndrome
Fatigue	Asthenia/fatigue; cough
Febrile neutropenia	Febrile neutropenia
Heart failure	Heart failure
Hyperbilirubimaemia	Hyperbilirubimaemia
Hypertension	Hypertension
Hypokalaemia	Hypokalaemia
Neuropathy	Neuropathy
Neutropenia	Neutropenia; leucopoenia
Pain	Arthralgia/myalgia; back pain; bone pain; headache; pain in extremity
Peripheral neuropathy	Peripheral neuropathy
Pulmonary embolism	Pulmonary embolism
Stomatitis	Mucosal inflammation; stomatitis
Thrombocytopenia	Thrombocytopenia
Urinary tract infection	Urinary tract infection
Vomiting	Constipation; nausea; vomiting

The list of model toxicities does include certain grade 3 and 4 toxicities not experienced by either treatment arm but have been included for extensibility.

For both eribulin and TPC, the reported event counts were summed for each toxicity grouping and divided by the number of initially treated patients to arrive at a proportion of patients experiencing each toxicity. For one-way sensitivity analyses the base-case values were varied by±20%; for probabilistic sensitivity analyses, standard errors were

calculated using a binary distribution. Base-case proportions and SEs used in PSA for each comparator are shown in Table 33. Ranges used in one-way sensitivity analysis are shown in the Appendix Section 9.14.

Individual adverse events were assumed to occur independently of one another, and the proportion of treated patients incurring adverse events was assumed constant over time.

Table 33: Percentages of patients experiencing grade 3 and 4 AEs occurring in 10% or more patients in eribulin or TPC arm for any grade

	Grade 3, % (SE)					Grade 4, % (SE)				
Toxicity	**Eribulin**	**TPC**	**gemcitabine**	**vinorelbine**	**capecitabine**	**Eribulin**	**TPC**	**gemcitabine**	**vinorelbine**	**capecitabine**
Anaemia	1.8 (0.6)	3.2 (1.1)	0.0 (0.0)	3.3 (2.3)	0.0 (0.0)	0.2 (0.2)	0.4 (0.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Anorexia	0.4 (0.3)	1.2 (0.7)	0.0 (0.0)	3.3 (2.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Diarrhoea	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Dyspnoea	3.6 (0.8)	2.4 (1.0)	6.5 (3.6)	3.3 (2.3)	0.0 (0.0)	0.0 (0.0)	0.4 (0.4)	0.0 (0.0)	1.6 (1.6)	0.0 (0.0)
Oedema	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Fatigue	8.2 (1.2)	10.1 (1.9)	13.0 (5.0)	9.8 (3.8)	6.8 (3.8)	0.6 (0.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Febrile neutropenia	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Heart failure	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Hyperbilirubimaemia	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Hypertension	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Hypokalaemia	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Neuropathy	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Neutropenia	33.0 (2.1)	19.4 (2.5)	6.5 (3.6)	37.7 (6.2)	2.3 (2.2)	26.2 (2.0)	7.7 (1.7)	0.0 (0.0)	9.8 (3.8)	0.0 (0.0)
Pain	4.2 (0.9)	5.3 (1.4)	2.2 (2.2)	8.2 (3.5)	11.4 (4.8)	0.2 (0.2)	0.8 (0.6)	0.0 (0.0)	1.6 (1.6)	0.0 (0.0)
Peripheral neuropathy	7.8 (1.2)	2.0 (0.9)	0.0 (0.0)	3.3 (2.3)	0.0 (0.0)	0.4 (0.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Pulmonary embolism	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Stomatitis	1.8 (0.6)	5.7 (1.5)	0.0 (0.0)	0.0 (0.0)	18.2 (5.8)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Thrombocytopenia	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Urinary tract infection	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Vomiting	2.6 (0.7)	4.5 (1.3)	0.0 (0.0)	4.9 (2.8)	6.8 (3.8)	0.2 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

Abbreviations: SE, Standard error.

6.3.3 Variation of transition probabilities over time

Transitions between the three health states of “Treated, “Progressive” and “Dead” were governed by probabilities of disease progression and death derived from Kaplan-Meier curves. As such, variation in the transition probabilities over the time horizon of the model has been included.

The proportions of patients who were responsive or stable in the “Treated” health state were assumed to be constant over the time horizon of the model. If this assumption is true then a person’s current health state (responsive or stable) should have no prognostic value, i.e. OS and PFS should be the same for patients in both states. Based on statistical analysis of OS and PFS amongst responsive and stable patients, there was found to be no significant difference of OS and PFS estimates between responsive and stable patients.

The proportion of treated patients incurring adverse events was also assumed constant over time, and was made in the absence of any evidence suggesting otherwise. This is consistent with the methods employed in other models that estimate AEs.

6.3.4 Linking intermediate outcome measures to final outcomes

No

6.3.5 Clinical experts

The study physicians on the EMBRACE study were used to provide information on the mapping of adverse events to adverse event groupings (Section 6.3.2).

Summary of selected values

6.3.6 Summary list of variables used

A list of all clinical variables used in the economic analysis is provided in Table 34.

Table 34: Summary of clinical variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Response to treatment			Trial results Section 5.5
Eribulin	0.111	0.017 (Beta)	
TPC	0.043	0.016 (Beta)	
Response to treatment		5.5	Trial results Section 5.5
Eribulin	0.078	0.038 (Beta)	
Gemcitabine	0	0 (Beta)	
Response to treatment		5.5	Trial results Section 5.5
Eribulin	0.149	0.037 (Beta)	
Vinorelbine	0.044	0.031 (Beta)	
Response to treatment		5.5	Trial results Section 5.5
Eribulin	0.097	0.053 (Beta)	
Capecitabine	0.091	0.061(Beta)	

Abbreviations: CI, Confidence interval.

Table 35: Summary of clinical variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Progression-free survival			Trial results Section 5.5
Eribulin	Kaplan-Meier		Independent Review
TPC	Kaplan-Meier		Independent Review
Eribulin Vs TPC HR Region 1	0.8930	(0.6960, 1.1450) (Normal)	Independent Review
Capecitabine	Kaplan-Meier	N/A	Independent Review
Eribulin Vs Capecitabine HR Region 1	xxxxxx	(x.xxxx, x.xxxx) (Normal)	Independent Review
Gemcitabine	Kaplan-Meier		Independent Review
Eribulin Vs Gemcitabine HR Region 1	xxxxxx	(x.xxxx, x.xxxx) (Normal)	Independent Review
Vinorelbine	Kaplan-Meier		Independent Review
Eribulin Vs Vinorelbine HR Region 1	xxxxxx	(x.xxxx, x.xxxx) (Normal)	Independent Review
Overall Survival			Trial results Section 5.5
Eribulin	Kaplan-Meier		
TPC	Kaplan-Meier		
Eribulin Vs TPC HR Region 1	0.7910	(x.xxxx, x.xxxx) (Normal)	
Capecitabine	Kaplan-Meier	N/A	
Eribulin Vs Capecitabine HR Region 1	Xxxxx	(x.xxxx, x.xxxx) (Normal)	
Gemcitabine	Kaplan-Meier		
Eribulin Vs Gemcitabine HR Region 1	Xxxxx	(x.xxxx,x.xxxx) (Normal)	
Vinorelbine	Kaplan-Meier		
Eribulin Vs Vinorelbine HR Region 1	xxxxx	(x.xxxx, x.xxxx) (Normal)	
Adverse events			See Table 33
Eribulin	See Table 33	Ranges used in sensitivity analysis are shown in the Appendix Section 9.14	
TPC	See Table 33		
Capecitabine	See Table 33		
Gemcitabine	See Table 33		
Vinorelbine	See Table 33		

Abbreviations: CI, Confidence interval.

6.3.7 Extrapolation of trial outcomes

A trial duration horizon is employed in the model. At the end of the duration of trial follow-up available to model (2.89 years) all patients not dead are transitioned to the terminal state.. Kaplan-Meier plots for PFS and OS from the EMBRACE trial are used to predict the numbers of people moving between the “Treated”, “Progressive” and “Dead” health states. The assumption that at the end of the time horizon for the available EMBRACE trial data, all remaining patients were assumed to transition to the “Dead” state avoids any need for extrapolation of trial outcomes . This is a conservative assumption since no further potential additive benefits of eribulin on survival are taken into consideration.

6.3.8 Summary of assumptions used

- Patients enter the model when they initiate treatment.
- Every 21 days, patients faced a risk of transition among health states based on tumour status or death, based on the length of the dosing cycle for eribulin.
- The “Treated” health state captures both stable disease and responsive disease, and assumes that treatment response is not a significant predictor for disease progression or death. The validity of this assumption was tested by examination of patient-level data from the EMBRACE trial.
- The proportion of treated patients with responsive disease is static over time. For a justification see Section 6.3.3.
- Patients in the “Treated” state may develop treatment-related toxicities, and the incidence of AEs is assumed constant over time. For a justification see Section 6.3.3.
- Patients in the “Progressive” state remain in this state until death.
- Patient utilities are a function of the health state they are in and the incidence of treatment-related toxicities.

6.4 Measurement and valuation of health effects

Patient experience

6.4.1 Affects of the condition on patients’ quality of life

The management of patients with metastatic breast cancer is a trade-off between the potential benefits (e.g. improvement in overall survival) and risk of unpleasant effects (side effect from drugs and the disease itself)

Overall survival is recognised as the most definitive cancer outcome (15, 16) and is of most importance to patients when making decisions regarding treatment options (17). Cancer symptoms can be severe including cancer-related fatigue and uncontrolled local disease, along with further complications relating to the organ(s) to which the cancer has spread (8). The tolerability of current treatments and responses to therapy vary. Side effects include peripheral neuropathy, alopecia, mucositis, nausea, vomiting, increased infection, and fatigue, and these can adversely affect a patients’ quality of life (30).

6.4.2 Change in HRQL over time

People with advanced breast cancer will generally suffer from a gradual reduction in HRQL as the disease progresses. People achieving disease control on treatment may benefit from HRQL improvements or a reduction in the detrimental effects of the disease of quality of life. However, these effects may only be transient until the disease progresses. This is supported by Phase II eribulin trial data which suggests that HRQL does not deteriorate and in many patients improves in patients who have objective positive tumour response to eribulin treatment, whereas patients who progress may suffer deterioration in their HRQL (See section 5.8).

HRQL data derived from clinical trials

6.4.3 Description of trial based HRQL data

Disease specific quality of life was collected in two of the phase II clinical trials directly by the patients. The questionnaires were the FACT-B and the EORTC-QOL Questionnaire C30. Generic instruments were not used. Although it may be possible to map scores of the EORTC-QOL to utilities, the absence of EQ-5D data from the trials and the non-randomised nature of the trials, these data were not used in any further analyses of HRQL.

Mapping clinical trial HRQL data

6.4.4 Description of mapping exercise

Mapping was not used to transform any of the quality of life data from the clinical trials as it was not appropriate to do so.

HRQL studies

6.4.5 Literature search to identify HRQL studies

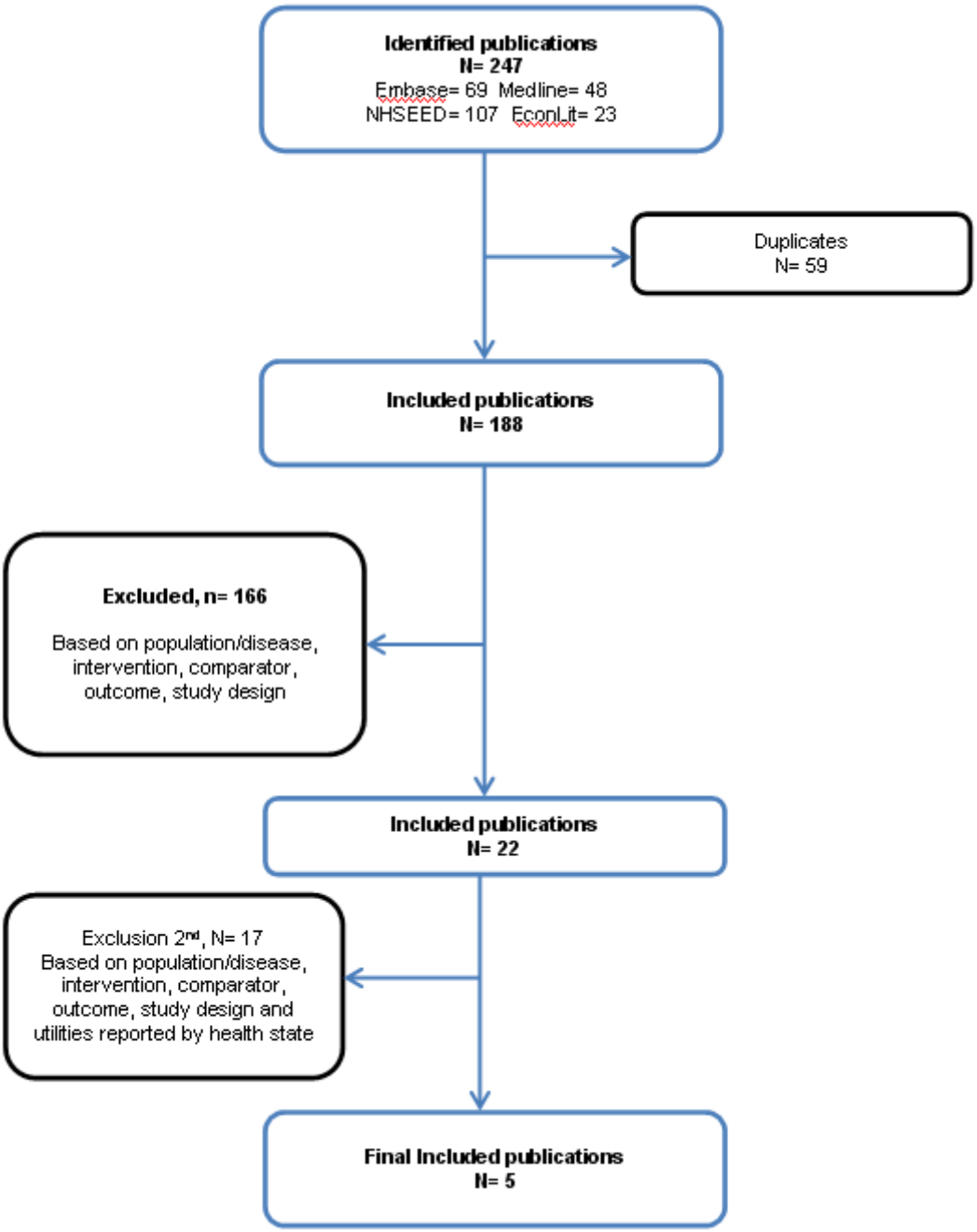
A systematic review was conducted to identify HRQL studies from the published literature relevant to the decision problem in order to identify appropriate utility data for the economic model. This was supplemented by extracting the utility values and sources from the cost effectiveness studies identified in Section 6.1.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for LABC/MBC and standard quality-of-life search filters were applied to the disease area search terms. The search strategy is provided in Section 9.12.

The inclusion and exclusion criteria were designed to identify all studies assessing a preference based measure of quality-of-life, either generic or valued in a separate study with appropriate methods (i.e. standard gamble or time trade off) or a non-preference quality-of-life measure (specifically, EQ-5D, SF-12 or SF-36) in LABC and/or MBC.

The results of these searches are reported within this section. The flow diagram for the systematic review is shown in Figure 13.

Figure 13: Flow diagram for the systematic review of HRQL studies



6.4.6 HRQL studies identified

Five studies of interest were identified by the searches and included in the present review (65-69). The remainder of the studies indentified for second pass were excluded on the basis of intervention, comparator, outcome, study design or because they did not report utilities by health state. A brief summary of the included studies is outlined in this section.

In summary, the most relevant study identified by the literature review was Lloyd et al (67). This study assessed UK-based societal preferences for different stages of

metastatic breast cancer (MBC) and toxicities. The reported utilities would be considered appropriate for populating a UK based economic model according the NICE reference case. The remainder of the studies assess patients in non-UK populations, and are therefore less relevant. These studies assessed utility in patients with breast cancer rather than eliciting values for the general public, or reported limited numbers of health states compared with those used in the current economic model.

Chie et al (65) aimed to assess utility in different clinical phases of breast cancer in Taiwanese patients. The study included 979 breast cancer patients admitted to the national Taiwan University Hospital from 1991 to 1995. The study identified six main clinical phases (screening, tumour finding and diagnosis, initial therapy, follow-up, recurrence and metastasis, and the terminal stage) and 17 sub phases which were assessed with VAS, standard gamble (SG) and TTO methods. The utility scores were highest during the screening phase, lower in the phases of incidental finding of the tumour and diagnosis, and lower still in the initial treatment phase. The utility score improved in follow-up phases. The utility scores assessed by SG and TTO were higher than those assessed by VAS.

Lidgren et al (66) aimed to assess HRQL in various clinical states in women with breast cancer using preference-based measures (EQ-5D and TTO). The patient population included in the analysis was consecutive breast cancer patients attending an outpatient clinic at Karolinska University hospital. Of the total 345 included breast cancer patients, 67 were diagnosed as metastatic. Patients with metastatic disease reported the lowest values. The mean EQ-5D index value reported for metastatic patients was 0.685 (95% CI 0.620-0.735); median, 0.725 (significant difference between the EQ-5D index value and TTO score, $p<0.05$) and the mean TTO value was 0.820 (95% CI 0.760-0.874), median, 0.850. Metastatic patients also reported the highest percentage (74%) compared with other disease states with moderate or severe pain and discomfort.

Lloyd et al (67) aimed to study UK-based societal preferences for different stages of MBC and toxicities. The health states were based on a literature review focussing on health related QoL burden in MBC and exploratory interviews. The study population was a sample of the general public from England and Wales. Standard gamble was used to determine health state utility, and the data was analysed with a mixed model analysis. The utility value for the base state reported as 0.715 and utility gain for treatment response reported as +0.075. The decrements associated with departures from health state were reported as -0.272 with progression; -0.150 with febrile neutropenia; -0.103 with diarrhoea and vomiting.

A health-related QoL valuation and/or utilities was carried out by Milne et al (68) for New Zealand (NZ) women for four clinical health states representative of LABC/MBC. A sample of 50 women, aged 25-69 years was randomly selected from the NZ general public. The valuations were based on TTO, VAS and EQ-5D (NZ and UK social tariffs). The mean TTO valuation response with chemotherapy reported as 0.46 (95% CI 0.41, 0.51), the mean EQ-5D values with chemotherapy for NZ and UK tariffs were 0.49 (95% CI 0.40, 0.57) and 0.48 (95% CI 0.43, 0.53) respectively, and mean VAS score with chemotherapy reported as 0.51 (95% CI 0.43, 0.59).

Sherrill et al (69) conducted a Q-TWiST (quality time without symptoms of toxicity) analysis to assess the overall benefit for patients using a single metric that included progression, survival, toxicities and QoL. Patients included in this analysis were taken from a phase III clinical trial of lapatinib combined with capecitabine compared with capecitabine alone in advanced or metastatic progressive breast cancer women. The overall average utility value observed during the TOX state (toxicities, Grade 3/4) was 0.59 with capecitabine monotherapy, and this value was similar between groups (0.60 with capecitabine plus lapatinib). Patient-reported utility weights for the TWiST states were less than one on average, consistent with the poor health of these patients even prior to progression. The TWiST utility values were similar in both treatment arms (0.66). Relapse utility scores were reported as 0.41 with capecitabine plus lapatinib and 0.44 with capecitabine. Combination therapy (capecitabine plus lapatinib) provided greater quality-adjusted survival than monotherapy with capecitabine.

In addition, utility values and their sources were extracted from the cost effectiveness studies identified in Section 6.1.2 in order to identify the most appropriate utility values for the economic model. The cost effectiveness studies, the utility values reported and the source and/or explanation of the utility study are outlined in Table 36.

The utility values reported by the economic studies appear to reference the same initial utility study carried out using values obtained from oncology nurses using standard gamble methodology. Cooper et al (55) reported mean values of several estimates sourced from previous cost effectiveness analyses (Brown and Hutton (70); Hutton et al (56); Launois (71)) and these values are subsequently used by Takeda et al (58) and CG81 (8). The utility values reported by Takeda et al (58) and CG81 (8) (as taken from Cooper et al (55)) have previously been accepted by NICE as they appropriate for use in an economic model according to the NICE methods guide. Brown and Hutton, and Launois et al ((70); (71)) were not included in the full review of economic studies identified in Section 6.1.1 as they were not UK studies and were therefore considered not to be relevant to decision making in England and Wales specifically. However, these studies were used to inform the upper and lower extremes in utility values for the economic model where necessary.

The most recent study by Benedict et al (53) sourced utilities from Lloyd et al (67), as identified during the HRQL systematic review, and Brown 2001 (54), as identified during the CE systematic review.

Table 36: Utility values reported in published cost effectiveness analyses

Study	Utility values	Source/explanation
Benedict et al, 2009 (53)	Model state = Utility Response (increment) = 0.07 No progression = 0.72 Progression (decrement) = -0.27 Mean AE utility reduction for Docetaxel = -0.07 Mean AE utility reduction for paclitaxel 175mg/m2 every 21 days = -0.06 Mean AE utility reduction for paclitaxel 90mg/m2 every 7 days = -0.06 Mean AE utility reduction for nano albumin-bound paclitaxel 260,g/m2 every 21 days = -0.07	Lloyd, 2006 (67) and Brown, 2001 (54).
Brown et al,	At start of second-line therapy = 0.64	Proxy utility values

Study	Utility values	Source/explanation
2001 (54)	Partial/complete response (P/CR) =0.84 Stable disease = 0.62 Progressive disease = 0.33 Terminal disease = 0.13 Peripheral neuropathy+PaR/CR = 0.62 Severe oedema+PaR/CR = 0.78 Severe skin condition+PaR/CR = 0.56 Febrile neutropenia with hospitalisation. = 0.24 Infection no hospitalisation. = 0.48 Death = 0	obtained from 30 oncology nurses from UK (base case) and 150 nurses from other western European countries (sensitivity analysis)
Cooper et al, 2003 (55)	Partial / Full response = 0.81 Partial / Full response with toxicity = 0.67 Stable disease = 0.65 Stable disease and febrile neutropenia or infection with non-hospitalisation = 0.60 Stable disease and febrile neutropenia or infection with hospitalisation = 0.44 Stable disease with toxicity = 0.54 Progressive disease = 0.45 Progressive disease with toxicity (assumption) = 0.35 Death = 0	Utilities taken from Brown and Hutton, 1998 (70), Hutton, 1996 (56), Launois, 1996 (71)
Hutton et al, 1996 (56)	Results from nurses from the UK PaR = 0.84 PaR + severe peripheral oedema = 0.78 SD = 0.62 Before second line therapy begins = 0.56 PaR + severe peripheral neuropathy = 0.62 PD = 0.33 Sepsis = 0.16 Terminal disease = 0.13 Utilities summed across nurses and countries PaR = 0.81 PaR + severe peripheral oedema = 0.75 SD = 0.62 Before second line therapy begins = 0.59 PaR + severe peripheral neuropathy = 0.53 PD = 0.41 Sepsis = 0.20 Terminal disease = 0.16	Descriptions were distributed to a sample of oncology nurses from centres in a number of countries. Standard gamble was used to obtain utility values for each of the health state descriptions. Eight of the health states are reported. The authors state that there was consistent ranking between the UK and other country analysis.
Jones et al, 2004 (52) HTA Based on Roche data	Base case Stable disease = 0.81 Progressive disease = 0.39 Scenario analyses (Launois et al) Stable disease (0.75) Progressive disease (0.65) Scenario analyses (Hutton et al) Stable disease = 0.62 Progressive disease = 0.41	Base case utilities estimated based on interviews of 25–30 oncology nurses from each of Germany, Italy, The Netherlands, Spain, the UK and the USA using standard gamble methodology. Scenario analyses was based on a survey of 20 French nurses using a

Study	Utility values	Source/explanation
		standard gamble methodology from Launois et al (71) and Hutton et al (56)
Jones et al, 2009 (57) HTA	Stable=0.80 Response=0.72 Progression=0.46	Not reported
Takeda et al, 2007 (58) HTA	Without toxicity Responsive = 0.81 Stable = 0.65 Progressive = 0.45 With toxicity Responsive = 0.67 Stable = 0.54 Progressive = 0.45	Cooper et al, 2003 (55)
NICE TA116 – taken from the ERG report (64)	Response = 0.8 Stable = 0.72 Progression = 0.46 Response with toxicity Febrile Neutropenia = 0.67 Diarrhoea/Vomiting = 0.71 Stomatitis = 0.67 Fatigue = 0.7 Hand/foot syndrome = 0.7 Neutropenia = 0.8 Hair loss = 0.7 Neuropathy = 0.7 Stable with toxicity Febrile Neutropenia = 0.58 Diarrhoea/Vomiting = 0.62 Stomatitis = 0.58 Fatigue = 0.61 Hand/foot syndrome = 0.61 Neutropenia = 0.72 Hair loss = 0.61 Neuropathy = 0.61 Progression with toxicity Neuropathy = 0.33	Utilities were taken from Narewska et al (a conference abstract which appears to have since been published as Lloyd 2006).
NICE CG81 (8)	Response = 0.81 Stabilisation = 0.65 Toxic hospitalisation = 0.44 Progressive disease = 0.45	Cooper et al, 2003 (55)

Abbreviations: PaR, Partial response; PD, Progressive disease; SD, Stable disease.

6.4.7 Comparison of HRQL data

Not applicable.

Adverse events

6.4.8 The impact of adverse events on HRQL

The tolerability of current treatments and responses to therapy vary. Side effects include peripheral neuropathy, alopecia, mucositis, nausea, vomiting, increased infection, and fatigue, and these can adversely affect a patients' quality of life (30).

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Summary of HRQL values used

The model assumes that patient HRQL is a function of current disease state and the presence of Grade 3 or Grade 4 treatment-related toxicities. To estimate QALYs, time spent in each health state was multiplied by a corresponding utility composed of the underlying state utility and the mean toxicity related decrement. Utility values were applied to each health state: "Treated", "Progressive", and "Terminal". For the "Treated" state, the assigned utility was an average of stable and responsive utilities, weighted by the ORR. An Terminal utility was assigned only in the final cycle before death; subsequent terminal utilities were assumed to be 0.The base-case utility values for the "Treated" (stable and responsive) and "Progressive" states, as well as decrements associated with toxicities, were based on a study by Lloyd et al in a UK population (67). The base-case Terminal utility was sourced from Hutton et al, 1996 (56) as this was not reported in the Lloyd study. Low and high estimates from alternative utility studies by Brown et al, Hutton et al, Lloyd et al and Launois et al (54, 56, 67, 71) were used as the bounds for one-way sensitivity analyses.

Grade 3 and Grade 4 adverse events were associated with utility decrements for the model cycle in which the event occurred. The decrements were added to the health state utility as described above. Decrements were based on a study of several toxicities and utility in breast cancer by Lloyd et al (67). Where available, the corresponding utility value was used; in cases where a utility for a specific adverse event was unavailable, the mean of the reported utilities was used. The rationale for this assumption was based in part on the study's conclusion that the range of adverse-event-related utilities is surprisingly narrow. One-way sensitivity analyses considered varying base-case values by ±20%.

The annual utility values for each health state and utility decrements for each adverse event are provided in Table 37.

Table 37: Summary of quality of life values for cost-effectiveness analysis

State	Utility value	Range	Reference to section in submission	Justification
Treated • Stable	0.715	0.620-0.810[†]	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches

State	Utility value	Range	Reference to section in submission	Justification
Treated • Responsive	0.790	0.790-0.840†	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches
Progressive	0.443	0.330-0.650†	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches
Terminal	0.160	0.130-0.250†	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches
Anaemia	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Anorexia	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Diarrhoea	-0.103	-0.13, -0.08‡	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches
Dyspnoea	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Oedema	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Fatigue	-0.115	-0.14, -0.09‡	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches
Febrile neutropenia	-0.150	-0.19, -0.11‡	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches
Heart failure	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Hyperbilirubimaemia	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Hypertension	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Hypokalemia	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Neuropathy	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Neutropenia	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Pain	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Peripheral neuropathy	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Pulmonary embolism	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Stomatitis	-0.151	-0.19, -0.11‡	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches
Thrombocytopenia	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches

State	Utility value	Range	Reference to section in submission	Justification
Urinary tract infection	-0.124	-0.16, -0.09‡	Mean of other adverse events	Most appropriate study identified in QoL searches
Vomiting	-0.103	-0.13, -0.08‡	Identified study reporting utility values in breast cancer section 6.4.6	Most appropriate study identified in QoL searches

Abbreviations: QoL, Quality of life.
†the ranges were based on the lowest and highest utility values for each of the health states from other studies identified through the literature search in Section 6.4.6; ‡range is ±20%

Additional analyses considered the application of NICE end-of-life criteria. Under the criteria, periods of survival beyond that achieved under the standard of care are assigned utility values equal to those of healthy members of the population of the same age and sex. The model used a utility value of 0.83 for all patients, calculated from UK female population values (72) weighted by the trial-start age distribution among EMBRACE participants, as shown in Table 38. In the end-of-life analyses, this utility was applied to patients in the eribulin arm beginning in the cycle in which the cumulative survival exceeds the cumulative total survival in the comparator arm.

Table 38: NICE end-of-life utilities

Age range	Patients (%)	Utility
< 25	0.0	0.94
25 – 34	2.6	0.93
35 – 44	13.1	0.91
45 – 54	30.6	0.85
55 – 64	33.9	0.81
65 – 74	17.5	0.78
≥ 75	2.4	0.71
Total	100.0	0.83

6.4.10 Input from clinical experts

None

6.4.11 HRQL experienced in each health state

Patients experience the utility of being in their current health state, that is “Treated” (stable and responsive) or “Progressive”. In addition, patients may experience treatment related adverse events. Therefore, disutilities were applied to patients on treatment who had an adverse event. The application of disutility due to adverse events covers the potential variances in quality of life whilst on treatment.

Patients’ quality of life toward the end of their life can also vary in the model according to the NICE end-of-life criteria.

6.4.12 Health effects excluded from the analysis

All health states in the model were assigned a utility value. All Grade 3 and 4 adverse events recorded in the clinical trial as described in Section 6.3.2 were assigned a utility and included in the analysis. Lower grade adverse events (Grade 1 and 2) were not expected to substantially affect patient's quality of life (or costs) and were therefore excluded from the analysis, in line with previous NICE appraisals such as TA116 (24).

6.4.13 Baseline HRQL

Not applicable.

6.4.14 Changes in HRQL over time

Depending on whether patients experience side-effects or not, their HRQL will vary within each cycle of the model. The number of side-effects experienced also affects HRQL.

6.4.15 Have the values in Sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 How is the clinical management of the condition currently costed in the NHS?

LABC/MBC is generally managed by a multi-disciplinary healthcare team in tertiary, secondary and primary care.

Chemotherapy drug administration would generally be carried out in secondary care. Oral administration of chemotherapy is covered by HRG code SB11Z (Deliver exclusively oral chemotherapy), while for chemotherapy drugs delivered intravenously HRG code SB15Z (Deliver subsequent elements of a chemotherapy cycle) was used. Although other HRG codes (SB12Z-SB14Z) are available for intravenously administered drugs, these cover first attendances for treatment. As a simplifying assumption, all chemotherapy was considered part of ongoing therapy, eliminating the need for separate initial and subsequent HRG codes.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Cancer services such as those for delivery of chemotherapy and radiotherapy are not currently covered by PbR Tariffs. As such NHS Reference costs have been used in the model, where appropriate.

Resource identification, measurement and valuation studies

6.5.3 Literature search to identify resource data

A brief literature review conducted in PubMed was carried out to identify studies of interest to inform the resource use data inputs for use in the model. The title and abstract (where available) of all publications were scanned and relevant publications were ordered and reviewed. Additional information was obtained from ancestral searches of reference lists from relevant publications and from separate internet searches.

6.5.4 Input from clinical experts

Clinical opinion was used to provide information on the type and quantity of resource use (Section 6.5.5). An advisory board meeting was conducted with five leading oncologists in the field of breast cancer which reviewed our draft NICE submission and provided expert opinion on how patients with metastatic breast cancer are managed in terms of resources at each state and how common toxicities are managed in clinical practice. In addition, seven oncologists whose principle interest is breast cancer were interviewed by our medical team on a face to face basis using a pre-specified proforma to capture the resources at each state and the management of common toxicities with chemotherapy agents. The results from both the advisory board and face to face meeting were very consistent and similar to other NICE submissions and these were used to inform the model.

Intervention and comparators' costs

6.5.5 Summary of cost used

Table 39 summarises the drug-related costs included in the model, including drug acquisition, pre-medication and administration. Costs shown are those applied per model cycle (21 days) for each individual drug. Ranges and distributions used in sensitivity analyses are ascribed to unit costs and are provided in Appendix, Section 9.14. Details of drug-related costs are provided in Table 39 to Table 43.

Table 39: Summary of drug-related costs per model cycle

Drugs	Cost, £			
	Drug acquisition	Pre-Medication	Administration	Total
Eribulin	[redacted]	0	420	[redacted]
TPC	£930	4	296	£1,335
Vinorelbine	£919	0	681	£1,599
Gemcitabine	£974	0	454	£1,428
Capecitabine	£531	0	210	£740
Taxanes	£1,584	18	227	£1,834
Docetaxel	£1,604	15	227	£1,847
Ixabepilone	-	--	--	£227
Paclitaxel	£1,644	30	227	£1,901
Nab-paclitaxel	£1,230	0	227	£1,457

Drugs	Cost, £			
	Drug acquisition	Pre-Medication	Administration	Total
Anthracyclines	£470	0	227	£696
Doxorubicin	£275	0	227	502
Liposomal doxorubicin	£1,394	0	227	1,620

Abbreviations: TPC, Treatment of Physician's Choice.

Unit drug costs

Drug costs were derived from dosing information provided in the relevant summaries of product characteristics, as presented in Table 40. The model assumed an average body surface area (BSA) of 1.74 m^2, based on the mean value reported in a study of UK women receiving chemotherapy (73). Each drug's dose per m^2 was multiplied by the mean BSA to determine the dose in mg.

Unit drug costs were based on published package costs from the British National Formulary (74). In the base case the median listed price for the largest available package size was used. For solutions and powders it was assumed that any drug leftover from a treatment was wasted; additional analyses considered per mg drug costs, i.e. an assumption of no wastage. Since Ixabepilone is not available in the UK a cost of £0 was applied in the model for this treatment. As such, the model analysis of Eribulin versus TPC can be deemed as being conservative.

The cost of vinorelbine is based on a patient having 140 mg as a combination of two tablets of 30mg and one tablet of 80mg. This equates of a cost of £919. In the model, it was necessary to assume patients take 30mg but that this costs £61.25 per tablet instead of £65.98 in order to generate the lower cost of £919.

The drug cost for the TPC arm considered as a whole was an average of the component costs weighted by the proportionate use of each drug in the EMBRACE trial (Table 41).

Table 40: Unit drug costs

Drugs	Package size	Cost per vial, £	Dose, mg/m^2	Cycle length, days	Doses per cycle	Infusion time, min	Notes
Eribulin (SPC, Appendix Section 9.1)	1 mg / 2 mL	[redacted]	1.4	21	2	5	
Vinorelbine (75)	30mg 80mg	65.98 175.92	80mg	7	1	0	Cost has been adjusted to account for the availability of an 80mg tablet
Gemcitabine (76)	1,000 mg	162.00	1250.0	21	2	30	
Capecitabine (51)	500 mg x 120	265.55	2500.0	21	14	0	
Taxanes							
Docetaxel (77)	80 mg / 2 mL	534.75	100.0	21	1	60	
Ixabepilone	NA	NA	NA	NA	NA	NA	Not approved in the UK
Paclitaxel (78)	30 mg / 5 mL	66.85	175.0	21	1	180	
Nab-paclitaxel (78)	100 mg	246.00	260.0	21	1	30	
Anthracyclines							
Doxorubicin (79)	200 mg / 100 mL	275.00	67.5	21	1	6.5	Dose: Mean of 60-75mg/m^2
Liposomal doxorubicin (80)	50 mg	464.50	67.5	21	1	60	Dose: Mean of 60-75mg/m^2

Table 41: Drug Unit Cost Calculation Component Shares
†

Drug	Share	Package size	Package type	Dose per treatment	Units Per cycle	Cycle length	Package size (mg)	Packages per treatment	Packages per cycle	Drug cost per cycle	Infusion Cost Per Cycle
Eribulin	NA	1mg / 2mL	Solution	2.436	2	21	1	3	6	[redacted]	£418
TPC										£934.44	£400
Vinorelbine	28.37%	30mg x 1	Tablet	139.2	1	7	30	5	5	£918.75	£680
Gemcitabine	21.40%	1000mg	Powder	2175	2	21	1000	3	6	£974.28	£454
Capecitabine	20.47%	500mg x 120	Tablet	4350	14	21	60000	1	2	£531.10	£209
Taxanes	19.07%									£1,606.72	£227
Docetaxel	24.39%	80mg / 2mL	Solution	174	1	21	80	3	3	£1,619.70	£227
Paclitaxel	63.41%	300mg / 50mL	Solution	304.5	1	21	300	2	2	£1,674.18	£227
Nab-paclitaxel	12.20%	100mg	Powder	452.4	1	21	100	5	5	£1,230.00	£227
Anthracyclines	10.70%									£469.52	£227
Doxorubicin	82.61%	200mg / 100mL	Solution	117.45	1	21	200	1	1	£275.00	£227
Liposomal doxorubicin	17.39%	50mg	Powder	117.45	1	21	50	3	3	£1,393.50	£227
Other	0.00%										

Based on individual monotherapies used as part of the TPC arm of the EMBRACE study. Values in parentheses are expressed as a percentage of the class of drugs, e.g. docetaxel use as a percentage of the taxane class.

The average cost of treatment in the TPC is calculated from a weighted average of the cost of drugs according to the usage of of drugs in the clinical trial. This weighting assumption was made because there is no reliable information on how patients in heavily pre-treated MBC are actually treated and, it was also felt that aligning the cost of the TPC closely to the efficacy is the most valid approach

Pre-medication drugs

People treated with taxanes also require pre-medication. Costs of pre-medication drugs were also included as specified by the relevant package inserts (Table 42). Unit drug costs were based on published package costs from the British National Formulary (74).

Table 42: Unit costs of pre-medication

Drugs	Pre-Medication	Package size	Unit cost, £	Dose (mg)	Units
Docetaxel	Dexamethasone	2 mg x 100	15.45	16	3
Paclitaxel	Cimetidine	12,000 mg / 300mL	14.24	300	1
	Dexamethasone	2 mg x 100	15.45	20	1

Administration

Drug administration costs were based on NHS Reference Costs (81). As a simplifying assumption, all chemotherapy was considered part of ongoing therapy, eliminating the need for separate initial and subsequent HRG codes. All chemotherapy was assumed to be delivered in the outpatient setting. Unit administration costs are presented in Table 43. Base-case costs were based on the mean reference cost; low and high costs for one-way sensitivity analyses were based on the lower and upper quartiles for this data. In the case of the upper bound for exclusively oral chemotherapy, the mean was used as it was greater than the upper quartile value (as is sometimes the case with reference costs). Drug administration costs for injectable chemotherapies were incurred at each treatment; for oral chemotherapies (e.g. capecitabine), the cost was assigned once per model cycle.

Table 43: Drug administration unit costs

HRG code	Description	Cost, £		
		Mean	Low	High
SB11Z	Deliver exclusively oral chemotherapy	208.92	103.02	208.92
SB15Z	Deliver subsequent elements of a chemotherapy cycle	226.83	120.69	236.41

Abbreviations: HRG, Healthcare Resource Group.

Health-state costs

6.5.6 Summary of costs used

Resource use and associated costs were dependent on the health state occupied by a patient and were assigned per model cycle. A summary of these costs are presented in Table 44. Resource use estimates are presented in Table 45. Unit costs for each resource were based on NHS reference costs for 2008-2009 (81) and are presented in Table 46. One-way sensitivity analyses were performed at the health-state level; low and high values were calculated by summing the respective low and high values for the unit resource costs (See Appendix, Section 9.14 for ranges).

Table 44: List of health states and associated costs in the economic model

Health states	Resource group	Cost, £	Reference to section in submission
Treated[†]		163	Table 45, Table 46
	Medical personnel	121	Table 45, Table 46
	Tests and diagnostics	43	Table 45, Table 46
	Radiotherapy	0	Table 45, Table 46
Progressive		233	Table 45, Table 46
	Medical personnel	160	Table 45, Table 46
	Tests and diagnostics	35	Table 45, Table 46
	Radiotherapy	38	Table 45, Table 46
Terminal[‡]		19,712	Table 45, Table 46
	Medical personnel	95	Table 45, Table 46
	Test and diagnostics	0	Table 45, Table 46
	Radiotherapy	20	Table 45, Table 46
	Care setting	19,596	Table 45, Table 46

[†] Stable and responsive assumed to incur the same resource use; [‡] Resources applied to the final model cycle prior to entering the "Dead" state.

Resource use

Per-cycle resource use estimates were developed for the "Treated" and "Progressive" health states; additional resource use estimates were applied to the final model cycle prior to entering the "Dead" state ("Terminal"). Utilisation and the consequent costs were assumed to occur independently of treatment assignment given lack of evidence to the contrary. Categories and components of resource use were defined for each of the three states ("Treated", "Progressive", and "Terminal") based on a literature review and clinical opinion solicited by Eisai, as described in Sections 6.5.3 and 6.5.4. A unit of consumption and probability of consumption was identified for each resource component over a 21 day cycle; the units were multiplied by the probability and the unit cost to calculate a net resource cost per model cycle. Base-case units and probabilities are presented in Table 45.

Table 45: Resource use

Health state	Resource group/resource item	Units	Probability, %	Source(s)
Treated				
	Medical personnel			
	Oncology nurse visit	0.00	0	Clinical opinion (Section 6.5.4)
	Oncologist visit	1.00	100	Clinical opinion (Section 6.5.4)
	Nurse home visit	0.00	0	Clinical opinion (Section 6.5.4)
	Tests and diagnostics			
	Chest x-ray	1.00	27	Clinical opinion (Section 6.5.4)
	CT scan	1.00	27	Clinical opinion (Section 6.5.4)
	Full blood count	2.00	100	Clinical opinion (Section 6.5.4)
	Liver function test	2.00	100	Clinical opinion (Section 6.5.4)
	Urea electrolyte test	2.00	100	Clinical opinion (Section 6.5.4)
	Radiotherapy	0.00	0	Clinical opinion (Section 6.5.4)
Progressive				
	Medical personnel			
	Oncology nurse visit	1.00	50	Clinical opinion (Section 6.5.4), (82)
	Oncologist visit	1.00	100	Clinical opinion (Section 6.5.4), (82)
	Nurse home visit	0.00	0	Clinical opinion (Section 6.5.4), (82)
	Tests and diagnostics			
	Chest x-ray	1.00	27	Clinical opinion (Section 6.5.4)
	CT scan	1.00	27	Clinical opinion (Section 6.5.4)
	Full blood count	1.00	100	Clinical opinion (Section 6.5.4)
	Liver function test	1.00	100	Clinical opinion (Section 6.5.4)
	Urea electrolyte test	1.00	100	Clinical opinion (Section 6.5.4)
	Radiotherapy	0.27	35	(82)
Terminal				
	Medical personnel			
	Oncology nurse visit	0.00	0	Clinical opinion (Section 6.5.4)
	Oncologist visit	1.00	20	Clinical opinion (Section 6.5.4), (82)
	Nurse home visit	3.00	60	Clinical opinion (Section 6.5.4), (82)
	Tests and diagnostics			
	Chest x-ray	0.00	0	Clinical opinion (Section 6.5.4)
	CT scan	0.00	0	Clinical opinion (Section 6.5.4)
	Full blood count	0.00	0	Clinical opinion (Section 6.5.4)
	Liver function test	0.00	0	Clinical opinion (Section 6.5.4)
	Urea electrolyte test	0.00	0	Clinical opinion (Section 6.5.4)
	Radiotherapy	1.00	5	(83)
	Care setting			

Health state	Resource group/resource item	Units	Probability, %	Source(s)
	Hospital day	0.00	0	Clinical opinion (Section 6.5.4)
	Hospital day, intensive	0.00	0	Clinical opinion (Section 6.5.4)
	Hospice inpatient	21.00	20	(82)
	Hospice outpatient	21.00	70	(82, 83)

Resource unit costs

Unit costs for each resource were based on NHS reference costs for 2008-2009 (81). Base-case costs reflect mean Reference Cost values; low and high values for one-way sensitivity analyses were based on the lower and upper quartiles. Unit costs are presented in Table 46.

Table 46: Resource unit costs

Resource group/resource item	Unit cost, £	Code	Description
Medical personnel			
Oncology nurse visit	78.49	370	Medical Oncology: Non-Consultant Led - Follow-up attendance non-admitted face-to-face
Oncologist visit	120.52	370	Medical Oncology: Consultant Led - Follow-up attendance non-admitted face-to-face
Nurse home visit	39.50	CN403CFO	Health Visiting Services: Core Services - Face to Face, One to One
Tests and diagnostics			
Chest x-ray	3.51	DAP482	Other pathology services
CT scan	100.14	RA08Z	Diagnostic Imaging: Outpatient -- Computerised Tomography Scan, one area, no contrast
Full blood count	2.97	DAP823	Haematology [Excluding Anti-Coagulant Services]
Liver function test	1.34	DAP841	Biochemistry
Urea electrolyte test	2.97	DAP823	Haematology [Excluding Anti-Coagulant Services]
Radiotherapy			
Total	406.18		
Visit	98.55	800	Clinical Oncology: Consultant Led - Follow up attendance non-admitted face to face
Planning	195.91	SC01Z	Define volume for SXR, DXR, electron or Megavoltage Radiotherapy without imaging and with simple calculation
Treatment	111.71	SC22Z	Outpatient Planning: Deliver a fraction of treatment on a megavoltage machine
Care setting‡			
Hospital day	901.74	XC05C - XC07C	Average of adult critical care (0-2 organs supported)
Hospital day, intensive	1,509.72	XC01C - XC04C	Average of adult critical care (3-6 organs supported)
Hospice inpatient	1,509.72	XC01C - XC04C	Average of adult critical care (3-6 organs supported)

Resource group/resource item	Unit cost, £	Code	Description
Hospice outpatient	901.74	XC05C - XC07C	Average of adult critical care (0-2 organs supported)

† Ultrasound is mean of reported codes; ‡ Mean of reported range of codes, weighted by reporting frequency.

Adverse-event costs

6.5.7 Summary of costs used

Unit costs for Grade 3 and Grade 4 adverse events were used in conjunction with adverse event rates (see Section 6.3.2, Treatment-Related Adverse Events) to estimate total adverse event costs. All costs were based on Day Case NHS Reference Cost data for 2008-2009 (81). Appropriate HRG codes were provided by expert clinical opinion solicited by Eisai. Base-case values reflected reported national means, while low and high values for one-way sensitivity analyses were based on lower and upper quartiles as reported in the Appendix, Section 9.14. Relevant HRG codes and costs are presented in Table 47.

Table 47: List of adverse events and summary of costs included in the economic model

Adverse events	Grade 3 cost, £	HRG Code	Description	Grade 4 cost, £	HRG Code	Description	Reference to section in submission
Anaemia	339	JA12A	Malignant breast disorders with major CC	339	JA12A	Malignant Breast Disorders with Major CC	See section 6.3.2
Anorexia	-	--	*No cost*	-	--	*No cost*	See section 6.3.2
Diarrhoea	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	339	JA12A	Malignant Breast Disorders with Major CC	See section 6.3.2
Dyspnoea	-	--	*No cost*	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	See section 6.3.2
Oedema	412	DZ20Z	Pulmonary oedema	412	DZ20Z	Pulmonary oedema	See section 6.3.2
Fatigue	-	--	*No cost*	-	--	*No cost*	See section 6.3.2
Febrile neutropenia	478	WA04U	Acute febrile illness with length of stay of 4 days or less without CC	478	WA04U	Acute febrile illness with length of stay of 4 days or less without CC	See section 6.3.2
Heart failure	-	--	*No cost*	680	EB03I	Heart failure or shock without CC	See section 6.3.2
Hyperbilirubimaemia	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	See section 6.3.2
Hypertension	-	--	*No cost*	-	--	*No cost*	See section 6.3.2
Hypokalemia	318	KC01C	Electrolyte disorders without CC	318	KC01C	Electrolyte disorders without CC	See section 6.3.2

Adverse events	Grade 3 cost, £	HRG Code	Description	Grade 4 cost, £	HRG Code	Description	Reference to section in submission
Neuropathy	-	--	*No cost*	339	JA12A	Malignant Breast Disorders with Major CC	See section 6.3.2
Neutropenia	-	--	*No cost*	339	JA12A	Malignant Breast Disorders with Major CC	See section 6.3.2
Pain	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	See section 6.3.2
Peripheral neuropathy	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	-	--	*No cost*	See section 6.3.2
Pulmonary embolism	359	DZ09B	Pulmonary embolus with CC	359	DZ09B	Pulmonary embolus with CC	See section 6.3.2
Stomatitis	393	WA21W	Other procedures and health care problems with CC	393	WA21W	Other procedures and health care problems with CC	See section 6.3.2
Thrombocytopenia	386	SA12F	Thrombocytopenia without CC	386	SA12F	Thrombocytopenia without CC	See section 6.3.2
Urinary tract infection	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	361	LA04G	Kidney or urinary tract infections with length of stay 1 day or less without CC	See section 6.3.2
Vomiting	121	370	Consultant Led: Follow-up attendance non-admitted face to face—medical oncology	339	JA12A	Malignant Breast Disorders with Major CC	See section 6.3.2

Abbreviations: CC, Co-morbidities or complications.

Miscellaneous costs

6.5.8 Summary of cost used

Not applicable.

6.6 Sensitivity analysis

6.6.1 Uncertainty around structural assumptions

The structure of the model was informed by several existing published economic evaluations to ensure that the structure closely matched clinical practice and was appropriate for use in economic modelling. Clinical trial data specific to the decision problem were used directly in the model to inform patient movement through the model. The structural uncertainty in the model was tested by using an alternative method of incorporating the clinical trial data on OS and PFS. Hazard Ratios (HRs) were used in place of the Kaplan Meier curves. See Section 5.5 for hazard ratio data used for the scenario analysis.

6.6.2 Deterministic sensitivity analysis

All parameters except PFS and OS were varied in one-way sensitivity analyses and the ten most influential variables were reported. PFS and OS were varied in probabilistic analysis. The rationale for this approach was that the PFS and OS are incorporated into the model using the clinical trial results in the form of Kaplan Meier curves and that one way sensitivity analysis is not appropriate on these parameters.

6.6.3 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis explored the variability in results over random sampling of all variables except the PFS and OS parameters from defined distributions. Drug costs were also omitted from the PSA as they were extensively tested individually within the one-way sensitivity anlaysis. In addition, list price is set for the treatments included therefore they are not expected to change. All other parameters including treatment dose were varied to ensure changes in the dosing practices would be taken into account. The standard errors and distributions used for each variable have been previously reported (See Appendix, Section 9.14). The results of 1,000 samples are presented.

6.7 Results

Clinical outcomes from the model

6.7.1 Summary of clinical outcomes from the model

Four scenarios were highlighted in the base case analysis. These were eribulin versus TPC as reported in the clinical trial and eribulin versus the three individual comparisons outlined in the scope, that is, capecitabine, vinorelbine and gemcitabine. In addition, the analysis focused on patients from region 1 (as detailed in Section 6.3.1) as this was the most appropriate patient group to consider. The clinical trial results compared with the model results for each of the comparisons is included in Table 48 to Table 50.

It is expected that the model values should closely approximate the empirical data as the inputs are effectively the same as the reported clinical data. Differences arise primarily from timing issues. That is, the EMBRACE trial data are a product of continuous analysis, whereas the model assesses health state transitions in accordance with the model cycle of 21 days. This validity of this scenario is dependent on the degree of right censoring from the trial, as it implicitly assumes that all patients enter the terminal state following the last observation.

Table 48: Summary of model results compared with clinical data for eribulin and TPC

Outcome	Clinical trial result		Model result		Difference[†]	
	Eribulin	TPC	Eribulin	TPC	Eribulin	TPC
Median PFS (days)	99	65	98	73	-0.8%	11.7%
PFS rate (proportion)						
3 months	0.536	0.406	0.530	0.406	-1.2%	0.0%
6 months	0.242	0.243	0.248	0.230	2.1%	-5.5%
9 months	0.113	0.042	0.115	0.037	2.0%	-13.1%
12 months	0.083	0.021	0.077	0.014	-6.9%	-34.4%
Median OS (days)	401	307	402	303	0.2%	-1.3%
OS rate (proportion)						
12 months	0.543	0.395	0.545	0.395	0.3%	0.0%
24 months	0.229	0.191	0.231	0.183	0.7%	-4.4%

Abbreviations: OS, Overall survival; PFS, Progression free survival; TPC, Treatment of Physician's Choice.
[†]The difference is calculated as: (model value – EMBRACE value) / (EMBRACE value).

Table 49: Summary of model results compared with clinical data for eribulin and gemcitabine

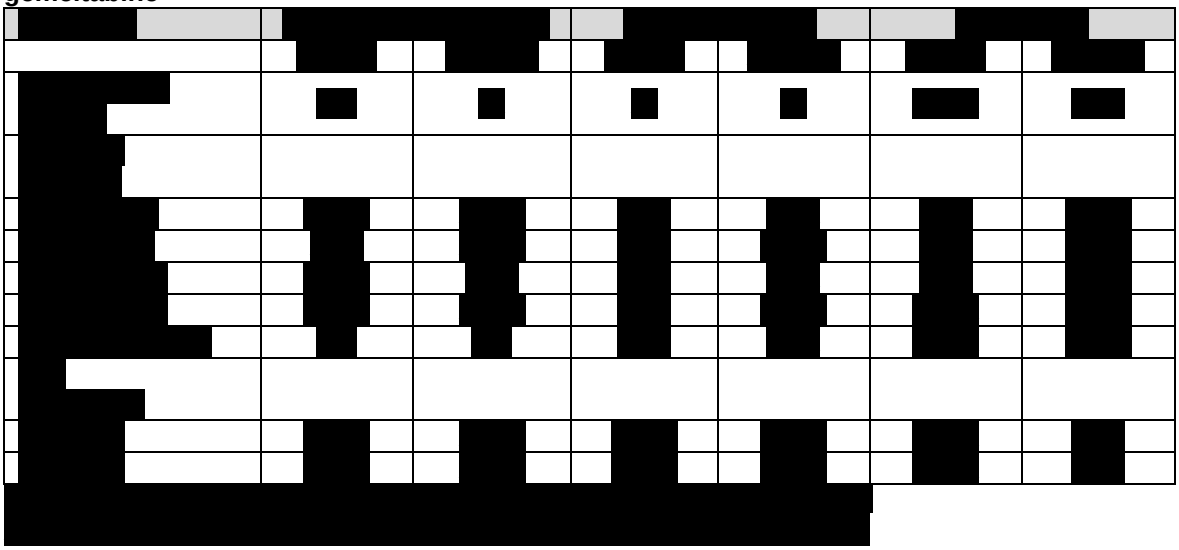


Table 52: Summary of model results compared with clinical data for eribulin and vinorelbine

[redacted]

Table 50: Summary of model results compared with clinical data for eribulin and capecitabine

[redacted]

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces were generated for each of the comparators in the four base case analyses and are presented here. Each of the comparator Markov traces is labelled TPC but the figure headings are representative of the analysis stated in the figure headings.

Eribulin vs. TPC comparison

Figure 14: Markov trace for eribulin

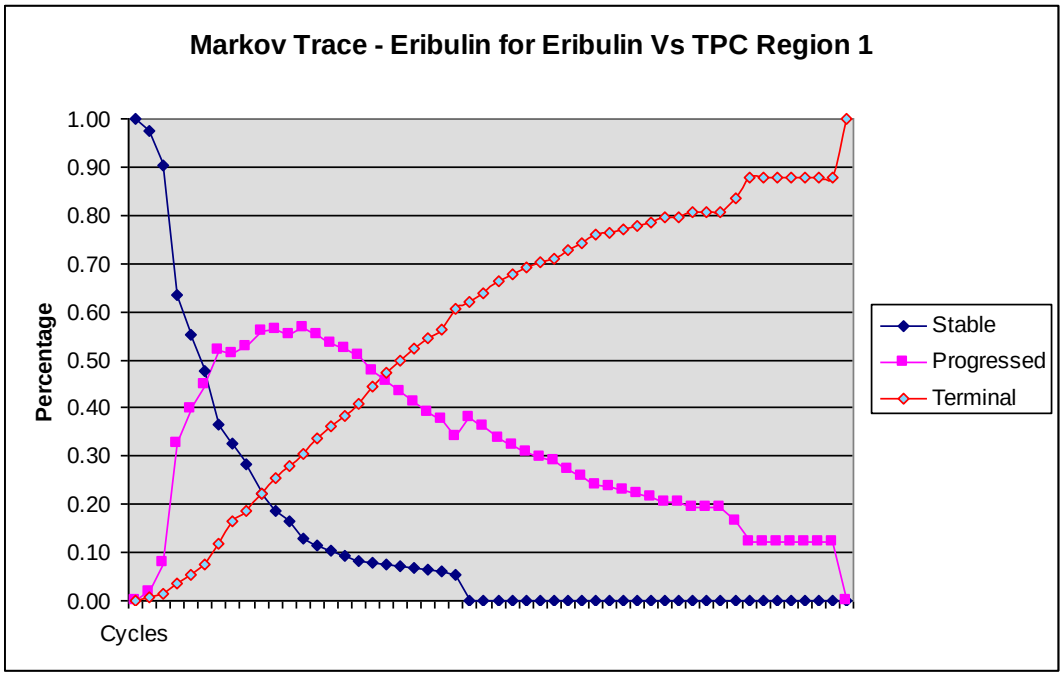
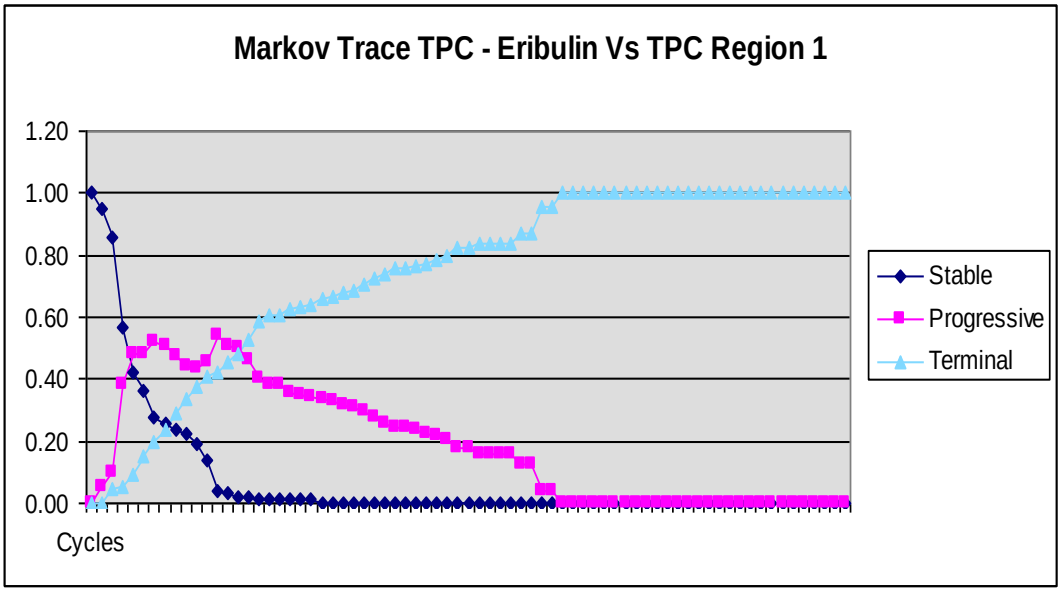


Figure 15: Markov trace for TPC



Eribulin vs. gemcitabine comparison

Figure 16: Markov trace for Eribulin (gemcitabine comparison)

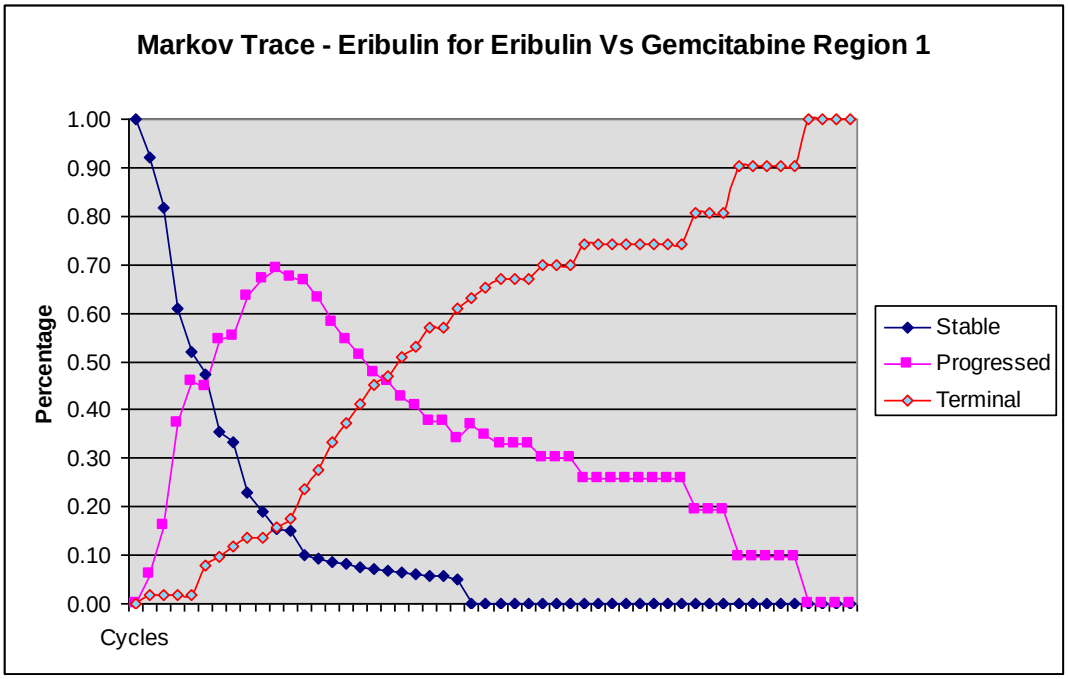
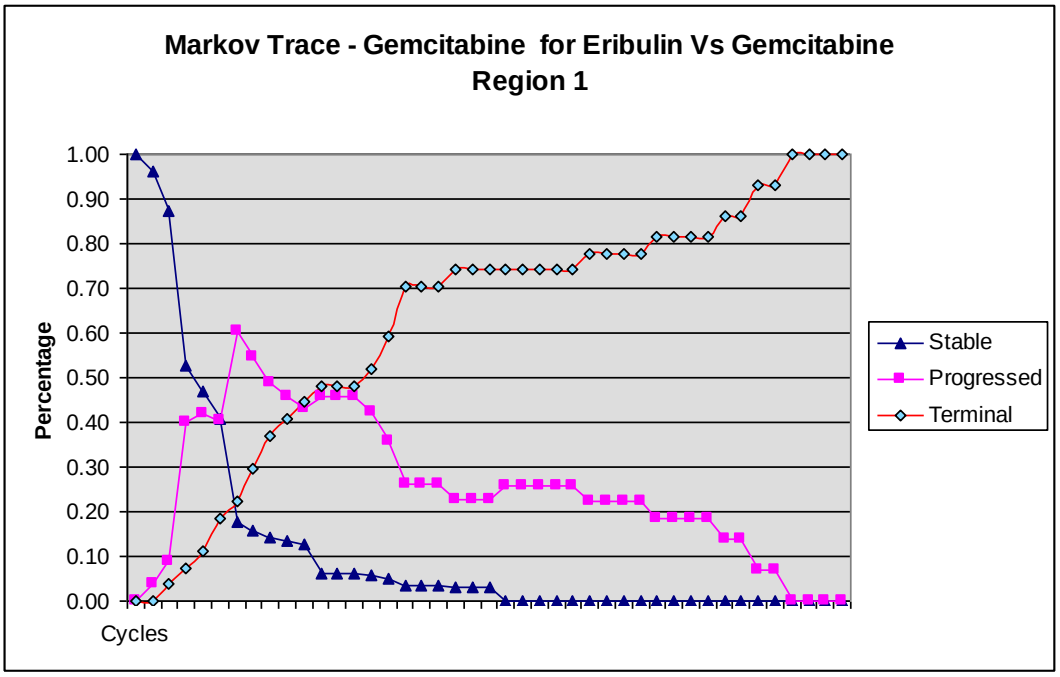


Figure 17: Markov trace for gemcitabine



Eribulin vs. vinorelbine comparison

Figure 18: Markov trace for Eribulin (vinorelbine comparison)

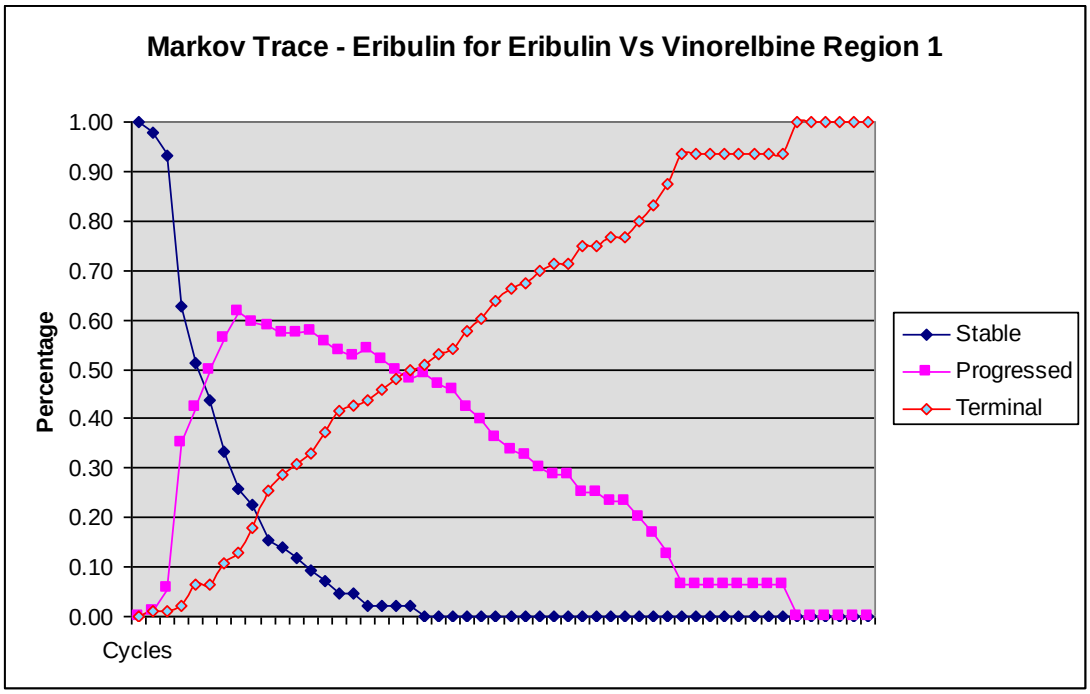
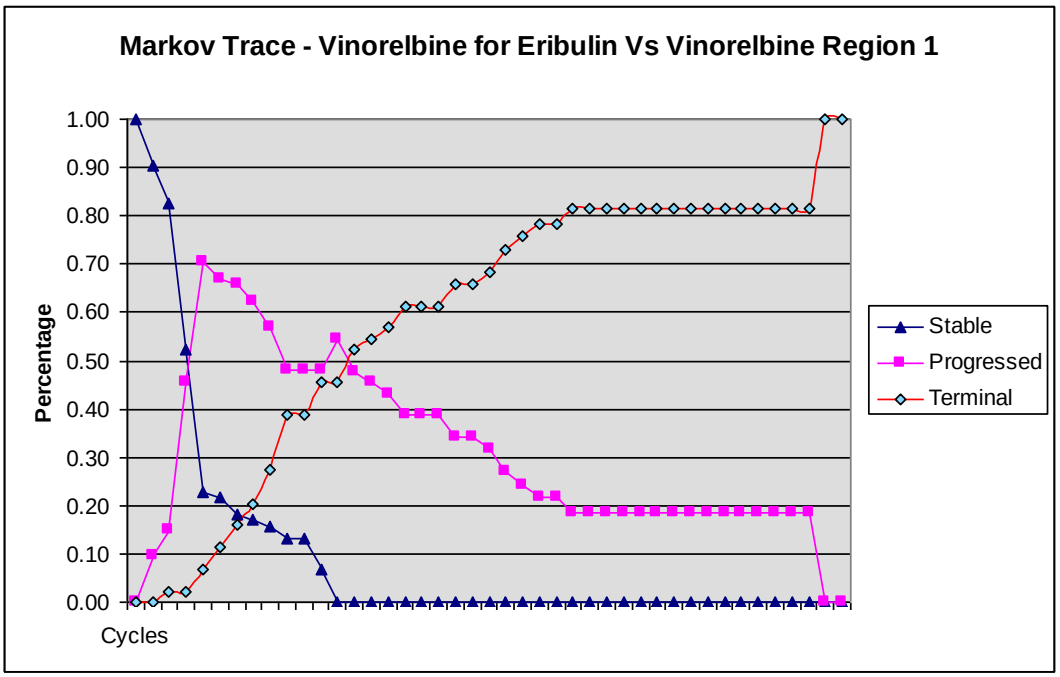


Figure 19: Markov trace for vinorelbine



Eribulin vs. capecitabine comparison

Figure 20: Markov trace for eribulin (capecitabine comparison)

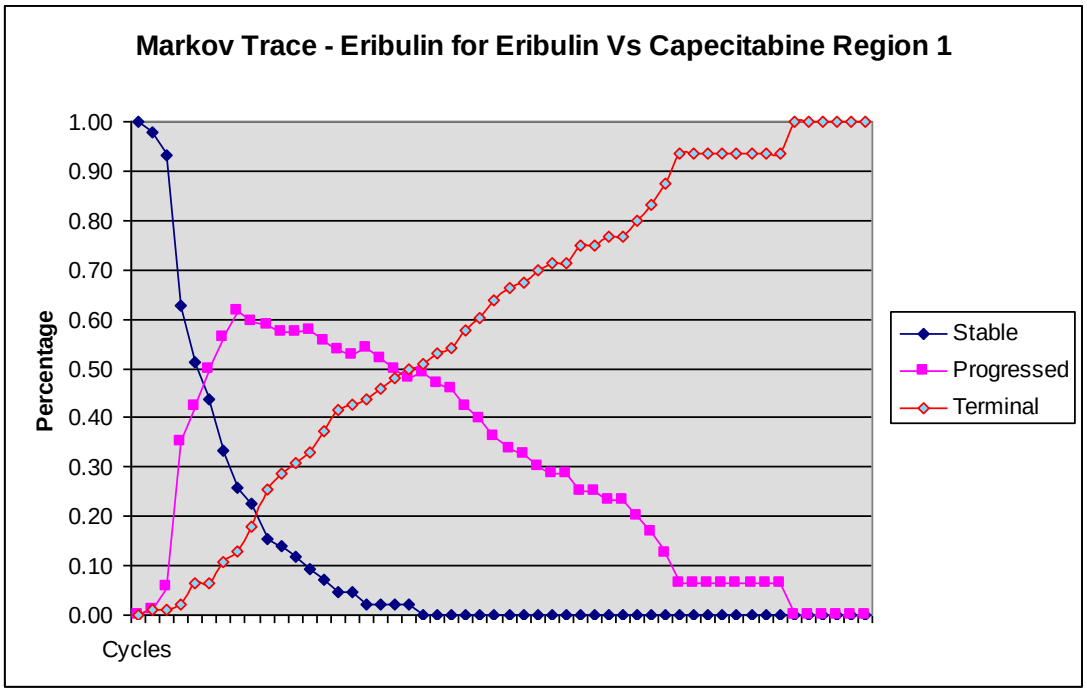
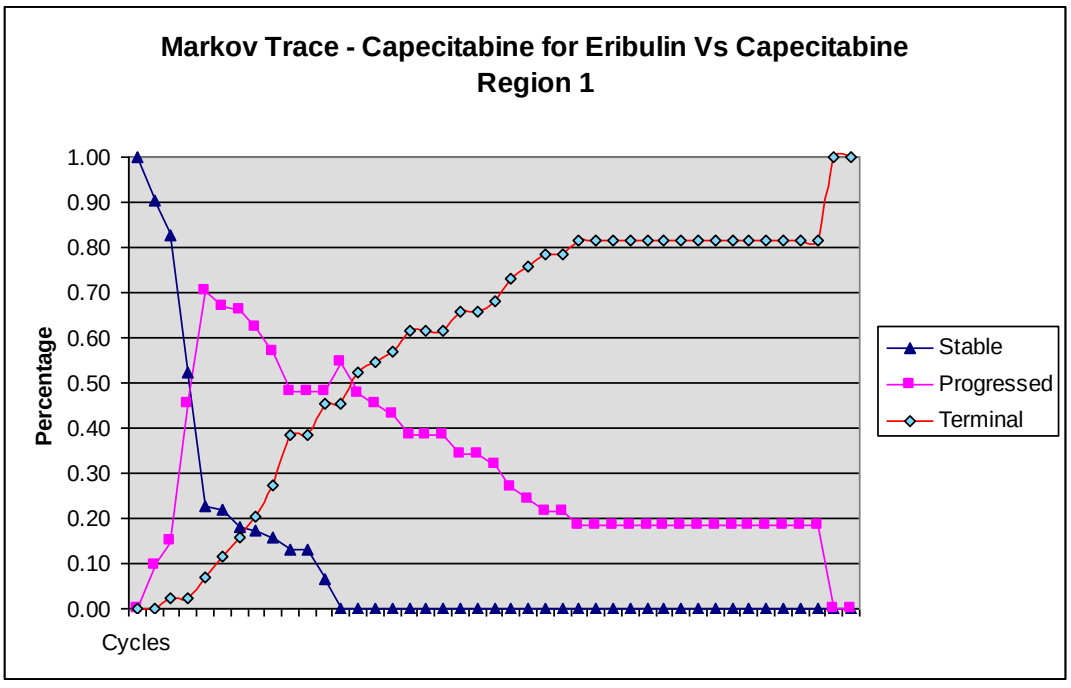


Figure 21: Markov trace for capecitabine



6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure 22: QALY Markov trace for eribulin (region1)

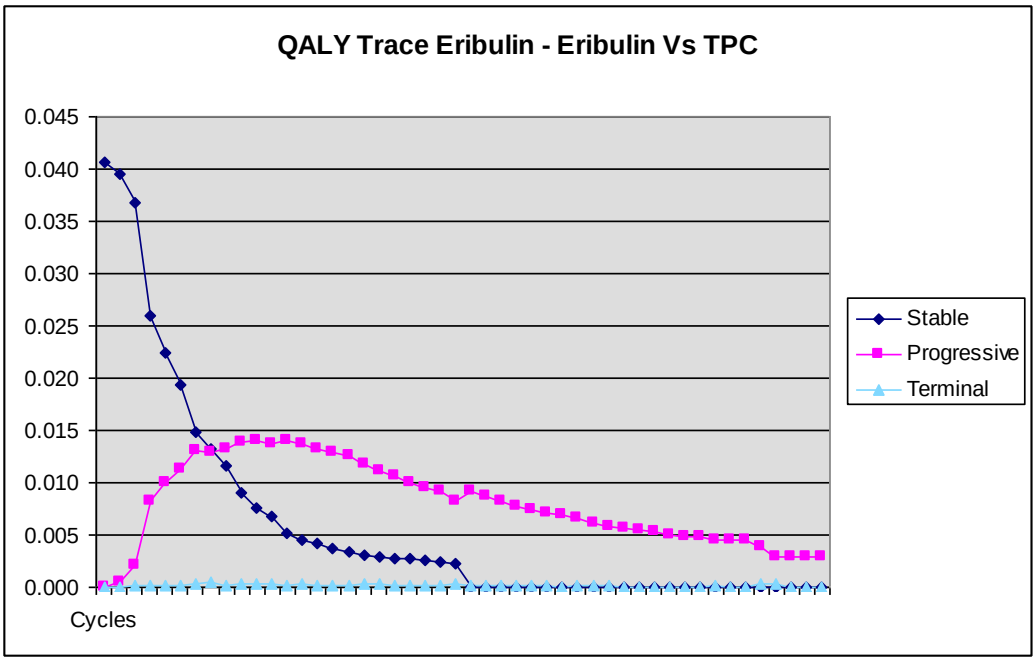


Figure 23: QALY Markov trace for TPC (region 1)

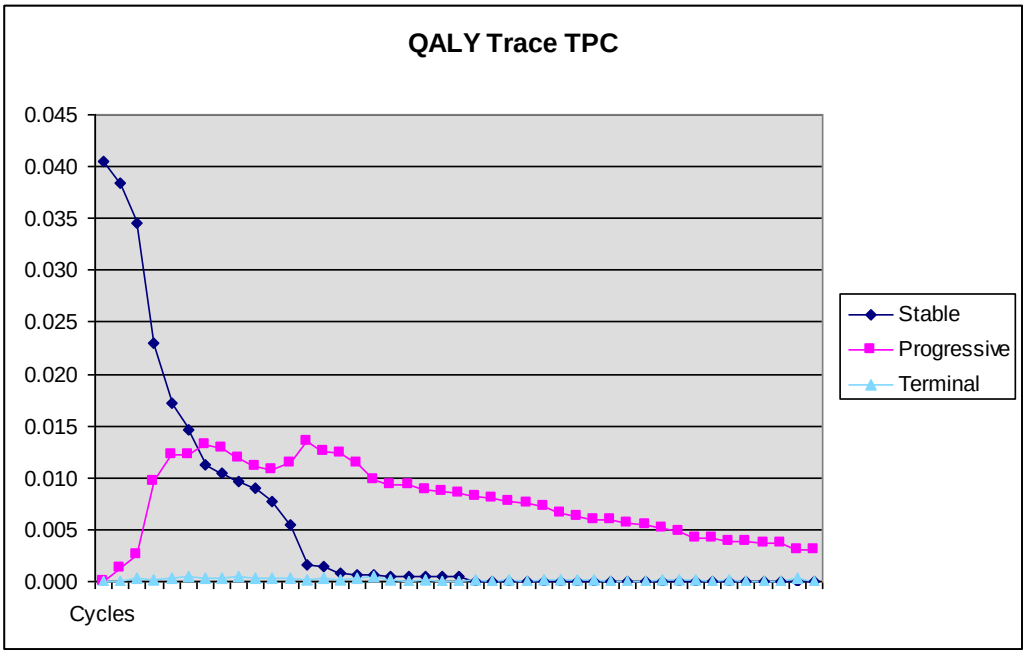


Figure 24: QALY Markov trace for eribulin in the gemcitabine comparison (region 1)

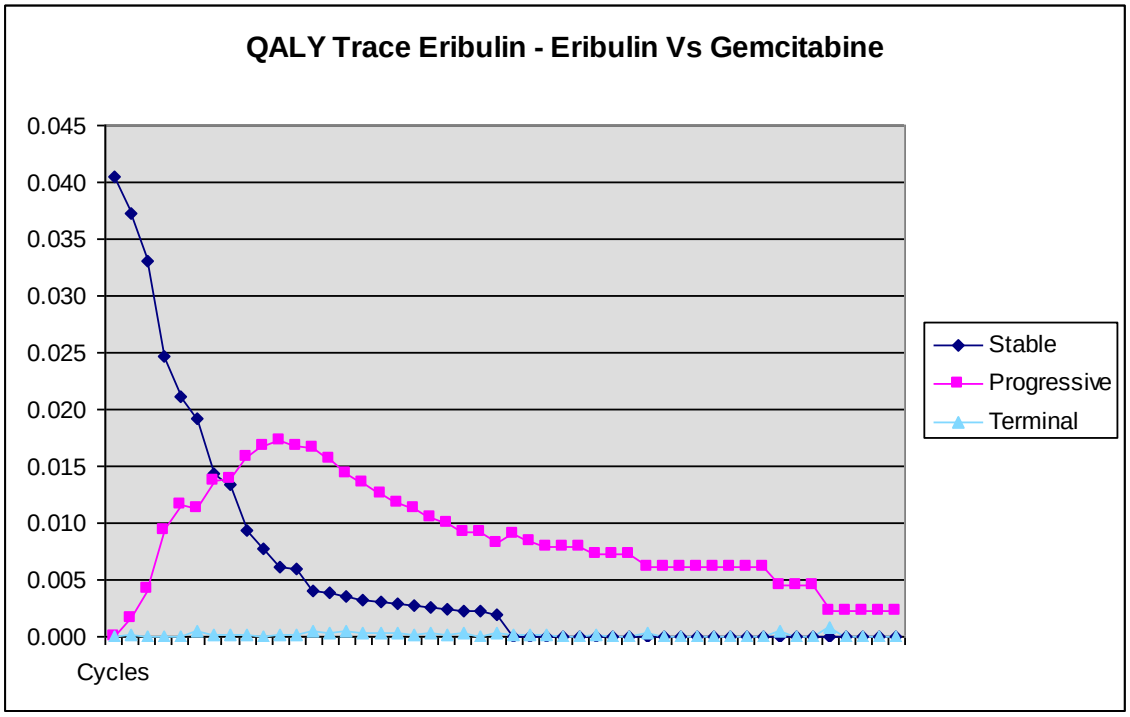


Figure 25: QALY Markov trace for gemcitabine (region 1)

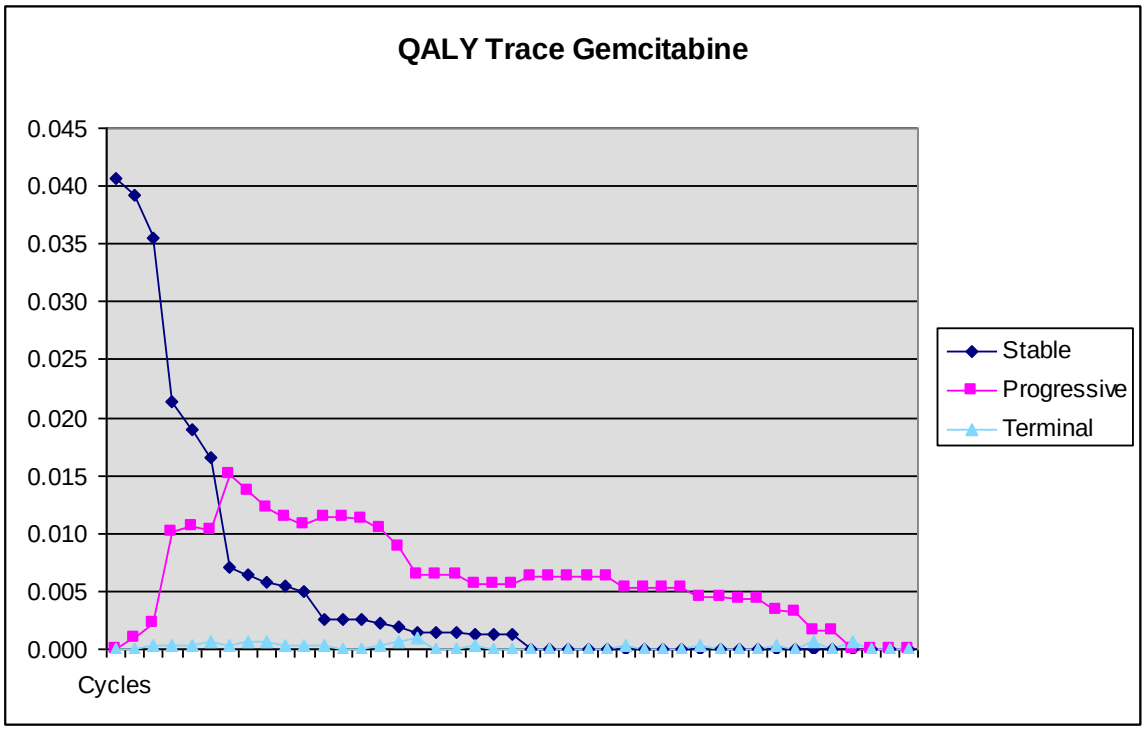


Figure 26: QALY Markov trace for eribulin in the vinorelbine comparison (region 1)

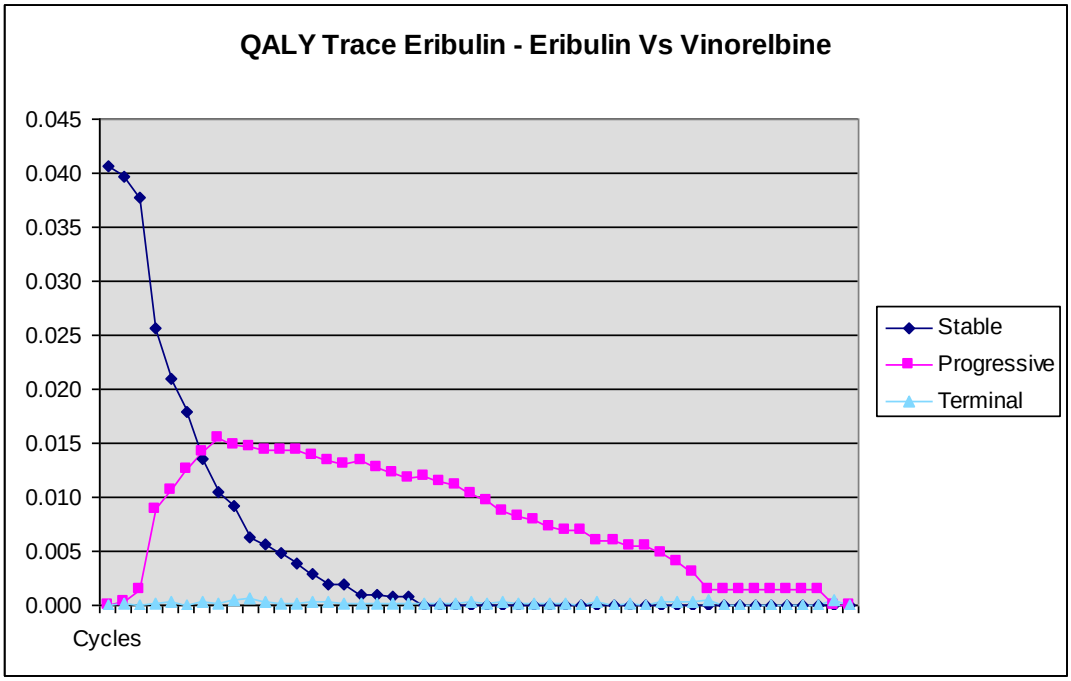


Figure 27: QALY Markov trace for vinorelbine (region 1)

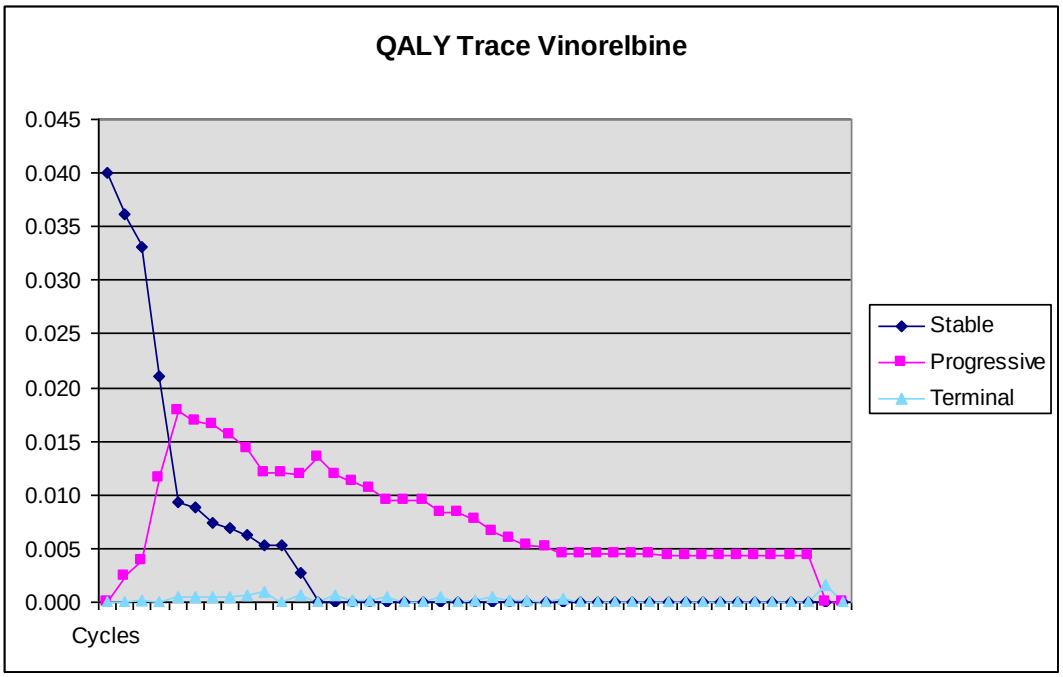


Figure 28: QALY Markov trace for eribulin in the capecitabine comparison (region1)

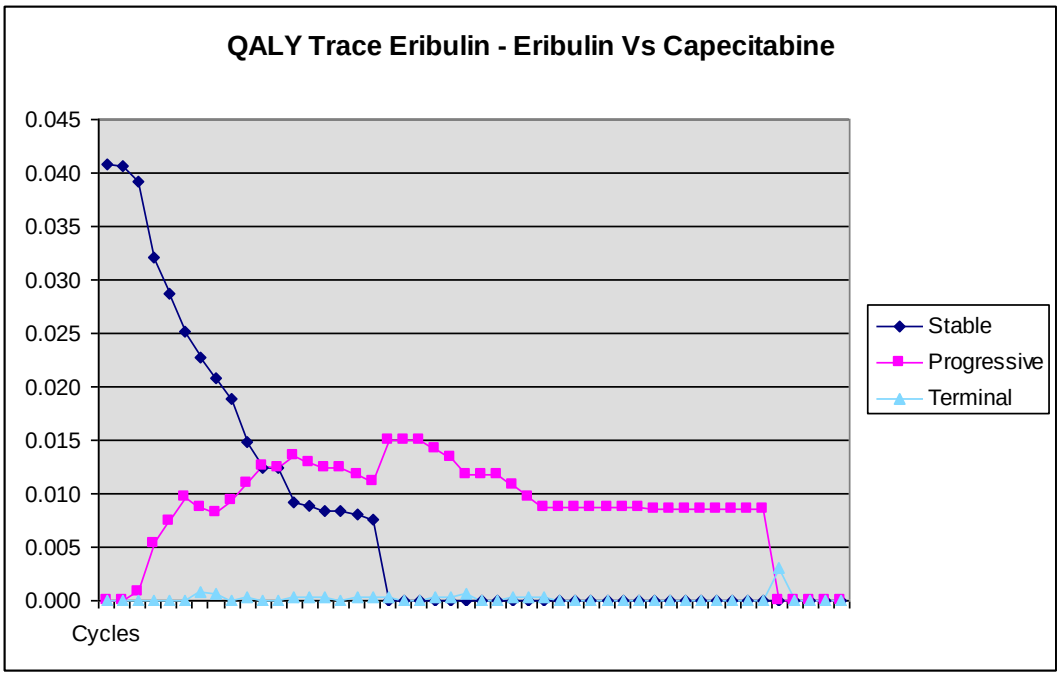
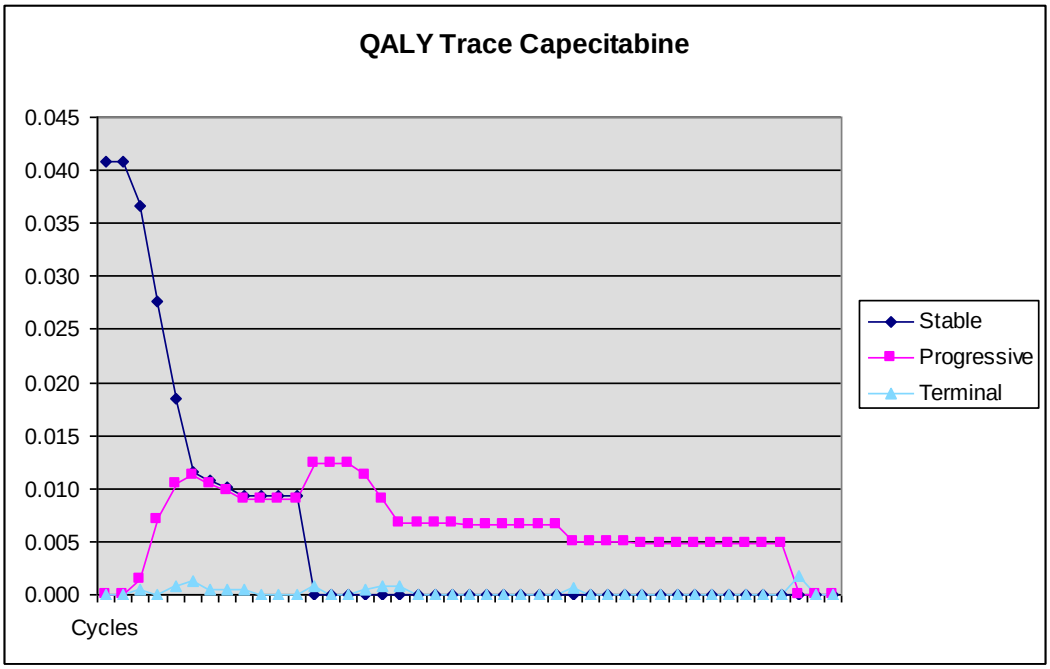


Figure 29: QALY Markov trace for capecitabine (region 1)



6.7.4 Life years and QALYs accrued for each clinical outcome

NA. The model was not set up to provide data in this format

6.7.5 Disaggregated incremental QALYs and costs

Table 51: Summary of QALY gain by health state for eribulin vs. TPC

Health state	QALY intervention (Eribulin)	QALY comparator (capecitabine)	Increment	Absolute increment	% absolute increment
Stable	0.287	0.229	0.058	0.058	47.69%
Progressive	0.393	0.329	0.063	0.063	52.25%
Terminal	0.009	0.009	0.000	0.000	0.06%
Total	0.689	0.567	0.121	0.121	100.00%

Abbreviations: QALY, quality-adjusted life year.

Table 52: Summary of QALY gain by health state for eribulin vs. capecitabine

Health state	QALY intervention (Eribulin)	QALY comparator (capecitabine)	Increment	Absolute increment	% absolute increment
Stable	0.359	0.234	0.125	0.125	46.46%
Progressive	0.417	0.274	0.144	0.144	53.48%
Terminal	0.009	0.009	0.000	0.000	0.06%
Total	0.785	0.517	0.268	0.269	100.00%

Abbreviations: QALY, quality-adjusted life year.

Table 53: Summary of QALY gain by health state for eribulin vs. vinorelbine

Health state	QALY intervention (Eribulin)	QALY comparator (vinorelbine)	Increment	Absolute increment	% absolute increment
Stable	0.247	0.182	0.064	0.064	56.69%
Progressive	0.373	0.324	0.049	0.049	43.25%
Terminal	0.009	0.009	0.000	0.000	0.05%
Total	0.629	0.516	0.114	0.114	100.00%

Abbreviations: QALY, quality-adjusted life year.

Table 54: Summary of QALY gain by health state for eribulin vs. gemcitabine

Health state	QALY intervention (Eribulin)	QALY comparator (gemcitabine)	Increment	Absolute increment	% absolute increment
Stable	0.268	0.222	0.046	0.046	24.08%
Progressive	0.412	0.267	0.145	0.145	75.85%
Terminal	0.009	0.009	0.000	0.000	0.06%
Total	0.688	0.498	0.190	0.191	100.00%

Abbreviations: QALY, quality-adjusted life year.

Table 55: Summary of costs by health state and cost category for eribulin vs. TPC

Costs	Cost intervention (Eribulin)	Cost comparator (TPC)	Increment	Absolute increment	% absolute increment
Infusion	£3,174	£2,250	£924	£924	15.63%
Drug	[redacted]	£5,251	xxxx	xxxxx	xxxxx
Stable	£1,141	£916	£224	£224	3.80%
Progressive	£3,596	£3,015	£581	£581	9.83%
Terminal	£18,819	£18,970	-£151	£151	2.55%
G3	£18	£30	-£12	£12	0.20%
G4	£54	£18	£36	£36	0.60%
Total	£36,035	£30,449	£5,586	£5,911	1.000

Abbreviations: G4, grade 4; G3, grade 3.

Table 56: Summary of costs by health state and cost category for eribulin vs. gemcitabine

Costs	Cost intervention (Eribulin)	Cost comparator (TPC)	Increment	Absolute increment	% absolute increment
Infusion	£2,970	£2,461	£509	£509	8.92%
Drug	[redacted]	xxxx	xxxx	xxxx	xxxx
Stable	£1,068	£885	£183	£183	3.21%
Progressive	£3,772	£2,447	£1,325	£1,325	23.21%
Terminal	£18,807	£19,072	-£265	£265	4.64%
G3	£18	£2	£16	£16	0.28%
G4	£52	£0	£52	£52	0.91%
Total	£35,329	£30,152	£5,177	£5,706	1.000

Abbreviations: G4, grade 4; G3, grade 3.

Table 57: Summary of costs by health state and cost category for eribulin vs. vinorelbine

Costs	Cost intervention (Eribulin)	Cost comparator (TPC)	Increment	Absolute increment	% absolute increment
Infusion	£2,726	£3,069	-£343	£343	6.86%
Drug	[redacted]	xxxx	xxxx	xxxx	xxxx
Stable	£980	£735	£244	£244	4.89%
Progressive	£3,420	£2,970	£450	£450	9.02%
Terminal	£18,887	£19,021	-£134	£134	2.68%
G3	£20	£20	£0	£0	0.00%
G4	£59	£24	£35	£35	0.70%
Total	£34,024	£29,982	£4,042	£4,995	1.000

Abbreviations: G4, grade 4; G3, grade 3

Table 58: Summary of costs by health state and cost category for eribulin vs. capecitabine

Costs	Cost intervention (Eribulin)	Cost comparator (TPC)	Increment	Absolute increment	% absolute increment
Infusion	£3,966	£1,190	£2,776	£2,776	20.50%
Drug	[redacted]	xxxx	xxxx	xxxx	xxxx
Stable	£1,425	£929	£497	£497	3.67%
Progressive	£3,823	£2,508	£1,316	£1,316	9.72%
Terminal	£18,713	£19,052	-£338	£338	2.50%
G3	£20	£63	-£43	£43	0.32%
G4	£59	£0	£59	£59	0.43%
Total	£39,545	£26,766	£12,779	£13,542	1.000

Abbreviations: G4, grade 4; G3, grade 3

Base-case analysis

6.7.6 Summary of results

Base case results are presented in Table 59 and Table 60 . The base case comparisons are versus TPC, and then versus each of the individual comparators listed in the scope for patients in region 1. An incremental analysis cannot be presented as the data in the eribulin arm is different for each comparison.

Table 59: Base-case results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£36,035	0.6887	£5,586	0.1213	£46,050

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 60: Base-case results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.6885	£5,177	0.1904	£27,183

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 61: Base-case results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.6291	£4,041	0.1136	£35,602

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 62: Base-case results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.7853	£12,779	0.2683	£47,631

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Sensitivity analyses

6.7.7 Deterministic sensitivity analysis

One-way deterministic sensitivity analysis was carried out on all model parameters except OS and PFS as previously explained in Section 6.6.2. The top ten parameters of influence are presented as tornado diagrams for each of the base case analyses.

Figure 30: Tornado diagram of eribulin vs. TPC

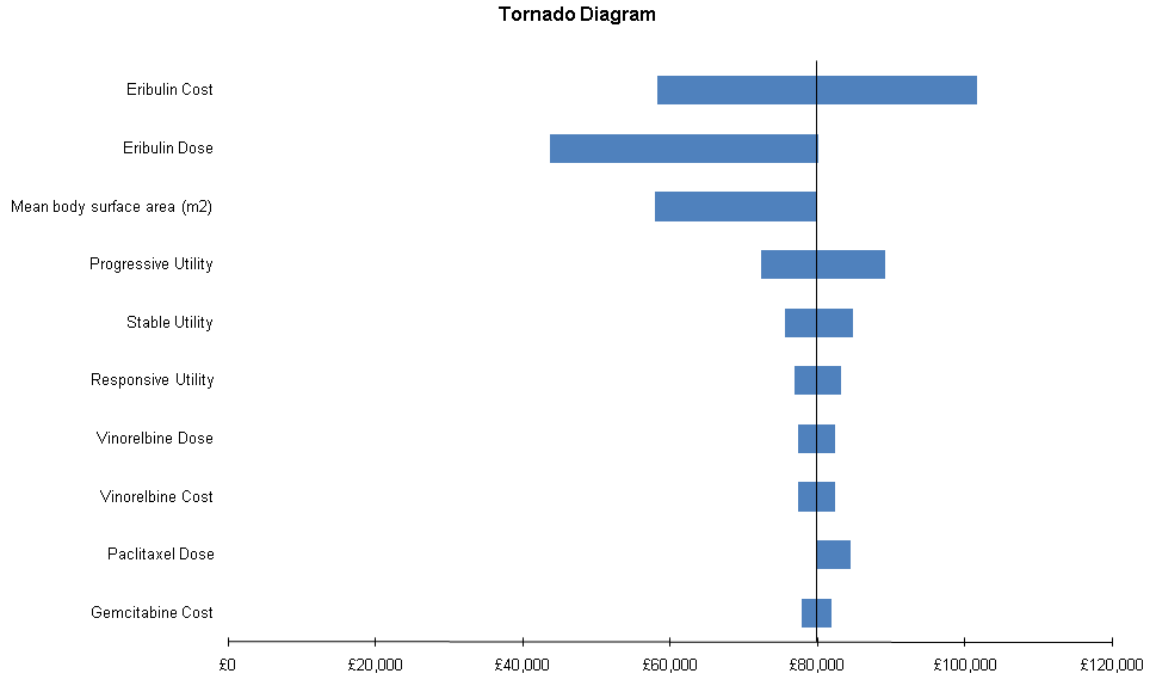


Figure 31: Tornado diagram of eribulin vs. gemcitabine

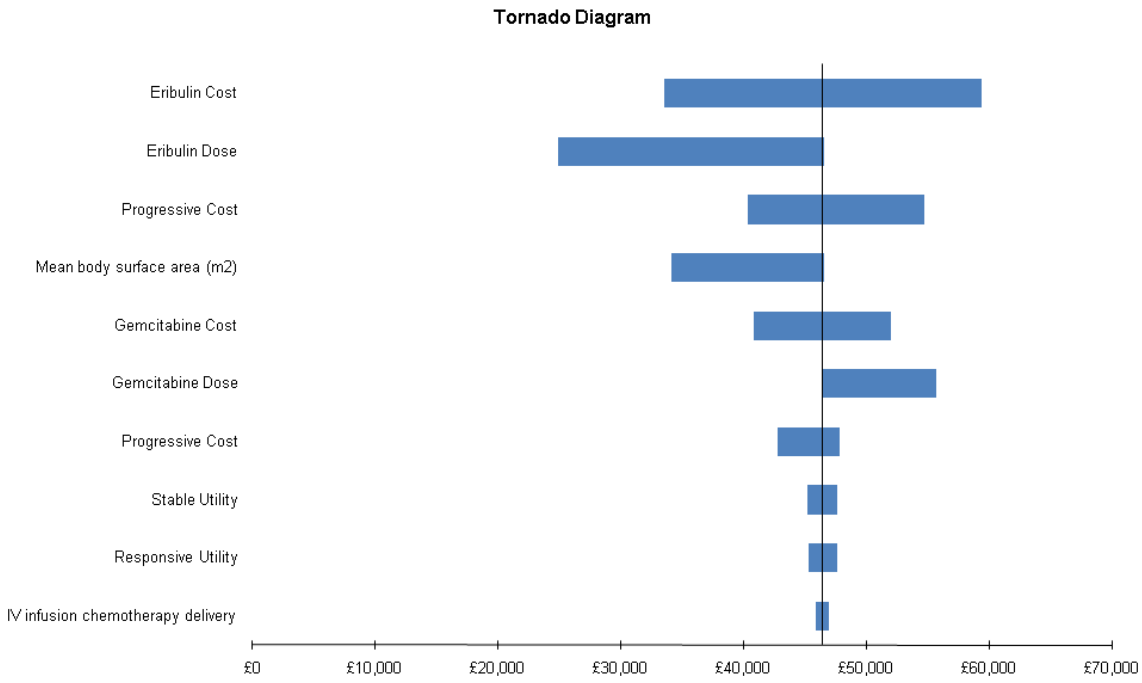


Figure 32: Tornado diagram of eribulin vs. vinorelbine

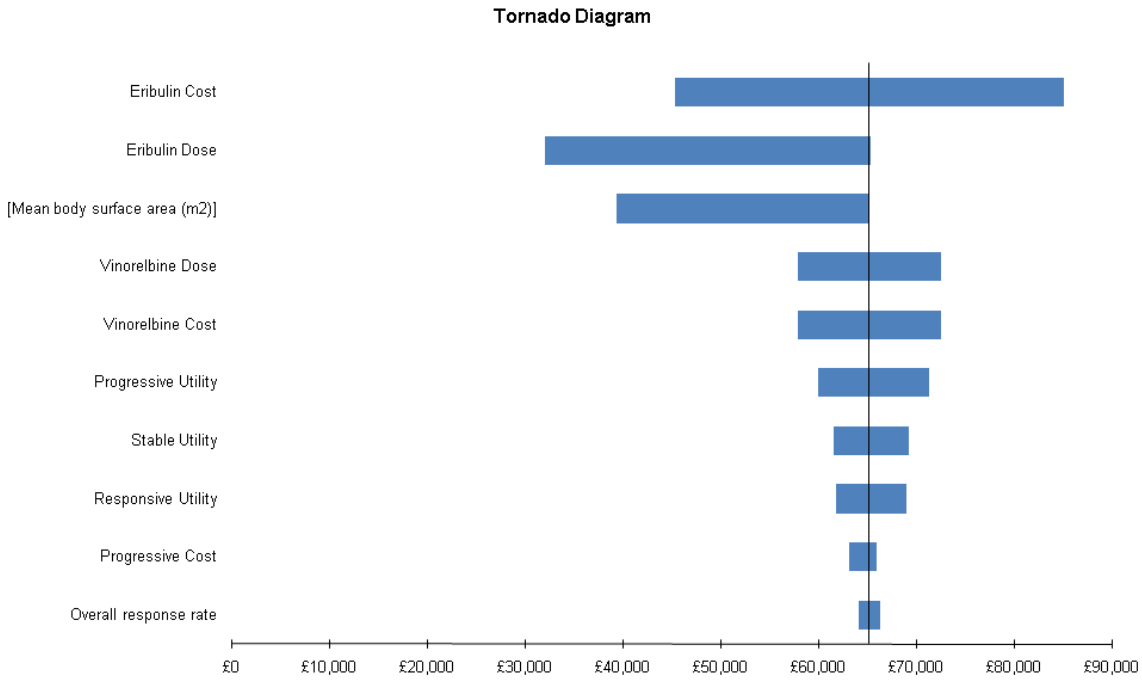
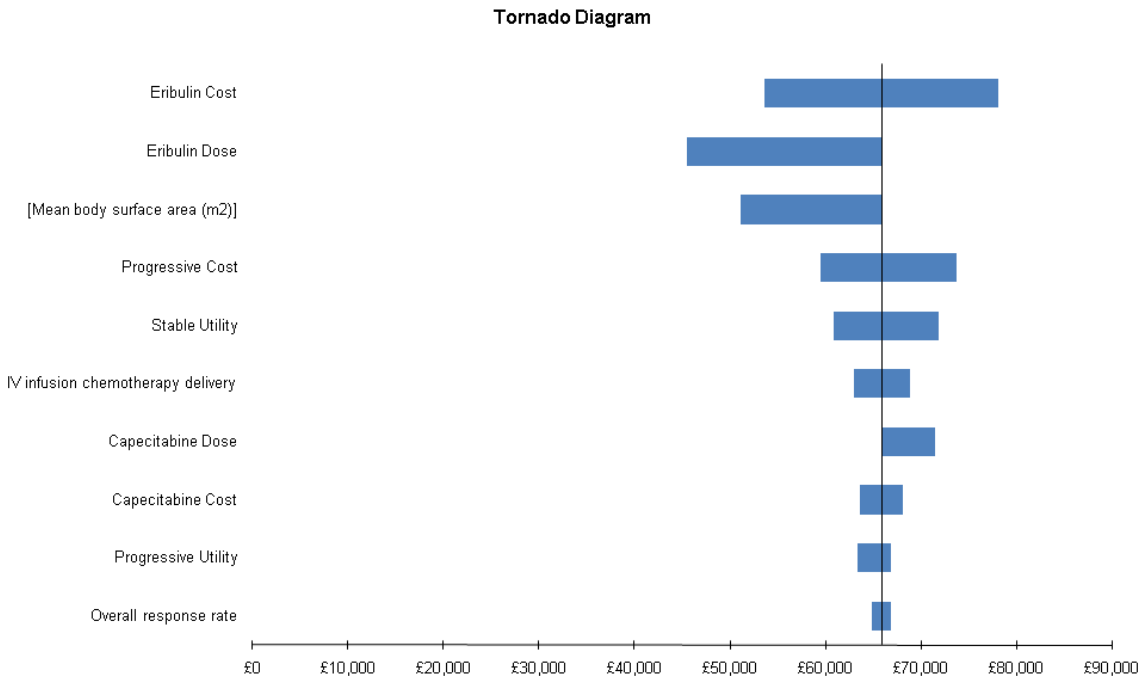


Figure 33: Tornado diagram of eribulin vs. capecitabine



6.7.8 Probabilistic sensitivity analysis

A probabilistic analysis was carried out for each of the four base case analyses as outlined in Section 6.6.3. These are presented here using tables to outline the mean total costs, QALYs and ICERs along with scatter plots and CEACs.

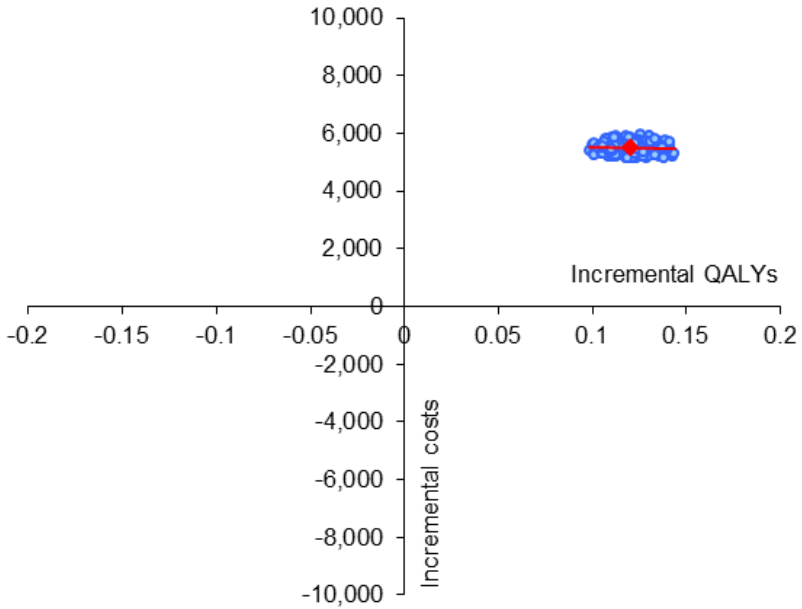
Eribulin vs. TPC

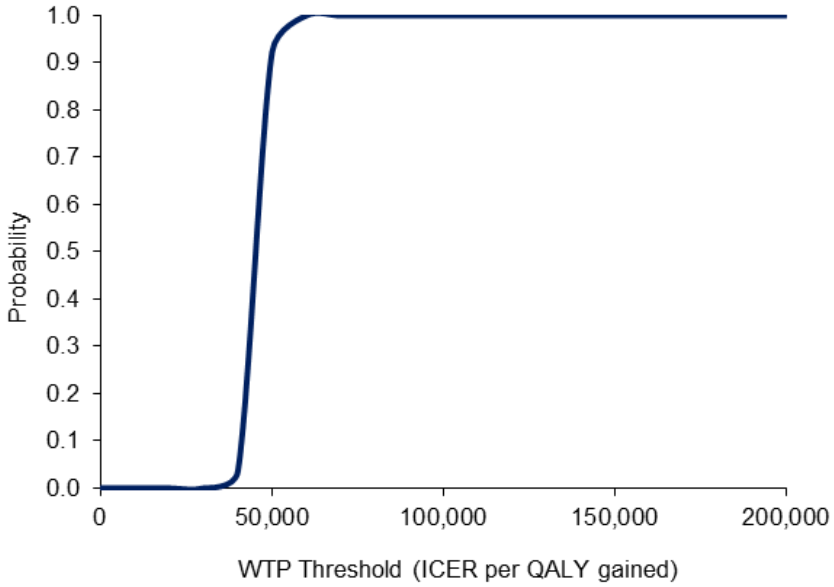
Table 63: PSA results for eribulin versus TPC

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£ £30,445	0.567694467			
Eribulin	£ £36,000	0.688710955	£ £5,556	0.121016488	£45,909

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 34: Cost effectiveness plane and CEAC of eribulin vs. TPC





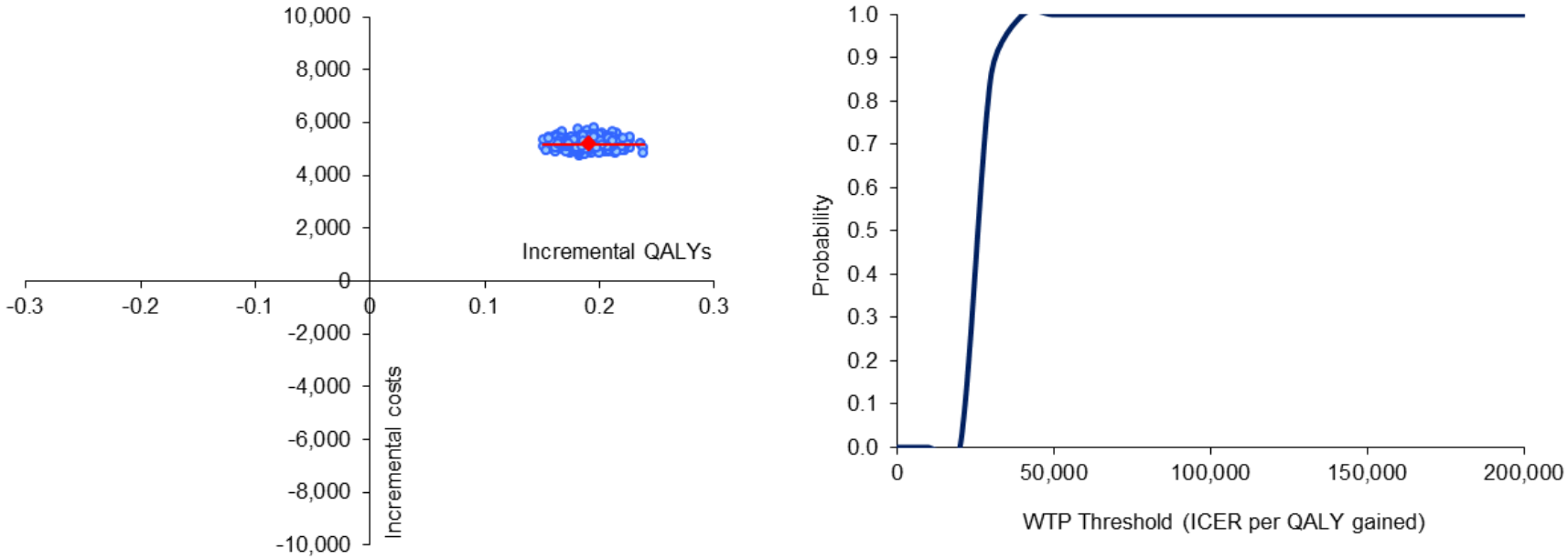
Eribulin vs. gemcitabine

Table 64: PSA results for eribulin versus gemcitabine

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£ 30341	0.4994			
Eribulin	£ 35511	0.6899	£5,170	0.190558118	£27,130

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 35: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine



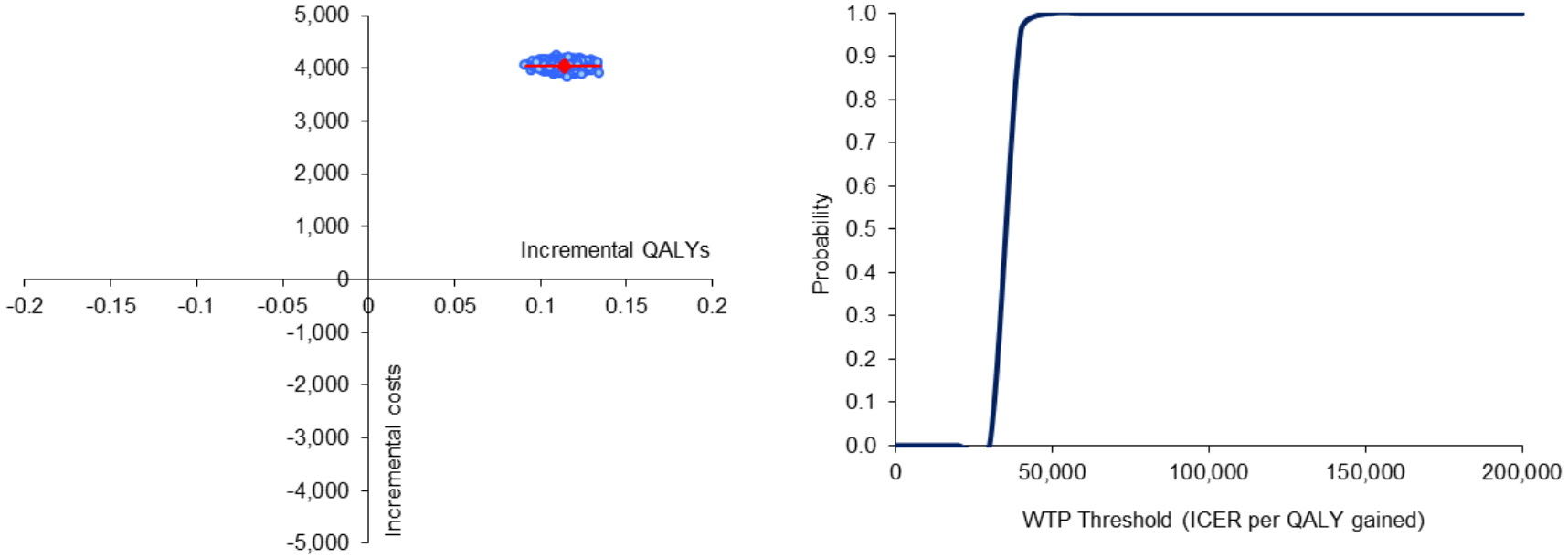
Eribulin vs. vinorelbine

Table 65: PSA results for eribulin versus vinorelbine

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£30,058	0.5158			
Eribulin	£34,105	0.6291	£4,047	0.1133	£35,719

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 36: Effectiveness plane showing scatter plot of eribulin vs. vinorelbine



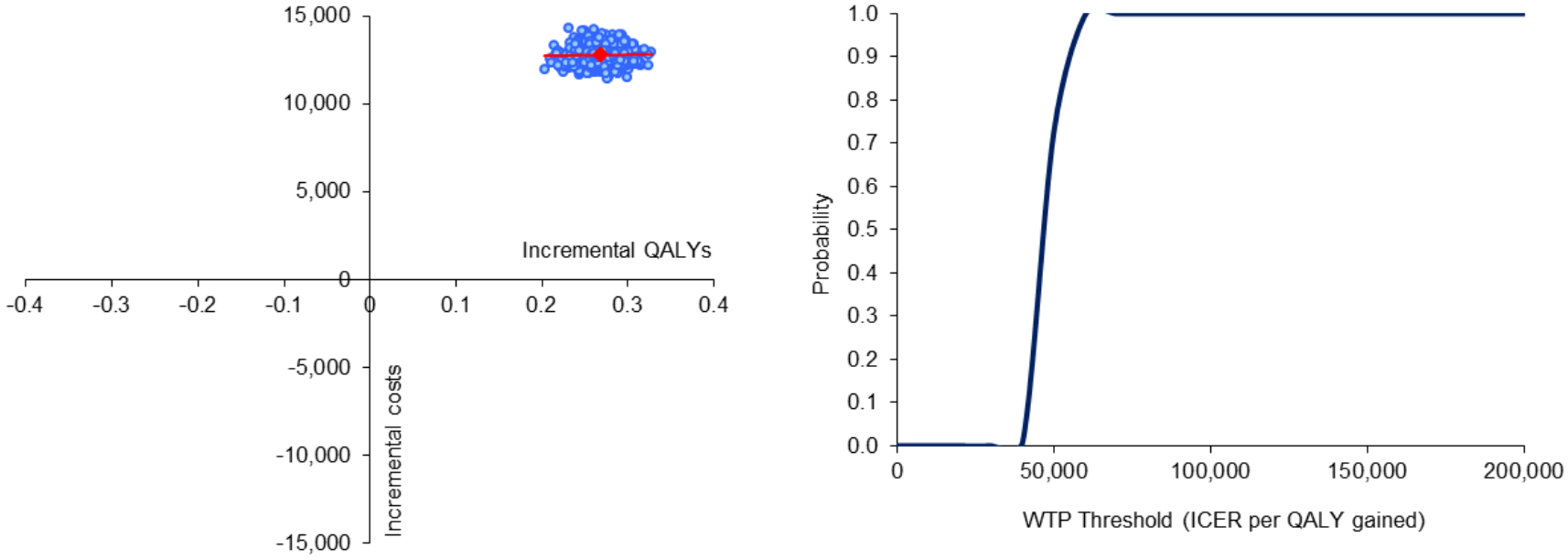
Eribulin vs. capecitabine

Table 66: PSA results for eribulin versus capecitabine

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,857	0.517898144			
Eribulin	£39,615	0.786238404	£12,758	0.26834026	£47,544

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 37: effectiveness plane showing scatter plot of eribulin vs. capecitabine



6.7.9 Scenario analysis

Several scenario analyses were carried out in order to demonstrate the cost effectiveness of eribulin in alternative settings. These analyses were as follows:

- Scenario analysis 1: End-of-life guidance applied
- Drug costs:
  - Scenario analysis 2: Price of eribulin calculated per mg rather than per vial
  - Scenario analysis 3: Price of vinorelbine calculated using the IV formula price
- Scenario analysis 4: All regions

In addition, an analysis to test the structural uncertainty within the model using hazard ratios to estimate survival in the model rather than Kaplan Meier curves was explored.

Scenario analysis 1: End-of-life guidance analysis

Eribulin meets the criteria for consideration under the Institute's end-of-life guidance. That is, eribulin is indicated for a relatively small number of patients who have LABC/MBC and have had a previous anthracycline and a taxane, the medicine is indicated for the treatment of patients with a diagnosis of a terminal illness and who are not, on average, expected to live for more than 24 months, and; eribulin is the only treatment in this setting to have de monstrated extension to life, compared to current NHS treatment (See Section 5.10.3). A scenario analysis was conducted on the assumption that eribulin qualifies for consideration under the end-of-life guidance, using the aforementioned full utility value of 0.83 for eribulin patients surviving beyond a certain number of days (the cumulative survival in the comparator arm) as shown in Table 67.

Table 67: Cumulative survival for comparators for end-of-life analysis

Comparator	Cumulative survival (number of days)
TPC	421
Vinorebine	392
Gemcitabine	363
Capecitabine	376

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

The analysis was conducted for the four base case analyses. Probabilistic results are also provided.

Table 68: End-of-life analysis results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£36,035	0.7775	£5,586	0.2101	£26,589

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 69: End-of-life analysis results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.8427	£5,177	0.3447	£15,019

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 70: End-of-life analysis results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.7092	£4,042	0.1937	£20,875

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 71: End-of-life analysis results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.9841	£12,779	0.4671	£27,356

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario analysis 1: End-of-life analysis – PSA results

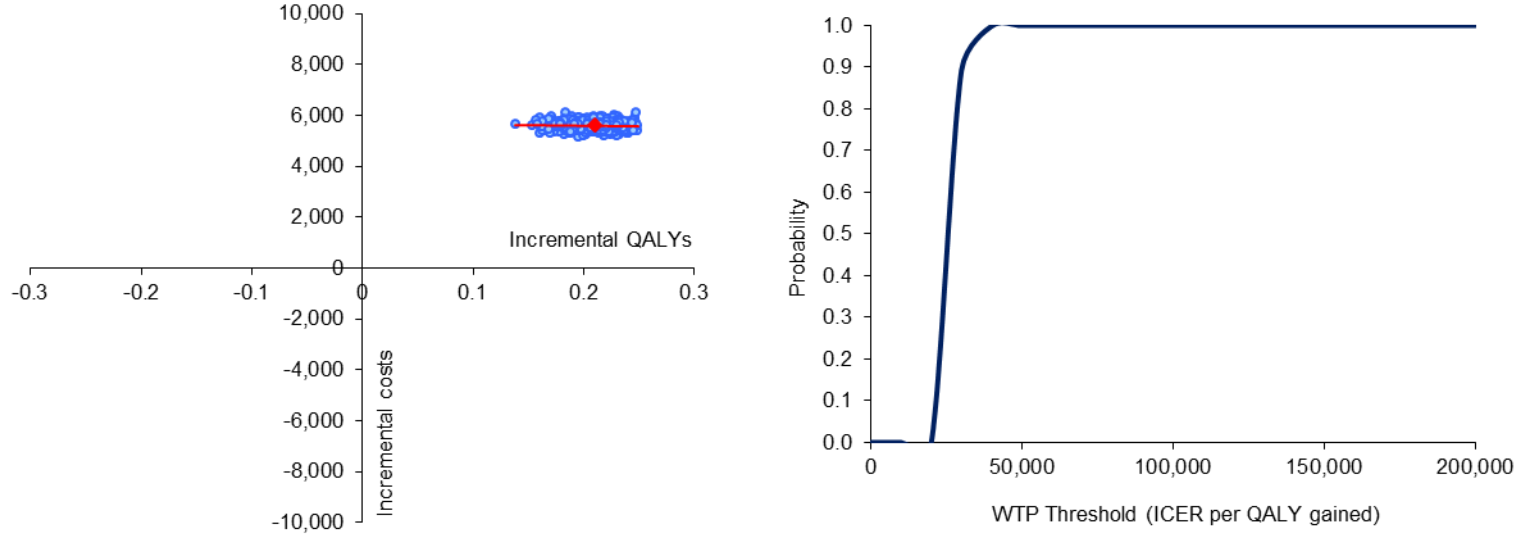
Eribulin vs. TPC

Table 72: PSA results for eribulin versus TPC end-of-life analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,323	0.567942892			
Eribulin	£36,090	0.777519366	£5,767	0.209576474	£27,516

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 38: Cost effectiveness plane and CEAC of eribulin vs. TPC end-of-life analysis



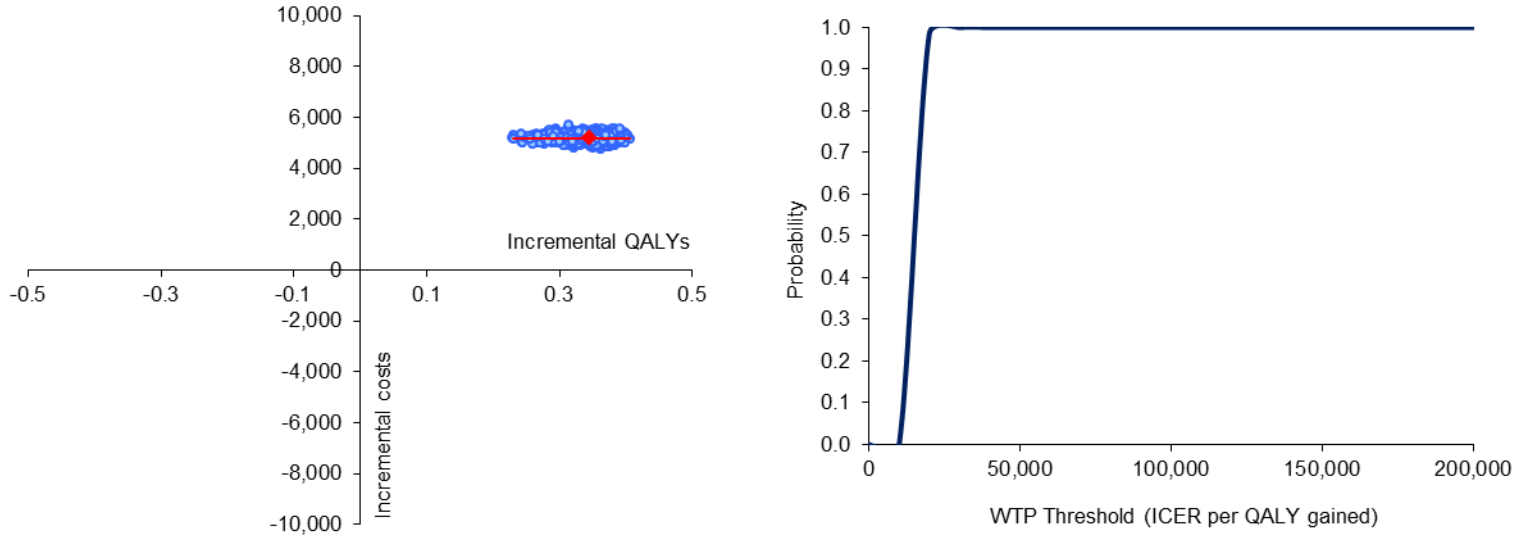
Eribulin vs. gemcitabine

Table 73: PSA results for eribulin versus gemcitabine end-of-life analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,073	0.4967			
Eribulin	£38,912	0.8409	£8,838	0.3442	£25,679

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 39: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine end-of-life analysis



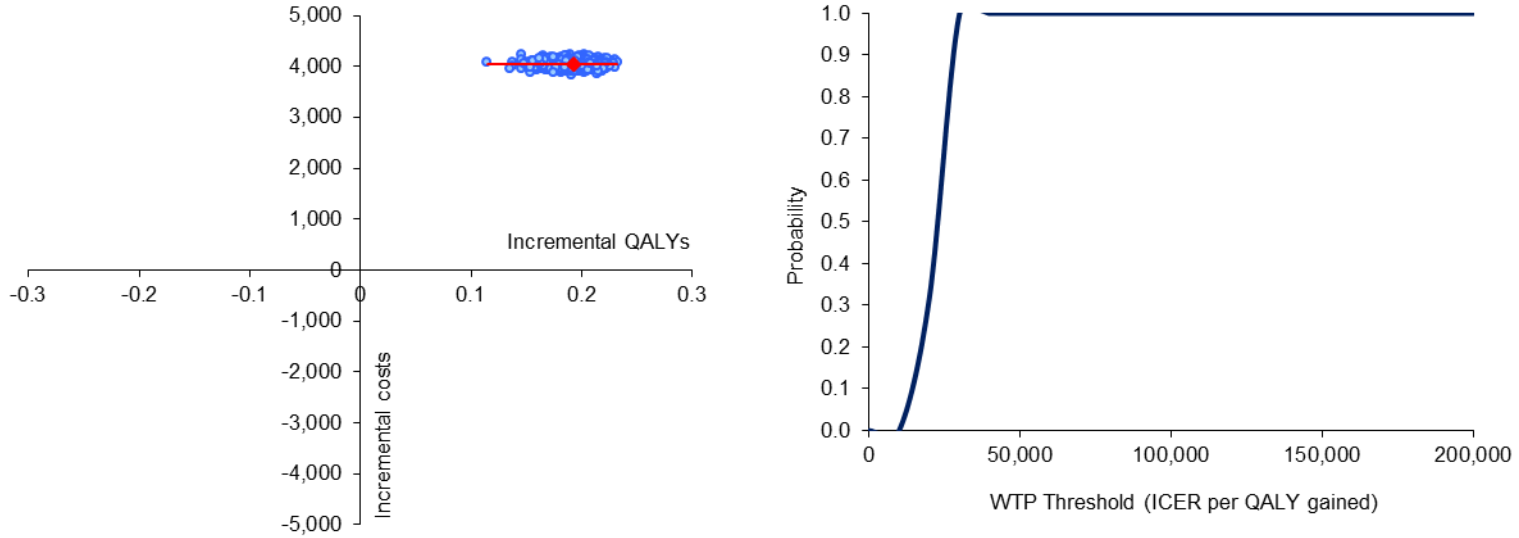
Eribulin vs. vinorelbine

Table 74: PSA results for eribulin versus vinorelbine end-of-life analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,941	0.514670945			
Eribulin	£33,984	0.706927015	£4,044	0.192256071	£21,032

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 40: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine end-of-life analysis



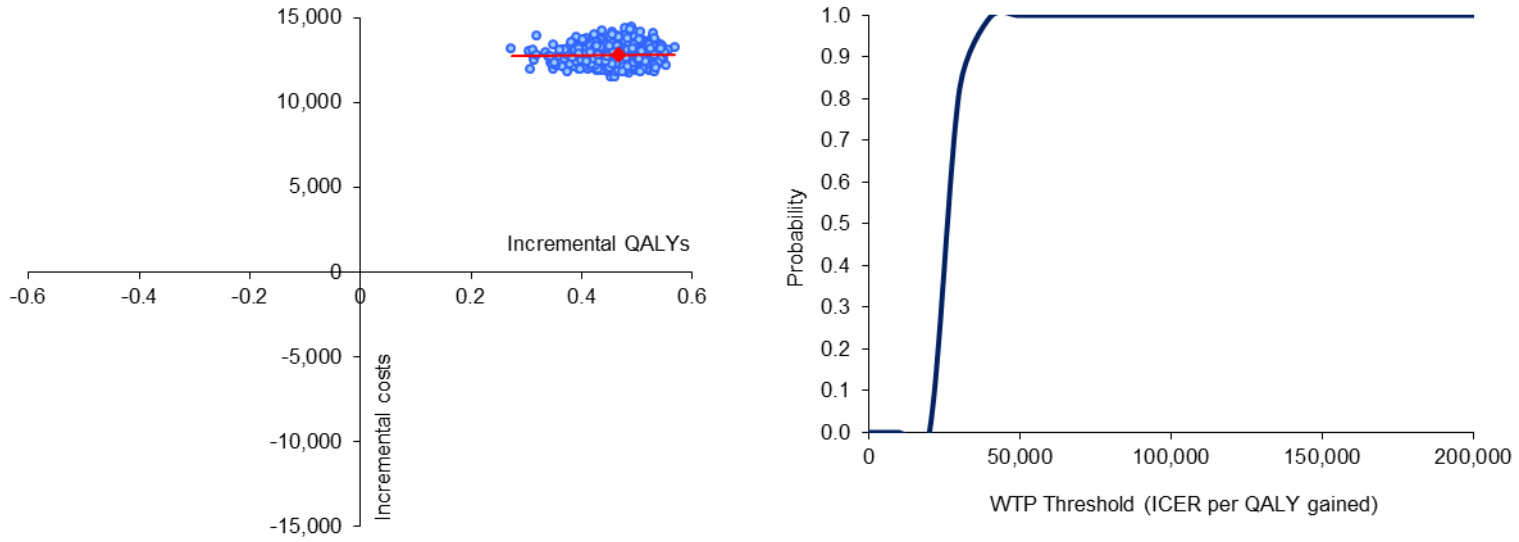
Eribulin vs. capecitabine

Table 75: PSA results for eribulin versus capecitabine end-of-life analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,648	0.519240717			
Eribulin	£39,484	0.985253511	£12,836	0.466012794	£27,545

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 41: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine end-of-life analysis



Scenario analysis 2: Drug costs – per milligram price for eribulin

A sensitivity analysis was carried out to determine the cost effectiveness of eribulin when drug costs were calculated using per-milligram (per mg) pricing and therefore assuming no wastage. The results for each of the base case analyses are presented here. Probabilistic results are also provided.

Table 76: Per mg analysis results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£29,123	0.5674			
Eribulin	£34,299	0.6887	£5,177	0.1213	£42,672

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 77: Per mg analysis results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£28,690	0.4980			
Eribulin	£33,704	0.6885	£5,014	0.1904	£26,330

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 78: Per mg analysis results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,981	0.5155			
Eribulin	£22,473	0.6291	£2,551	0.1136	£22,473

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 79: Per mg analysis results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£25,280	0.5170			
Eribulin	£37,376	0.7853	£12,096	0.2683	£45,085

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario analysis 2: Drug costs – per milligram price of eribulin analysis – PSA results

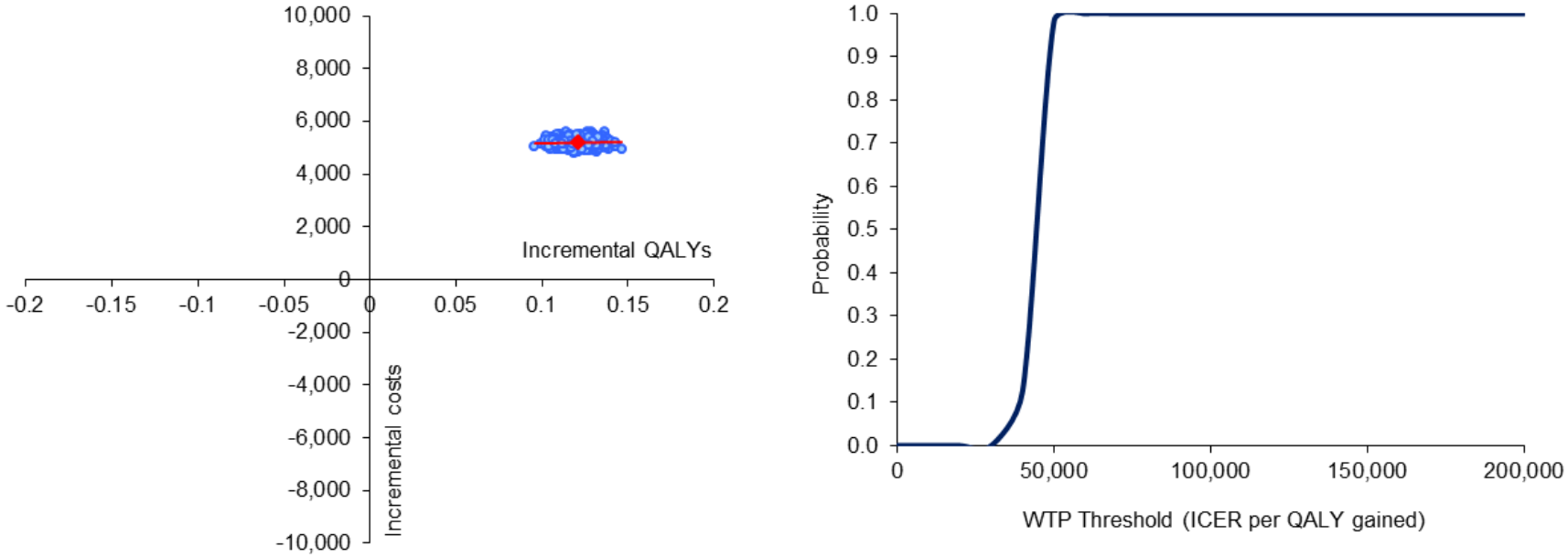
Eribulin vs. TPC

Table 80: PSA results for eribulin versus TPC - per mg analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£29,303	0.564111669			
Eribulin	£34,595	0.684830674	£5,292	0.120719005	£43,836

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 42: Cost effectiveness plane and CEAC of eribulin vs. TPC - per mg analysis



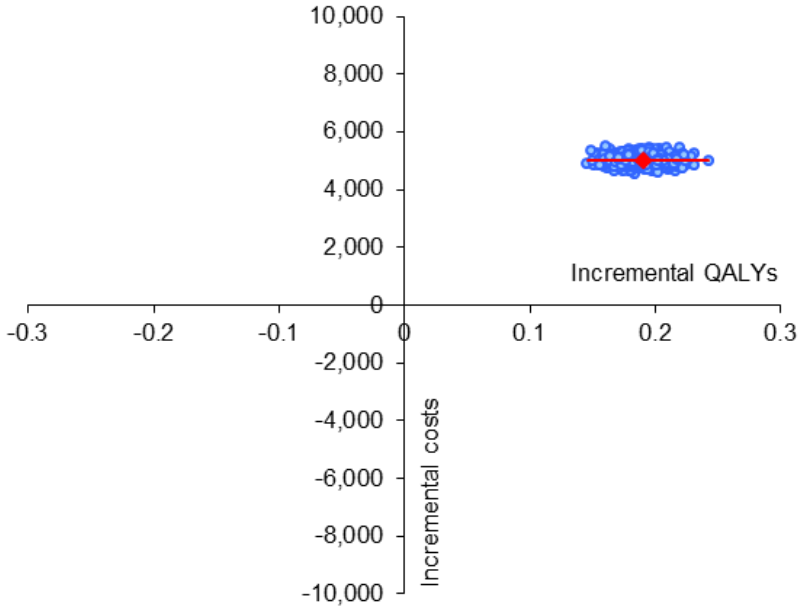
Eribulin vs. gemcitabine

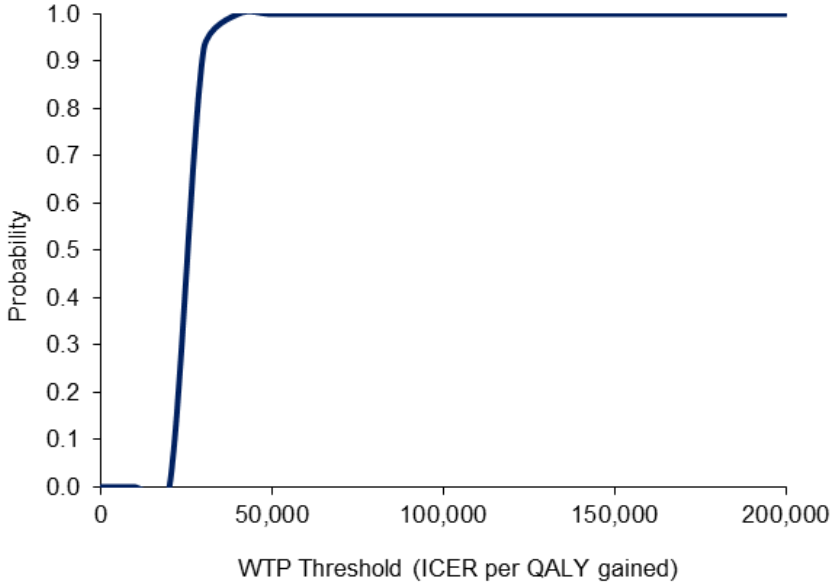
Table 81: PSA results for eribulin versus gemcitabine - per mg analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£28,766	0.497992087			
Eribulin	£33,766	0.688361669	£5,000	0.190369582	£26,267

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 43: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine - per mg analysis





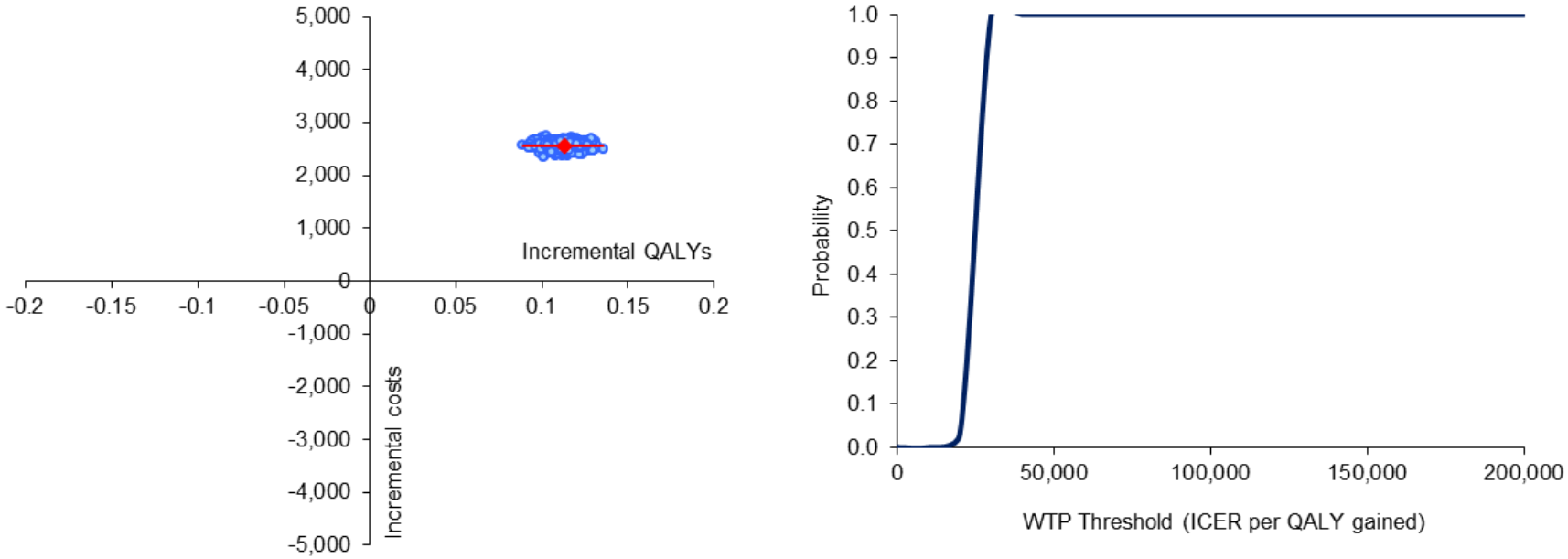
Eribulin vs. vinorelbine

Table 82: PSA results for eribulin versus vinorelbine - per mg analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£30,162	0.514668446			
Eribulin	£32,695	0.627895287	£2,533	0.113226841	£22,369

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 44: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine - per mg analysis



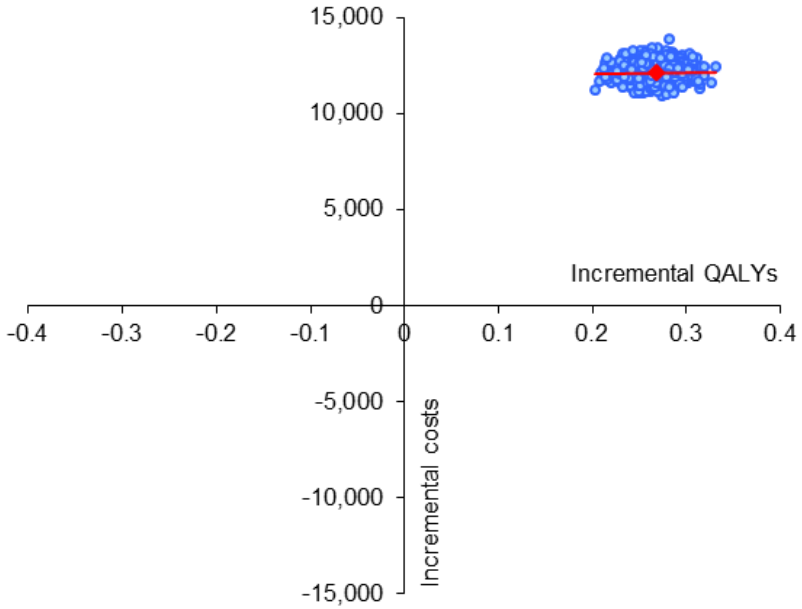
Eribulin vs. capecitabine

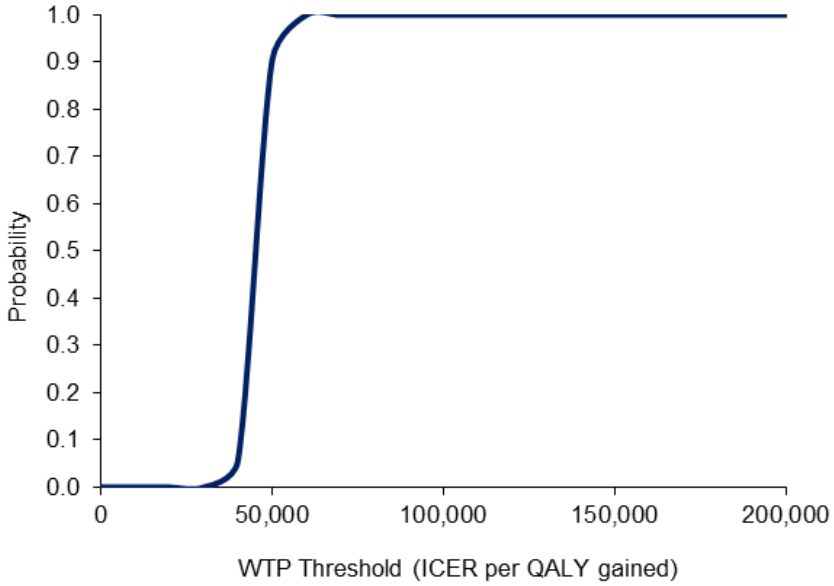
Table 83: PSA results for eribulin versus capecitabine - per mg analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£25,226	0.52			
Eribulin	£37,320	0.79	£12,094	0.27	£45,035

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 45: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine - per mg analysis





Scenario analysis 3: Drug costs – IV vinorelbine price

In addition, the cost of vinorelbine was uncertain in the model as some centres use the IV formulation and others use the oral formulation. As these formulations have substantially different prices, an analysis was carried out using the IV cost of vinorelbine to show the effect of this uncertainty on the cost effectiveness results. Only the TPC and vinorelbine comparisons will be affected by this change in the model, therefore only these comparisons are presented. Probabilistic results are also presented.

Table 84: Vinorelbine IV price analysis results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£29,678	0.567408			
Eribulin	£36,035	0.688718	£6,357	0.121309	£52,407

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; IV, intravenous

Table 85: Vinorelbine IV price analysis results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£27,801	0.5155			
Eribulin	£34,024	0.6291	£6,223	0.1136	£54,817

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; IV, intravenous

Scenario analysis 2: Drug costs – vinorelbine IV price – PSA results

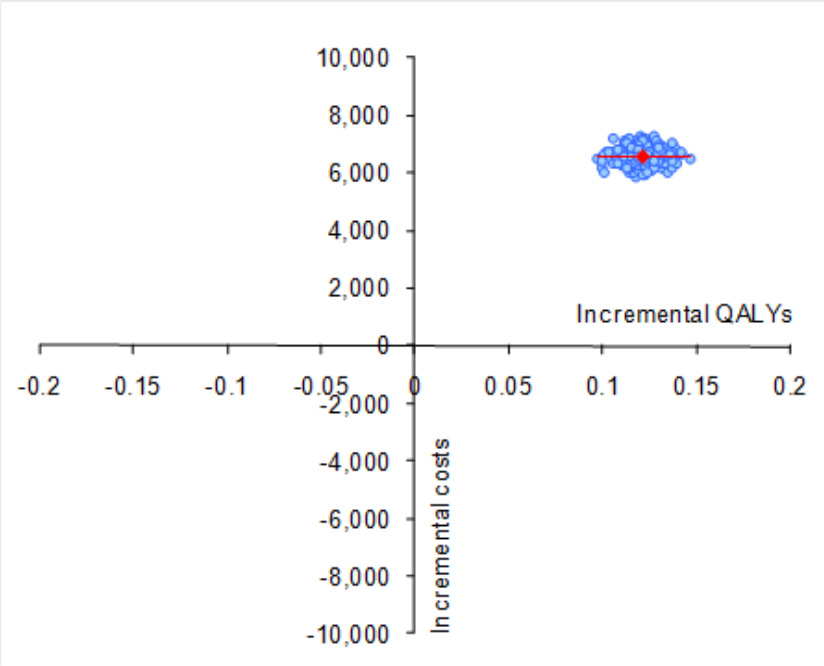
Eribulin vs. TPC

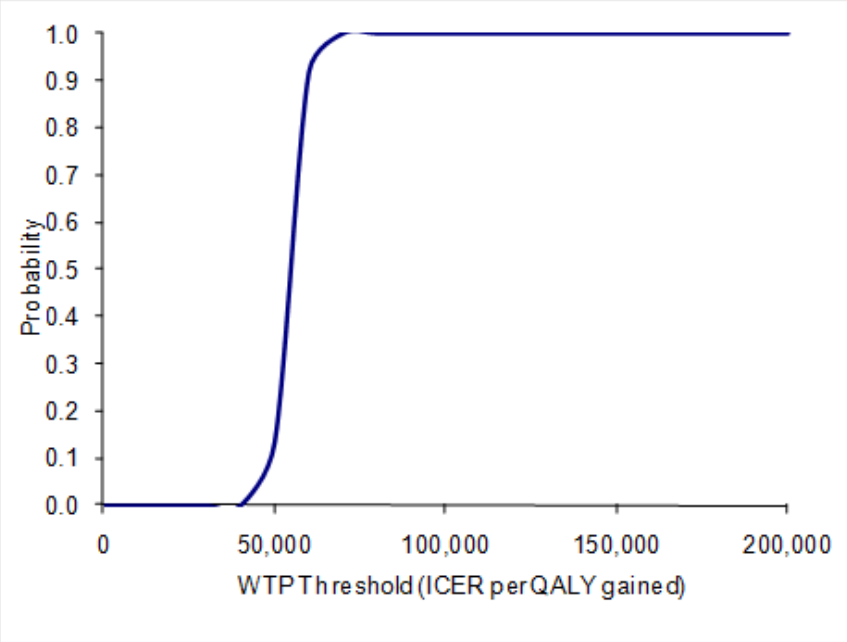
Table 86: PSA results for eribulin versus TPC – vinorelbine IV price

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£29,400	0.568456863			
Eribulin	£35,908	0.689938549	£6,508	0.121481685	£53,574

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; IV, intravenous

Figure 46: Cost effectiveness plane and CEAC of eribulin vs. TPC - vinorelbine IV price





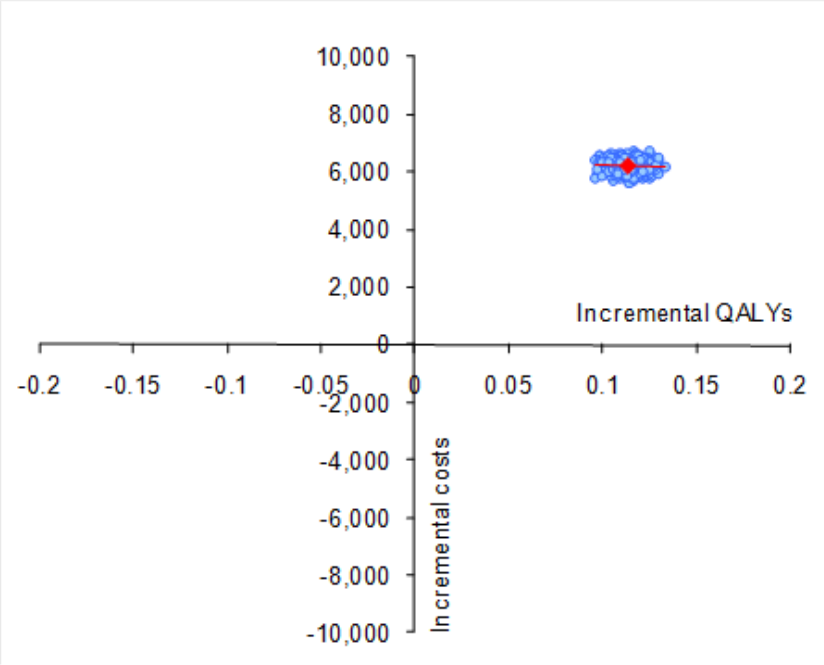
Eribulin vs. vinorelbine

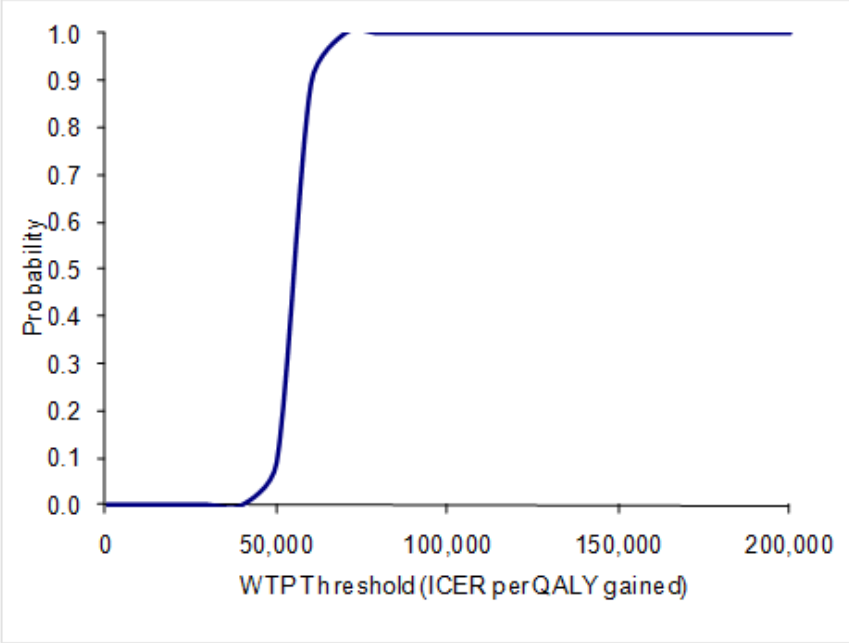
Table 87: PSA results for eribulin versus vinorelbine - vinorelbine IV price

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£27,745	0.5142			
Eribulin	£33,967	0.627593975	£6,222	0.113359453	£54,890

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; IV, intravenous

Figure 47: Cost effectiveness plane and CEAC of eribulin vs. vinorelbine - vinorelbine IV price





Scenario analysis 4: all regions

A scenario analysis was carried out to examine the cost effectiveness of eribulin versus TPC when using data for all regions in the clinical trial. Probabilistic results are also presented.

Table 88: All regions analysis results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£32,095	0.6018			
Eribulin	£36,670	0.6932	£4,575	0.0914	£50,059

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 89: All regions analysis results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£32,437	0.5411			
Eribulin	£36,313	0.6888	£3,877	0.1477	£26,242

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 90: All regions analysis results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£31,258	0.5392			
Eribulin	£34,417	0.6158	£3,159	0.0766	£41,276

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 91: All regions analysis results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£29,199	0.6634			
Eribulin	£38,226	0.7614	£9,028	0.0980	£92,084

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario analysis 4: all regions – PSA results

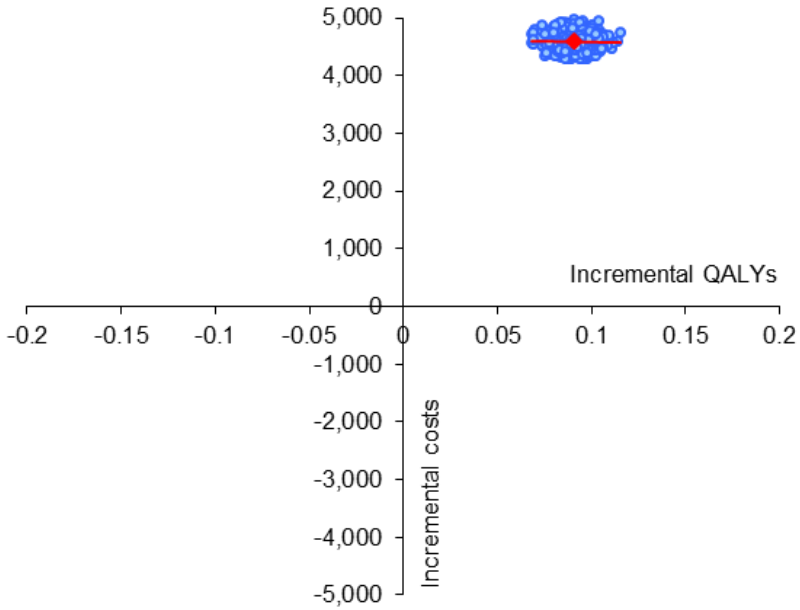
Eribulin vs. TPC

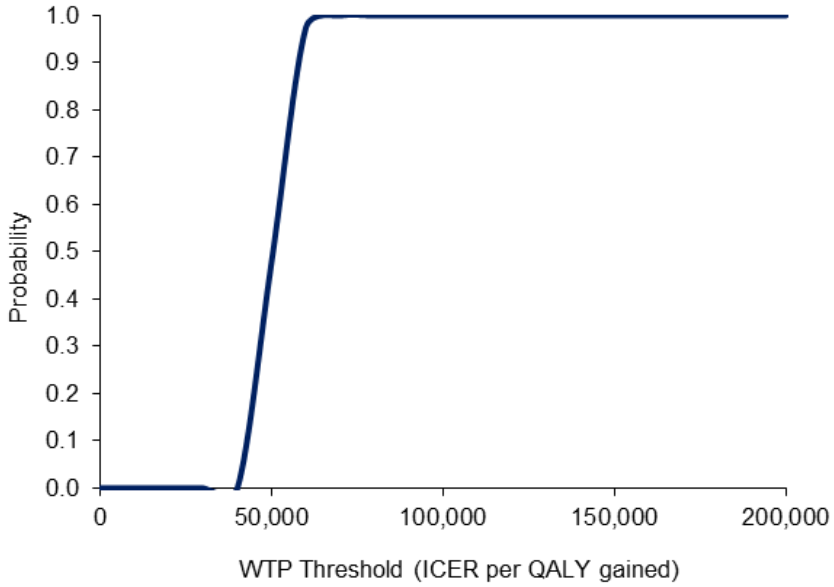
Table 92: PSA results for eribulin versus TPC - all regions analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£32,164	0.6015			
Eribulin	£36,599	0.6928	£4,583	0.0913	£50,245

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 48: Cost effectiveness plane and CEAC of eribulin vs. TPC - all regions analysis





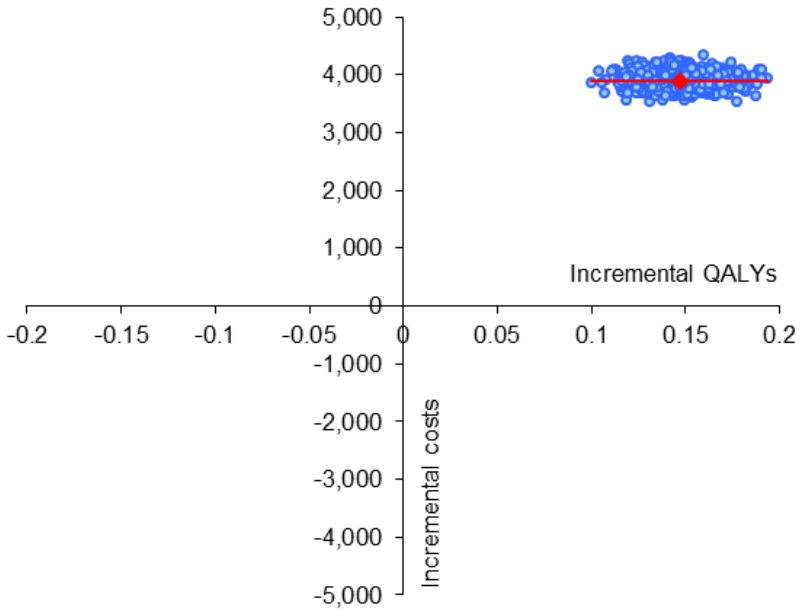
Eribulin vs. gemcitabine

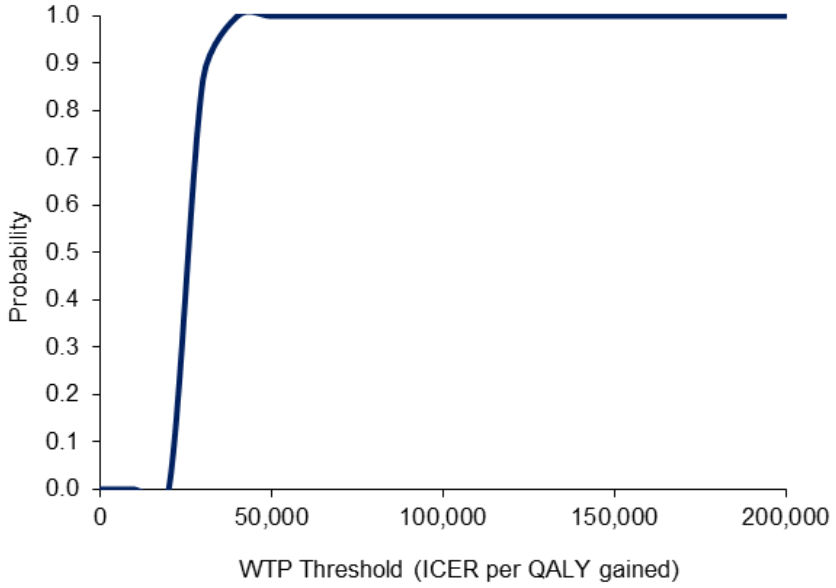
Table 93: PSA results for eribulin versus gemcitabine - all regions analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£32,542	0.536341792			
Eribulin	£36,403	0.683732292	£3,861	0.1473905	£26,194

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 49: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine - all regions analysis





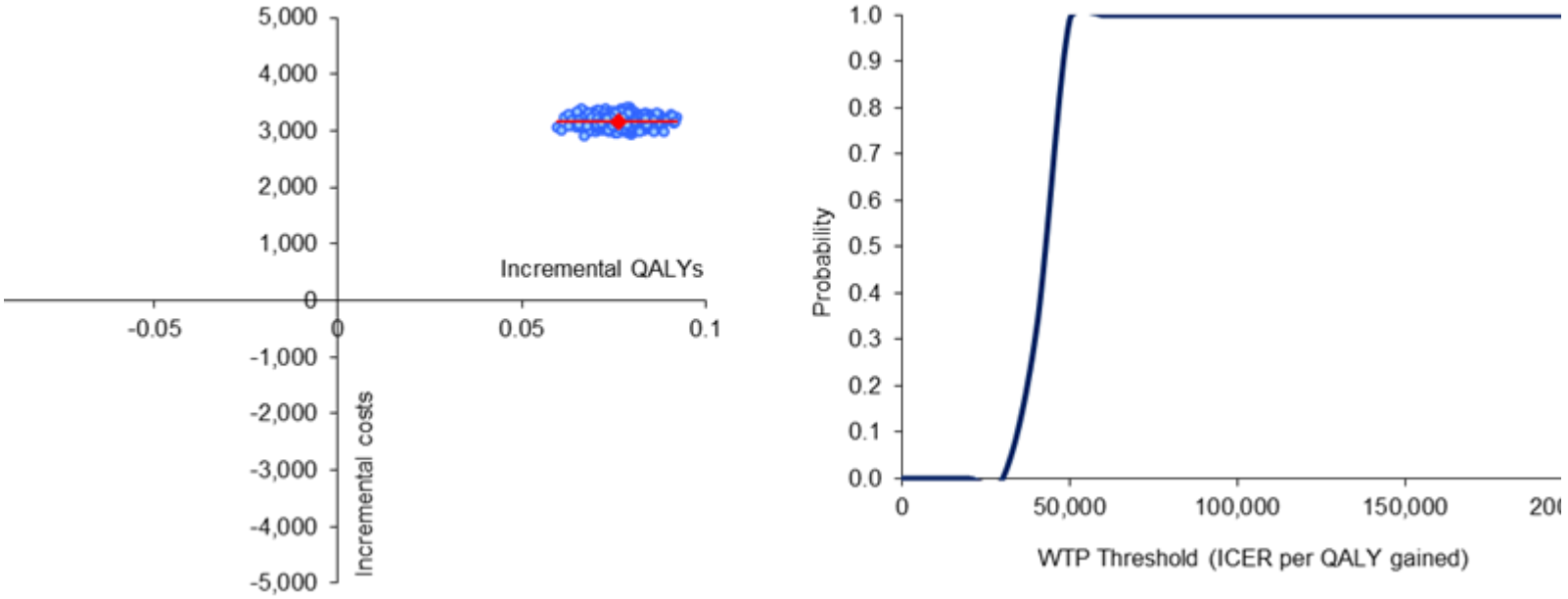
Eribulin vs. vinorelbine

Table 94: PSA results for eribulin versus vinorelbine - all regions analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£31,274	0.5365			
Eribulin	£34,450	0.6127	£3,177	0.076	£41,542

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 50: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine - - all regions analysis



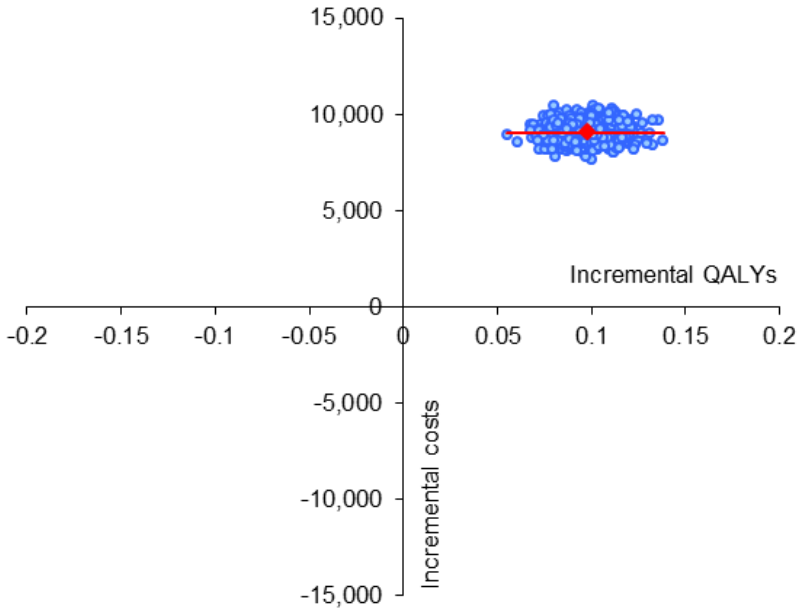
Eribulin vs. capecitabine

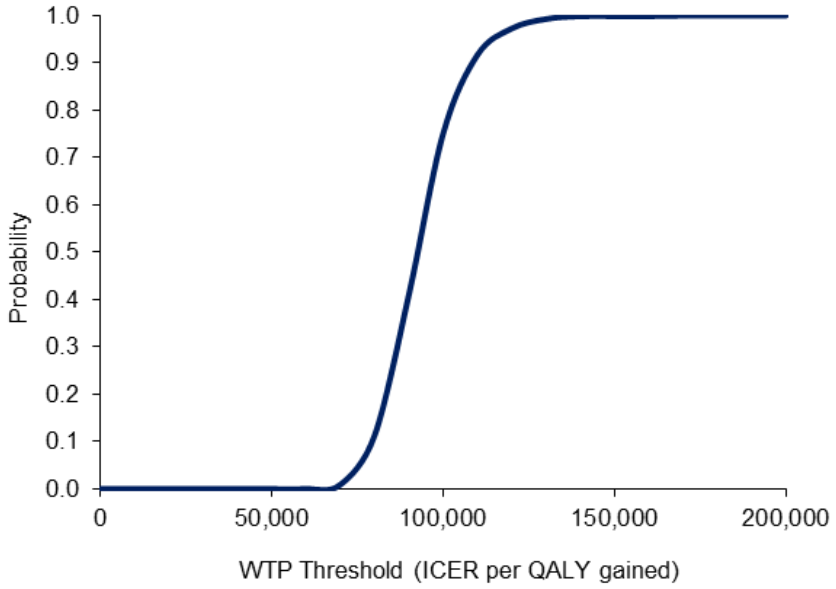
Table 95: PSA results for eribulin versus capecitabine - all regions analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£29,271	0.648			
Eribulin	£38,301	0.7627	£9,029	0.0978	£91,402

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 51: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine - all regions analysis





Structural sensitivity analysis

A structural sensitivity analysis was carried out by using hazard ratios calculated from the clinical trial to estimate the survival of patients in each of the treatment arms instead of using Kaplan Meier curves. The results of this analysis are shown here.

To demonstrate how the HR model predicts the trial results tables showing the median PFS and OS in days and the PFS and OS rate for specific time periods has been reported in Table 96 to Table 98. In general, this analysis shows that the Kaplan Meier curves present a better estimate of the outcomes from the clinical trial.

Table 96: HR analysis - summary of model results compared with clinical data for eribulin and TPC

Outcome	Clinical trial result		Model result		Difference[†]	
	Eribulin	TPC	Eribulin	TPC	Eribulin	TPC
Median PFS (days)	99	65	78	73	-20.74%	11.71%
PFS rate (proportion)						
3 months	0.536	0.406	0.447	0.406	-16.69%	0.00%
6 months	0.242	0.243	0.272	0.230	12.16%	-5.51%
9 months	0.113	0.042	0.053	0.037	-53.00%	-13.09%
12 months	0.083	0.021	0.023	0.014	-72.38%	-34.42%
Median OS (days)	401	307	335	303	-16.44%	-1.29%
OS rate (proportion)						
12 months	0.543	0.395	0.480	0.395	-11.72%	0.00%
24 months	0.229	0.191	0.260	0.183	13.53%	-4.37%

Abbreviations: OS, Overall survival; PFS, Progression free survival; TPC, Treatment of Physician's Choice.
[†]The difference is calculated as: (model value – EMBRACE value) / (EMBRACE value).

Table 100: HR analysis - summary of model results compared with clinical data for eribulin and gemcitabine

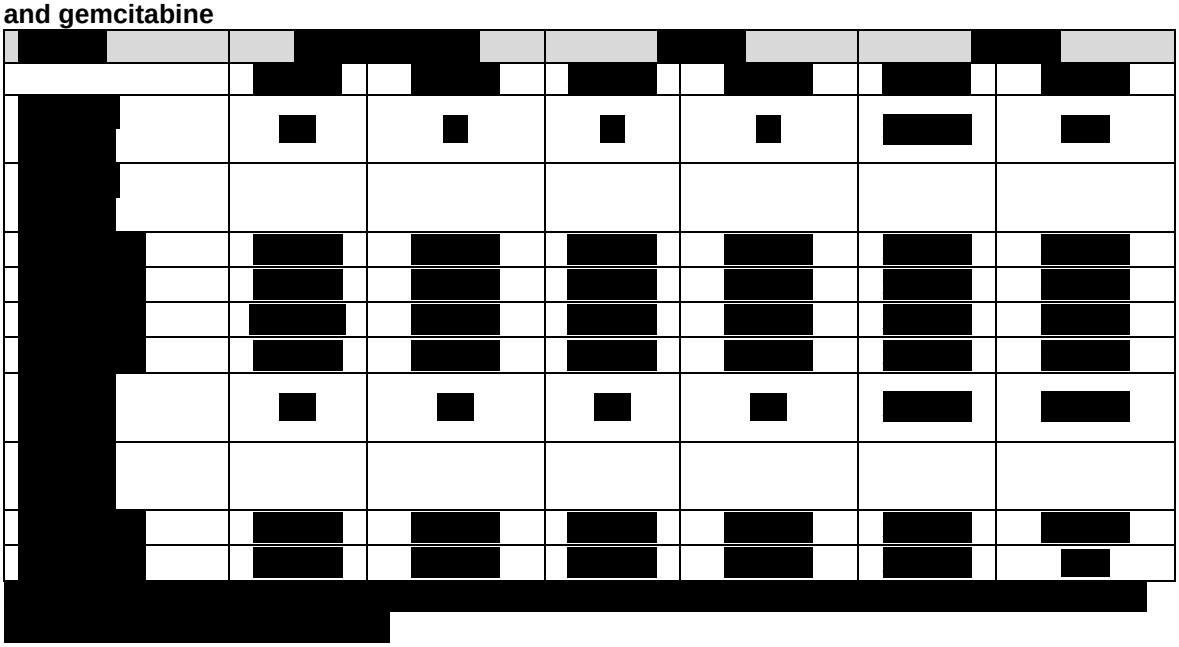


Table 97: HR analysis - summary of model results compared with clinical data for eribulin and vinorelbine

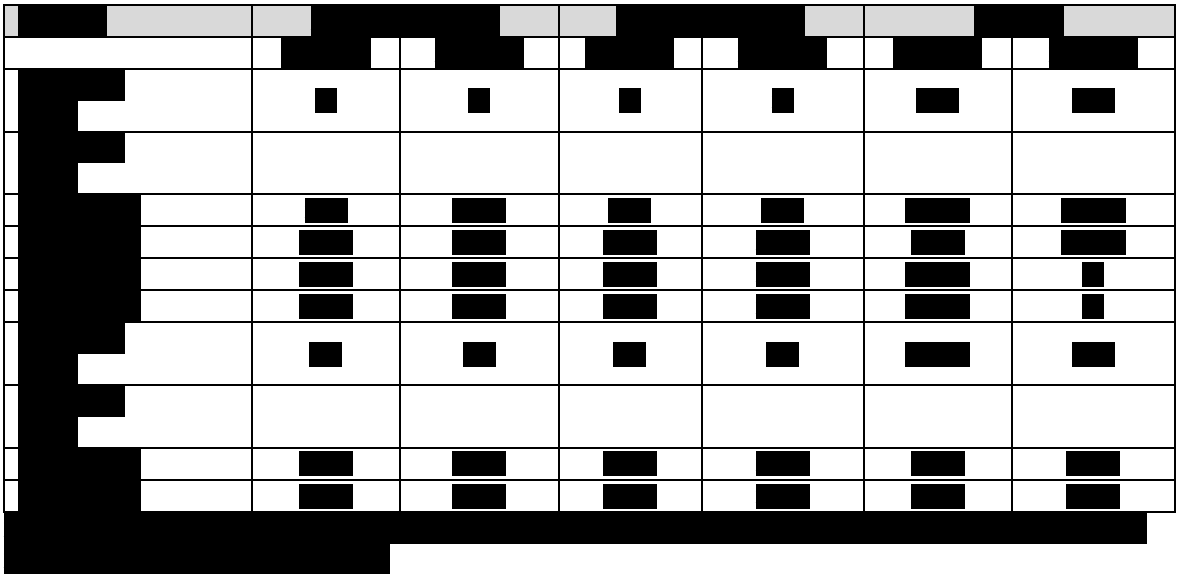
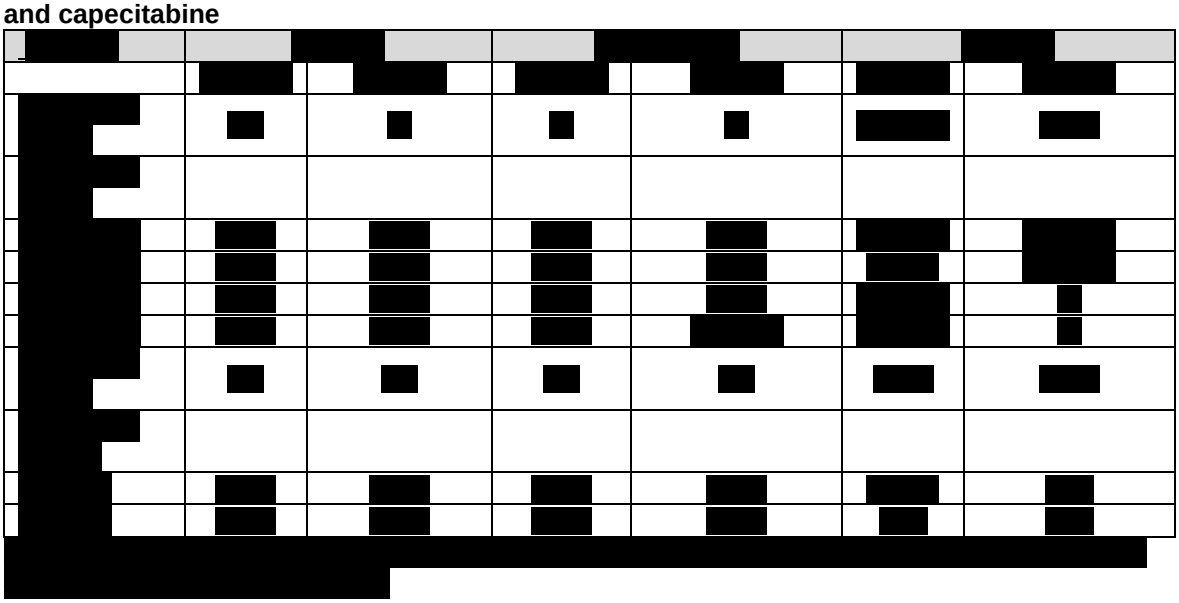


Table 98: HR analysis - summary of model results compared with clinical data for eribulin and capecitabine



The cost effectiveness results for each of the comparisons using HRs rather than Kaplan Meier curves to estimate the OS and PFS in the model is shown in Table 99 to Table 102. Probabilistic results are also presented.

Table 99: HR analysis results for eribulin versus TPC

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£34,303	0.6475	£3,854	0.0801	£48,110

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 100: HR analysis results for eribulin versus gemcitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£34,631	0.6181	£4,479	0.1201	£37,292

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 101: HR analysis results for eribulin versus vinorelbine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£33,958	0.688	£3,976	0.1729	£22,996

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 102: HR analysis results for eribulin versus capecitabine

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£37,548	0.8207	£10,782	0.3037	£35,493

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

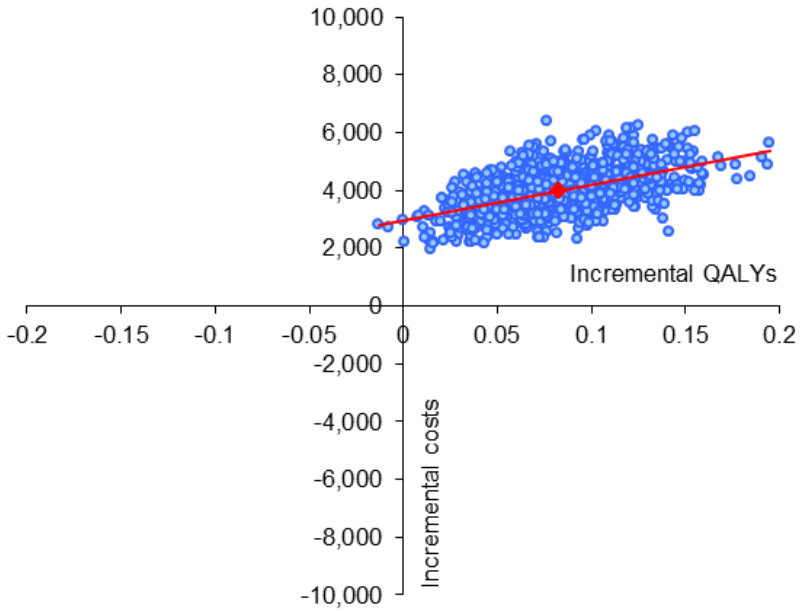
Structural sensitivity analysis – PSA results

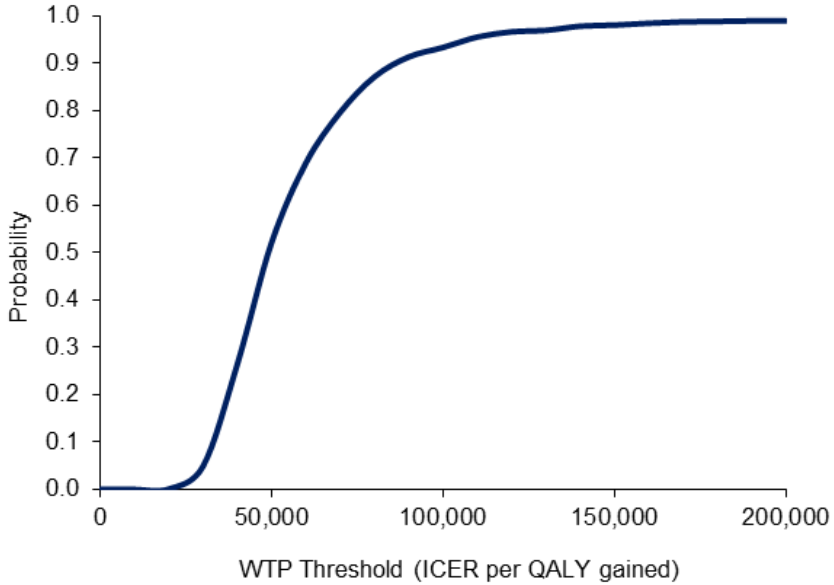
Table 103: PSA results for eribulin versus TPC – HR analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,406	0.5658			
Eribulin	£34,296	0.6467	£3,891	0.0808	£48,101

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 52: Cost effectiveness plane and CEAC of eribulin vs. TPC – HR analysis





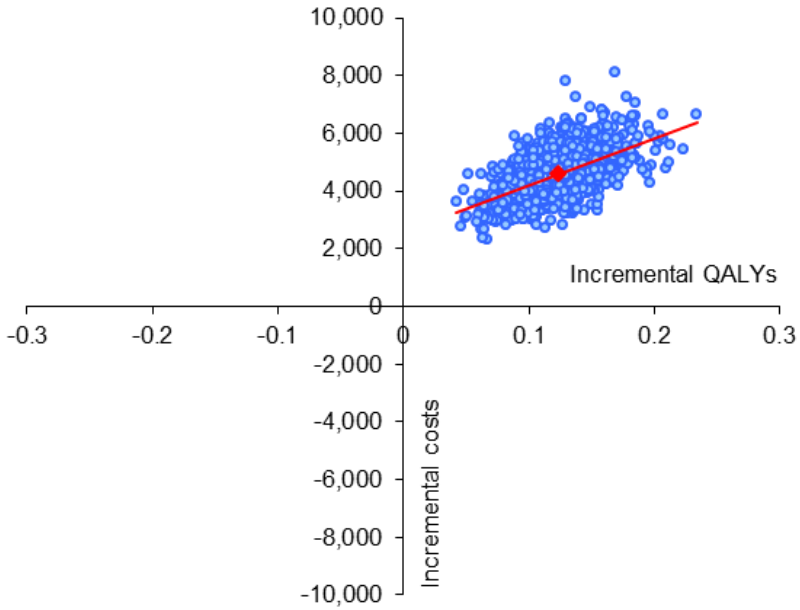
Eribulin vs. gemcitabine

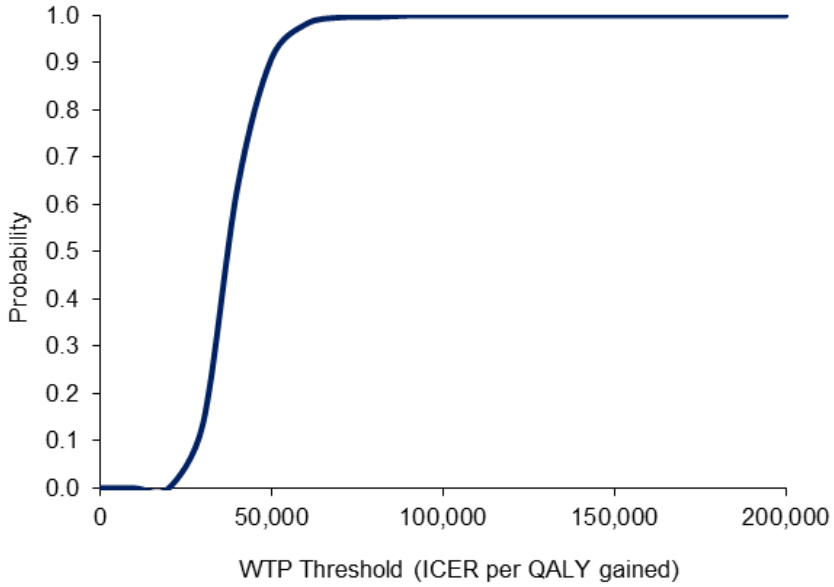
Table 104: PSA results for eribulin versus gemcitabine – HR analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,218	0.4967			
Eribulin	£34,812	0.6227	£4,594	0.1260	£36,456

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 53: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine – HR analysis





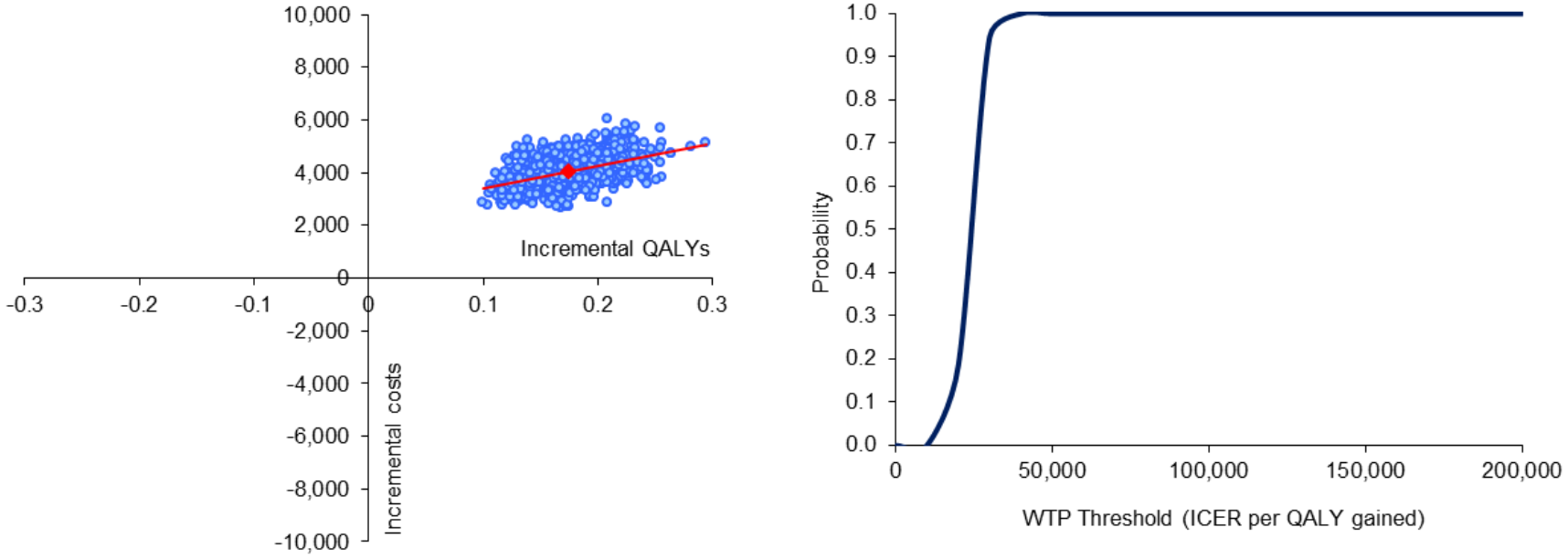
Eribulin vs. vinorelbine

Table 105: PSA results for eribulin versus vinorelbine – HR analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,928	0.5240			
Eribulin	£33,947	0.7038	£4,019	0.1797	£22,360

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 54: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine – HR analysis



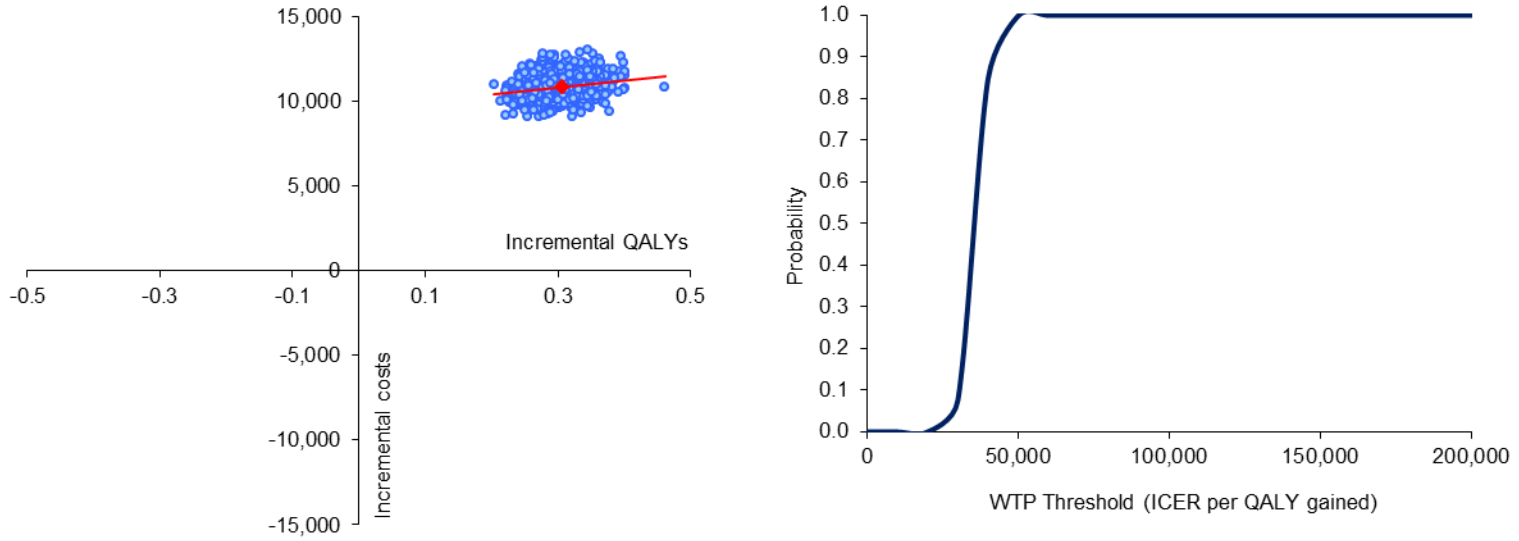
Eribulin vs. capecitabine

Table 106: PSA results for eribulin versus capecitabine – HR analysis

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,952	0.523687268			
Eribulin	£37,722	0.830125307	£10,770	0.306438039	£35,145

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 55: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine – HR analysis



6.7.10 Summary of main findings from sensitivity analysis

Base case results show that eribulin versus TPC results in a cost per QALY of £46,050. For the comparators outlined in the NICE scope, the cost per QALY ranges from £27,183to £47,631. PSA demonstrates a low level of uncertainty around the base case results.

The application of end-of-life guidance reduces the ICER substantially to £26,589compared with TPC and ranges from £15,019 to £27,356 when compared with individual components of the TPC as outlined in the NICE scope.

Applying the cost per milligram for eribulin in the model (representing the practices of the most efficient centres) also reduces the ICER to £42,672 compared with TPC and to £26,330-£45,085 when compared with individual comparators.

If centres were only to use vinorelbine in its IV formulation at a higher cost than the oral formulation, the cost per QALY would increase from that demonstrated in the base case to £52,407 compared with TPC and to £54,817 compared with vinorelbine.

6.7.11 Key drivers of the cost-effectiveness results

The one-way sensitivity analysis showed the results of the model to be most sensitive to a range of parameters depending on the treatment comparison. The general trends show that drug cost, utility of the health states and the cost of the health states consistently appeared in the top ten most influential variables for the comparisons presented.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The methodlogical approach taken to modelling this cost effectiveness of Eribulin was validated by a Professor of Health Economics based at a UK University.

Validating of data inputs, such as cost of treatment for health states and choices for dosing and formulation was done by consultation with UK clinicians and commissioners of concology treatment services servies.

Basici quality control checking was conducted as follows:

- Desk checking of individual calculations, including use of Excel's 'Formula Auditing' tool to trace formulas and performing manual calculations on key parameters; and
- Testing of extreme values, which involve entering 'unlikely' low or high values into each input field to check for any potential errors or inaccuracies

QC checks were also performed along the project lifecycle. These were performed independently by modelers: (1) one modeler from the project team who has been directly involved with programming the model and (2) a second modeler who is not on the project team and who has not been exposed to the model and (3) a third modeler for suitability of model for NICE submission. This ensures a more balanced review process. If the quality assurance check revealed formula errors or inaccuracies with the model, we made the necessary corrections, followed by a second quality assurance check.

Below is the QC check list, all of which were performed:

QC Check List

Functionality
Check that navigation buttons work
Check that worksheet is locked and protected in the appropriate areas
Custom cells are unlocked and functioning
Check that all drop down boxes work and contain the correct variables
Test extreme low and high values to check for calculation errors
Check that custom cells can be restored properly
Confirmed that all screens are formatted for printing

Clarity
Confirm that overview screen effectively describes model
Check model assumptions

Accurracy
Check that input parameters have been verified by source documentation
Verify all equations using the formula auditing tool (trace dependents of inputs, trace precedents of results)
Ensure that named ranges and "look ups" have valid and accurate cell

references
Check that proportions and probabilities sum to 1 where appropriate and are between 0 and 1
Check calculations (e.g. dosing, costs, ICERs, etc.)
Check that results reflect what is expected (e.g. if costs increase for intervention then ICER should decrease, etc)
Check results for sensitivity analyses

Consistency
All worksheets are formatted for printing
Naming conventions are consistent across worksheets
Check consistency of outputs (e.g. graphs are consistent with tabled results)
Check spelling and grammar
Consistent use of fonts, colors, and logos
Check that all abbreviations are footnoted

Validity
Benchmark model outputs against published estimates (e.g. costs, survival, ICERs, etc.)
Engage KOL to validate model structure, assumptions, and inputs.

Platform
Model maintains functionality and format in both Excel 2003 and 2007
Check that file properties contain appropriate information
Check that file name uses the appropriate naming convention

6.9 Subgroup analysis

6.9.1 Rationale for subgroup analysis

N/A

6.9.2 Subgroup patient characteristics

N/A

6.9.3 Please describe how the statistical analysis was undertaken.

N/A

6.9.4 Results of subgroup analyses

N/A

6.9.5 Relevant subgroups not considered

N/A

6.10 Interpretation of economic evidence

6.10.1 Comparison with published economic literature

Only one study was identified that assessed the cost effectiveness of treatment for third line MBC in the literature review (Section 6.1). This study did not include eribulin as a comparator therefore the results of the cost effectiveness analysis provided in this submission cannot be compared to the published literature.

6.10.2 Relevance of the economic evaluation to all patient groups

The model uses data directly from the clinical trial which was specifically designed to represent patients in whom eribulin is indicated. The model results are therefore directly applicable to the patient group outlined in the decision problem.

6.10.3 Strengths and weaknesses of the evaluation

Model Strengths

The model directly reflects the treatment pathway by using the trial results of a pragmatic and good quality RCT containing all the relevant comparators given in clinical practice. The model specifically uses trial data that represents patients in the UK and the treatments they are most likely to receive.

The model incorporates the benefit of the treatment to patients in terms of quantity and quality of life and also appropriately takes into account the potential affect on quality of life of adverse events.

The model enables a sensitivity analysis to the estimation of transition probabilities using either hazard ratios applied proportionally to the comparator Kaplan meier curve or the two Kaplan Meier curves from each treatment group.

The model appropriately assigned non-drug costs to the each health state, reflecting a closer approximation of the real world setting.

Model limitations

The model uses data from EMBRACE to estimate the PFS and OS inputs for each of the comparators. These are calculated from the underlying KM estimates, which in turn are calculated from the patient-level data. There is a slight difference in the PFS and OS data used as model inputs compared with the OS and PFS data reported directly from the clinical trial. This minor limitation could be caused by a number of issues, the most likely being that the clinical study report may average survival over the observation period unit (1 day) to calculate the KM curves, whereas the model uses the survival value at the beginning of the cycle due to the short observation period unit. This limitation is likely to have a very minor effect as the differences between the trial report and model inputs was very small (1-2 days).

There is uncertainty regarding the extrapolation of outcomes beyond trial follow-up due to lack of long-term observational data. Therefore the model employs the conservative assumption of no treatment benefit following the end of trial follow-up.

The model relied on clinical expert opinion to define resource use for each health state. Published literature was either out-of-date or not relevant to the U.K. population. Additional resource use data

Utilities were obtained from the literature, rather than being trial based.

Applying the hazard ratio to the Kaplan Meier curve of the comparator group assumes the proportionality constant is independent of time.

No patients are assumed to die as a result of anything other than breast cancer as a result of progression. This is a simplifying assumption which is unlikely to change the overall results of the model.

6.10.4 Further analyses

Extensive sensitivity analyses have been presented in this submission.

Further analyses combining the scenarios outlined in Section 6.7.9 could be performed and will be made available on request, for example a scenario using both end-of-life criteria and the HR methods for efficacy inputs could be presented.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Table 107 outlines the number of patient eligible for treatment with eribulin. The patient population is determined as follows:

- Around 42,600 people were newly diagnosed with breast cancer in England and Wales during 2008 (4).
- It is estimated that 5% (n=2,130) of patients initially presenting with breast cancer will be diagnosed with LABC/MBC (8).
- In addition, around 35% (n=14,165) of those with a primary diagnosis of breast cancer at an earlier stage, will develop metastases in the future (8) (42,600 - 2,130 x 35%), equating to a total of 16,295 (14,165 + 2,130) patients with LABC/MBC.
- Based on the indication, eribulin monotherapy will be given to patients with LABC or MBC who have progressed after at least two chemotherapeutic regimens for advanced disease. Assuming that all patients receive active treatment (e.g. chemotherapy, biologic therapy, hormonal therapy), it is estimated that 61.8% (n=10,070) of these will receive first-line chemotherapy for LABC/MABC (16,295 x 61.8%) (20).
- Of those treated with chemotherapy at first-line, around 16.8% will go on to receive chemotherapy at third-line or later (20), equating to 1,692 patients who would be eligible for treatment with eribulin (10,070 x 16.8%).
- There is currently no cure for LABC/MBC and the long-term prognosis is poor. Five-year survival in those diagnosed with metastatic disease is low, around 13% (13). For the purposes of estimating eligble patients for eribulin treatment it is assumed that the mortality rate and those newly diagnosed with breast cancer is equivalent.

Table 107: Estimation of patients eligible for treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Newly diagnosed with breast cancer	42,600	42,600	42,600	42,600	42,600
Newly diagnosed initially presenting with LABC/MBC	2,130	2,130	2,130	2,130	2,130
Newly diagnosed with early stage breast cancer	40,470	40,470	40,470	40,470	40,470

	Year 1	Year 2	Year 3	Year 4	Year 5
People with primary diagnosis of early breast cancer who develop LABC/MABC	14,165	14,165	14,165	14,165	14,165
Net population with LABC/MBC	16,295	16,295	16,295	16,295	16,295
Net population receiving first-line chemotherapy for LABC/MBC	10,070	10,070	10,070	10,070	10,070
Net population receiving chemotherapy at third-line or later and therefore eligible for eribulin treatment	1,692	1,692	1,692	1,692	1,692

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

The budget impact of eribulin use over the next 5 years has been calculated based on the expected market share of eribulin and the eribulin cost per year. The cost of eribulin per year is calculated as follows:

- Cost per vial = [redacted]
- Cost per cycle = [redacted] (based on 3 vials per dose, and 2 doses per cycle)
- Cost per year = [redacted] (based on an average of 5 cycles in the EMBRACE trial)

These estimates are a potential over estimate of the cost of eribulin since some patients will be given lower doses.

7.3 What assumption(s) were made about market share (when relevant)?

The market uptake for eribulin is assumed to be 10% each year (cumulative 50% at year 5). Table 108 outlines the cumulative market uptake of eribulin over the next 5 years, based on the number of eligible patients presented in Table 107. This assumes a positive recommendation for eribulin use at third-line, consistent with it's licensed indication (following disease progression after at least two chemotherapeutic regimens for advanced disease).

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

No other significant costs are associated with treatment.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

No unit costs were assumed other than the drug costs outlined in Section 7.2.

7.6 Were there any estimates of resource savings? If so, what were they?

No, the budget impact presented here represents drug costs only.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 108: Budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Cumulative uptake	10%	20%	30%	40%	50%
Cumulative patients treated with eribulin	169	338	508	677	846
Cumulative net cost	xxxx	xxxx	xxxx	xxxxx	xxxxx

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Eribulin is provided as a ready to use solution, avoiding the need for reconstitution or dilution associated with many IV chemotherapeutic agents. The majority of chemotherapy regimens require IV administration and vary in their infusion times. Eribulin may be administered as a quick and convenient 2-5 minute IV infusion with no special handling or tubing required. Therefore, it is likely that additional resource savings will be generated, compared with some chemotherapeutic agents, through the reduction in staff administration time.

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9 Appendices

9.1 Appendix 1: Eribulin, Summary of Product Characteristics.

1. NAME OF THE MEDICINAL PRODUCT

HALAVEN 0.44 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 0.44 mg of eribulin (as mesylate)
Each 2 ml vial contains 0.88 mg of eribulin (as mesylate)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Solution for injection.

Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HALAVEN monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

4.2 Posology and method of administration

HALAVEN should be administered in units specialised in the administration of cytotoxic chemotherapy and only under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products.

Posology

The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesylate) which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.

Patients may experience nausea or vomiting. Antiemetic prophylaxis including corticosteroids should be considered.

Dose delays during therapy

The administration of HALAVEN should be delayed on Day 1 or Day 8 for any of the following:

- Absolute neutrophil count (ANC) < 1 x 10^9/l
- Platelets < 75 x 10^9/l
- Grade 3 or 4 non-hematological toxicities.

Dose reduction during therapy

Dose reduction recommendations for retreatment are shown in the following table.

Dose reduction recommendations

Adverse reaction after previous HALAVEN administration	**Recommended dose**
Haematological:	
ANC < 0.5 x 10^9/l lasting more than 7 days	0.97 mg/m^2
ANC < 1 x 10^9/l neutropenia complicated by fever or infection	
Platelets < 25 x 10^9/l thrombocytopenia	
Platelets < 50 x 10^9/l thrombocytopenia complicated by haemorrhage or requiring blood or platelet transfusion	
Non-haematological:	
Any Grade 3 or 4 in the previous cycle	
Reoccurrence of any haematological or non-haematological adverse reactions as specified above	
Despite reduction to 0.97 mg/m^2	0.62 mg/m^2
Despite reduction to 0.62 mg/m^2	Consider discontinuation

Do not re-escalate the eribulin dose after it has been reduced.

Patients with hepatic impairment

Impaired liver function due to metastases:
The recommended dose of eribulin in patients with mild hepatic impairment (Child-Pugh A) is 0.97 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of eribulin in patients with moderate hepatic impairment (Child-Pugh B) is 0.62 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.
Severe hepatic impairment (Child-Pugh C) has not been studied but it is expected that a more marked dose reduction is needed if eribulin is used in these patients.

Impaired liver function due to cirrhosis:
This patient group has not been studied. The doses above may be used in mild and moderate impairment but close monitoring is advised as the doses may need readjustment.

Patients with renal impairment

Patients with severely impaired renal function (creatinine clearance <40 ml/min) may need a reduction of the dose (See section 5.2). The optimal dose for this patient groups remains to be established. Caution and close safety monitoring as advised. No specific dose adjustments are recommended for patients with mild to moderate renal impairment.

Elderly patients

No specific dose adjustments are recommended based on the age of the patient (see section 4.8).

Paediatric patients

There is no relevant use of HALAVEN in children and adolescents in the indication of breast cancer.

Method of administration

The dose may be diluted in up to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. It should not be diluted in glucose 5% infusion solution. For instructions on the dilution of the medicinal product before administration, see section 6.6. Good peripheral venous access, or a patent central line, should be ensured prior to administration. There is no evidence that eribulin mesylate is a vesicant or an irritant. In the event of extravasation, treatment should be symptomatic. For information relevant to the handling of cytotoxic drugs see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Breast feeding

4.4 Special warnings and precautions for use

Haematology

Myelosuppression is dose dependent and primarily manifested as neutropenia (section 4.8). Monitoring of complete blood counts should be performed on all patients prior to each dose of eribulin. Treatment with eribulin should only be initiated in patients with ANC values ≥ 1.5 x 10^9/l and platelets > 100 x 10^9/l.

Febrile neutropenia occurred in < 5% of breast cancer patients treated with eribulin. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, should be treated according to the recommendations in section 4.2.

Patients with ALT or AST >3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines (see section 5.1).

Peripheral neuropathy

Patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of dose (see section 4.2)

In clinical trials, patients with pre-existing neuropathy greater than Grade 2 were excluded. However, patients with pre-existing neuropathy Grade 1 or 2 were no more likely to develop new or worsening symptoms than those who entered the study without the condition.

QT prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Hypokalemia or hypomagnesemia should be corrected prior to initiating HALAVEN and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome.

Use in combination with anti-HER2 therapy

There is no experience of using eribulin in combination with anti-HER2 therapy in clinical trials.

Excipients

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

4.5 Interaction with other medicinal products and other forms of interaction

Eribulin is mainly (up to 70%) eliminated through biliary excretion. The transport protein involved in this process is unknown. Complete inhibition of the transport could in theory give rise to a more than 3-fold increase in plasma concentrations. It is not recommended to use substances which are inhibitors of hepatic transport proteins such as organic anion-transporting proteins (OATPs), P-glycoprotein (Pgp), multidrug resistant proteins (MRPs) etc concomitantly with eribulin. Inhibitors of such transporters include but are not limited to: cyclosporine, ritonavir, saquinavir, lopinavir and certain other protease inhibitors, efavirenz, emtricitabine, verapamil, clarithromycin, quinine, quinidine, disopyramide etc.

Concomitant treatment with enzyme inducing substances such as rifampicin, carbamazepine, phenytoin, St John´s wort (Hypericum perforatum) is not recommended as these drugs are likely to give rise to markedly reduced plasma concentrations of eribulin.

No drug-drug interactions are expected with CYP3A4 inhibitors unless they are potent inhibitors of Pgp. Eribulin exposure (AUC and C_{max}) was unaffected by ketoconazole, a CYP3A4 inhibitor.

Effects of eribulin on the pharmacokinetics of other drugs

Eribulin may inhibit the important drug metabolising enzyme CYP3A4. This is indicated by in vitro data and no in vivo data is available. Concomitant use with substances that are mainly metabolised by CYP3A4 should be made with caution and it is recommended that the patient is closely monitored for adverse effects due to increased plasma concentrations of the concomitantly used substance. If the substance has a narrow therapeutic range, concomitant use should be avoided.

Eribulin does not inhibit the CYP enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 at relevant clinical concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no information on the use of eribulin in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats. HALAVEN should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Women of childbearing age must be advised to avoid becoming pregnant whilst they or their male partner are receiving HALAVEN and should use effective contraception during and up to 3 months after treatment.

Breastfeeding

There is no information on the excretion of eribulin or its metabolites in human or animal breast milk. A risk to newborns or infants cannot be excluded and therefore HALAVEN must not be used during breastfeeding (see section 4.3).

Fertility

Testicular toxicity has been observed in rats and dogs (see section 5.3). Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with HALAVEN.

4.7 Effects on ability to drive and use machines

HALAVEN may cause adverse reactions such as tiredness and dizziness which may lead to a minor or moderate influence on the ability to drive or use machines. Patients should be advised not to drive or use machines if they feel tired or dizzy.

4.8 Undesirable effects

The most commonly reported adverse reactions to eribulin are shown in the table below.

The following table shows the incidence rates of adverse reactions observed in 827 breast cancer patients who received the recommended dose in two Phase 2 and one Phase 3 study. Frequency categories are defined as: very common (≥ 1/10), common

(≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Actual frequencies are shown where Grade 3 or 4 reactions occurred with a frequency of ≥ 1%.

System Organ Class	**Adverse Reactions – all Grades**		**Grade 3 and 4 Reactions ≥ 1% Frequency %**
	Very Common (Frequency %)	**Common (Frequency %)**	
Infections and infestations		Urinary tract infection Oral candidiasis Upper respiratory tract infection Nasopharyngitis Rhinitis	
Blood and lymphatic disorders	Neutropenia (54.5%) Leukopenia (22.1%) Anaemia (20.3%)	Febrile neutropenia (4.7%) Thrombocytopenia Lymphopenia	Neutropenia 48.3% Leukopenia 14% Febrile neutropenia 4.6%[a] Anaemia 1.4%
Metabolism and nutrition disorders	Decreased appetite	Hypokalaemia Hypomagnesaemia Dehydration Hyperglycaemia Hypophosphataemia	
Psychiatric disorders		Insomnia Depression	
Nervous system disorders	Peripheral neuropathy [b] (32.0%) Headache	Dysgeusia Dizziness Hypoaesthesia Lethargy Neurotoxicity	Peripheral neuropathy [b] 6.9%
Eye disorders		Lacrimation increased Conjunctivitis	
Ear and Labyrinth Disorders		Vertigo	
Cardiac disorders		Tachycardia	
Vascular disorders		Hot flush	
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough Oropharyngeal pain Epistaxis Rhinorrhoea	
Gastrointestinal disorders	Nausea (35.1%) Constipation Diarrhoea Vomiting	Abdominal pain Stomatitis Dry mouth Dyspepsia Gastrooesophageal reflux disease Mouth ulceration Abdominal distension	Nausea 1.1%[c]

System Organ Class	Adverse Reactions – all Grades		Grade 3 and 4 Reactions ≥ 1% Frequency %
	Very Common (Frequency %)	Common (Frequency %)	
Hepatobiliary disorders		Alanine aminotransferase increased (3.0%) Aspartate aminotransferase increased	Alanine aminotransferase increased 1.1%[c]
Skin and subcutaneous tissue disorders	Alopecia	Rash Pruritus Nail disorder Night sweats Palmar plantar erythrodysaesthesia Dry skin Erythema Hyperhidrosis	
Musculoskeletal and connective tissue disorders	Arthralgia and Myalgia	Pain in extremity Muscle spasms Musculoskeletal pain and Musculoskeletal chest pain Muscular weakness Bone pain Back pain	
General disorders and administration site conditions	Fatigue/Asthenia (52.8%) Pyrexia	Mucosal Inflammation (9.8%) Peripheral oedema Pain Chills Influenza like illness Chest Pain	Fatigue/Asthenia 8.4% Mucosal Inflammation 1.3%[c]
Investigations		Weight decreased	

[a] Includes 1 Grade 5
[b] Includes preferred terms of peripheral neuropathy, peripheral motor neuropathy, polyneuropathy, paraesthesia, peripheral sensory neuropathy, peripheral sensorimotor neuropathy and demyelinating polyneuropathy
[c] No Grade 4

In the same breast cancer population in clinical trials the following medically significant adverse reactions were reported as uncommon (≥ 1/1,000 to < 1/100)

Infection and infestations: Pneumonia, Neutropenic sepsis, Oral herpes, Herpes zoster
Ear and labyrinth disorders: Tinnitus
Vascular disorders: Deep vein thrombosis, pulmonary embolism
Respiratory, thoracic and mediastinal disorders: Interstitial lung disease
Hepatobiliary disorders: Hyperbilirubinaemia
Skin and subcutaneous tissue disorder: Angioedema
Renal disorders: Dysuria, Haematuria, Proteinuria, Renal failure

Selected adverse reactions

Neutropenia
The neutropenia observed was reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (< 0.5 x 10^9/l) was 8 days.
Neutrophil counts of < 0.5 x 10^9/l that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin.
Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% of breast cancer patients treated in a phase 3 study with eribulin received G-CSF.
Neutropenia resulted in discontinuation in < 1% of patients receiving eribulin.
Peripheral neuropathy
In the 827 breast cancer patients the most common adverse reaction resulting in discontinuation of treatment with eribulin was peripheral neuropathy (4%). The median time to Grade 2 peripheral neuropathy was 85 days (post 4 cycles).
Development of Grade 3 or 4 peripheral neuropathy occurred in 7% of eribulin treated breast cancer patients. In clinical trials, patients with pre-existing neuropathy were as likely to develop new or worsening symptoms as those who entered the study without the condition.
In patients with pre-existing Grade 1 or 2 peripheral neuropathy the frequency of treatment-emergent Grade 3 peripheral neuropathy was 10%.

Special populations

Elderly population
In studies of 1,222 patients treated with eribulin, 244 patients (20.0%) were > 65 - 75 years of age and 66 patients (5.4%) were > 75 years of age. Among the 827 of these patients who received the recommended dose of eribulin in the Phase 2/3 breast cancer studies, 121 patients (14.6%) were > 65 - 75 years of age and 17 patients (2.1%) were > 75 years of age. The safety profile of eribulin in elderly patients (> 65 years of age) was similar to that of patients ≤ 65 years of age. No dose adjustments are recommended for the elderly population.

Patients with hepatic impairment
Patients with ALT or AST > 3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin > 1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia (see also sections 4.2 and 5.2).

4.9 Overdose

In one case of overdose the patient inadvertently received 8.6 mg of eribulin mesylate (approximately 4 times the planned dose) and subsequently developed a hypersensitivity reaction (Grade 3) on Day 3 and neutropenia (Grade 3) on Day 7. Both adverse reactions resolved with supportive care.

There is no known antidote for eribulin overdose. In the event of an overdose, the patient should be closely monitored. Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX41

HALAVEN (eribulin mesylate) is a non-taxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G_2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

Clinical experience

The efficacy of HALAVEN in breast cancer is supported by two single-arm Phase 2 studies and a randomized Phase 3 comparative study.

The 762 patients in the pivotal Phase 3 EMBRACE study had locally recurrent or metastatic breast cancer, and had previously received at least two and a maximum of five chemotherapy regimens, including an anthracycline and a taxane (unless contraindicated). Patients must have progressed within 6 months of their last chemotherapeutic regimen. They were randomized 2:1 to receive either HALAVEN at a dose of 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesylate) on Days 1 and 8 in a 21-day cycle administered intravenously over 2 to 5 minutes, or treatment of physician's choice (TPC), defined as any single-agent chemotherapy, hormonal treatment, or biologic therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, reflecting local practice. The TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), or 3% hormonal therapy.

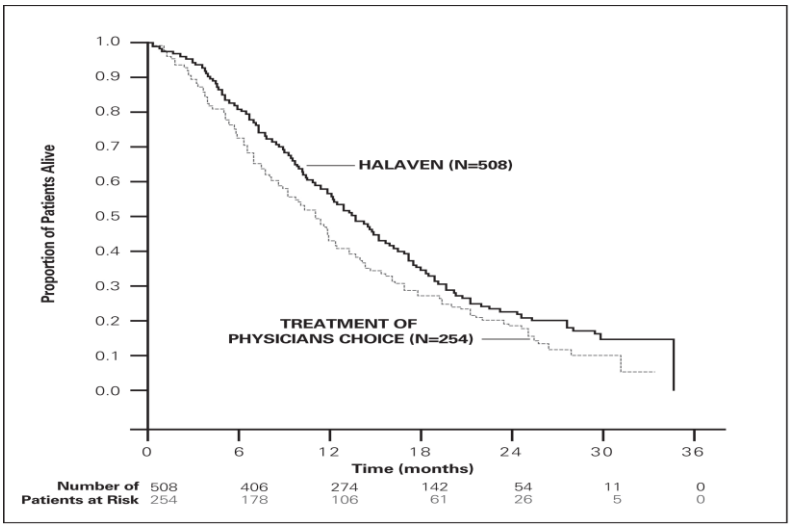
The study met its primary endpoint with an overall survival result that was statistically significantly better in the eribulin group compared to TPC at 55% of events. The median survival of the HALAVEN group (median: 399 days/13.1 months) compared with the TPC group (median: 324 days/10.6 months) improved by 75 days/2.5 months (HR 0.809, 95% CI: 0.660, 0.991, p=0.041). This result was confirmed with an updated overall survival analysis carried out at 77% of events with the median survival of the HALAVEN group (median: 403 days/13.2 months) compared with the TPC group (median: 321 days/10.5 months) improved by 82 days/2.7 months (HR 0.805, 95% CI: 0.677, 0.958, nominal p=0.014).

Efficacy of HALAVEN versus Treatment of Physician's Choice – Updated Survival Analysis in the ITT Population

Efficacy Parameter	HALAVEN (n = 508)	TPC (n = 254)
Overall Survival		
Number of Events	**386**	**203**
Median	**403 days**	**321 days**
95% CI	**(367,438)**	**(281,365**
Hazard Ratio (95% CI)[a]	**0.805**	
(Cox proportional hazards)	**(0.677, 0.958)**	
Nominal *P*-value (log-rank)[a]	**0.014**	

[a] Stratified by geographic region, HER2/neu status, and prior capecitabine therapy.

Kaplan-Meier Analysis of OS-Update Data (ITT Population)



At the time of the original cut-off, analysis of progression free survival by independent and investigator review is shown in the following table.

Efficacy of HALAVEN versus Treatment of Physician's Choice – Progression Free Survival

	HALAVEN n=508	**TPC n=254**
Independent		
Number of events	357	164
Median	113 days	68 days
(95% CI)	(101 - 118)	(63 – 103)
Hazard Ratio[a] (95% CI)	0.865 (0.714 – 1.048)	
p-value[b] (Log rank)	0.137	
Investigator		
Number of events	429	206
Median	110 days	66 days
(95% CI)	(100 - 114)	(60 – 79)
Hazard Ratio[a] (95% CI)	0.757 (0.638 – 0.900)	
p-value[b] (Log rank)	0.002	
[a] For the hazard ratio, a value less than 1.00 favours eribulin [b] Stratified by geographic region, HER2/neu status, and prior capecitabine use.		

In response evaluable patients who received HALAVEN, the objective response rate by the RECIST criteria was 12.2% (95% CI: 9.4%, 15.5%) by independent review and 13.2% (95% CI: 10.3%, 16.7%) by investigator review. The median response duration in this population by independent review was 128 days (95% CI: 116, 152 days) (4.2 months).

The positive effect on OS and PFS was seen in both taxane-refractory and non-refractory groups of patients. In the OS update, the HR for eribulin versus TPC was 0.90 (95% CI 0.71, 1.14) in favour of eribulin for taxane-refractory patients and 0.73 (95% CI 0.56, 0.96) for patients not taxane-refractory. In the Investigator assessment-based analysis of PFS (based on original data cut-off), the HR was 0.77 (95% CI 0.61, 0.97) for taxane-refractory patients and 0.76 (95% CI 0.58, 0.99) for patients not taxane-refractory.

The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The analysis of updated OS showed a survival benefit for the eribulin group compared to TPC both in capecitabine pre-treated patients with a HR of 0.787 (95% CI 0.645, 0.961), and for the capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI 0.606, 1.233). Investigator assessment-based analysis of PFS (based on original data cut-off), also showed a positive effect in the capecitabine pre-treated group with a HR of 0.68 (0.56, 0.83). For the capecitabine-naïve group the corresponding HR was 1.03 (0.73, 1.45).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with eribulin in all subsets of the paediatric population in the indication of breast cancer.

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of eribulin are characterized by a rapid distribution phase followed by a prolonged elimination phase, with a mean terminal half-life of approximately 40 h. It has a large volume of distribution (range of means 43 to 114 l/m^2).

Eribulin is weakly bound to plasma proteins. The plasma protein binding of eribulin (100-1000 ng/ml) ranged from 49% to 65% in human plasma.

Biotransformation

Unchanged eribulin was the major circulating species in plasma following administration of ^{14}C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin.

Elimination

Eribulin has a low clearance (range of means 1.16 to 2.42 l/h/m^2). No significant accumulation of eribulin is observed on weekly administration. The pharmacokinetic properties are not dose or time dependent in the range of eribulin mesylate doses of 0.25 to 4.0 mg/m^2.

Eribulin is eliminated primarily by biliary excretion. The transport protein involved in the excretion is presently unknown. Preclinical studies indicate that eribulin is transported by Pgp. However, it is unknown whether Pgp is contributing to the biliary excretion of eribulin.

After administration of ^{14}C-eribulin to patients, approximately 82% of the dose was eliminated in faeces and 9% in urine indicating that renal clearance is not a significant route of eribulin elimination.

Unchanged eribulin represented most of the total radioactivity in faeces and urine.

Hepatic impairment

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=4) hepatic impairment due to liver metastases. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 3-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 0.97 mg/m^2 to patients with mild hepatic impairment and 0.62 mg/m^2 to patients with moderate hepatic impairment resulted in a somewhat higher exposure than after a dose of 1.23 mg/m^2 to patients with normal hepatic function. HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C). There is no study in patients with hepatic impairment due to cirrhosis. See section 4.2 for dosage recommendation.

Renal impairment

A study in patients with different degrees of impaired renal function showed that the exposure of eribulin in patients with moderate renal function (creatinine clearance ≥ 40 to 59 ml/min, n=6) was similar to patients with normal renal function while the exposure in

patients with severe impairment was increased by 75% (creatinine clearance < 40 ml/min, n=4). See section 4.2 for treatment recommendations.

5.3 Preclinical safety data

Eribulin was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test). Eribulin was positive in the mouse lymphoma mutagenesis assay and was clastogenic in the *in vivo* rat micronucleus assay.

No carcinogenicity studies have been conducted with eribulin.

A fertility study was not conducted with eribulin, but based on non-clinical findings in repeated-dose studies where testicular toxicity was observed in both rats (hypocellularity of seminiferous epithelium with hypospermia/aspermia) and dogs, male fertility may be compromised by treatment with eribulin.. An embryofoetal development study in rat confirmed the developmental toxicity and teratogenic potential of eribulin mesylate. Pregnant rats were treated with 0.01, 0.03, 0.1 and 0.15 mg/kg at gestation days 8, 10 and 12. Dose related increased number of resorptions and decreased foetal weight were observed at doses ≥ 0.1 mg/kg and increased incidence of malformations (absence of lower jaw, tongue, stomach and spleen) was recorded at 0.15 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol anhydrous
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

4 years.

In-use shelf life

From a microbiological point of view unless the method of opening precludes the risk of microbial contamination the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

If not used immediately HALAVEN as the undiluted solution in a syringe should not normally be stored longer than 4 hours at 25°C and ambient lighting, or 24 hours at 2°C - 8°C.

Diluted solutions of HALAVEN (0.018 mg/ml to 0.18 mg/ml in sodium chloride 9 mg/ml (0.9%)) solution for injection should not be stored longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the opened and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml type I glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal, containing 2 ml of solution.

The pack sizes are cartons of 1 or 6 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

HALAVEN is a cytotoxic anticancer medicinal product and, as with other toxic compounds, caution should be exercised in its handling. The use of gloves, goggles, and protective clothing is recommended. If the skin comes into contact with the solution it should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. HALAVEN should only be prepared and administered by personnel appropriately trained in handling of cytotoxic agents. Pregnant staff should not handle HALAVEN.

Using aseptic technique HALAVEN can be diluted up to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection. It must not be mixed with other medicinal products and should not be diluted in glucose 5% infusion solution.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

9.2 Appendix 2: Search strategy for Section 5.1 (Identification of studies)

9.2.1 Databases searched

Studies of interest were identified by searching the following electronic databases with no restrictions on date or language of publication.

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid)
- The Cochrane Library (incorporating the Central Register of Controlled Trials, CENTRAL)

9.2.2 Date on which the search was conducted

All databases were searched on 27/08/2010.

9.2.3 Date span of the search

- Ovid MEDLINE(R) 1950 to present (27/08/2010).
- EMBASE (Ovid), 1980 to 2010 Week 33, searched on the 27/08/10.
- The Cochrane Library, to present (27/08/10).

9.2.4 Search strategy

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present (searched on 27/08/2010)

	Searches	Results
1	(eribulin or eribulin mesylate).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	22
2	halaven.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	0
3	(E7389 or E-7389 or ER086526 or ER-086526).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	22
4	halichondrin b analog*.mp.	8
5	1 or 2 or 3 or 4	35

EMBASE 1980 to 2010 Week 33 (searched on 27/08/2010)

	Searches	Results
1	eribulin mesylate.mp. or exp eribulin/	65
2	halaven.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	0
3	halichondrin b analog*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	13

4	(E7389 or E-7389 or ER086526 or ER-086526).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	89
5	1 or 2 or 3 or 4	110

Cochrane Library (searched on 27/08/2010)

ID	Search	Hits
#1	eribulin OR eribulin mesylate	1
#2	halaven	0
#3	E7389 or E-7389 or ER086526 or ER-086526	0
#4	halichondrin b analog*	0
#5	(#1 OR #2 OR #3 OR #4)	1

9.2.5 Additional searches

Additional studies were identified by hand searching the following resources:

- www.clinicaltrials.gov

Clinicaltrials.gov was searched for completed studies of eribulin/E7389 for locally advanced or metastatic breast cancer. Searched on 07/09/2010.

- Conference proceedings

ASCO annual meetings and breast cancer symposia (http://www.asco.org/ASCOv2/Meetings/Abstracts) were searched on 03/09/2010 for eribulin or E7389 in breast cancer.

All completed studies from the eribulin clinical trial programme were also assessed for inclusion, including any unpublished studies and additional information that Eisai were aware of.

9.2.6 Inclusion and exclusion criteria.

	Description	Justification
Inclusion criteria		
Population	Patients with locally advanced or metastatic breast cancer	As specified by the NICE scope
Interventions	Eribulin (or various names thereof, e.g. E7389)	Technology under appraisal
Outcomes	Overall survival, progression-free survival, response rate, adverse effects of treatment, HR-QL	As specified by the NICE scope

	Description	Justification
Study design	RCTs (Phase II-III), observational studies	RCTs prioritised as per STA guidance. Non-randomised evidence (e.g. observational data, open label clinical trials) were also identified by the search for possible inclusion.
Language restrictions	None	
Exclusion criteria		
Population	Patients with any other disease, including earlier stages of breast cancer	As specified by the NICE scope
Interventions	Other interventions used for the treatment of locally advanced or metastatic breast cancer	No further evidence for comparator treatments was sought, due to the availability of head to head data from the pivotal Phase III RCT for eribulin
Outcomes	Pharmaco-kinetic, -dynamic outcomes (bioavailability, dose ranging)	Not relevant to the decision problem
Study design	Letters, Reviews	These types of records represent lower levels of evidence and were excluded to minimise potential sources of bias.
Language restrictions	None	

9.2.7 Data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template.

9.2.8 List of excluded studies.

Listed below are all excluded records (n=107; not including duplicates of the same record).

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3. Fortman JL, Sherman DH. Utilizing the power of microbial genetics to bridge the gap between the promise and the application of marine natural products. ChemBioChem. [Review]. 2005 Jun;6 (6):960-78.
4. Jain R. Marine life: New hope for cancer drugs. Indian Journal of Cancer. [Letter]. 2009 01;46 (3):243-4.
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6. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. Nature Reviews Cancer. [Review]. 2004 Apr;4 (4):253-65.

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9.3 Appendix 3: Quality assessment of RCT(s)

Study name: EMBRACE (Study 305)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	For all patients, the agent chosen for the arm receiving TPC was first defined and confirmed by the investigator using an interactive voice response system. Patients were pre-stratified according to geographical region, HER2 status, and prior treatment with capecitabine, and then randomised in a 2:1 ratio to receive either eribulin or TPC according to a randomisation schedule.	Yes
Was the concealment of treatment allocation adequate?	Investigators and patients were not blinded to study treatment as this was an open-label study.	NA
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The two treatment groups were well matched in terms of demographic characteristics, prior chemotherapy regimens, and baseline disease and tumour characteristics (e.g. HER2 status, ER/PR status, and site of disease), with the exception of cancer staging at diagnosis.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Investigators and patients were not blinded to study treatment as this was an open-label study. However, the Eisai study team was blinded to data for the primary outcome (OS) until database lock to avoid potential bias. Independent statisticians conducted an interim analysis – after 50% of the planned deaths had been observed – and assisted with queries surrounding all death events. The primary outcome of OS is precise, being documented by the date of death and would therefore not be subject to assessment bias by unblinded investigators. An independent, blinded review of tumour scanning data was performed for outcomes of tumour response (e.g. PFS, ORR), in addition to the investigator review.	NA
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexplained differences	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes measured were presented in the CSRs.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary analysis of the primary outcome (OS) was compared between the eribulin and TPC groups in the ITT population, with patients for whom a date of death was not recorded being censored at the time of last contact. Secondary outcomes were also measured in the ITT population, with secondary analyses being performed in the PP population.	Yes

Abbreviations: CSR, Clinical study report; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; ITT, Intent-to-treat; ORR, Objective response rate; OS, Overall survival; PFS, Progression free survival; PR, Progesterone receptor; PP, Per protocol; TPC, Treatment of Physician's Choice.

9.4 Appendix 4: Search strategy for Section 5.7 (Indirect and mixed treatment comparisons)

N/A

9.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 5.7

N/A

9.6 Appendix 6: Search strategy for Section 5.8 (Non-RCT evidence)

The clinical search described in Section 5.1 and Section 9.2 was also designed to identify eligible non-RCT studies for eribulin.

9.7 Appendix 7: Quality assessment of non-RCT(s) in Section 5.8

Quality assessment based on Chambers et al, 2009 (84).

	Grade (yes/no/not clear/NA)		
Study question	**Study 201**	**Study 211**	**Study 221**
Were selection/eligibility criteria adequately reported?	Yes	Yes	Yes
Was the selected population representative of that seen in normal practice?	Yes	Yes	Yes
Was an appropriate measure of variability reported?	Yes	Yes	Yes
Was loss to follow-up reported or explained?	Yes	Yes	Yes
Were at least 90% of those included at baseline followed up?	Yes	Yes	Yes
Were patients recruited prospectively?	Yes	Yes	Yes
Were patients recruited consecutively?	Not clear, but given the Phase II design presumably so	Not clear, but given the Phase II design presumably so	Not clear, but given the Phase II design presumably so
Did the study report relevant prognostic factors?	Yes	Yes	Yes

9.8 Appendix 8: Search strategy for Section 5.9 (Adverse events)

The clinical search described in Section 5.1 and Section 9.2 was also designed to identify eligible studies for adverse events associated with eribulin.

9.9 Appendix 9: Quality assessment of adverse event data in Section 5.9

Quality assessments of the EMBRACE study and relevant non-RCTs can be found in Section 9.3 and Section 9.7, respectively.

9.10 Appendix 10: Search strategy for Section 6.1 (Cost-effectiveness studies)

9.10.1 Databases searched

Studies of interest were identified by searching the following electronic databases with no restrictions on date or language of publication.

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid)
- NHS-Economic Evaluation Database (NHS-EED, as part of The Cochrane Library)
- EconLit (Ovid)

9.10.2 Date on which the search was conducted

All databases were searched on 13/09/2010.

9.10.3 Date span of the search

- Ovid MEDLINE(R) 1950 to present (13/09/2010).
- EMBASE (Ovid), 1980 to 2010 Week 36 (13/09/10).
- NHS EED (The Cochrane Library), to present (13/09/10).
- EconLit (Ovid), 1969 to present (13/09/2010).

9.10.4 Search strategy

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present; Date searched on 13/09/2010

	Searches	Results
1	breast cancer.mp. or exp Breast Neoplasms/	199697
2	(breast* or mamma*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	562120
3	(metastat* or advanc*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	449210
4	exp Neoplasm Metastasis/ or metastatic.mp.	208799
5	(cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2451842
6	2 and 5	274537
7	1 or 6	274616
8	3 or 4	539394
9	7 and 8	50510
10	decision support techniques/	8351
11	markov.mp.	10195

12	exp models economic/	7377
13	decision analysis.mp.	2879
14	cost benefit analysis/	49225
15	10 or 11 or 12 or 14	69046
16	9 and 15	273

EMBASE 1980 to 2010 Week 36; Date searched on 13/09/2010

	Searches	Results
1	breast cancer.mp. or exp breast cancer/	226070
2	(breast* or mamma*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	606257
3	(metastat* or advanc*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	515614
4	exp metastasis/ or metastatic.mp.	310496
5	(cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	2672296
6	2 and 5	314482
7	1 or 6	315755
8	3 or 4	683980
9	7 and 8	70663
10	decision support techniques/	8121
11	markov.mp.	8481
12	exp models economic/	68992
13	decision analysis.mp.	3245
14	cost benefit analysis/	53411
15	10 or 11 or 12 or 13 or 14	137392
16	9 and 15	556

Cochrane Library (NHS-EED); Date searched on 13/09/2010

ID	Search	Hits
#1	metasta* OR advanc*	30572
#2	cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*	75884
#3	breast* or mamma*	19079
#4	(#2 AND #3)	14607
#5	(#1 AND #4)	5357

#6	decision support techniques	3251
#7	markov:ti,ab,kw	1303
#8	"models economic"	1461
#9	"decision analysis"	769
#10	"cost benefit analysis"	16609
#11	(#6 OR #7 OR #8 OR #9 OR #10)	19591
#12	(#5 AND #11)	237
	There are 128 results out of 237 records for: "(#5 AND #11) in NHS Economic Evaluation Database"	128

Econlit 1969 to August 2010; Date searched on 13/09/2010

	Searches	Results
1	breast cancer.mp. or exp Breast Neoplasms/	150
2	(breast* or mamma*).mp. [mp=heading words, abstract, title, country as subject]	378
3	(metastat* or advanc*).mp. [mp=heading words, abstract, title, country as subject]	12591
4	exp Neoplasm Metastasis/ or metastatic.mp.	9
5	(cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*).mp. [mp=heading words, abstract, title, country as subject]	718
6	2 and 5	169
7	1 or 6	169
8	3 or 4	12591
9	7 and 8	21

9.10.5 Additional searches

A supplementary search of the NICE website was carried out to identify any appraisals or guidelines which used economic models to support their recommendations.

A table of the completed appraisals and guidelines listed on the NICE website has been included in this section. Clinical guideline CG81 was identified which examined the clinical and economic evidence for treatments for advanced breast cancer as were the appraisals for gemcitabine (TA116) and were reviewed in full. The trastuzumab appraisal was not reviewed in detail as the patient population is less relevant to the current submission.

	Include?	Comment
Guidelines		
Breast cancer (advanced)	Yes	Relevant to the decision problem

	Include?	Comment
Guidelines		
Breast cancer (early & locally advanced)	No	Not relevant patient population
Familial breast cancer	No	Not relevant patient population
Appraisals		
Breast cancer (advanced & metastatic) - bevacizumab	No	Terminated appraisal
Breast cancer (early) – docetaxel	No	Not relevant patient population
Breast cancer (early) - hormonal treatments	No	Not relevant patient population
Breast cancer (early) – paclitaxel	No	Not relevant patient population
Breast cancer (early) – trastuzumab	No	Not relevant patient population
Breast cancer - capecitabine (replaced by CG81)	No	CG81 reviewed
Breast cancer - gemcitabine	Yes	Not reviewed by CG81 and relevant to the decision problem

9.10.6 Inclusion and exclusion criteria.

Inclusion

- Patients with advanced/metastatic breast cancer and;
- Either a cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility study.

Exclusion

- Not breast cancer.
- Not a cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility study.
- Studies not relevant to the UK.

9.10.7 The data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Data were extracted from eligible publications into a pre-defined Microsoft Word® document by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies

Study name: Benedict, 2009 (53)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Cost-effectiveness modelling examines the relative value of treatments by providing an estimation of the value gained for money spent. The cost effectiveness of docetaxel against the paclitaxel and against nano albumin paclitaxel is also presented.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	

Study name: Benedict, 2009 (53)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Patients with metastatic breast cancer or locally advanced disease whose cancer progressed after anthracycline chemotherapy.
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	The treatment administration costs were calculated using a report from the Avon, Somerset, Wiltshire Cancer services and NHS reference costs.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	Markov model developed to assess the cost effectiveness of different taxane regimens.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The model tracks health status of the patients (no progression/progression/death) in a 3-weekly cycles. It also accounts for adverse events, dose reductions and type of further therapy after a taxane regimen has failed.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	10 years
23. Was the discount rate stated?	Yes	Costs and outcomes were discounted at 3.5% annually.
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	Sensitivity analysis tested the scenarios of varying treatment cycles probabilistically and of fixed

Study name: Benedict, 2009 (53)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
		therapy duration of six cycles.
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparisons were made between all modules of docetaxel and paclitaxel.
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Docetaxel compared with paclitaxel is estimated to have a cost-effectiveness ratio that falls within the acceptable threshold in the UK.
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Brown, 2001 (54)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	Restrictions of healthcare budgets and importance of QoL in terminally ill patients have led to development of cost-effectiveness models.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	

Study name: Brown, 2001 (54)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Docetaxel, paclitaxel and vinorelbine-licensed in UK; major salvage chemotherapy options for patients with breast cancer.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost utility.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Utility takes into account of both survival and quality of life; utility measures an individual preference for time spent in different health states with varying QoL.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Individual studies from a systematic review informed a pooled analysis of the efficacy and safety of the comparators.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	It appears that a naïve pooled analysis was carried out; no formal meta-analysis was carried out.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Utilities were obtained from UK and Western European nurses.
14. Were productivity changes (if included) reported separately?	NA	The authors state that productivity losses were not included in the analyses except where incorporated into the utilities.
15. Was the relevance of productivity changes to the study question discussed?	NA	As above.
16. Were quantities of resources reported separately from their unit cost?	No	Not all unit costs used were listed separately and numbers of test required per cycle etc were not reported separately (see Table 3 of study).

Study name: Brown, 2001 (54)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
17. Were the methods for the estimation of quantities and unit costs described?	Yes	National databases, communication with specific hospitals and MIMS.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	Markov.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	In the base case, only the costs were discounted (6%). Costs and benefits were discounted in a sensitivity analysis (both at 6%).
24. Was the choice of rate justified?	Not clear	The discount rate for costs was justified but the exclusion of discounting for benefits was not explained.
25. Was an explanation given if cost or benefits were not discounted?	No	Benefits were not discounted in the base case. No explanation for this is reported.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	Probabilistic analysis was not carried out.
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Not clear	The authors report that sensitivity analysis were carried out to test the robustness of the model and validity of the results, however, the rationale behind the specific analyses chosen was not reported.
29. Were the ranges over which the parameters were varied stated?	Not clear	Only scenarios were reported
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Incremental analyses between docetaxel and vinorelbine and for docetaxel and paclitaxel were reported. However, the alternatives were not ranked and assessed in terms of dominance and extended dominance.

Study name: Brown, 2001 (54)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
31. Was an incremental analysis reported?	No	As above.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Total per patient costs and utilities were presented as well as incremental costs and utilities and ICERs. The clinical outcomes such as survival were not reported.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Not clear	An incremental analysis was not performed.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations were outlined in the discussion section.
36. Were generalisability issues addressed?	No	There is no discussion on the patient population from which the clinical effectiveness data were collected and whether this is appropriate for a UK cost effectiveness analysis.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Cooper, 2003 (55)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	The main aim of the study was to demonstrate how probabilistic Markov models can be implemented from a Bayesian perspective for both the synthesis of relevant evidence input into the model and the evaluation of the model itself. The study details an application to assessing the cost effectiveness of taxanes for the second-line treatment of advanced breast cancer compared with conventional treatment.
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the	Not clear	Not explicitly stated as the UK NHS

Study name: Cooper, 2003 (55)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
analysis clearly stated and justified?		perspective.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The cost effectiveness of taxanes is used as an illustrative example of the use of different model methodologies.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	Effectiveness data were based on pooled analysis of published studies.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	Utility values and sources outlined in an appendix.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	NA	Productivity changes were not included.
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	

Study name: Cooper, 2003 (55)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	NA	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Not clear	Not explicitly stated. Authors report that it was assumed that individuals were only allowed a maximum of seven cycles of treatment and that the model followed individuals for a maximum of 28 further cycles after the end of the treatment period.
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	Likely to be because of the relatively short time horizon, but not stated.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	NA	Ranges not required as model was fully probabilistic.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study	Yes	

Study name: Cooper, 2003 (55)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
question given?		
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Hutton, 1996 (56)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	Increasing pressure on healthcare budgets, developers of new treatments are more frequently required to justify the use clinically and economically.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Docetaxel may produce a significant advance in clinical management of metastatic breast cancer, and socio-economic impact of this drug therefore warrants investigation.
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	Yes	Cost utility.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Increasing pressure on healthcare budgets; new treatments; realisation of QoL is as important as survival appraised methods for measuring the effectiveness of the treatment.
Data collection		

Study name: Hutton, 1996 (56)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Not clear	Results based on literature review and consultation with three practising oncologists; no details provided.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Costs; QALYs; Cost per patient.
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	The study considered a hypothetical, but representative, female patient.
14. Were productivity changes (if included) reported separately?	No	No description.
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	Resource costs associated with the treatment of metastatic breast cancer; table 5 of the publication.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	National databases and published literature; National health service hospital and community health service inflation index; Prices for drugs obtained from MIMS, May 1996.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	Decision analysis model; Markov model.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost	Yes	Treatment delivered for 6 cycles

Study name: Hutton, 1996 (56)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
and benefits stated?		repeated at 3-week intervals.
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	NA	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No statistical analysis carried out.
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	Along with the robustness of the cost utility results, sensitivity analyses showed an increased response with docetaxel compared with paclitaxel in different scenarios.
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Incremental cost utility analysis of docetaxel versus paclitaxel.
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Response rates; individual utilities; overall treatment cost/per patient; QALYs and incremental costs reported.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Not clear	
35. Were conclusions accompanied by the appropriate caveats?	Yes	The model assumed that neither docetaxel nor paclitaxel resulted in survival gains for patients (but only quality of life gains), that the median survival is the same (43%) for both treatment options. However, none of these assumptions was based on clear evidence. The pooling of the individual studies was unclear, as is whether the search mechanism was comprehensive or systematic.
36. Were generalisability issues addressed?	Not clear	

Study name: Hutton, 1996 (56)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Jones, 2004 (52)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Owing to the small number of studies included in the review and the heterogeneity between the studies, statistical pooling was inappropriate, so statistical chi-squared tests of heterogeneity were not performed.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Appropriate comparators were vinorelbine and best supportive care (NICE).
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Monte-Carlo simulation helps to generate cost-effectiveness curves and the impact of differences in health-care QoL on cost-effectiveness.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an	Yes	Systematic review; Limited data for Capecitabine monotherapy, and Capecitabine in combination with

Study name: Jones, 2004 (52)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
overview of a number of effectiveness studies)?		docetaxel reported data from one RCT abs (Roche submission).
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Quality-adjusted life-years (QALYs) were used as the measure of effectiveness for the economic evaluation.
12. Were the methods used to value health states and other benefits stated?	Yes	Response to treatment, Survival, QoL.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Women with locally advanced or metastatic stages IIIa and IIIb, and metastatic cancer to stage IV breast cancer were included.
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	Costs for hospitalisation, consultation and drug treatment were reported.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Personal Social Services Research Unit (PSSRU), 2000; alternative cost for the various specialities could have been obtained from the Chartered Institute of Public Finance and Accounting (CIPFA).
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	There were insufficient data identified during the course of this review to allow an independent economic model to be developed. The economic evaluation of capecitabine monotherapy in this report was, therefore, based on the data reported in the Roche submission to NICE [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished]. Monte Carlo simulation to generate cost-effectiveness acceptability curves and the impact of differences in health-related QoL on

Study name: Jones, 2004 (52)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
		cost-effectiveness.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	No discounting was undertaken due to the limited expected lifespan of patients in this setting.
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	Unclear	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Due to limited data no probabilistic analysis could be done
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Unclear	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Incremental QALY gain for treatments was reported.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	From the evidence available from the single trial, capecitabine in combination with docetaxel appears to be more effective than single-agent docetaxel in terms of overall survival, time to disease progression, time to treatment failure and overall tumour response (complete response plus partial response).
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	RCTs investigating capecitabine in combination with docetaxel

Study name: Jones, 2004 (52)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
		compared to alternative second-line therapies are required. From the limited evidence it would appear that capecitabine in combination with docetaxel is more effective. The method of calculation of QALYs ignores the potential for differences in adverse events between treatments to alter QoL estimates.
36. Were generalisability issues addressed?	Unclear	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: NICE CG81 (full guideline) (8)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	A review of previous economic evaluations has been reported.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	

Study name: NICE CG81 (full guideline) (8)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Studies were appropriately reported.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	An indirect comparison was carried out for first line treatment.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	Utility values were reported to be taken from Cooper et al.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Oncology nurses using standard gamble technique.
14. Were productivity changes (if included) reported separately?	NA	Productivity changes were not included.
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	No	This is not explicitly reported. Assumed to be related to survival.
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	NA	
25. Was an explanation given if cost	Yes	The authors report that discounting

Study name: NICE CG81 (full guideline) (8)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
or benefits were not discounted?		was not expected to have much impact on the results of the model since many of the possible pathways through the model are associated with survival of less than 24 months.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Not clear	Further explanation of the choice of parameters investigated in sensitivity analysis would have been useful.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Not clear	The authors do not appear to have discussed the generalisability of the clinical data but do discuss other issues of generalisability in the discussion. It may be assumed that the relevance and appropriateness of the clinical data have been discussed elsewhere in the guideline.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: NICE TA116 (ERG report) (64)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	This may be considered implicit - analysis carried out at NICE's request.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost utility analysis.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	This may be considered implicit - cost-utility assessments are required for NICE submission.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Method of pooling questionable.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	This is not reported in the ERG report.
14. Were productivity changes (if included) reported separately?	NA	Productivity changes were not included.
15. Was the relevance of productivity changes to the study question discussed?	NA	

Study name: NICE TA116 (ERG report) (64)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	3.5% for costs and benefits applied.
24. Was the choice of rate justified?	Not clear	This may be considered implicit – the discount rate is specified by NICE but has not been reported in the ERG report.
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Not clear	Not reported in the ERG report.
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Not clear	Extent of analyses may be considered limited.
29. Were the ranges over which the parameters were varied stated?	Not clear	Not reported in the ERG report but likely to have been reported in the submission.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented	Yes	

Study name: NICE TA116 (ERG report) (64)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Not clear	Not reported in the ERG report.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Takeda, 2007 (58)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	Cost-effectiveness of gemcitabine and paclitaxel in combination compared with paclitaxel alone as treatment for women with metastatic breast cancer.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Gemcitabine and paclitaxel for people diagnosed with Stage IV metastatic breast cancer who have previously been treated with anthracycline based therapies.
5. Were the alternatives being compared clearly described?	Yes	Gemcitabine, in combination with paclitaxel, is licensed for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness.
7. Was the choice of form of	Yes	State transition model.

Study name: Takeda, 2007 (58)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
economic evaluation justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Systematic review.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	The included study reports were tabulated and synthesised in a narrative summary. Meta-analysis was not appropriate for this report, due to the limited data identified.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	ICERs; QALYs.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	Costs for consultation, CT administration, Drugs and toxicities was reported.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Published studies, BNF 50, NHS pay and prices index.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Inflated costs based on inputs from various sources using the NHS Pay and Prices Index.
20. Were details of any model used given?	Yes	Markov state transition model.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		

Study name: Takeda, 2007 (58)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime.
23. Was the discount rate stated?	Yes	The model with costs and outcomes discounted at 3.5%.
24. Was the choice of rate justified?	Yes	NICE 2004.
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	No analysis possible because of limited data.
27. Was the approach to sensitivity analysis described?	Yes	Sensitivity analysis based on only six cycles of chemotherapy, responsive and stable disease patients.
28. Was the choice of variables for sensitivity analysis justified?	Yes	Consulted clinical oncologist from a teaching hospital for inputs and variables.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Reports total costs, life-years and quality-adjusted life-years for each treatment group and incremental cost-effectiveness ratios.
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	The systematic review was restricted by the lack of published evidence for gemcitabine's licensed indication. In the absence of any fully published studies, data from three abstracts were used to form the basis of the review of clinical effectiveness.
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008)		

Study name: Takeda, 2007 (58)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.12 Appendix 12: Search strategy for Section 6.4 (Measurement and valuation of health effects)

9.12.1 Databases searched

Studies of interest were identified by searching the following electronic databases with no restrictions on date or language of publication.

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid)
- NHS-EED (The Cochrane Library)
- EconLit (Ovid)

9.12.2 Date on which the search was conducted

All databases were searched on 01/09/2010.

9.12.3 Date span of the search

- Ovid MEDLINE(R) 1950 to present (01/09/2010).
- EMBASE (Ovid), 1980 to 2010 Week 34 (01/09/10).
- NHS-EED (The Cochrane Library), to present (01/09/10).
- EconLit (Ovid), 1969 to present (01/09/2010).

9.12.4 Search strategy

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present; Date searched on 01/09/2010

	Searches	Results
1	breast cancer.mp. or exp breast cancer/	198869
2	exp metastasis/ or metastatic.mp.	208155
3	(breast* or mamma*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	559606
4	(cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2446113
5	(metasta* or advanc*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	617766
6	3 and 4	273529
7	1 or 6	273608
8	2 or 5	622125
9	7 and 8	60681
10	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	10767

11	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1525
12	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2052
13	(Health utilities index or HUI).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	759
14	(time trade off or TTO).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	734
15	(standard gamble or SG).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4565
16	10 or 11 or 12 or 13 or 14 or 15	19161
17	9 and 16	48

EMBASE 1980 to 2010 Week 34; Date searched on 01/09/2010

	Searches	**Results**
1	breast cancer.mp. or exp breast cancer/	224991
2	(breast* or mamma*).mp.	603806
3	(metastat* or advanc*).mp.	512857
4	exp metastasis/ or metastatic.mp.	309367
5	(cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adencarcinoma* or polyp*).mp.	2661683
6	2 and 5	313022
7	1 or 6	314284
8	3 or 4	680642
9	7 and 8	70351
10	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	14162
11	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1929
12	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	2635
13	(Health utilities index or HUI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1577
14	(time trade off or TTO).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	859
15	(standard gamble or SG).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	5228
16	10 or 11 or 12 or 13 or 14 or 15	24864

17	9 and 16	66

NHS-EED; Date searched on 01/09/2010

ID	Search	Hits
#1	metasta* OR advanc*	30542
#2	cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*	75850
#3	breast* or mamma*	19067
#4	(#2 AND #3)	14596
#5	(#1 AND #4)	5347
#6	quality of life	29482
#7	short form 36 or shortform 36 or SF-36 or SF36 or SF 36	5356
#8	short form 12 or shortform 12 or SF12 or SF-12 or SF 12	10735
#09	Euroqol 5D or EQ-5D or EQ5D or Euroqol	1121
#10	Health utilities index or HUI	5669
#11	time trade off or TTO	603
#12	standard gamble or SG	4263
#13	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)	41534
#14	(#5 AND #13)	742
	There are 107 results out of 742 records for: "(#5 AND #13) in NHS Economic Evaluation Database"	107

Econlit 1969 to August 2010; Date searched on 01/09/2010

	Searches	Results
1	breast cancer.mp. or exp breast cancer/	150
2	exp metastasis/ or metastatic.mp.	9
3	(breast* or mamma*).mp. [mp=heading words, abstract, title, country as subject]	378
4	(cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*).mp. [mp=heading words, abstract, title, country as subject]	718
5	(metasta* or advanc*).mp. [mp=heading words, abstract, title, country as subject]	12602
6	3 and 4	169
7	1 or 6	169
8	2 or 5	12602
9	7 and 8	23

9.12.5 Additional searches

No additional searches were carried out. However, additional data for utility values were extracted from the cost effectiveness studies (see section 6.1.2).

9.12.6 Inclusion and exclusion criteria.

Inclusion

- Women with advanced/metastatic breast cancer and;
- A study which used a preference based measure of QoL;
  - Either generic or valued using standard gamble or time-trade off; or
- A non preference based measure, specifically EQ-5D, SF-12 or SF-36.

Exclusion

- Not breast cancer.
- Did not report utility values for model health states.

9.12.7 The data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Data were extracted from eligible publications into a pre-defined Microsoft Word® document by a reviewer. This was designed to capture study design, patient characteristics, demographics and results. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

9.13 Appendix 13: Search strategy for Section 6.5 (Resource identification, measurement and valuation)

A formal systematic literature search for resource use was not completed. Please see Section 6.5.3 for details of the searches carried out for resource use data.

9.13.1 Databases searched

NA

9.13.2 Date on which the search was conducted

NA

9.13.3 Date span of the search

NA

9.13.4 Search strategy

NA

9.13.5 Additional searches

NA

9.13.6 The inclusion and exclusion criteria.

NA

9.13.7 The data abstraction strategy.

NA

9.14 Appendix 14: Economic evaluation; Ranges and distributions used in sensitivity analysis

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Drug costs, drug dosing, drug ingredient costs, pre-medication costs, health state costs, toxicity costs, utility values and discounting					
Drug Costs					
Drug Dose per Treatment (mg/m^2)					
[Mean body surface area (m^2)]	1.7	1.3	2.1	0.2	Beta
Eribulin	1.4	1.1	1.8	0.1	Beta
Vinorelbine	80.0	80	80	8.0	Beta
Gemcitabine	1,250.0	937.5	1,562.5	125.0	Beta
Capecitabine	2,500.0	1,875.0	3,125.0	250.0	Beta
Taxanes					
Docetaxel	100.0	75.0	125.0	10.0	Beta
Ixabepilone	40.0	30.0	50.0	4.0	Beta
Paclitaxel	175.0	131.3	218.8	17.5	Beta
Nab-paclitaxel	260.0	195.0	325.0	26.0	Beta
Anthracyclines					
Doxorubicin	67.5	50.6	84.4	6.8	Beta
Liposomal doxorubicin	67.5	60.0	75.0	6.8	Beta
Drug Ingredient Cost (per vial)					
Eribulin	£[redacted]				
Vinorelbine	£61.25				
Gemcitabine	£162.00				
Capecitabine	£265.55				
Taxanes					
Docetaxel	£534.75				
Ixabepilone	£-				
Paclitaxel	£822.25				
Nab-paclitaxel	£246.00				
Anthracyclines					
Doxorubicin	£275.00				
Liposomal doxorubicin	£464.50				
Pre-Medication Cost (per vial)					
Cimetidine	£14.24				
Dexamethasone	£15.45				
Infusion Costs					
Exclusively oral chemotherapy delivery	£209.93	£103.02	£209.93	£20.99	Gamma
IV infusion chemotherapy delivery	£226.88	£120.69	£236.41	£22.69	Gamma
Resource Costs					
Health state costs					
Stable	£163	£ 95	£ 193	£ 16	Gamma
Responsive	£163	£ 95	£ 193	£ 16	Gamma
Progressive	£233	£ 111	£ 282	£ 23	Gamma
Terminal	£19,712	£15,722	£23,177	£1,971	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Grade 3 toxicity costs					
Anaemia	£339	£ 161	£ 395	£ 34	Gamma
Anorexia	£0	£-	£-	£-	Gamma
Diarrhoea	£121	£ 67	£ 145	£ 12	Gamma
Dyspnoea	£0	£-	£-	£-	Gamma
Oedema	£412	£ 231	£ 467	£ 41	Gamma
Fatigue	£0	£-	£-	£-	Gamma
Febrile neutropenia	£478	£ 309	£ 564	£ 48	Gamma
Heart failure	£0	£-	£-	£-	Gamma
Hyperbilirubimaemia	£121	£ 67	£ 145	£ 12	Gamma
Hypertension	£0	£-	£-	£-	Gamma
Hypokalaemia	£318	£ 187	£ 345	£ 32	Gamma
Neuropathy	£0	£-	£-	£-	Gamma
Neutropenia	£0	£-	£-	£-	Gamma
Pain	£121	£ 67	£ 145	£ 12	Gamma
Peripheral neuropathy	£121	£ 67	£ 145	£ 12	Gamma
Pulmonary embolism	£359	£ 246	£ 359	£ 36	Gamma
Stomatitis	£393	£ 261	£ 401	£ 39	Gamma
Thrombocytopenia	£386	£ 229	£ 457	£ 39	Gamma
Urinary tract infection	£121	£ 67	£ 145	£ 12	Gamma
Vomiting	£121	£ 67	£ 145	£ 12	Gamma
Grade 4 toxicity costs					
Anaemia	£339	£ 161	£ 395	£ 34	Gamma
Anorexia	£0	£-	£-	£-	Gamma
Diarrhoea	£339	£ 161	£ 395	£ 34	Gamma
Dyspnoea	£121	£ 67	£ 145	£ 12	Gamma
Oedema	£412	£ 231	£ 467	£ 41	Gamma
Fatigue	£0	£-	£-	£-	Gamma
Febrile neutropenia	£478	£ 309	£ 564	£ 48	Gamma
Heart failure	£680	£ 277	£ 942	£ 68	Gamma
Hyperbilirubimaemia	£121	£ 67	£ 145	£ 12	Gamma
Hypertension	£0	£-	£-	£-	Gamma
Hypokalaemia	£318	£ 187	£ 345	£ 32	Gamma
Neuropathy	£339	£ 161	£ 395	£ 34	Gamma
Neutropenia	£339	£ 161	£ 395	£ 34	Gamma
Pain	£121	£ 67	£ 145	£ 12	Gamma
Peripheral neuropathy	£0	£-	£-	£-	Gamma
Pulmonary embolism	£359	£ 246	£ 359	£ 36	Gamma
Stomatitis	£393	£ 261	£ 401	£ 39	Gamma
Thrombocytopenia	£386	£ 229	£ 457	£ 39	Gamma
Urinary tract infection	£361	£ 258	£ 385	£ 36	Gamma
Vomiting	£339	£ 161	£ 395	£ 34	Gamma
Utilities					
Beginning therapy	0.72	0.56	0.86	0.07	Beta
Stable	0.72	0.62	0.81	0.07	Beta
Responsive	0.79	0.79	0.84	0.08	Beta
Progressive	0.44	0.33	0.65	0.04	Beta
Terminal	0.16	0.13	0.25	0.02	Beta
NICE End-of-Life	0.83	0.62	1.00	0.08	Beta
w/ Anaemia	-0.12	-0.16	-0.09	0.01	Normal

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
w/ Anorexia	-0.12	-0.16	-0.09	0.01	Normal
w/ Diarrhoea	-0.10	-0.13	-0.08	0.01	Normal
w/ Dyspnoea	-0.12	-0.16	-0.09	0.01	Normal
w/ Oedema	-0.12	-0.16	-0.09	0.01	Normal
w/ Fatigue	-0.12	-0.14	-0.09	0.01	Normal
w/ Febrile neutropenia	-0.15	-0.19	-0.11	0.02	Normal
w/ Heart failure	-0.12	-0.16	-0.09	0.01	Normal
w/ Hyperbilirubimaemia	-0.12	-0.16	-0.09	0.01	Normal
w/ Hypertension	-0.12	-0.16	-0.09	0.01	Normal
w/ Hypokalaemia	-0.12	-0.16	-0.09	0.01	Normal
w/ Neuropathy	-0.12	-0.16	-0.09	0.01	Normal
w/ Neutropenia	-0.12	-0.16	-0.09	0.01	Normal
w/ Pain	-0.12	-0.16	-0.09	0.01	Normal
w/ Peripheral neuropathy	-0.12	-0.16	-0.09	0.01	Normal
w/ Pulmonary embolism	-0.12	-0.16	-0.09	0.01	Normal
w/ Stomatitis	-0.15	-0.19	-0.11	0.02	Normal
w/ Thrombocytopenia	-0.12	-0.16	-0.09	0.01	Normal
w/ Urinary tract infection	-0.12	-0.16	-0.09	0.01	Normal
w/ Vomiting	-0.10	-0.13	-0.08	0.01	Normal
Discounts					
Costs discount	3.5%	2.6%	4.4%	0.4%	Beta
Effects discount	3.5%	2.6%	4.4%	0.4%	Beta
Efficacy and safety variables for each comparison					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Eribulin vs TPC					
Eribulin Efficacy & Safety					
Efficacy & Survival					
Overall response rate	0.110769	0.076647	0.144891	0.017409	Beta
Hazard ratio (PFS)	0.893	0.696	1.145	0.0893	Normal
Hazard ratio (OS)	0.791	0.639	0.981	0.0791	Normal
Grade 3 toxicity rates					
Anaemia	0.017893	0.013419	0.022366	0.005911	Gamma
Anorexia	0.003976	0.002982	0.00497	0.002806	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.035785	0.026839	0.044732	0.008282	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.081511	0.061133	0.101889	0.0122	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.33002	0.247515	0.412525	0.020966	Gamma
Pain	0.04175	0.031312	0.052187	0.008918	Gamma
Peripheral neuropathy	0.077535	0.058151	0.096918	0.011924	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0.017893	0.013419	0.022366	0.005911	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Vomiting	0.025845	0.019384	0.032306	0.007075	Gamma
Grade 4 toxicity rates					
Anaemia	0.001988	0.001491	0.002485	0.001986	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0	0	0	0	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.005964	0.004473	0.007455	0.003433	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.262425	0.196819	0.328032	0.019617	Gamma
Pain	0.001988	0.001491	0.002485	0.001986	Gamma
Peripheral neuropathy	0.003976	0.002982	0.00497	0.002806	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.001988	0.001491	0.002485	0.001986	Gamma
TPC Efficacy & Safety					
Efficacy & Survival					
Overall response rate	0.042945	0.011821	0.074068	0.015879	Beta
Grade 3 toxicity rates					
Anaemia	0.032389	0.024291	0.040486	0.011264	Gamma
Anorexia	0.012146	0.009109	0.015182	0.00697	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.024291	0.018219	0.030364	0.009796	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.101215	0.075911	0.126518	0.019191	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.194332	0.145749	0.242915	0.025177	Gamma
Pain	0.052632	0.039474	0.065789	0.014208	Gamma
Peripheral neuropathy	0.020243	0.015182	0.025304	0.008961	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0.05668	0.04251	0.07085	0.014713	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.044534	0.033401	0.055668	0.013125	Gamma
Grade 4 toxicity rates					
Anaemia	0.004049	0.003036	0.005061	0.00404	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Dyspnoea	0.004049	0.003036	0.005061	0.00404	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0	0	0	0	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.076923	0.057692	0.096154	0.016955	Gamma
Pain	0.008097	0.006073	0.010121	0.005702	Gamma
Peripheral neuropathy	0	0	0	0	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0	0	0	0	Gamma
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Eribulin vs gemcitabine					
Eribulin Efficacy & Safety					
Efficacy & Survival					
Overall response rate	xxxx	xxxx	xxxx	xxxx	Beta
Hazard ratio (PFS)	xxxx	xxxx	xxxx	xxxx	Normal
Hazard ratio (OS)	xxxx	xxxx	xxxx	xxxx	Normal
Grade 3 toxicity rates					
Anaemia	0.017893	0.013419	0.022366	0.005911	Gamma
Anorexia	0.003976	0.002982	0.00497	0.002806	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.035785	0.026839	0.044732	0.008282	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.081511	0.061133	0.101889	0.0122	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.33002	0.247515	0.412525	0.020966	Gamma
Pain	0.04175	0.031312	0.052187	0.008918	Gamma
Peripheral neuropathy	0.077535	0.058151	0.096918	0.011924	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0.017893	0.013419	0.022366	0.005911	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.025845	0.019384	0.032306	0.007075	Gamma
Grade 4 toxicity rates					
Anaemia	0.001988	0.001491	0.002485	0.001986	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0	0	0	0	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Oedema	0	0	0	0	Gamma
Fatigue	0.005964	0.004473	0.007455	0.003433	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.262425	0.196819	0.328032	0.019617	Gamma
Pain	0.001988	0.001491	0.002485	0.001986	Gamma
Peripheral neuropathy	0.003976	0.002982	0.00497	0.002806	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.001988	0.001491	0.002485	0.001986	Gamma
Gemcitabine Efficacy & Safety					
Efficacy & Survival					
Overall response rate	0	0	0	0	Beta
Grade 3 toxicity rates					
Anaemia	0	0	0	0	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.065217	0.048913	0.081522	0.036405	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.130435	0.097826	0.163043	0.049656	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.065217	0.048913	0.081522	0.036405	Gamma
Pain	0.021739	0.016304	0.027174	0.021502	Gamma
Peripheral neuropathy	0	0	0	0	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0	0	0	0	Gamma
Grade 4 toxicity rates					
Anaemia	0	0	0	0	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0	0	0	0	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0	0	0	0	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0	0	0	0	Gamma
Pain	0	0	0	0	Gamma
Peripheral neuropathy	0	0	0	0	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0	0	0	0	Gamma
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Eribulin vs vinorelbine					
Eribulin Efficacy & Safety					
Overall response rate	xxxx	xxxx	xxxx	xxxx	Beta
Hazard ratio (PFS)	xxxx	xxxx	xxxx	xxxx	Normal
Hazard ratio (OS)	xxxx	xxxx	xxxx	xxxx	Normal
Grade 3 toxicity rates					
Anaemia	0.017893	0.013419	0.022366	0.005911	Gamma
Anorexia	0.003976	0.002982	0.00497	0.002806	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.035785	0.026839	0.044732	0.008282	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.081511	0.061133	0.101889	0.0122	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.33002	0.247515	0.412525	0.020966	Gamma
Pain	0.04175	0.031312	0.052187	0.008918	Gamma
Peripheral neuropathy	0.077535	0.058151	0.096918	0.011924	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0.017893	0.013419	0.022366	0.005911	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.025845	0.019384	0.032306	0.007075	Gamma
Grade 4 toxicity rates					
Anaemia	0.001988	0.001491	0.002485	0.001986	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0	0	0	0	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.005964	0.004473	0.007455	0.003433	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.262425	0.196819	0.328032	0.019617	Gamma
Pain	0.001988	0.001491	0.002485	0.001986	Gamma
Peripheral neuropathy	0.003976	0.002982	0.00497	0.002806	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.001988	0.001491	0.002485	0.001986	Gamma
Vinorelbine Efficacy & Safety					
Efficacy & Survival					
Overall response rate	0.044444	0	0.104657	0.030721	Beta
Grade 3 toxicity rates					
Anaemia	0.032787	0.02459	0.040984	0.022801	Gamma
Anorexia	0.032787	0.02459	0.040984	0.022801	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.032787	0.02459	0.040984	0.022801	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.098361	0.07377	0.122951	0.03813	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.377049	0.282787	0.471311	0.062053	Gamma
Pain	0.081967	0.061475	0.102459	0.035122	Gamma
Peripheral neuropathy	0.032787	0.02459	0.040984	0.022801	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.04918	0.036885	0.061475	0.027687	Gamma
Grade 4 toxicity rates					
Anaemia	0	0	0	0	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.016393	0.012295	0.020492	0.016259	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0	0	0	0	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.098361	0.07377	0.122951	0.03813	Gamma
Pain	0.016393	0.012295	0.020492	0.016259	Gamma
Peripheral neuropathy	0	0	0	0	Gamma
Pulmonary embolism	0	0	0	0	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0	0	0	0	Gamma
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Eribulin vs capecitabine					
Eribulin Efficacy & Safety					
Efficacy & Survival					
Overall response rate	xxxx	xxxx	xxxx	xxxx	Beta
Hazard ratio (PFS)	xxxx	xxxx	xxxx	xxxx	Normal
Hazard ratio (OS)	xxxx	xxxx	xxxx	xxxx	Normal
Grade 3 toxicity rates					
Anaemia	0.017893	0.013419	0.022366	0.005911	Gamma
Anorexia	0.003976	0.002982	0.00497	0.002806	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0.035785	0.026839	0.044732	0.008282	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.081511	0.061133	0.101889	0.0122	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.33002	0.247515	0.412525	0.020966	Gamma
Pain	0.04175	0.031312	0.052187	0.008918	Gamma
Peripheral neuropathy	0.077535	0.058151	0.096918	0.011924	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0.017893	0.013419	0.022366	0.005911	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.025845	0.019384	0.032306	0.007075	Gamma
Grade 4 toxicity rates					
Anaemia	0.001988	0.001491	0.002485	0.001986	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0	0	0	0	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.005964	0.004473	0.007455	0.003433	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.262425	0.196819	0.328032	0.019617	Gamma
Pain	0.001988	0.001491	0.002485	0.001986	Gamma
Peripheral neuropathy	0.003976	0.002982	0.00497	0.002806	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma

Model variables					
Variable	**Base**	**Min**	**Max**	**SE**	**Distribution**
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.001988	0.001491	0.002485	0.001986	Gamma
Capecitabine Efficacy & Safety					
Efficacy & Survival					
Overall response rate	xxxx	xxxx	xxxx	xxxx	Beta
Grade 3 toxicity rates					
Anaemia	0	0	0	0	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0	0	0	0	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0.068182	0.051136	0.085227	0.037999	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0.022727	0.017045	0.028409	0.022468	Gamma
Pain	0.113636	0.085227	0.142045	0.047845	Gamma
Peripheral neuropathy	0	0	0	0	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0.181818	0.136364	0.227273	0.058146	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0.068182	0.051136	0.085227	0.037999	Gamma
Grade 4 toxicity rates					
Anaemia	0	0	0	0	Gamma
Anorexia	0	0	0	0	Gamma
Diarrhoea	0	0	0	0	Gamma
Dyspnoea	0	0	0	0	Gamma
Oedema	0	0	0	0	Gamma
Fatigue	0	0	0	0	Gamma
Febrile neutropenia	0	0	0	0	Gamma
Heart failure	0	0	0	0	Gamma
Hyperbilirubimaemia	0	0	0	0	Gamma
Hypertension	0	0	0	0	Gamma
Hypokalaemia	0	0	0	0	Gamma
Neuropathy	0	0	0	0	Gamma
Neutropenia	0	0	0	0	Gamma
Pain	0	0	0	0	Gamma
Peripheral neuropathy	0	0	0	0	Gamma
Pulmonary embolism	0	0	0	0	Gamma
Stomatitis	0	0	0	0	Gamma
Thrombocytopenia	0	0	0	0	Gamma
Urinary tract infection	0	0	0	0	Gamma
Vomiting	0	0	0	0	Gamma

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the

specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of

any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

CONFIDENTIAL

1 July 2011

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Dear Carole

Patient Access Scheme – Halaven – advanced breast cancer

Further to my letter of 11th March, which confirmed that the Department was content for a PAS proposal to be considered in the appraisal of Halaven (eribulin) in the treatment of locally advanced or metastatic breast cancer, Eisai have now requested that the level of discount offered through the scheme should remain confidential and should not be published in NICE guidance.

The Department is content in this case for the level of discount to remain confidential in the draft guidance for Halaven. NICE must of course be satisfied that sufficient information can be communicated to stakeholders to explain an appraisal recommendation. In this regard, what constitutes a sufficient level of transparency is a matter for the Institute to determine in developing its guidance. In addition, the NHS must have access to the discount price when final NICE guidance is made available, so Trusts and commissioners are able to properly account for the PAS.

Yours sincerely

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Patient access scheme submission template

Halaven® (eribulin mesylate)

For the treatment of locally advanced/metastatic breast cancer

Submitted to NICE 11th March 2011 as part of the STA process

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The 'Specification for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Halaven® (eribulin mesylate).

Disease area: Locally advanced breast cancer (LABC)/metastatic breast cancer (MBC).

Eribulin monotherapy is indicated for the treatment of patients with LABC or MBC who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

Suitable comparators for eribulin include gemcitabine, vinorelbine and capecitabine.

3.2 Please outline the rationale for developing the patient access scheme.

To facilitate earlier patient access to eribulin.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Financially based scheme – straight discount off the list price.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme applies to the whole licensed population.

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3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The patient access scheme applies to the population from the date of NICE recommendation and is not dependent on criteria, for example, degree of response.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

N/A as outlined in 3.5.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The discount of the list price will apply at point of sale. The current list price is £313 per vial and with the patient access scheme the price per vial will be xxxx xxxxxxxx xx x xxxx xxxxxxxx. Hospitals will be charged the discount price directly when they order eribulin

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No administration of the scheme is required as this is a straight discount off list price.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

N/A straight discount off the list price.

3.10 Please provide details of the duration of the scheme.

The scheme will be in place until NICE review eribulin.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues that relate to the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

N/A straight discount off list price.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

N/A.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

N/A the population to whom the scheme applies is presented in the main manufacturer submission of evidence.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

N/A this scheme is not been submitted at the end of the technology appraisal process.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

N/A straight discount off the list price.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

N/A straight discount off the list price.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

N/A straight discount of the list price, therefore no costs associated with the implementation and operation of the patient access scheme. Hospitals will procure eribulin in the same way that they receive any other current Eisai product through our distributor and the distributor will invoice the hospital the discounted price

Table 1 Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	Reference source
Stock management		
Administration of claim forms		
Staff training		
Other costs…		
…		
…		
Total implementation/ operation costs		

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

N/A straight discount of the list price, therefore no additional treatment-related costs for the intervention both with and without the patient access scheme.

Table 2 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Intervention without PAS		Intervention with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Interventions					
Monitoring tests					
Diagnostic tests					
Appointments					
Other costs…					
…					
…					
Total treatment-related costs					

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[a]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[a] For outcome-based schemes, please see section 5.2.8 in appendix B.

Results for the intervention *without* the patient access scheme

Table 3.1 Base-case cost-effectiveness results *without* patient access scheme – TPC (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£39,939	0.6887	£9,490	0.1213	£78,228

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Table 3.2 Base-case cost-effectiveness results *without* patient access scheme – Gemcitabine (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£38,982	0.6885	£8,830	0.1904	£46,366

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Table 3.3 Base-case cost-effectiveness results *without* patient access scheme – Vinorelbine (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£37,377	0.6291	£7,394	0.1136	£65,135

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Table 3.4 Base-case cost-effectiveness results *without* patient access scheme – Capecitabine (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£44,423	0.7853	£17,657	0.2683	£65,812

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Results for the intervention *with* the patient access scheme

Table 3.5 Base-case cost-effectiveness results *with* patient access scheme – TPC (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£36,035	0.6887	£5,586	0.1213	£46,050

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Table 3.6 Base-case cost-effectiveness results *with* patient access scheme – Gemcitabine (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.6885	£5,177	0.1904	£27,183

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Table 3.7 Base-case cost-effectiveness results *with* patient access scheme – Vinorelbine (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.6291	£4,041	0.1136	£35,602

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Table 3.8 Base-case cost-effectiveness results *with* patient access scheme – Capecitabine (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.7853	£12,779	0.2683	£47,631

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

4.8 Please present in separate tables the incremental results as follows. [b]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

An incremental analysis of each comparison is presented in section 4.7. An incremental analysis of all the individual treatments included in the model is not possible as the inputs and outcomes for the

[b] For outcome-based schemes, please see section 5.2.9 in appendix B.

intervention group (eribulin) differs for each of the comparator analyses.

Table 4.1 Base-case incremental results *without* patient access scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4.2 Base-case incremental results *with* patient access scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

One-way deterministic sensitivity analysis was carried out on all model parameters. The top ten parameters of influence are presented as tornado diagrams for each of the base case analyses.

*All the results presented in this section are from the base case analyses in the main submission and **do not** take the discounted price of eribulin into account.*

Figure 1: Tornado diagram of eribulin vs. TPC *without* the PAS

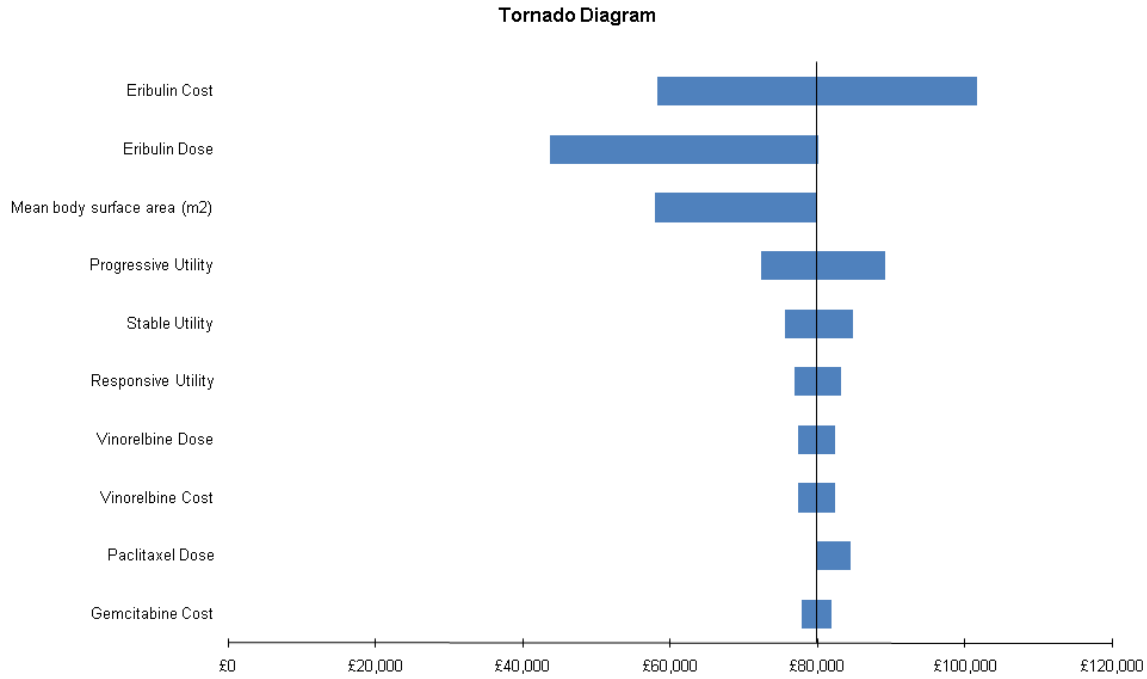


Figure 2: Tornado diagram of eribulin vs. gemcitabine *without* the PAS

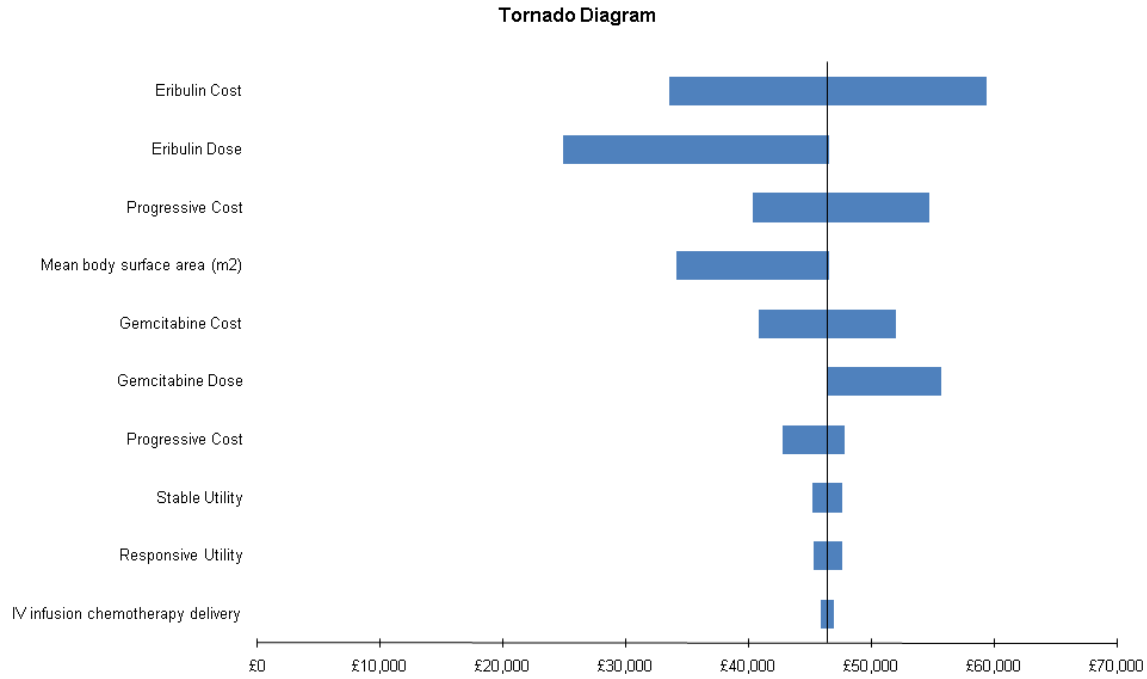


Figure 3: Tornado diagram of eribulin vs. vinorelbine *without* the PAS

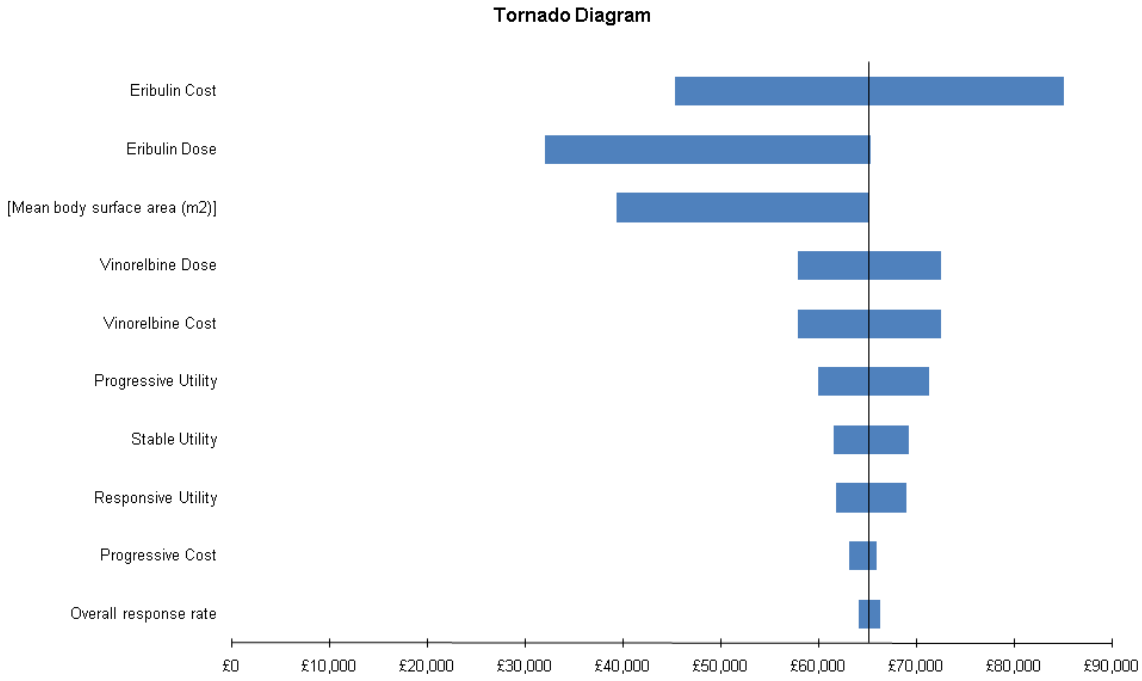
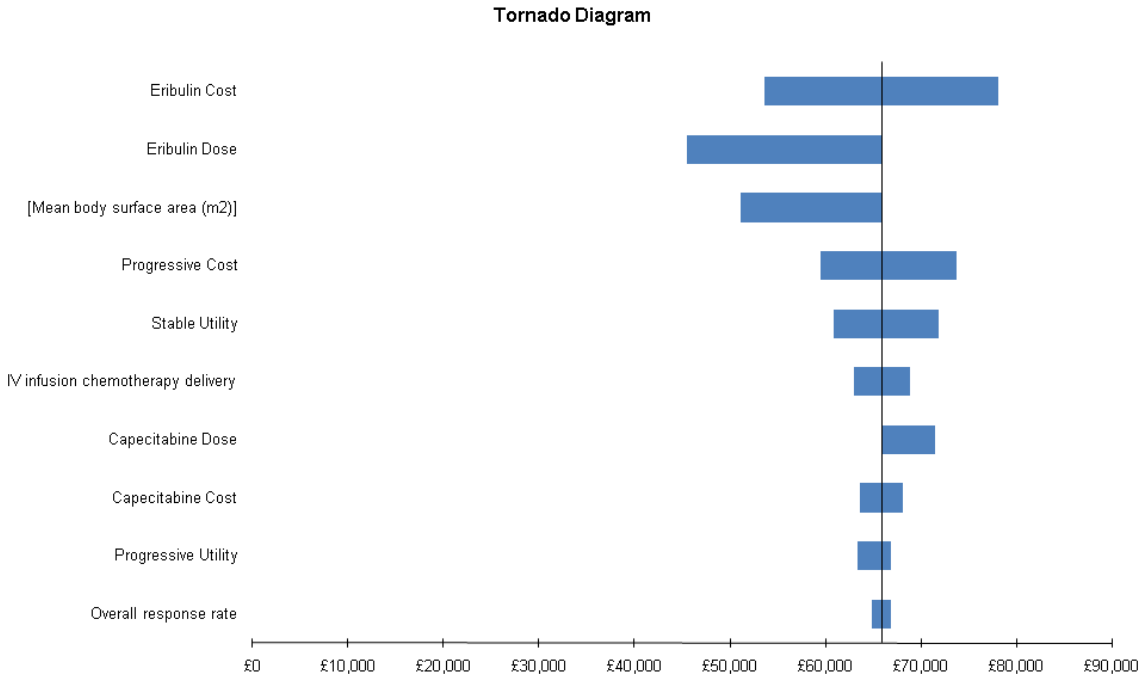


Figure 4: Tornado diagram of eribulin vs. capecitabine *without* the PAS



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

A probabilistic analysis was carried out for each of the four base case analyses. These are presented here using tables to outline the mean total costs, QALYs and ICERs along with scatter plots and CEACs.

*All the results presented in this section are from the base case analyses in the submission and **do not** take the discounted price of eribulin into account.*

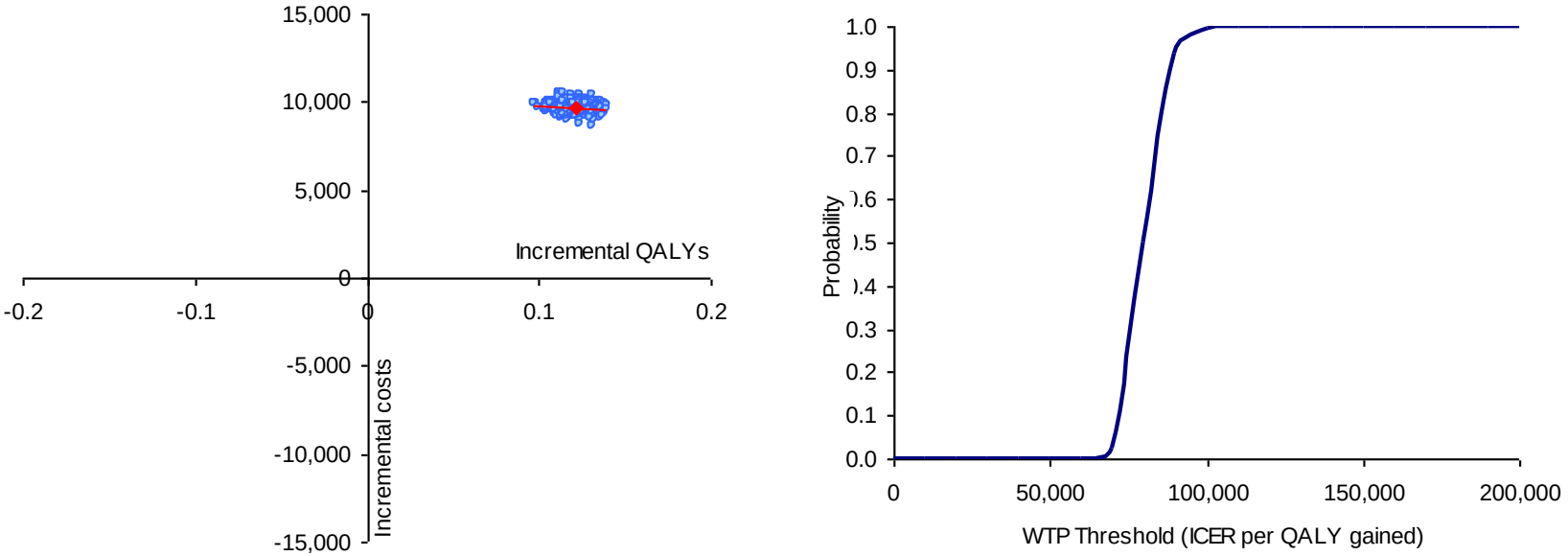
Eribulin vs. TPC

Table 1: PSA results for eribulin versus TPC *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,266	0.5694			
Eribulin	£39,895	0.6912	£9,629	0.1218	£79,049

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 5: Cost effectiveness plane and CEAC of eribulin vs. TPC *without* the PAS



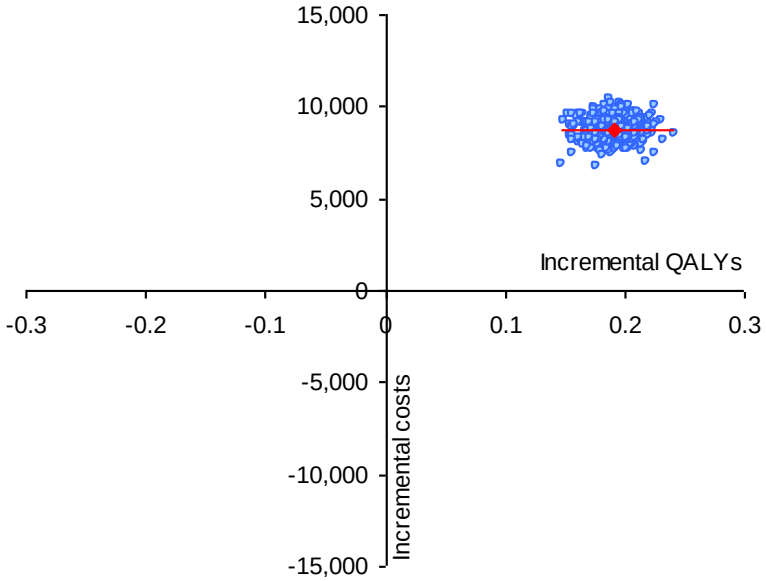
Eribulin vs. gemcitabine

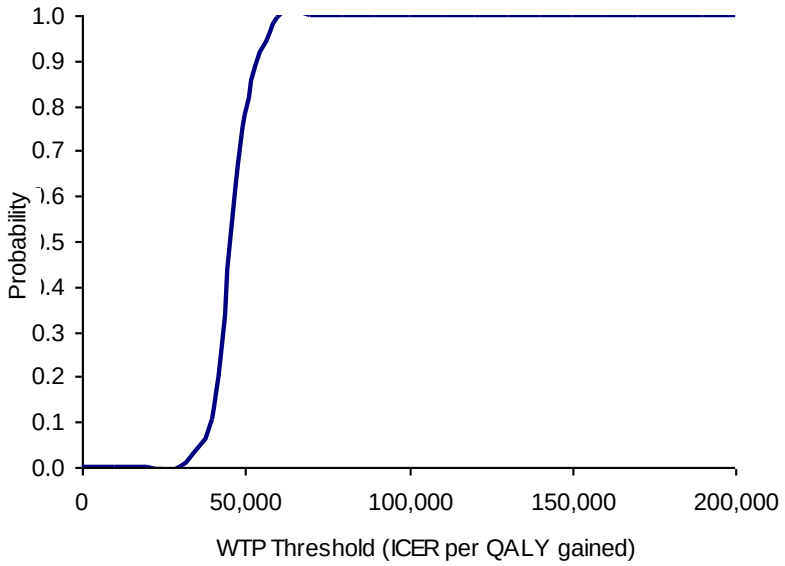
Table 2: PSA results for eribulin versus gemcitabine *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,227	0.4996			
Eribulin	£38,980	0.6903	£8,753	0.1907	£45,896

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 6: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine *without* the PAS





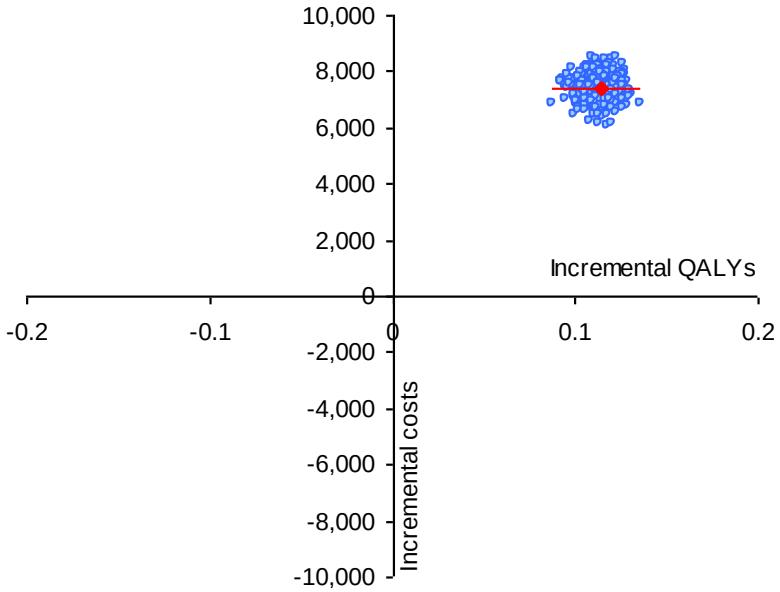
Eribulin vs. vinorelbine

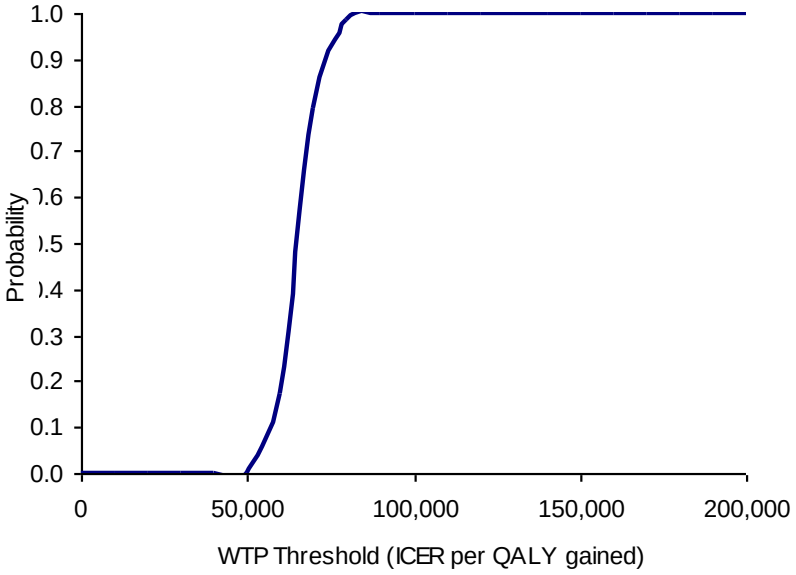
Table 3: PSA results for eribulin versus vinorelbine *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£30,059	0.5139			
Eribulin	£37,462	0.6270	£7,402	0.1131	£65,459

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 7: Effectiveness plane showing scatter plot of eribulin vs. vinorelbine *without* the PAS





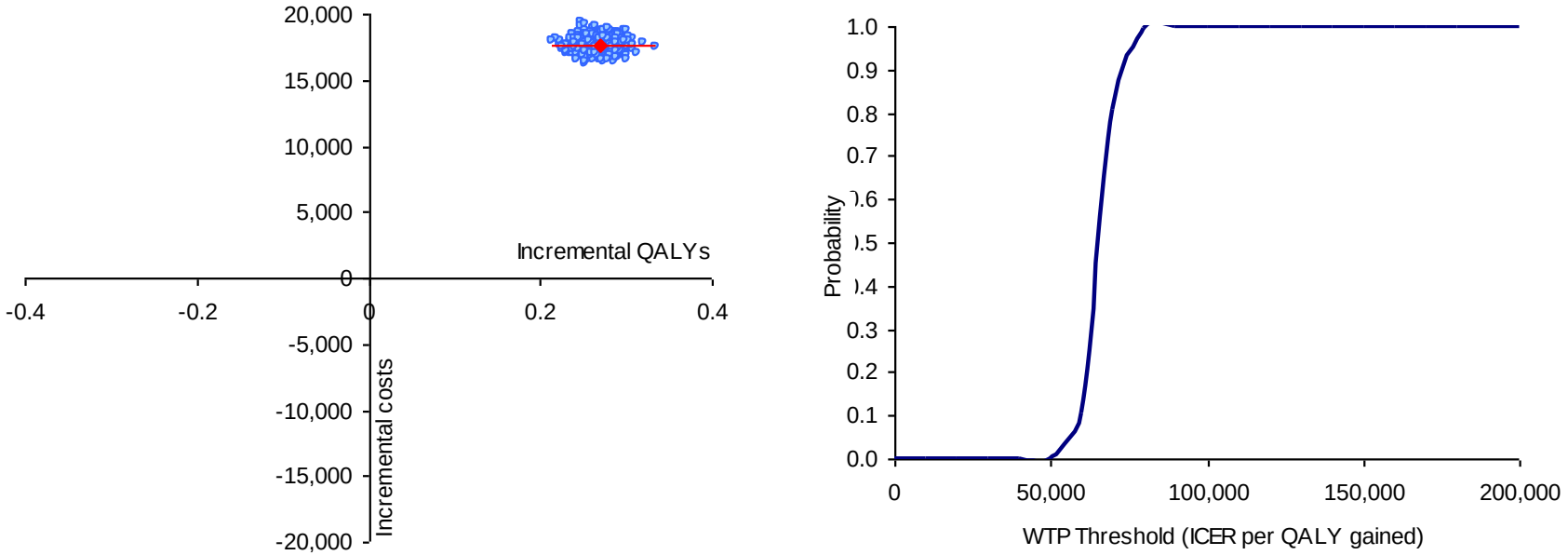
Eribulin vs. capecitabine

Table 4: PSA results for eribulin versus capecitabine *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,885	0.5177			
Eribulin	£44,542	0.7863	£17,657	0.2686	£65,748

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 8: effectiveness plane showing scatter plot of eribulin vs. capecitabine *without* the PAS



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

*Several scenario analyses were carried out in order to demonstrate the cost effectiveness of eribulin in alternative settings. All the results presented in this section are from the main submission and **do not take** into account the discounted price of eribulin (results with the PAS for the below deterministic analyses are presented in section 4.13)*

These analyses were as follows:

- *End of life guidance applied*
- *Drug costs: price of eribulin calculated per mg rather than per vial*
- *All region analysis*

In addition, an analysis to test the structural uncertainty within the model using hazard ratios to estimate survival in the model rather than Kaplan Meier curves was explored.

End of life guidance analysis

Eribulin meets the criteria for consideration under the Institute's end of life guidance. That is, eribulin is indicated for a relatively small number of patients who have LABC/MBC and have had a previous anthracycline and a taxane, the medicine is indicated for the treatment of patients with a diagnosis of a terminal illness and who are not, on average, expected to live for more than 24 months, and; eribulin is the only treatment in this setting to have demonstrated extension to life, compared to current NHS treatment (See Section 5.10.3 of the manufacture's submission). A scenario analysis was conducted on the assumption that eribulin qualifies for consideration under the end-of-life guidance, using the aforementioned full utility value of 0.83 for eribulin patients surviving beyond a certain number of days (the cumulative survival in the comparator arm) as shown in Table 5.

Table 5: Cumulative survival for comparators for EOL analysis

Comparator	Cumulative survival (number of days)
TPC	421
Vinorebine	392
Gemcitabine	363
Capecitabine	376

The analysis was conducted for the four base case analyses. Probabilistic results are also provided.

Table 6: End of life analysis results for eribulin versus TPC *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£39,939	0.7775	£9,490	0.2101	£45,168

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 7: End of life analysis results for eribulin versus gemcitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£38,982	0.8427	£8,830	0.3447	£25,618

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 8: End of life analysis results for eribulin versus vinorelbine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,982	0.5155			
Eribulin	£37,377	0.7092	£7,394	0.1937	£38,193

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 9: End of life analysis results for eribulin versus capecitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£44,423	0.9841	£17,657	0.4671	£37,798

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

End of life analysis – PSA results

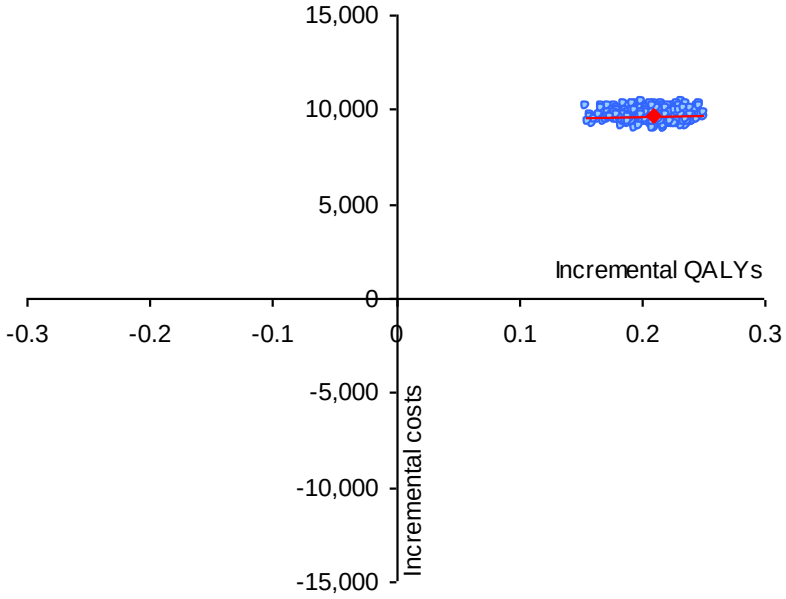
Eribulin vs. TPC

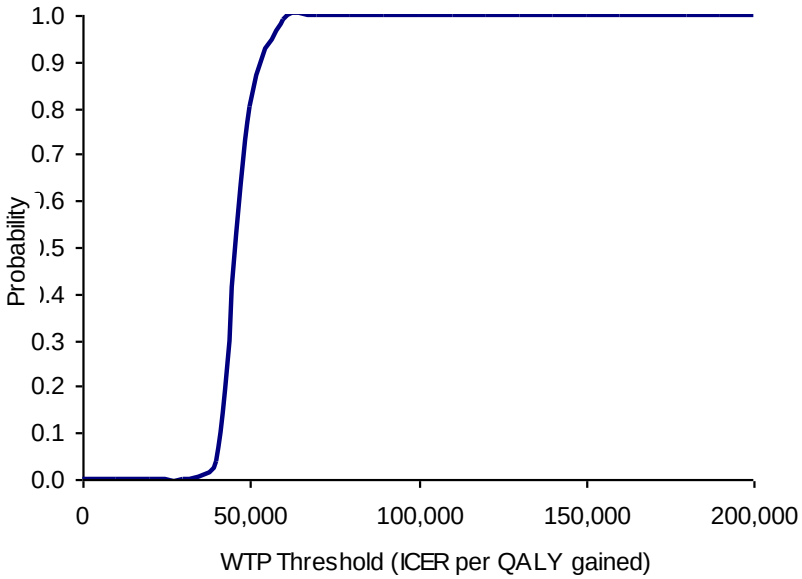
Table 10: PSA results for eribulin versus TPC end of life analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,173	0.5663			
Eribulin	£39,796	0.7770	£9,624	0.2107	£45,684

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 9: Cost effectiveness plane and CEAC of eribulin vs. TPC end of life analysis *without* the PAS





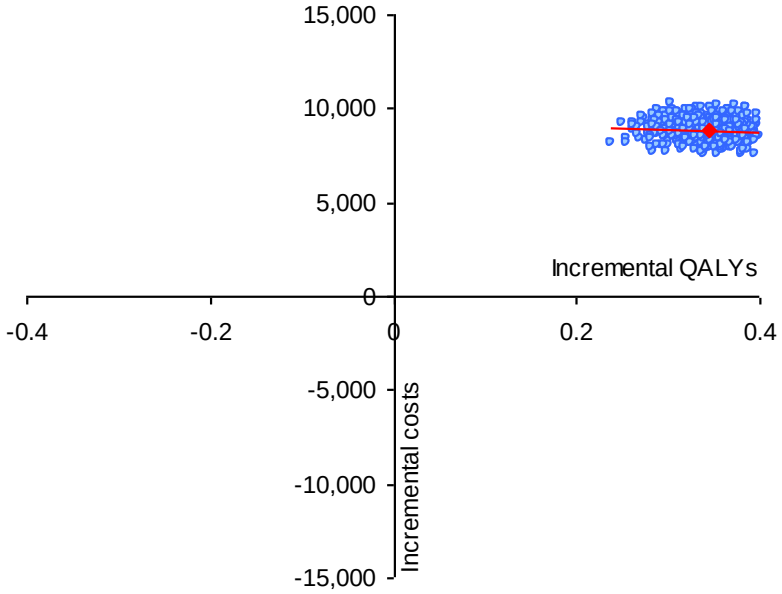
Eribulin vs. gemcitabine

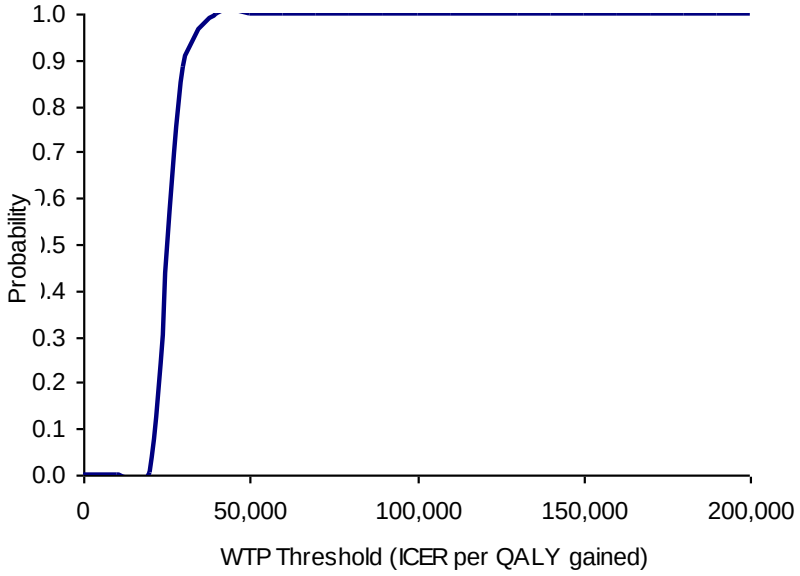
Table 11: PSA results for eribulin versus gemcitabine end of life analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,073	0.4967			
Eribulin	£38,912	0.8409	£8,838	0.3442	£25,679

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 10: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine end of life analysis *without* the PAS





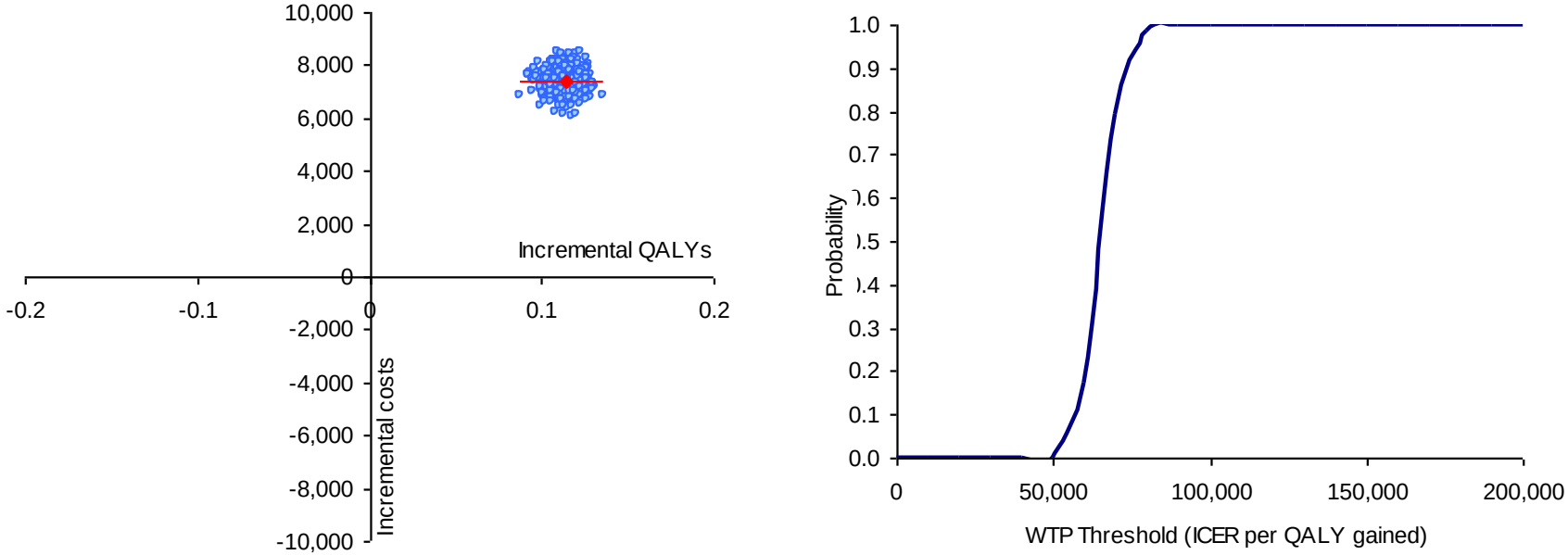
Eribulin vs. vinorelbine

Table 12: PSA results for eribulin versus vinorelbine end of life analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£30,295	0.5174			
Eribulin	£37,704	0.7112	£7,409	0.1938	£38,225

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 11: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine end of life analysis *without* the PAS



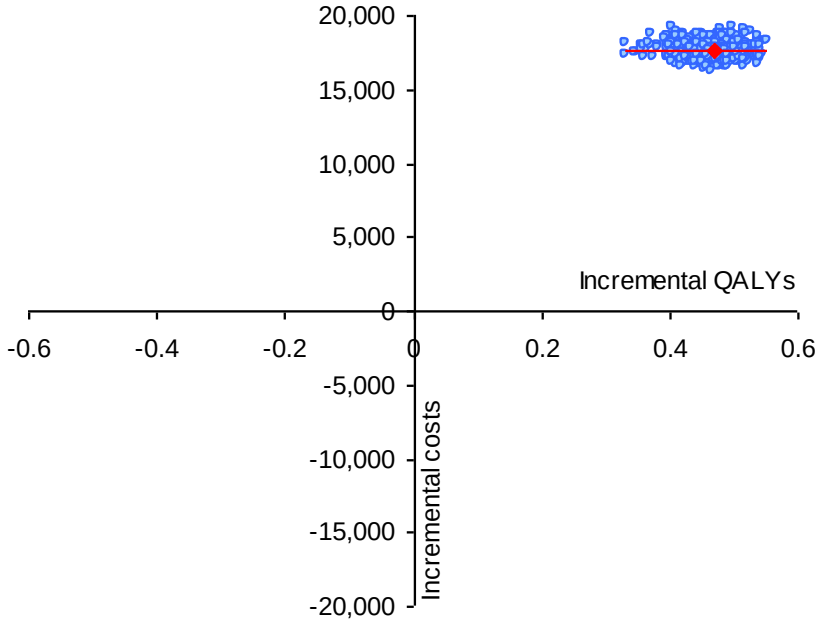
Eribulin vs. capecitabine

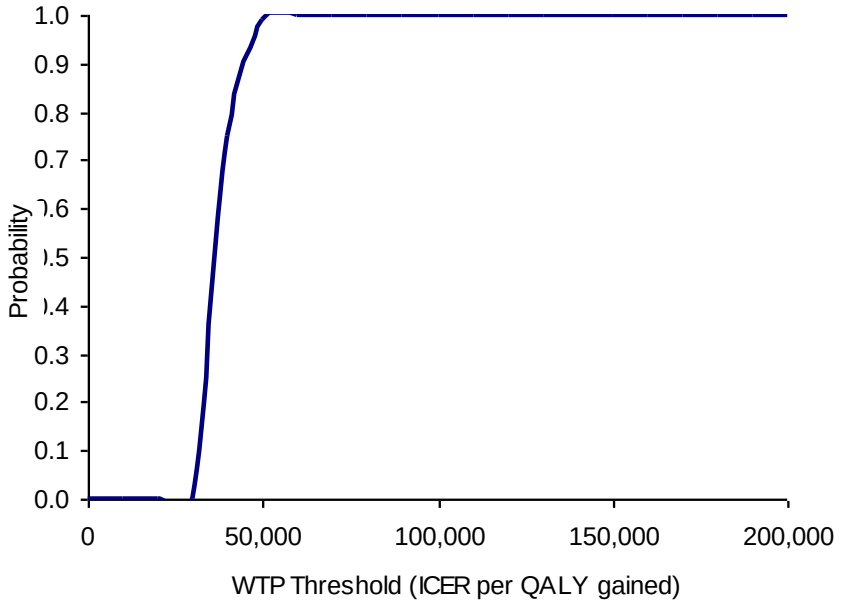
Table 13: PSA results for eribulin versus capecitabine end of life analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,708	0.5138			
Eribulin	£44,372	0.9817	£17,664	0.4679	£37,756

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 12: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine end of life analysis *without* the PAS





Drug costs – per milligram price for eribulin

A sensitivity analysis was carried out to determine the cost effectiveness of eribulin when drug costs were calculated using per-milligram (per mg) pricing and therefore assuming no wastage. The results for each of the base case analyses are presented here. Probabilistic results are also provided.

Table 14: Per mg analysis results for eribulin versus TPC *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£29,123	0.5674			
Eribulin	£37,469	0.6887	£8,346	0.1213	£68,801

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 15: Per mg analysis results for eribulin versus gemcitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£28,690	0.4980			
Eribulin	£36,670	0.6885	£7,981	0.1904	£41,907

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 16: Per mg analysis results for eribulin versus vinorelbine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,981	0.5155			
Eribulin	£35,255	0.6291	£5,274	0.1136	£46,428

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 17: Per mg analysis results for eribulin versus capecitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£25,280	0.5170			
Eribulin	£41,337	0.7853	£16,057	0.2683	£59,848

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Drug costs – per milligram price of eribulin analysis – PSA results

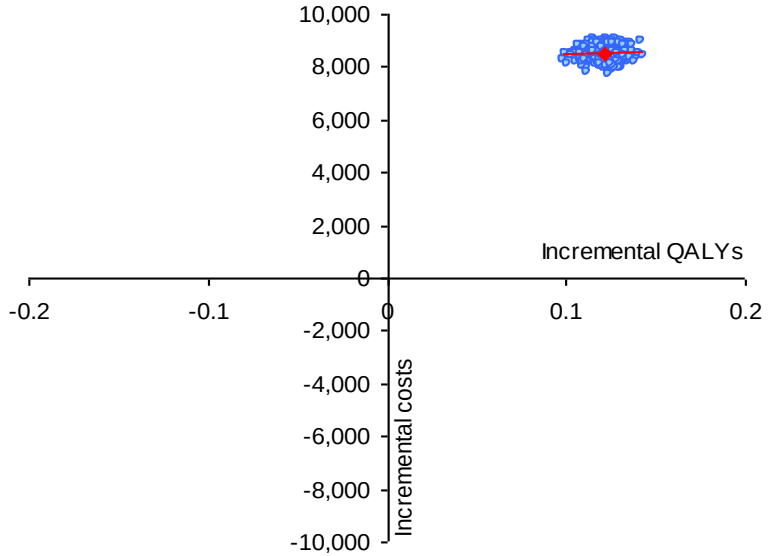
Eribulin vs. TPC

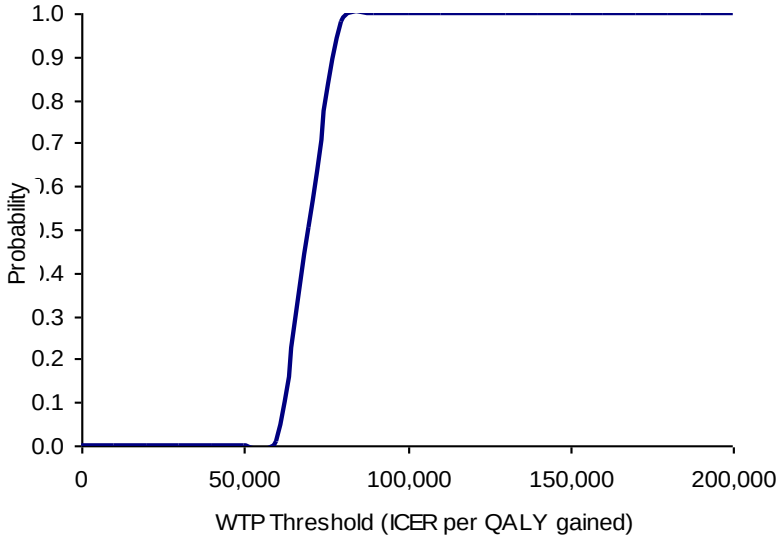
Table 18: PSA results for eribulin versus TPC - per mg analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£28,961	0.5691			
Eribulin	£37,481	0.6909	£8,520	0.1218	£69,969

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 13: Cost effectiveness plane and CEAC of eribulin vs. TPC - per mg analysis *without* the PAS





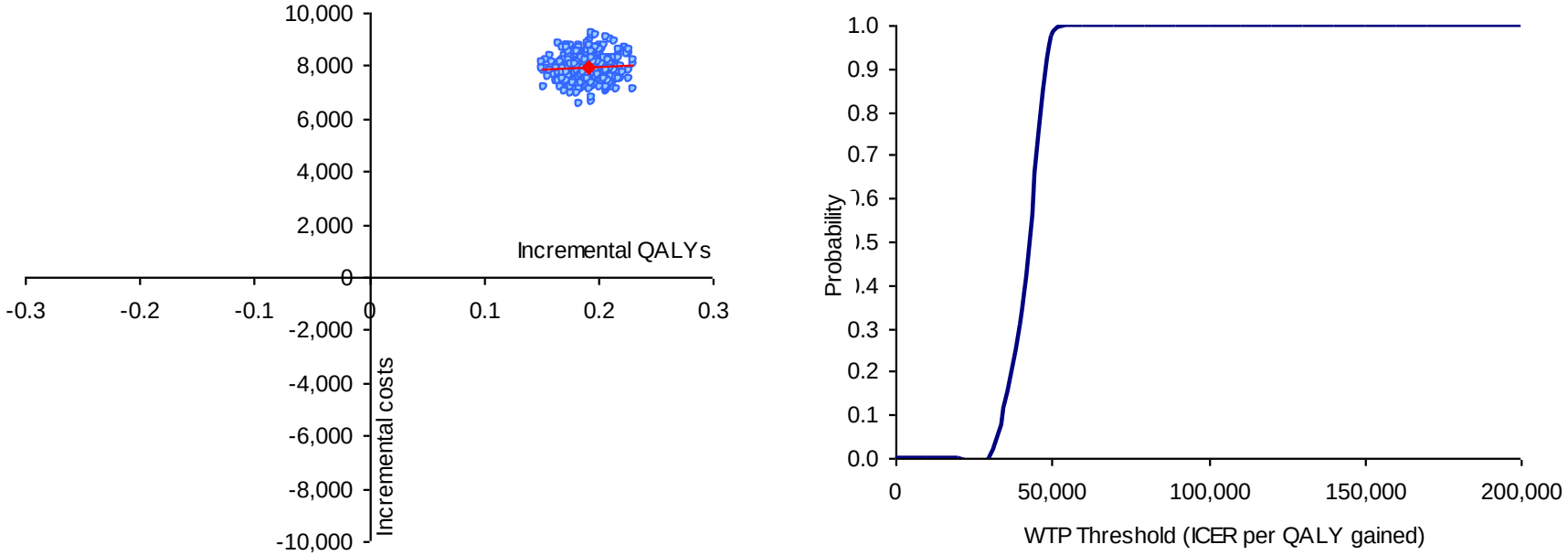
Eribulin vs. gemcitabine

Table 19: PSA results for eribulin versus gemcitabine - per mg analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£28,634	0.4964			
Eribulin	£36,582	0.6868	£7,947	0.1904	£41,747

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 14: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine - per mg analysis *without* the PAS



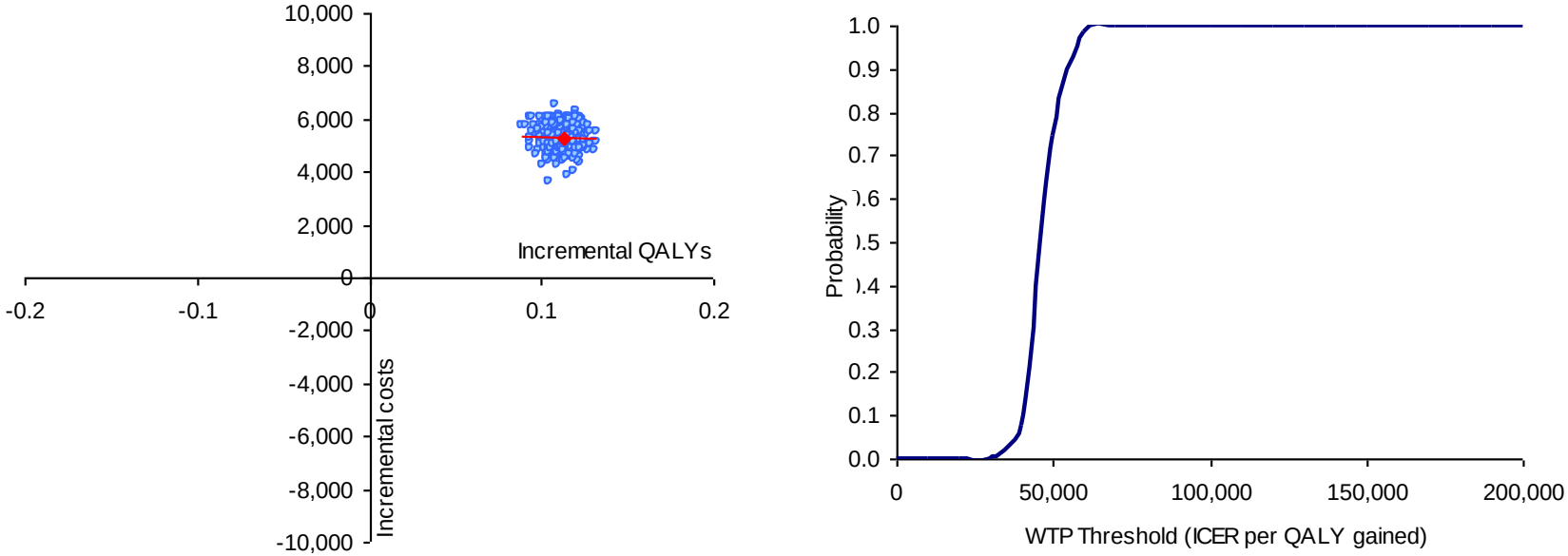
Eribulin vs. vinorelbine

Table 20: PSA results for eribulin versus vinorelbine - per mg analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,941	0.5138			
Eribulin	£35,228	0.6268	£5,287	0.1130	£46,769

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 15: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine - per mg analysis *without* the PAS



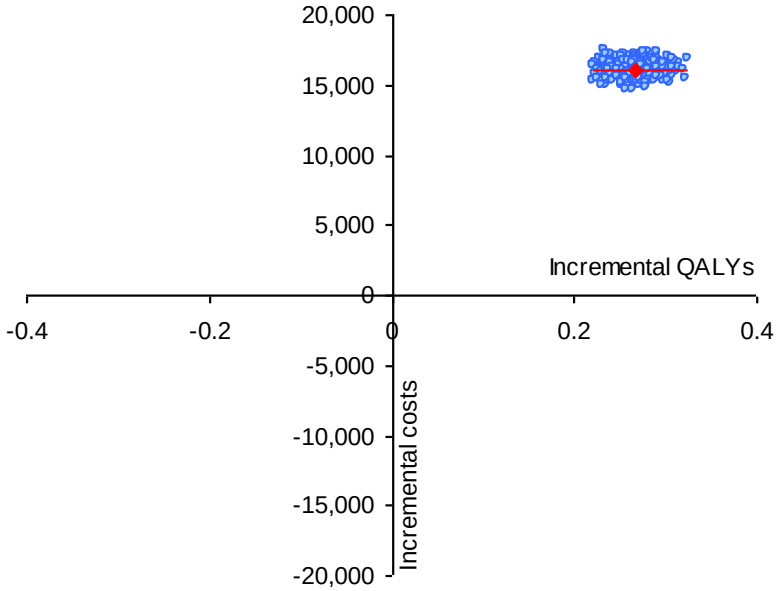
Eribulin vs. capecitabine

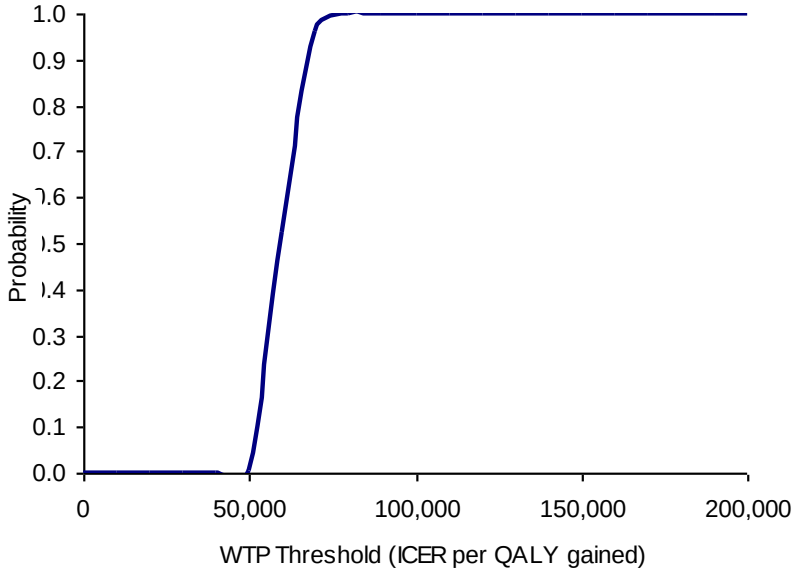
Table 21: PSA results for eribulin versus capecitabine - per mg analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£25,410	0.5165			
Eribulin	£41,485	0.7845	£16,074	0.2680	£59,972

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 16: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine - per mg analysis *without* the PAS





All regions analysis

A scenario analysis was carried out to examine the cost effectiveness of eribulin versus TPC when using data for all regions in the clinical trial. Probabilistic results are also presented.

Table 22: All regions analysis results for eribulin versus TPC *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£32,095	0.6018			
Eribulin	£40,786	0.6932	£8,856	0.0914	£95,088

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 23: All regions analysis results for eribulin versus gemcitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£32,437	0.5411			
Eribulin	£40,313	0.6888	£7,876	0.1477	£53,314

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 24: All regions analysis results for eribulin versus vinorelbine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£31,258	0.5392			
Eribulin	£37,944	0.6158	£6,685	0.0766	£87,352

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 25: All regions analysis results for eribulin versus capecitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£29,199	0.6634			
Eribulin	£42,708	0.7614	£13,509	0.0980	£137,795

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario analysis 4: all regions – PSA results

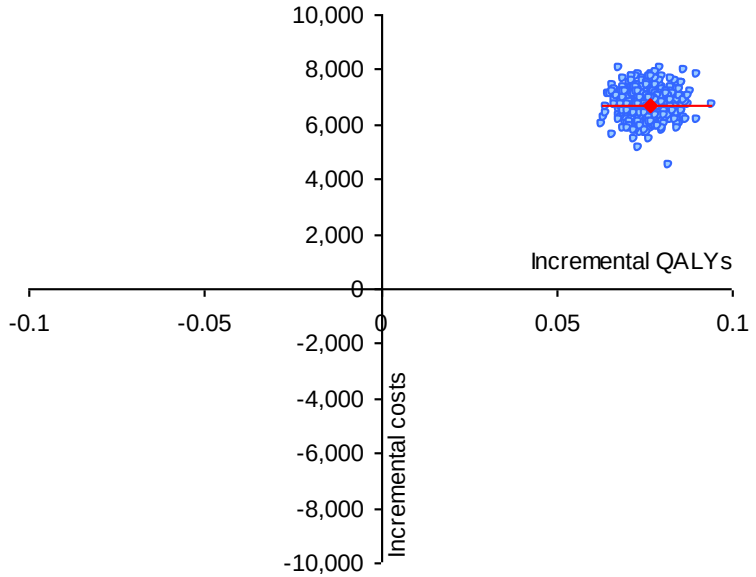
Eribulin vs. TPC

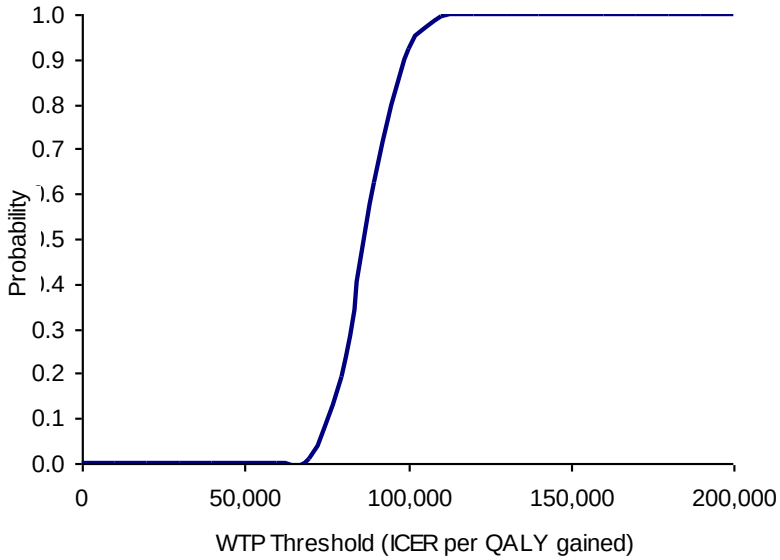
Table 26: PSA results for eribulin versus TPC - all regions analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£32,164	0.6015			
Eribulin	£40,864	0.6928	£8,700	0.0913	£95,010

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 17: Cost effectiveness plane and CEAC of eribulin vs. TPC - all regions analysis *without* the PAS





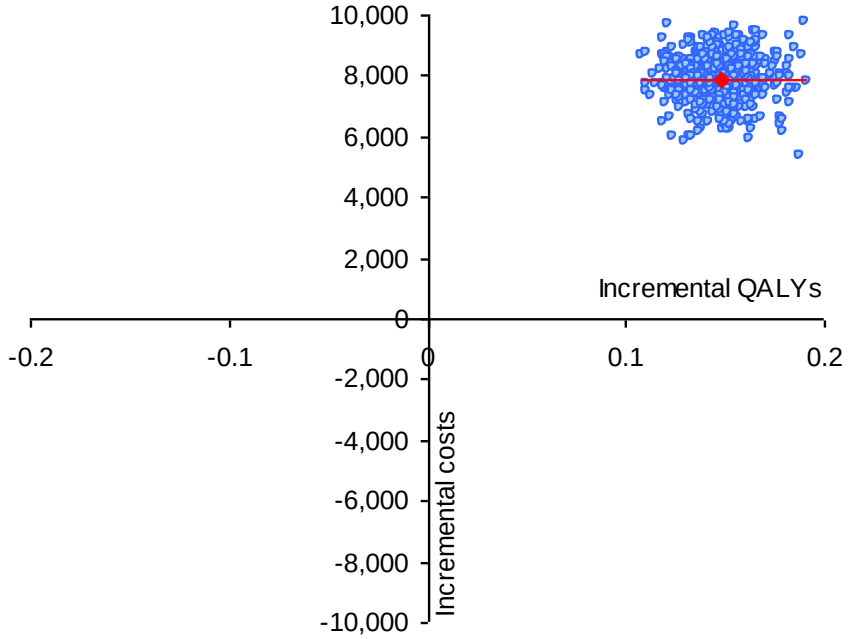
Eribulin vs. gemcitabine

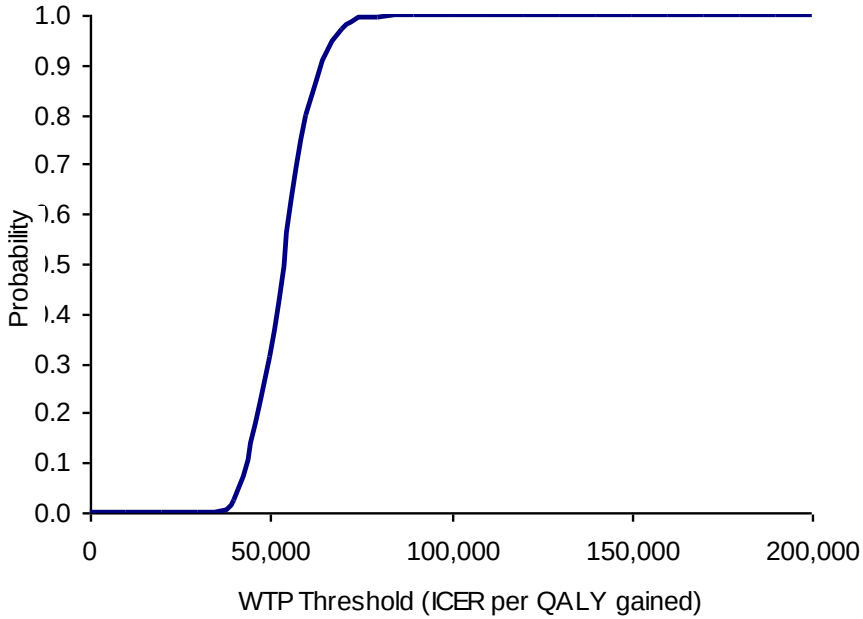
Table 27: PSA results for eribulin versus gemcitabine - all regions analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£32,285	0.5434			
Eribulin	£40,151	0.6914	£7,867	0.1479	£53,174

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 18: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine - all regions analysis *without* the PAS





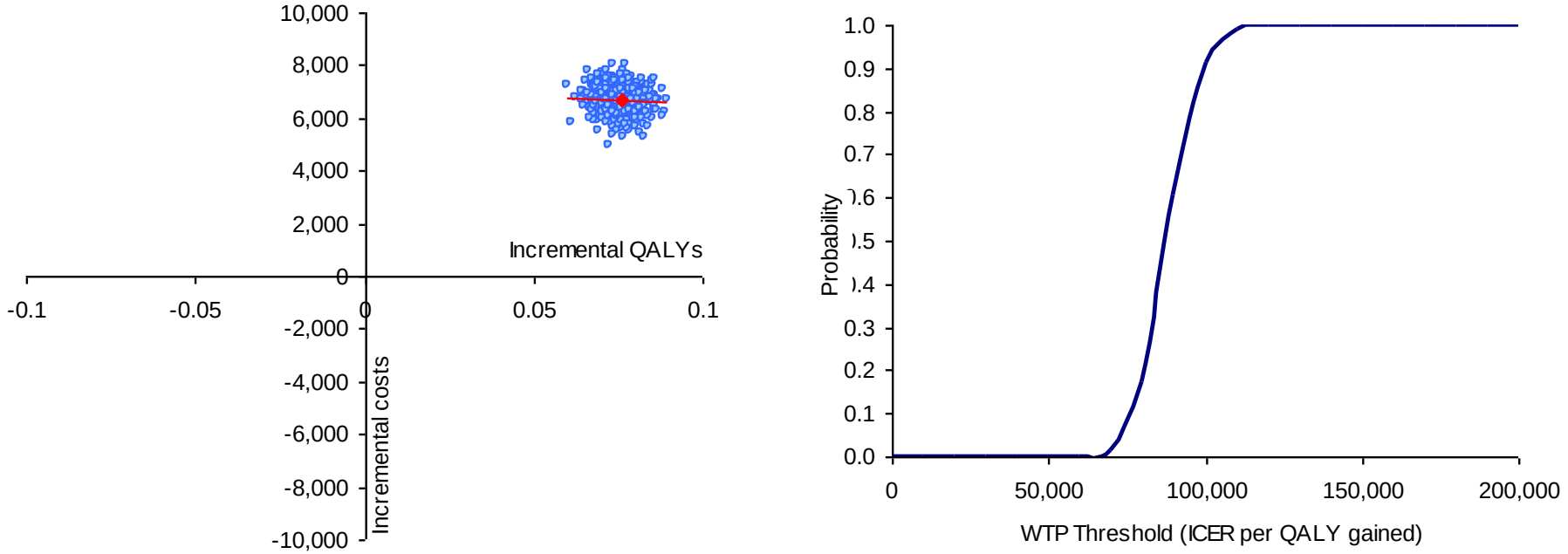
Eribulin vs. vinorelbine

Table 28: PSA results for eribulin versus vinorelbine - all regions analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£31,168	0.5365			
Eribulin	£37,895	0.6127	£6,726	0.0761	£88,284

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 19: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine - - all regions analysis *without* the PAS



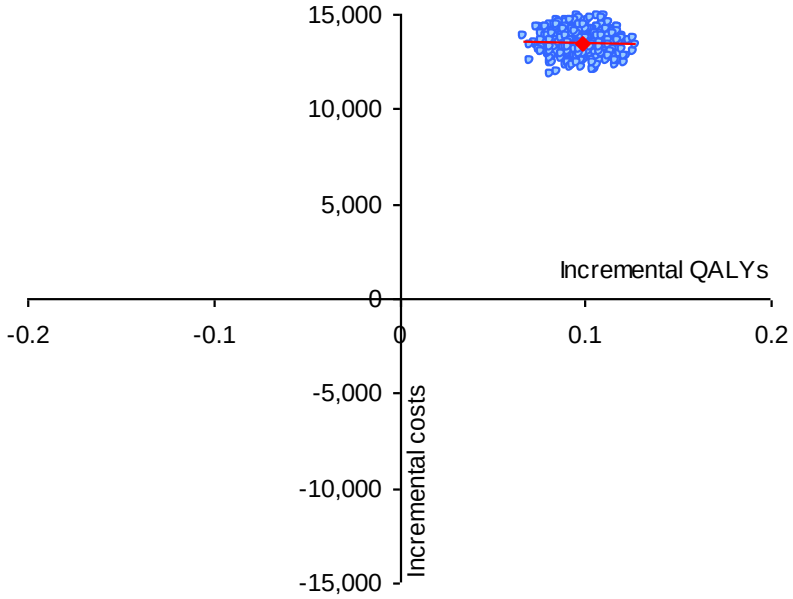
Eribulin vs. capecitabine

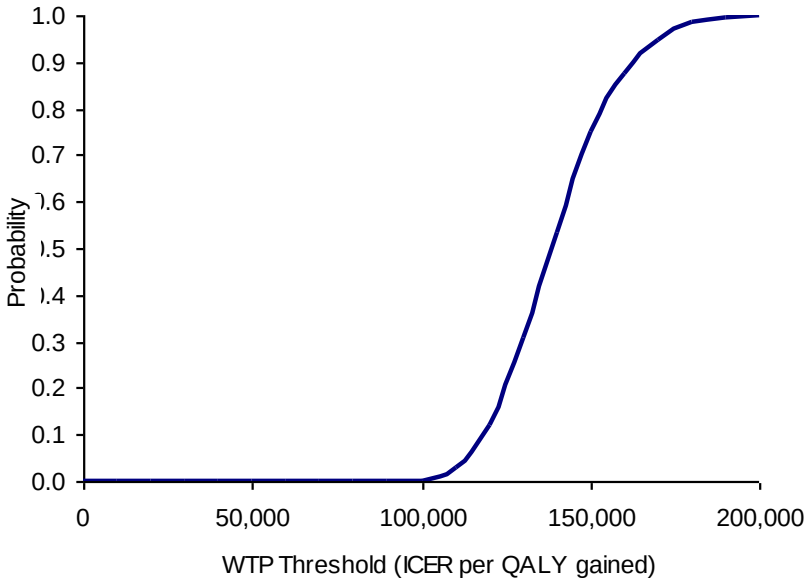
Table 29: PSA results for eribulin versus capecitabine - all regions analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£29,155	0.6648			
Eribulin	£42,654	0.7627	£13,499	0.0978	£137,907

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 20: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine - all regions analysis *without* the PAS





Structural sensitivity analysis

A structural sensitivity analysis was carried out by using hazard ratios calculated from the clinical trial to estimate the survival of patients in each of the treatment arms instead of using Kaplan Meier curves. The manufacturer's submission contains further details on how the HR model predicts the trial results in section 6.7.9.

The cost effectiveness results for each of the comparisons using HRs rather than Kaplan Meier curves to estimate the OS and PFS in the model is shown in Table 30 to Table 33. Probabilistic results are also presented.

Table 30: HR analysis results for eribulin versus TPC *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,449	0.5674			
Eribulin	£37,704	0.6475	£7,255	0.0801	£90,569

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 31: HR analysis results for eribulin versus gemcitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,152	0.4980			
Eribulin	£38,226	0.6181	£8,074	0.1201	£67,223

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 32: HR analysis results for eribulin versus vinorelbine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,983	0.5155			
Eribulin	£37,128	0.6884	£7,146	0.1729	£41,330

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 33: HR analysis results for eribulin versus capecitabine *without* the PAS

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,766	0.5170			
Eribulin	£41,622	0.8207	£14,856	0.3037	£48,905

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

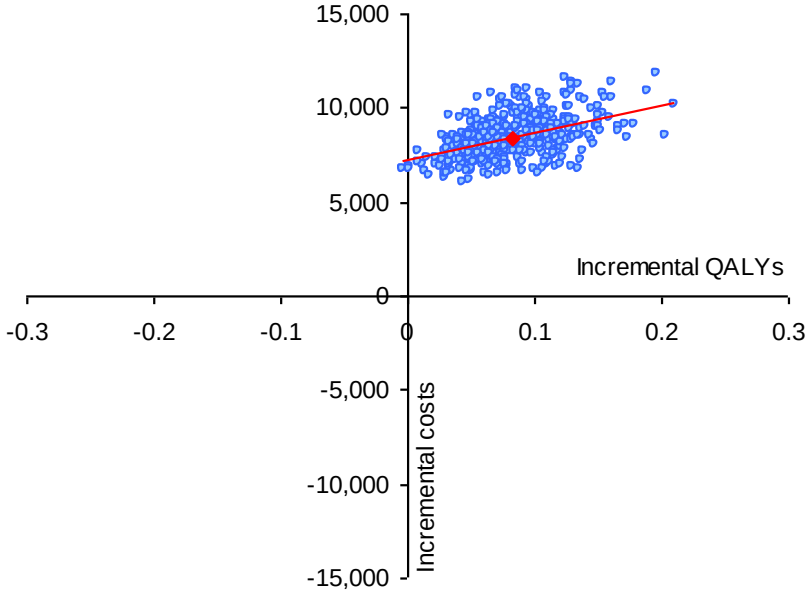
Structural sensitivity analysis – PSA results

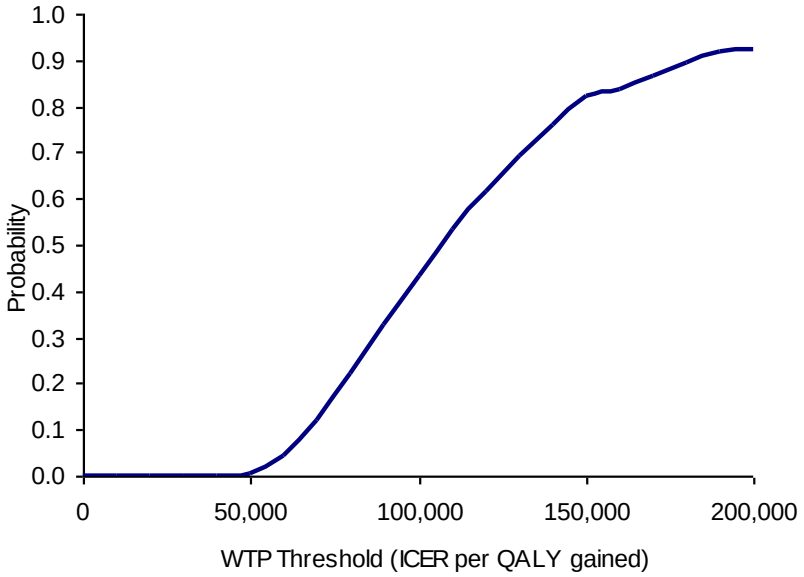
Table 34: PSA results for eribulin versus TPC – HR analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
TPC	£30,469	0.5670			
Eribulin	£37,802	0.6477	£7,333	0.0806	£90,878

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 21: Cost effectiveness plane and CEAC of eribulin vs. TPC – HR analysis *without* the PAS





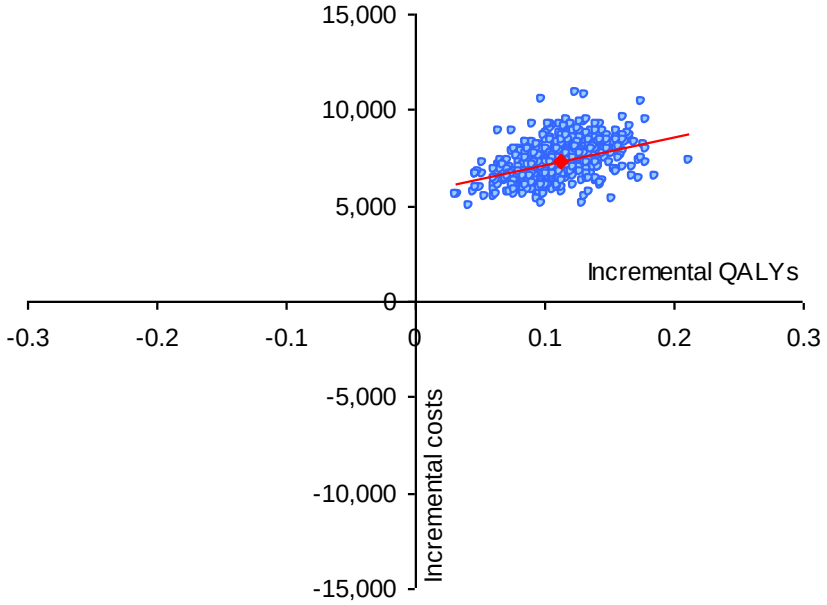
Eribulin vs. gemcitabine

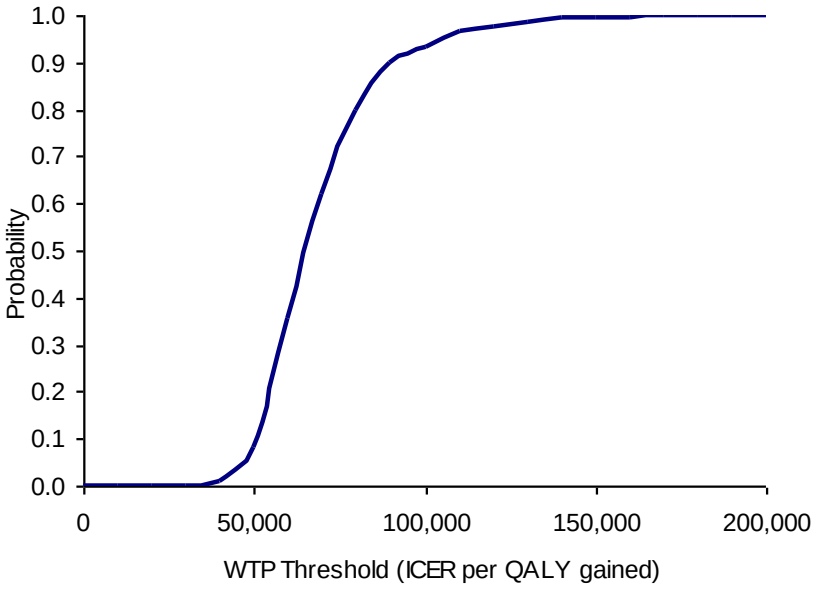
Table 35: PSA results for eribulin versus gemcitabine – HR analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Gemcitabine	£30,099	0.4976			
Eribulin	£37,385	0.6099	£7,286	0.1122	£64,920

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 22: Cost effectiveness plane and CEAC of eribulin vs. gemcitabine – HR analysis *without* the PAS





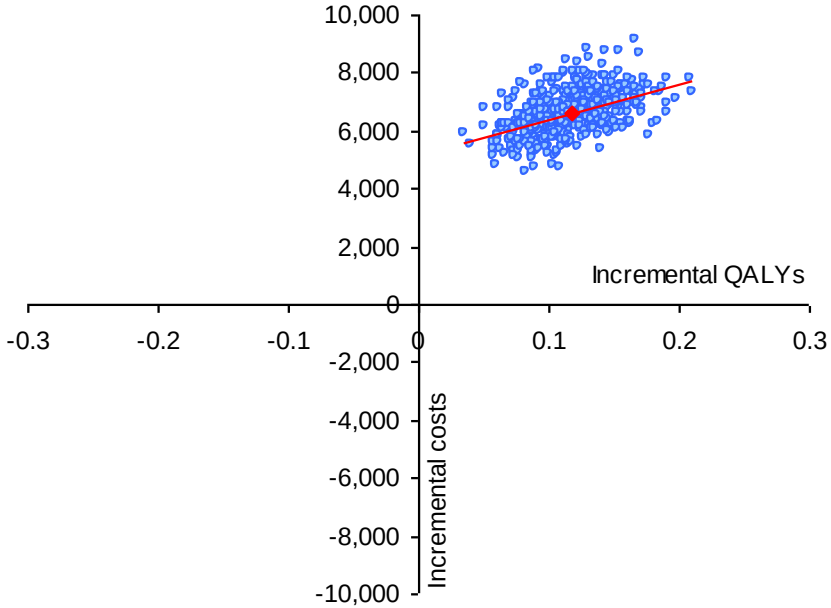
Eribulin vs. vinorelbine

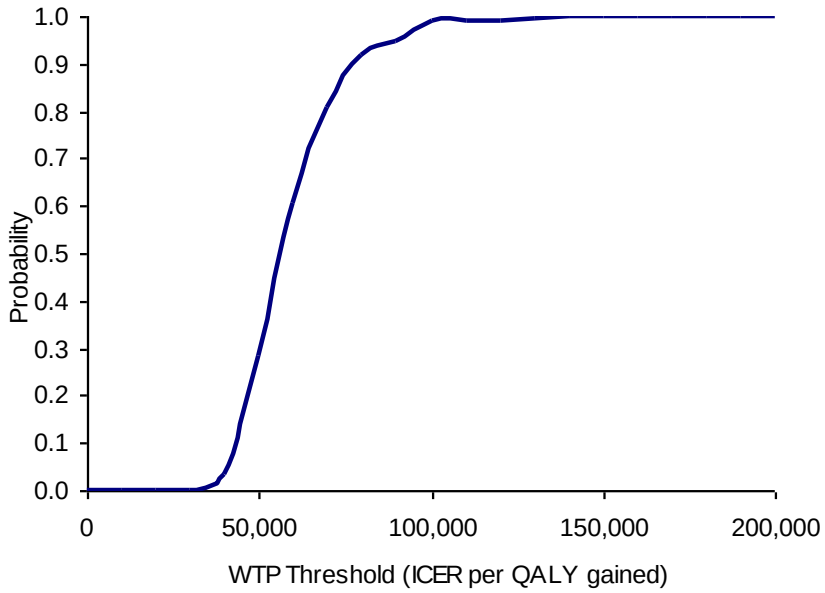
Table 36: PSA results for eribulin versus vinorelbine – HR analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Vinorelbine	£29,555	0.5141			
Eribulin	£36,641	0.6884	£7,094	0.1736	£40,851

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 23: Cost effectiveness plane showing scatter plot of eribulin vs. vinorelbine – HR analysis *without* the PAS





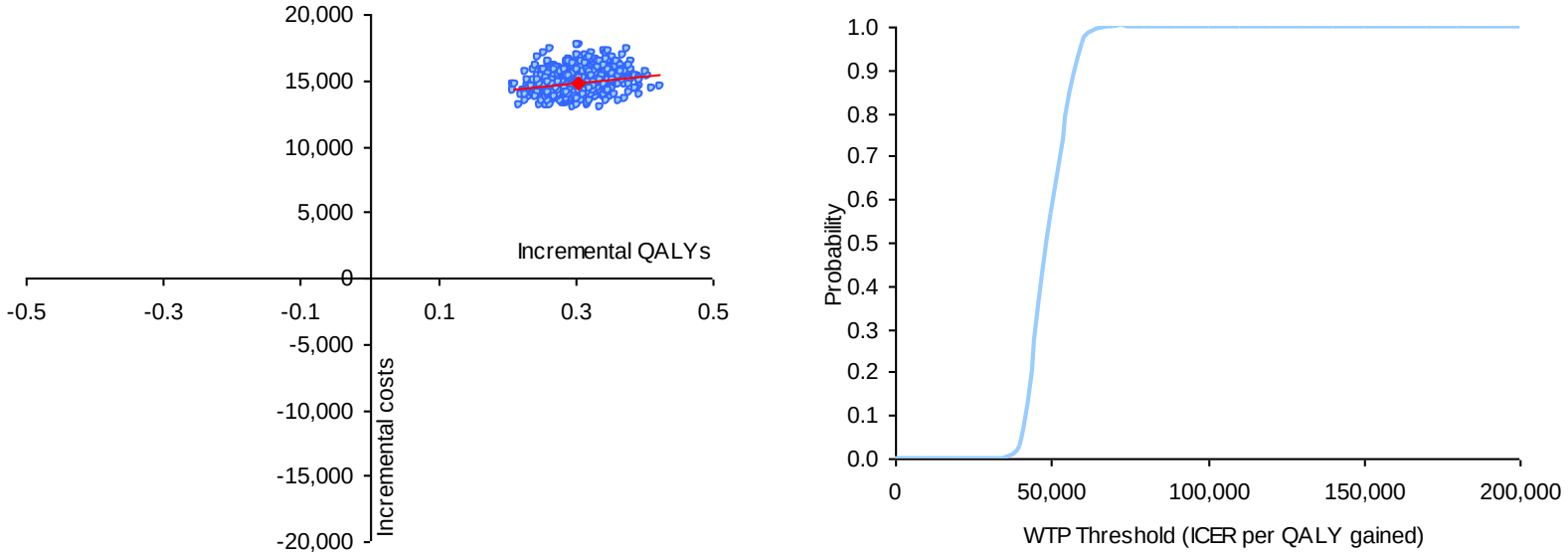
Eribulin vs. capecitabine

Table 37: PSA results for eribulin versus capecitabine – HR analysis *without* the PAS

Technologies	Mean totals		Incremental		Mean ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental
Capecitabine	£26,865	0.5173			
Eribulin	£41,609	0.8189	£14,743	0.3016	£48,879

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 24: Cost effectiveness plane showing scatter plot of eribulin vs. capecitabine – HR analysis *without* the PAS



4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

N/A straight discount off the list price.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

All ICERs presented in this section are deterministic model results.

Table 5.1 Results showing the impact of patient access scheme on ICERs – TPC

	ICER for intervention versus: TPC	
	Without PAS	**With PAS**
Base case (region1)	£79,049	£45,909
EOL criteria	£45,168	£27,516
Cost per mg analysis	£69,829	£42,672
All region analysis	£95,088	£50,059
HR analysis	£90,569	£57,916

Table 5.2 Results showing the impact of patient access scheme on ICERs – Gemcitabine

	ICER for intervention versus: Gemcitabine	
	Without PAS	**With PAS**
Base case (region1)	£46,366	£26,330
EOL criteria	£25,618	£15,019
Cost per mg analysis	£41,907	£26,330
All region analysis	£53,314	£26,242
HR analysis	£67,233	£37,292

Table 5.3 Results showing the impact of patient access scheme on ICERs – Vinorelbine

	ICER for intervention versus: Vinorelbine	
	Without PAS	**With PAS**
Base case (region1)	£65,135	£35,602
EOL criteria	£38,193	£20,875
Cost per mg analysis	£46,461	£22,473
All region analysis	£87,352	£41,276
HR analysis	£41,330	£22,996

Table 5.4 Results showing the impact of patient access scheme on ICERs – Capecitabine

	ICER for intervention versus: Capecitabine	
	Without PAS	**With PAS**
Base case (region1)	£65,812	£47,631
EOL criteria	£37,798	£27,356
Cost per mg analysis	£59,848	£45,085
All region analysis	£137,795	£92,084
HR analysis	£48,905	£35,493

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim

forms/rebate forms, guides for pharmacists and physicians, patient information documents.

N/A straight discount off list price.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

N/A.

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

N/A.

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

N/A.

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

N/A.

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

N/A.

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

N/A.

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

N/A.

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

N/A.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

N/A.

6th April 2011

NHS
National Institute for Health and Clinical Excellence

NICE
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

Tel: 0161 870 3154
Fax: 020 7061 9792

Email: kate.moore@nice.org.uk

www.nice.org.uk

Dear [redacted],

Re: Single Technology Appraisal – eribulin for the treatment of locally advanced breast cancer or metastatic breast cancer

The Evidence Review Group (Liverpool Reviews and Implementation Group) and the technical team at NICE have now had an opportunity to take a look at submission received on the 11th March 2011 by Eisai. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **12:00, 20 April 2011**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Raisa Sidhu – Technical Lead (raisa.sidhu@nice.org.uk). Any procedural questions should be addressed to Kate Moore – Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely,

Frances

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on clinical effectiveness data

A1. Please provide a fully-functioning version of the Clinical Study Report (CSR) as the links to the tables and appendices in the CSR for the EMBRACE trial do not appear to work.

A2. Please provide a copy of the statistical analysis plan for the EMBRACE trial.

A3. It is noted that evidence is cited from a report by Synovate Healthcare (reference 20 in the manufacturer's submission). Please clarify how the data in the Synovate file provided relates to the information presented in Section 2.2 and Section 7 of the manufacturer's submission.

A4. It is noted that the manufacturer's submission presents patient details for the overall trial population. Please provide patient details by each Region i.e. from Region 1, Region 2 and Region 3 for each of the following:

i) patient demographics (as in Table 7)

ii) baseline characteristics (as in Table 8)

iii) prior chemotherapy regimens (as in Table 9)

A5. It is noted that in the manufacturer's submission, overall survival data is presented for Region 1 by treatment of physicians choice (TPC), as in table 21. Please provide tables of patient details (patient demographics, baseline characteristics and prior chemotherapy regimens as requested in A4) by TPC (i.e. capecitabine, vinorelbine and gemcitabine).

A6. Regarding the statement on page 28, that the use of TPC as a comparator in the EMBRACE trial was agreed with the EMA, please clarify as to whether the EMA stipulated the use of TPC or whether the EMA agreed that TPC was the most useful comparator.

A7. Please provide information on protocol violations in the EMBRACE trial. Please provide the number and type of violations for each arm of the trial for the whole trial population.

A8. It is noted that no data regarding post-progression treatments given to patients in the EMBRACE trial has been provided. Please provide information on the post-progression treatments given to patients in both arms of the trial and the number of patients who received each treatment.

A9. Please provide clarification of the numbers of HER2+ patients in each arm of the EMBRACE trial who received pre-treatment with trastuzumab (i.e. prior to entering the trial).

A10. Please provide further information regarding adverse events for the EMBRACE trial population, including a summary of treatment-emergent adverse events in the eribulin group by CTCAE grade with an incidence of at least 1% in either treatment group.

Section B: Clarification on cost-effectiveness data

B1. All analyses and tables in the original submission should be updated to incorporate the discounted price of eribulin (as in the DH-approved patient access scheme).

B2. Please provide a revised copy of the raw trial data matrix in the submitted model (range B1221:S1985 of the "Data Trial" worksheet) with 4 additional columns as follows:

- PFS days based on Investigator Assessment

- PFS censored based on Investigator Assessment

- Days on treatment

- Days until response occurs (for responders CR/PR only)

This is to allow the Evidence Review Group to be able to examine the sensitivity of model results to different assumptions about the definition of disease progression, the duration of treatment and the timing of treatment response.

Eisai Limited

Ms Kate Moore
NICE
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

18th April 2011

Dear Kate

Re: Single Technology Appraisal – eribulin for the treatment of locally advanced breast cancer or metastatic breast cancer

Please find Eisai's response to the letter dated 6th April. In this version 'academic/ commercial in confidence' material has been removed as indicated in the confidential information checklist

Section A: Clarification on clinical effectiveness data

A1. Please provide a fully-functioning version of the Clinical Study Report (CSR) as the links to the tables and appendices in the CSR for the EMBRACE trial do not appear to work.

A fully functioning CSR has been send on CD to Kate Moore on Monday 18th by special delivery

A2. Please provide a copy of the statistical analysis plan for the EMBRACE trial.

Confidential report provided

A3. It is noted that evidence is cited from a report by Synovate Healthcare (reference 20 in the manufacturer's submission). Please clarify how the data in the Synovate file provided relates to the information presented in Section 2.2 and Section 7 of the manufacturer's submission.

No robust published estimates are available for the number of patient eligible for treatment for breast cancer after two previous treatments in a metastatic setting and after an anthracycline and a taxane. Data have to be drawn from various sources, one of which is a market research database, generated by Synovate. Data obtained from the Synovate database are combined with published epidemiological data to improve the accuracy of the final estimate. Of particular use is the estimate of the number of patients actually treated for MBC and data on treatment rates according to number of previous treatments (line of therapy) in MBC. As shown in the submission, these data were combined with published estimates of patients that progress to metastatic disease to generate an estimate for total patients eligible.

A4. It is noted that the manufacturer's submission presents patient details for the overall trial population. Please provide patient details by each Region i.e.from Region 1, Region 2 and Region 3 for each of the following:

i) patient demographics (as in Table 7)

ii) baseline characteristics (as in Table 8)

iii) prior chemotherapy regimens (as in Table 9)

Tables provided as academic in confidence

A5. It is noted that in the manufacturer's submission, overall survival data is presented for Region 1 by treatment of physicians choice (TPC), as in table 21. Please provide tables of patient details (patient demographics, baseline characteristics and prior chemotherapy regimens as requested in A4) by TPC (i.e. capecitabine, vinorelbine and gemcitabine).

The answer to this is incorporated in the Region 1 file above

A6. Regarding the statement on page 28, that the use of TPC as a comparator in the EMBRACE trial was agreed with the EMA, please clarify as to whether the EMA stipulated the use of TPC or whether the EMA agreed that TPC was the most useful comparator.

Confidential report provided

A7. Please provide information on protocol violations in the EMBRACE trial. Please provide the number and type of violations for each arm of the trial for the whole trial population.

Confidential report provided

A8. It is noted that no data regarding post-progression treatments given to patients in the EMBRACE trial has been provided. Please provide information on the post-progression treatments given to patients in both arms of the trial and the number of patients who received each treatment.

Confidential report provided

A9. Please provide clarification of the numbers of HER2+ patients in each arm of the EMBRACE trial who received pre-treatment with trastuzumab (i.e. prior to entering the trial).

Academic in confidence report provided

A10. Please provide further information regarding adverse events for the EMBRACE trial population, including a summary of treatment-emergent adverse events in the eribulin group by CTCAE grade with an incidence of at least 1% in either treatment group.

Confidential report provided

Section B: Clarification on cost-effectiveness data

B1. All analyses and tables in the original submission should be updated to incorporate the discounted price of eribulin (as in the DH-approved patient access scheme).

Revised submission submitted incorporating patient access scheme

B2. Please provide a revised copy of the raw trial data matrix in the submitted model (range B1221:S1985 of the "Data Trial" worksheet) with 4 additional columns as follows:

- PFS days based on Investigator Assessment

- PFS censored based on Investigator Assessment

- Days on treatment

- Days until response occurs (for responders CR/PR only)

Patient level data provide

Yours sincerely

Eisai Limited

National Institute for Health and Clinical Excellence

NICE
Level 1A, City Tower
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Fax: 020 7061 9792

Email: kate.moore@nice.org.uk

www.nice.org.uk

Dear [redacted],

Thank you for your responses to our clarification questions. We have a further query regarding question B2 and would appreciate you getting back to us on this by **Friday 6 May 2011 at the latest**.

According to the protocol, trial treatments should be discontinued when (among other events) disease progression occurs; as assessed by the investigator according to RECIST criteria or clinical evidence. However, when comparing the investigator 'PFS days' variable and the 'Time on treatment' variable, there are 103 patients who appear to have continued on treatment for 30 days up to a maximum of 259 days beyond the time the investigator considered that their disease had progressed. As an example: Patient 19031014 is shown in the IPD extract to have had 183 days of PFS (independent assessment) or 266 days of PFS (investigator assessment). However, in CSR Table 16.2.1.2 page 95 she is shown receiving TPC (capecitabine) up to day 423, which is 157 days after PFS ends (i.e. date of progression). Therefore, there appear to be protocol violations not identified elsewhere in the CSR.

It is unclear as to whether the data reported reflect the clinical events and their timing accurately, or if it is a consequence of some inconsistency of definition or calculation affecting one of more of the IPD variables supplied. Therefore, could you please confirm whether other treatments were allowed after progression for the 103 patients, and if so, why and where in the study protocol the criteria for these treatments are specified?

Kind Regards

Kate Moore
Technology Appraisals Project Manager - Committee D
0161 870 3154

Dear Kate
The discrepancy in relation to question B2 is as a result of the progression/censoring rules associated with PFS as per the FDA guidance. If the investigator calls progression due to progressive disease (PD) without confirmatory scans then the PFS date used is the date of the last tumour assessment prior to discontinuation. Similarly, if the progression date follows missed assessments then the progression date used will be the last scan date prior to the missed assessments. If the patient lack any post baseline tumour assessments then this could result in progressive disease being deemed to occur at day 1 (to avoid the introduction of negative integers).
In short : the investigator will continue to treat the patient until they deem progression, however the date of progression used in the analysis (based upon the FDA guidance) could be earlier than that deemed by the investigator at the time of study conduct .
The rules were prospectively agreed with the regulatory agencies and as they apply to both treatment arms equally then there will be no treatment arm bias.
After discontinuation of study drug (eribulin or TPC), the Investigators were required to provide the date of the first new anticancer treatment in order to be able to censor for PFS. Investigators chose treatment based on what they thought was appropriate and there were no specific criteria in the selection of this treatment
Kind regards
[redacted]

Eisai Limited
Registered in England No. 2242511
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Please note our new telephone no. is +44 (0) 845 676 1400 and the fax is +44 (0) 845 676 1401

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Eribulin for the treatment of locally advanced or metastatic breast cancer

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: [redacted], [redacted] and [redacted]

Name of your organisation: Breast Cancer Care jointly with Breakthrough Breast Cancer and Breast Cancer Campaign

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?

√ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Eribulin for the treatment of locally advanced or metastatic breast cancer

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. Advantages

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

This review considers eribulin as a monotherapy for the treatment of women with locally advanced or metastatic breast cancer, whose disease has progressed after at least two chemotherapy treatments (including an anthracycline and a taxane). Therefore, if eribulin was approved it would offer an additional option for patients whose previous chemotherapy regimen had failed. This is important as metastatic breast cancer is not curable and many of the treatments available for advanced or metastatic breast cancer are increasingly available for use in the primary setting. When early breast cancer is treated by these therapies the patient will have an increased risk of drug resistance. This can reduce the treatment options available to them in the metastatic setting, demonstrating the importance of the availability of additional treatments.

Eribulin has been shown to offer significant benefits in overall survival and has been reported to be the only single agent to date to show a prolonged overall survival effect in patients with heavily pre-treated metastatic breast cancer.[1] In the Phase III EMBRACE trial a statistically significant survival advantage of 2.5 months was observed in patients receiving eribulin compared to other treatments of physician's choice[2] [3]. One year survival was also reported to be better for the patients who received eribulin (53.9% vs 43.7%).[4] This clearly demonstrates an important advantage the technology has for the treatment of metastatic breast cancer since even a survival benefit of a few months is known to be important for this patient group where the median survival time from diagnosis is typically just 2-4 years.[5]

Eribulin exerts its effect by disrupting microtubule formation of cancer cells during cell division which triggers programmed cell death. This mode of action allows eribulin to target many different forms of breast cancer and has the potential to be effective in cases where the cancer has failed to respond to other treatments. Additionally,

[1] Gradishar, W., 2011. The place for Eribulin in the treatment of metastatic breast cancer. i*Current Oncology Reports*, 13(1):11-16.
[2] Twelves, C. *et al.* 2010. Phase III trials of Eribulin Mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. *Clinical Breast Cancer*, 10(2):160-163.
[3] Mani, S. and Swami, U., 2010. Eribulin mesilate, a halichondrin B analogue, in the treatment of breast cancer. *Drugs of Today*, 46(9):641-53.
[4] Abraham, J., 2011. Eribulin in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *Community Oncology*, 8(1)15-19.
[5] Chung, C. T. and Carlson, R. W., 2003. Goals and Objectives in the management of metastatic breast cancer. *Oncologist*, 8(6)514-20.

eribulin has the added advantage of being effective in patients whose disease is resistant to other tubulin targeting agents.[6]

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

When compared to treatment of physicians' choice eribulin has been shown to significantly improve overall survival in patients with metastatic breast cancer who have previously undergone two other chemotherapy regimes. Patients' response rate was also significantly higher than the control group (12.2% vs 4.7%).[7] The clinical benefit rate (rates of complete plus partial response and stable disease $\geq$ 6 months) also favoured patients receiving eribulin compared to physicians choice (22.6% vs 16.8%).[8] Additionally, progression free survival is reported to be higher in those receiving eribulin although it should be noted this improvement was not statistically significant upon independent review.[9]

The enhanced survival benefit of this technology has obvious benefits for patients as it will allow them additional time to spend with their families and loved ones. For patients with metastatic breast cancer the importance of this should not be ignored.

Also symptom control including pain control was reported as having been improved.[10] [11] This has the potential to offer improvements in quality of life, including social functioning and quality time with family and friends.

[6] Twelves, C. *et al.* 2010. Phase III trials of Eribulin Mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. *Clinical Breast Cancer*, 10(2):160-163.
[7] Abraham, J., 2011. Eribulin in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *Community Oncology*, 8(1)15-19.
[8] Ibid.
[9] Ibid.
[10] Twelves, C. *et al.* 2010. Phase III trials of Eribulin Mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. *Clinical Breast Cancer*, 10(2):160-163.
[11] Cortes, J. *et al.* 2010. Phase II study of the halichondrin B Analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with anthracycline, a taxane and capecitabine. *ASCO American Society of Clinical Oncology conference*

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What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)

2. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

Eribulin, like all chemotherapy agents, has associated side effects, but the ones associated with this technology are acceptable for a standard regimen. Side effects consist mainly of neutropenia (low number of neutrophils) and fatigue.[12] [13] [14] A low incidence of peripheral neuropathy (damage of nerves in peripheral nervous system) and febrile neutropenia has been reported.[15] Additionally, there appears to be minimal chances of drug-drug interactions and hypersensitivity.[16] In general the side effect profile of this technology is likely to be manageable for patients in this setting making it another feasible option as a treatment for patients in the metastatic setting.

Metastatic breast cancer patients have limited treatment options and so may tolerate the side effects of chemotherapy if it means they will see benefits such as better quality of life or longer survival.

'All drugs have some side effects and as long as the benefit outweighs the risk then I'd be happy to receive it' – breast cancer patient (and Breakthrough Breast Cancer supporter).

Eribulin currently has to be administered in hospital as it requires a short intravenous (iv) infusion. This may be of concern for some needle phobic patients. Additionally, travel to a hospital may be inconvenient for the patient (and carer) as they will need

[12] Mani, S. and Swami, U., 2010. Eribulin mesilate, a halichondrin B analogue, in the treatment of breast cancer. *Drugs of Today*, 46(9):641-53.
[13] Morris, P. G., 2010. Advances in therapy: eribulin improves survival for metastatic breast cancer. *Anti-cancer Drugs*, 21(10):885-9.
[14] Cigler, T. and Vahdat, L. T., 2010. Eribulin mesylate for the treatment of breast cancer. *Expert Opinion in Pharmacotherapy,* 11(9):1587-93.
[15] Morris, P. G., 2010. Advances in therapy: eribulin improves survival for metastatic breast cancer. Anti-*cancer Drugs*, 21(10):885-9.
[16] Mani, S. and Swami, U., 2010. Eribulin mesilate, a halichondrin B analogue, in the treatment of breast cancer. *Drugs of Today*, 46(9):641-53.

to go to the hospital, possibly take time off work and organise transportation which is likely to incur costs.

However, while issues such as time, costs and stress do commonly inconvenience patients they are the same as nearly all other chemotherapy agents. Therefore, eribulin is not considered significantly different in its use.

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

None we are aware of.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Eribulin is a novel chemotherapy agent and is not specific to a particular type of tumour. It therefore has the potential to benefit all patients with advanced breast cancer suitable for treatment with chemotherapy whose cancers have already been treated with, and failed to respond to, other targeted therapies. This would include metastatic breast cancer patients whether they are hormone sensitive, HER2 positive or triple negative. Again this is important as it expands the treatment options available in a setting which has limited options.

Special consideration should be given to patients with hepatic impairment as eribulin exposure increases with deceasing hepatic function.[17] Dose modification is recommended in these patients.[18]

Future studies into the applications of eribulin will investigate its potential role in other settings including for early breast cancer, to ascertain how best to incorporate this new agent into current treatment paradigms.[19]

[17] Roche. http://www.herceptin.net/portal/eipf/pb/herceptin/trastuzumab
[18] Abraham, J., 2011. Eribulin in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *Community Oncology*, 8(1)15-19.
[19] Morris, P. G., 2010. Advances in therapy: eribulin improves survival for metastatic breast cancer. *Anti-cancer Drugs*, 21(10):885-9.

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Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

Upon progression of breast cancer, standard lines of chemotherapy include capecitabine, vinorelbine, taxane/gemcitabine combinations and platinum-based regimens. In Europe, treatment with combination regimens tends to be favoured to maximise the probability of response. In the UK, many clinicians favour sequential use of single agent regimens in the interests of balancing disease control and quality of life. Taxane and anthracycline containing regimens are often received in standard practice but may be inappropriate comparators in this appraisal as the relevant population are patients who must have already received these technologies and thus failed to respond to such treatments.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

Eribulin has been shown to provide benefits for patients with metastatic or advanced disease who have previously received and stopped responding to other chemotherapy agents. Overall survival as well as patients response rate was found to be statistically better in those patients receiving eribulin. .

In the EMBRACE trial Eribulin was administered iv over 2-5 minutes on days one and eight of a 21 day cycle.[20] This duration of infusion has advantages over other chemotherapy agents as it is very short, for example HER2 positive patients receiving trastuzumab are given an initial iv infusion of 90 minutes, reducing to 30 minutes on subsequent infusions if well tolerated.[21] The process of receiving chemotherapy is not a pleasant one for the patient so the shorter the duration of infusion the better. This makes eribulin a more convenient option over other iv chemotherapy agents and has the added advantage that patients will be required to spend less time in hospital.

[20] Abraham, J., 2011. Eribulin in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *Community Oncology*, 8(1)15-19.
[21] Witteveen, P. et al. 2010. Eribulin mesylate pharmacokinetics in patients with hepatic impairment. *Journal of Clinical Oncology* 28:15s

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The side effects caused by this treatment are known to be manageable compared to other therapies. Common side effects include fatigue and neutropenia. However, these represent a manageable profile making this therapy an attractive option for many patients in the metastatic setting.

Some patients have told us that given the choice they prefer regular visits to the hospital rather than to receive treatment at home as they are in more contact with their health care team and can have treatment administered by a health care professional. Eribulin administration meets the needs of these patients as it requires a short iv infusion by a chemotherapy team.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe

Eribulin is administered intravenously and will therefore require the patient to attend hospital. Travel and associated costs including financial costs and inconvenience may thus disadvantage the patient and their carer.

Furthermore, as eribulin is administered intravenously it may be an unattractive option for a small number of needle phobic patients.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

We are unaware of patients receiving this treatment outside the context of a clinical trial.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

None known

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Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

None known

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

Eribulin may provide an addition to the existing treatment options that are available for women with advanced or metastatic breast cancer, particularly where the breast cancer is resistant to other chemotherapies. Patients with this condition typically have limited treatment options and those with resistant tumours will have even further limitations on their options. It is important that a range of treatments be made available as not all will meet the needs of the individual patient. Furthermore, patients with locally advanced or metastatic breast cancer, understandably, want access to treatments that will give them the chance of both an increased length of survival and improved quality of life to spend more quality time with their friends and families, something this technology can provide.

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

If eribulin is not made available on the NHS this would limit the effective treatment options available for these patients in the advanced or metastatic disease setting. More importantly it would deny patients a treatment option which has proven benefits in improvements in life expectancy.

Are there groups of patients that have difficulties using the technology?

None known

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Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?

It is essential that clinically effective drugs are available through the NHS to all patients who may benefit from them and NICE approval for eribulin would achieve this outcome. The introduction of the Cancer Drugs Fund is a welcome route of access to those drugs that have not been approved by NICE, but there is not necessarily the consistency of availability across the different regions via the Cancer Drugs Fund in comparison to NICE approval. If eribulin were to be approved it would help ensure that, where clinically appropriate, patients would be able to receive this treatment equally, regardless of where they live.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

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

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

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

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation [redacted]

Commenting on behalf of the Royal College of Pathologists

Are you (tick all that apply):

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

I am a specialist breast pathologist involved in the assessment of surgical specimens as well as breast clinical trials and translational research.

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

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

The technology appears to provide a new avenue for the treatment of locally advanced or metastatic breast carcinoma in heavily pre-treated patients. The technology is a drug from a new class of compounds. As such, it offers a previously unavailable line of therapy. It would be used in addition to current therapies; either before, instead of, or after.

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

All subgroups could potentially benefit.

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

It would be administered in secondary care.

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

The technology is not currently available in the NHS.

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

The management of locally advanced or metastatic breast carcinoma is dealt with in NICE clinical guideline 81.

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The advantages and disadvantages of the technology

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

This technology is in a new class and will, therefore, be an adjunct to, rather than an alternative to, current therapies. It should be no more difficult to use than the currently available drugs used in this patient group (see NICE clinical guideline 81).

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

The rules would be the same as for other drugs used for the patients in this group as defined by NICE clinical guideline 81.

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

As far as I am aware the clinical trial conditions reflect clinical practice. The majority of the trial patients (64%) were recruited from North America, Western Europe and Australia suggesting that this reflects UK practice. The most important outcome is the statistically significant increase in overall survival in the Eribulin treated group. Overall survival is not a surrogate marker and indicates a significant benefit from this technology.

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

The adverse event frequency was similar between the technology and current therapy. However, there was a higher incidence of bone marrow suppression and neuropathy in the Eribulin treated group.

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Any additional sources of evidence

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

No.

Implementation issues

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

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

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

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

NHS staff would require training on the indications, administration and adverse effects profile of this technology. This would not need to be lengthy or involved.

It is unlikely that additional facilities or equipment would be needed over and above those necessary for a modern oncology centre.

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Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?

None.

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

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

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

Please do not exceed the 8-page limit.

About you

Your name: [redacted] submitting comments on behalf of the following organisations:

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

Comments coordinated by [redacted]

Are you (tick all that apply):

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

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Eribulin for the treatment of locally advanced or metastatic breast cancer

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

Locally recurrent or metastatic breast cancer is treated with sequential chemotherapy or, in the case of oestrogen receptor positive disease, sequential endocrine therapy. The practice across the UK is generally to treat with sequential single agent chemotherapy regimes in fitting with current NICE guidance (Clinical Guideline 81, Advanced Breast Cancer) which states:
'for patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

first line: single-agent docetaxel
second line: single-agent vinorelbine or capecitabine
third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).'

With increased use of combined taxanes and anthracyclines in the adjuvant setting, patients who relapse are often part-way down this pathway from the outset and therefore have more limited options down the line.
The choice between capecitabine and vinorelbine as second line treatment is sometimes directed by side-effect profile, but is often a personal preference of different oncologists or departments. Most patients will go on to have the other drug as third line treatment.

Eribulin, a non-taxane microtubule inhibitor, is another option in this advanced setting. The phase III registration study (EMBRACE; Cortes et al, Lancet 2001; 377:914-23) compared eribulin with treatment of physicians choice (TPC) in patients who had previously been exposed to anthracyclines and taxanes. All patients had received 2 and 5 previous courses of chemotherapy (at least 2 in the advanced setting) including an anthracycline and a taxane (unless contraindicated). 762 patients were enrolled and randomised 2:1 in favour of eribulin. The choice of agents used in the TPC arm was mainly vinorelbine (25%), gemcitabine (19%), capecitabine (18%) or further taxanes (15%). No patients received only supportive care, although 4% did not receive chemotherapy and were treated with endocrine therapy instead. The overall survival was significantly improved in the eribulin arm (13.1 months versus 10.6 months, HR 0.81, p=0.041), at the expense of increased fatigue, neutropaenia and peripheral neuropathy.

Given the broad range of patients entered into the study (both in terms of degree of pre-treatment and in tumour characteristics such as hormone and Her-2 receptor profile) it is difficult to identify a subgroup that would especially benefit from this technology. The choice of TPC as the comparator arm does reflect clinical practice in the UK, and the drugs that were chosen by treating physicians in this group do compare well with the options used in practice. However it does make any direct clinical and economic comparisons difficult. Nevertheless, it is very unusual for a

chemotherapy trial in advanced breast cancer to show an overall survival benefit, so these results are a positive step forward. The difficulty is in deciding exactly where to position eribulin in treatment pathway, but it would seem reasonable to consider as a 3rd or 4th line option after capecitabine and/or vinorelbine.

The advantages and disadvantages of the technology

Eribulin is given by a short intravenous infusion on day 1 and 8 of a 21-day cycle, which would entail a similar administration burden to the NHS as vinorelbine, one of its main comparators (another comparator, capecitabine is an oral medication).
The side effect profile of eribulin was worse than the combined TPC group, although individual toxicities would vary with the choice of TPC drug. The neutropaenia rate was relatively high in the eribulin group (45% grade 3 or 4) and 18% received granulocyte colony stimulating factors (an additional cost), although the febrile neutropaenia rate was low at 5% so there is not a large expected burden of extra hospital admissions. Other toxicities of concern are fatigue (54% all grades) and peripheral neuropathy (35% all grades).

In the phase III trial, the chemotherapy was continued until progression of disease, intolerance or patient choice. The median duration of treatment with eribulin was 3.9 months (approximately 5 cycles, range 1-23 cycles). No additional imaging tests are expected compared with other chemotherapy schedules.

The trial does reflect UK practice, with a wide range of 2nd-5th line chemotherapy used in different centres. Eribulin appears to provide an additional chemotherapy option in this setting. Other chemotherapy regimens used after capecitabine and vinorelbine might include gemcitabine/carboplatin, repeat taxane or anthracycline exposure, liposomal anthracyclines, mitomycin/mitoxantrone/methotrexate combination.

The most important outcomes (overall survival and toxicity) were measured. There is no other chemotherapy with a proven survival benefit in this setting.

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Any additional sources of evidence

None known

Implementation issues

Approval of this technology would give a further effective option for advanced metastatic breast cancer patients. It is not likely to result in an extra line of therapy in patients who wouldn't otherwise receive more chemotherapy, but instead might replace a variety of unproven and difficult to define 3rd and 4th line regimes. The apparent survival benefit would clearly be attractive to both patients and physicians, and might result in more conformity of care across the UK.

The number of cycles required is poorly defined, with treatment until progression or intolerance, but in reality patients in this setting are often maintained on other chemotherapy agents, with widely varying practices of when to stop treatment, usually dictated by symptomatic control.

No extra training or education of staff will be needed. No additional resources are required.

Equality

There are no issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality.

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Eribulin for the treatment of locally advanced or metastatic breast cancer

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Primary Care Trusts (PCTs) provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a PCT perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation NHS Camden

Please indicate your position in the organisation:

- commissioning services for the PCT in general?
- commissioning services for the PCT specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery in the PCT (e.g. medical director, public health director, director of nursing)?
- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify) [redacted]

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

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

NHS Camden funds chemotherapy for this indication in line with NICE guidance. Any funding requests for drugs outside NICE, would be considered as individual funding requests where the London Cancer Prioritisation Programme ratings are used to inform funding decisions.

To what extent and in which population(s) is the technology being used in your local health economy? Not in the health economy yet.

- is there variation in how it is being used in your local health economy? Not aware of this due to lack of data completed by Provider organisations
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

According to NICE's estimates, a population of 100,000 may expect to treat 23 cases of advanced breast cancer per year. This includes the 5% of all invasive cancers that are advanced on diagnosis and the proportion of locally or advanced cancers that progress in a year. Only a small proportion of these will require third line therapy

There are few options for women who have received two or more chemotherapy regimens for locally advanced or metastatic disease and alongside effectiveness a comparison of safety and adverse events will also be important.

An indirect comparison and/or sub-group analyses are required to assess the effectiveness of eribulin against the specified (current) comparators vinorelbine, capecitabine, and gemcitabine. The manufacturer's submission should provide more

complete data from two phase III trials to facilitate this. There is no direct evidence comparing alternative chemotherapy sequences and NICE's recommendation for single agent docetaxel, followed by capecitabine (or vinorelbine) monotherapy followed by vinorelbine (or capecitabine) monotherapy after failure of anthracyclines is based on a cost-effectiveness analysis of the sequencing of post-anthracycline first, second and third line treatments

The cost of eribulin is not yet known and it is unclear whether the treatment will be appraised according to NICE's policy for treatments that extend life in patients with a short life-expectancy. Although published data are limited, eribulin appears to extend overall survival by 2.5 months (median survival: 13.1 months with eribulin vs. 10.6 months with control; HR 0.81, 95% CI 0.66 to 0.99; p=0.041) in a subset of women with metastatic breast cancer compared to other second line, post-anthracycline regimens. The control group in the landmark phase III trial EMBRACE was treatment of physician's choice. This control arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy) and 3% hormonal therapy. Data from phase II studies suggests that median overall survival is comparable to that seen with capecitabine or vinorelbine monotherapy in this population group (9.4 to 18.1 months with capecitabine and 6 months with vinorelbine).

If this combination is to be funded according to NICE's end of life policy, evidence will be needed to show that:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- an extension to life, normally of at least an additional 3 months, compared to current NHS treatment is seen in the treated group and
- that the treatment is licensed or otherwise indicated, for small patient populations

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

All prescribing and monitoring in secondary care only – no prescribing or monitoring in primary care.

This will be a PbR exclusion and hence secondary care will receive payment for it if used in line with NICE from the commissioners. It requires IV administration so additional costs such as administration costs would be charged back to the commissioner. However, it is administered over 2-5 minutes but it is not known how long the patient will need to be present in the specialist clinic for (e.g. for any pre-medication, monitoring post injection etc).

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Single Technology Appraisal (STA)

Eribulin for the treatment of locally advanced or metastatic breast cancer

Some information on treatment is missing e.g. length of treatment cycles, frequency of administration, total number of cycles expected etc. Thus it is difficult to estimate the additional resources, and linked to it the additional opportunity costs attached to this regime.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

Chemotherapy is a PbR exclusion so secondary care would receive funding if use is in line with NICE and any local agreements. The cost of eribulin is not yet known so it is not possible to know the true financial impact of a positive NICE recommendation. There is information missing related to the costs associated with administration, monitoring, number of cycles, etc… therefore cannot estimate the likely budget impact nor the currently available services this is likely to displace.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

There is a possibility that the use of eribulin may displace current options, since NICE does not provide decommissioning advice for commissioners.

Would there be any need for education and training of NHS staff?

Not sure- best to ask the specialists

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Eribulin for the treatment of locally advanced or metastatic breast cancer

Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?

The PCT's concern that access to treatments that offer a small benefit (overall survival) and incur high costs displace access to other clinically and cost-effective treatments / services within the NHS's finite budget.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

Aspects of prioritization that are applied to the (Interim) Cancer Drugs Fund put emphasis on clinical effectiveness and outcomes, e.g. robust trial data, effective comparators (including current clinical practice) and overall survival; Appraisals that apply different thresholds to this does raise confusion amongst both patients and clinicians, and few understand the displaced access to effective treatments in the aftermath.

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Eribulin for the treatment of locally advanced or metastatic breast cancer

This report was commissioned by the NIHR HTA Programme as project number 10/19

Completed May 24th 2011

CONTAINS IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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Date completed: 24th May 2011

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 10/19

Declared competing interests of the authors: None

Acknowledgements:

Thanks to Dr Helen Innes and the BMJ TAR group who provided feedback on the clinical (HI and BMJ) and economic sections (BMJ) of the report

Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors

This report should be referenced as follows:

Greenhalgh J, Bagust A, Boland A, Oyee J, Trevor N, Dundar Y, Fleeman N, Davis H, O'Reilly S. Eribulin for the treatment of advanced or metastatic breast cancer: A Single Technology Appraisal. LRiG, The University of Liverpool, 2011

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Janette Greenhalgh	Project lead, drafted the clinical results section and supervised the production of the final report
Adrian Bagust	Critical appraisal of the economic model
Angela Boland	Critical appraisal of the economic evidence
James Oyee	Critical appraisal of clinical statistical approach
Nicola Trevor	Critical appraisal of the economic evidence
Yenal Dundar	Cross checking of manufacturer's search strategies
Nigel Fleeman	Summary and critical appraisal of the clinical evidence
Helen Davis	Critical appraisal of the manufacturer's submission
Susan O'Reilly	Critical appraisal of the clinical sections of the manufacturer's submission

All authors read and commented on draft versions of the ERG report.

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Abbreviations

AC	Appraisal Committee
AE(s)	adverse event(s)
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CTX	chemotherapy
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Co-operative Oncology Group
EMA	European Medicines Agency
EMBRACE	Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389
ER	oestrogen receptor
ERG	Evidence Review Group
FACT-B	Functional Assessment of Cancer Therapy - Breast
FDA	Food and Drug Administration
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
IRC	Independent Review Committee
ITT	intention to treat
IV	intravenous
LABC/MBC	locally advanced or metastatic breast cancer
LYG	life years gained
MS	manufacturer's submission
NICE	National Institute for Health and Clinical Excellence
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression- free survival
PP	per protocol
PR	partial response
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life years
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SA	sensitivity analysis
SD	stable disease
SPC	Summary of Product Characteristics
STA	single technology appraisal
TPC	treatment of physician's choice
vs	versus
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE from Eisai Ltd in support of the use of eribulin (Halaven®) as a treatment for patients with locally advanced or metastatic breast cancer (LABC/MBC). The manufacturer's submission (MS) describes the use of single agent eribulin for patients who have received two or more chemotherapy (CTX) regimens for LABC/MBC.

Eribulin has a marketing authorisation in Europe. It is licensed for use in the treatment of patients with LABC/MBC who have progressed after at least two CTX regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

1.2 Summary of submitted clinical-effectiveness evidence

The main source of clinical evidence described in the MS is derived from the EMBRACE trial. The EMBRACE trial is a phase III, open-label randomised controlled trial (RCT) that included 762 patients who have received two or more CTX regimens for LABC/MBC. Patients were randomised 2:1 to receive eribulin or treatment of physician's choice (TPC). The manufacturer reports clinical effectiveness results for two populations, the overall intention to treat (ITT) population of the EMBRACE trial and a subset (n=488) of the overall ITT population, patients from Region 1 only (North America, Western Europe and Australia). For the primary endpoint of OS, the manufacturer reports clinical effectiveness results at two time points: the primary analysis (protocol specified after 55% of patients had died) and an updated analysis (requested by regulatory authorities and conducted after 77% of patients had died). The results of all secondary endpoints are reported from the time of the primary analysis. In the overall ITT population, treatment with eribulin was associated with a statistically significant improvement in OS compared with treatment with TPC in both primary (difference in median OS 2.5 months/75 days [HR=0.81; 95% CI 0.66 to 0.99]) and updated analyses (difference in median OS 2.7 months/82 days [HR=0.81; 95% CI 0.67 to 0.96]). Treatment with eribulin was associated with a statistically significant improvement in PFS compared with treatment with TPC when assessed by the investigator (difference in median PFS 1.48 months/45 days [HR=0.76; 95% CI 0.64 to 0.90]) but not for the independently-assessed data (difference in median PFS 1.44 months/44 days [HR=0.87; 95% CI 0.71 to1.05]).The objective response rate (ORR) was statistically significantly different in favour of eribulin compared with TPC for both independent (12.2% [95% CI 9.4 to 15.5] vs 4.7% [95% CI 2.3 to 8.4] p=0.002) and investigator-based assessments (13.2% [95% CI 10.3 to 16.7] vs 7.5% [95% CI 4.3 to 11.9] p=0.028]). The clinical

benefit rate (CBR) for the eribulin arm was greater than in the TPC arm for both independent-based assessment (22.6% [95% CI 18.9 to 26.7] vs 16.8% [95% CI 12.1 to 22.5]) and investigator-based assessment (27.8 [95% CI 23.8 to 32.1] vs 20.1% [95% CI 14.9 to 26.1]). Median duration of response was not significantly different between to the two arms of the trial.

In the analysis of Region 1 only patients, treatment with eribulin was associated with a statistically significant improvement in OS compared with treatment with TPC in both primary (difference in median OS 3.06 months/93 days [HR=0.72; 95% CI 0.57 to 0.92]) and updated analyses (difference in median OS 3.09 months/94 days [HR= 0.79; 95% CI 0.64 to 0.98]). The manufacturer reports the results of *post-hoc* subgroup analyses of median OS by TPC subgroup for both the overall EMBRACE ITT population and the Region 1 patient subset. The health-related quality of life (HRQoL) data derived from phase II trial data suggest that QoL may be improved in patients whose tumour responds to eribulin treatment. The most frequently reported serious adverse events (SAEs) in the eribulin arm were febrile neutropenia (4.2%) and neutropenia (1.8%); the most common AE leading to treatment discontinuation in the eribulin arm was peripheral neuropathy.

1.3 Summary of submitted cost-effectiveness evidence

In the absence of any relevant UK economic evaluations, the manufacturer submitted a *de novo* economic evaluation comparing eribulin vs TPC for patients with LABC/MBC whose disease had progressed after at least two prior CTX regimens for advanced disease. Eribulin has recently been approved by the Department of Health and the lower Patient Access Scheme (PAS) price of eribulin is used in the economic model. The manufacturer constructed a semi-Markov state transition model in Microsoft Excel to model the lifetime clinical and economic outcomes for a hypothetical cohort of patients with LABC/MBC. The manufacturer's submitted economic model is based on the clinical effectiveness data from Region 1 only; however, the model includes options to use the full ITT dataset. The ERG notes that a trial duration time horizon is adopted in the model. This means that at the end of the duration of the trial (2.89 years), all patients that are alive are transitioned into a "terminal" state and no extrapolation of trial outcomes is undertaken. The model assumes an average body surface area (BSA) of 1.74m^2 for estimating treatment costs. The model consists of three main health states: treated, progressive and dead. All patients in the model were initially assigned to the "treated" health state which comprises both stable and responsive patients. The perspective adopted in the economic evaluation was that of the NHS and Personal Social Services (PSS) and costs and benefits were discounted at 3.5% per annum. Clinical-effectiveness data from Region 1of the EMBRACE trial were used to populate the base-case analysis in the submitted economic model. Quality adjusted life years (QALYs) are NICE's preferred measure of health related quality of life; EQ-5D data were not collected during the EMBRACE trial and QALYs were estimated using utility values from published literature. The manufacturer's base-case incremental cost-effectiveness ratio

(ICER) for eribulin vs TPC (Region1) is £46,050 per QALY gained. The manufacturer also presents the following ICERs: eribulin vs gemcitabine (£27,183 per QALY gained); eribulin vs vinorelbine (£35,602 per QALY gained) and eribulin vs capecitabine (£47,631 per QALY gained). The manufacturer showed the ICERs to be robust when subjected to extensive deterministic and probabilistic sensitivity analysis (PSA). The manufacturer also claims that eribulin (vs any comparator using data from ITT population or Region 1 data) meets NICE's 'End of Life' criteria.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The manufacturer cites evidence from a well-designed trial (EMBRACE) of the clinical benefit of eribulin vs TPC as a treatment for LABC/MBC following treatment failure with an anthracycline and a taxane. The trial is large, multi-centred and international with a robust primary outcome of OS.

1.4.2 Weaknesses

There is only a single RCT (EMBRACE) which compares eribulin to TPC described in the MS. Analyses of eribulin vs individual TPCs are presented, but due to the small number of patients in each group and the *post-hoc* nature of these analyses, the reliability of these results is questionable.

The conduct of the trial may be of some concern as the manufacturer's clinical data show that a substantial number of patients did not receive all routine assessment scans required by the protocol.

No HRQoL data were collected during the EMBRACE trial. In the clinical section of the MS the manufacturer relies on HRQoL data collected from two single arm phase II studies.

The main weakness in the economic evaluation is related to the manufacturer's inaccurate costing of comparators to eribulin. The submitted model does not take account of BSA differences between patients and instead uses a fixed average value for all patients. The administration costs of CTX drugs are also flawed – out of date NHS Reference Costs are used, all CTX drugs are assumed to be administered in an out-patient setting and differential healthcare resource group (HRG) costs are ignored.

1.4.3 Areas of uncertainty

The key area of uncertainty is whether or not the clinical effectiveness data from Region 1 patients only are preferred to data from the ITT population. In the EMBRACE trial, Region 1 patients are from North America, Western Europe and Australia and the manufacturer asserts that this patient population is of direct relevance to patients in the NHS in England and Wales. In the eribulin vs TPC comparison, the incremental OS gain is higher in Region 1 patients compared with the incremental

OS gain in patients in the ITT population. As a result, the ICER in the Region 1 population is lower than the ICER in the ITT population. The ERG considers that eribulin compared with TPC meets NICE 'End of Life' criteria only when data for Region 1 are employed.

The final scope issued by NICE specified three subgroup comparisons, defined by the intended treatment (eribulin vs gemcitabine, vs vinorelbine and vs capecitabine). In each case the number of patients is small, and the ERG does not consider these analyses to provide convincing evidence of clinical or cost-effectiveness differences between eribulin and these three comparators.

The ERG is of the opinion that it is valid to project OS estimates beyond the trial data; this leads to a gain in OS for all patients especially for patients in Region 1. The ERG's estimates of OS for Region 1 patients and patients in the overall ITT population are larger than the estimates submitted by the manufacturer. Whether or not the ERG's method of projection is appropriate is open to debate.

1.5 Key issues

Whether or not clinical data from Region 1 are preferred to clinical data from the ITT population is a key issue. Limiting the clinical evidence base to data from Region 1 appears to reduce the size of the ICER and allows the manufacturer to claim that eribulin should be appraised according to the 'End of Life' criteria.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

In the context section of the MS (section 2) the manufacturer describes the key issues relating to the underlying health problem and associated risk factors. The MS provides an overview of the clinical problem, including epidemiology and prognosis for breast cancer. A summary of this section is provided in Box 1and Box 2. All information is taken directly from the MS unless otherwise stated.

Box 1 Epidemiology

Breast cancer is the most common malignancy in women in the UK; it accounts for around 1 in 3 cases of cancer in women and the lifetime risk of developing breast cancer for a woman is 1 in 8.[1] The incidence has almost doubled over the last three decades,[1] with around 42,300 women (> 99% of cases) and 300 men (< 1%) newly diagnosed with breast cancer in England and Wales during 2008.[1] The risk of developing breast cancer is strongly correlated with age; 81% of cases in the UK occur in women aged 50 years and over.[1]

Box 2 Prognosis

Locally advanced and metastatic breast cancer (LABC/MBC), is the most advanced form of breast cancer, where the cancer is no longer localised to the breast and has spread to other parts of the body, commonly the lungs, liver, brain and bone.[2] Although few patients are diagnosed with MBC (around 5%[3]), the risk of recurrence persists for many years following remission of non-metastatic disease. It is estimated that 30%, 46%, and 71% of patients initially diagnosed with stages I, II, and III disease, respectively, will eventually progress to metastatic disease.[3]

There is currently no cure for LABC/MBC and the long-term prognosis is poor. Whereas 5-year survival rates of 92% have been reported for tumours diagnosed at the earliest stage, 5-year survival in those diagnosed with metastatic disease is low, around 13%.[4] As reported in the recent NICE assessment report, the average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving CTX.[5] At the point in therapy where eribulin will be used the length of survival would be expected to be even less.

The ERG is of the opinion that the manufacturer's description of the underlying health problem is an accurate account.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer provides a summary of approaches to the treatment of LABC/MBC (Box 3) and describes current NICE guidance relevant to the treatment of LABC/MBC (Table 1). The manufacturer describes the proposed place of eribulin in the treatment pathway (Box 4) and presents an estimate of the number of patients in the UK who would be eligible for treatment with eribulin.

Box 3 Summary of treatment approaches

The management of LABC/MBC is complex and diverse, with treatment options combined in a multi-disciplinary approach; treatment choice for physicians and patients will depend upon a number of factors, including: exposure and response to therapy at earlier stages of treatment, menopausal status, ER/PR and HER2 status, tolerability, patient preference, availability of drugs, quality of life, performance status, age, site of disease or treatment goals.

Systemic therapy, in the form of hormonal therapies, CTX agents, and targeted/biologic agents, are

current treatment options. There are a variety of single and combination therapies that can be used in a sequential regimen approach; therefore, when disease progression occurs during first-line treatment a second is tried, and so on.

Pre-treated patients (those who have already received treatment with anthracyclines and taxanes), are a particularly challenging subgroup to manage effectively since by this stage patients will have progressed despite treatment, and further treatment options will have limited effectiveness. Treatment for this advanced stage of the disease is focused on prolonging survival, while controlling the symptoms and improving quality of life.[6] Overall survival (OS) is recognised as the most definitive cancer outcome[7, 8] and is of most importance to patients when making decisions regarding treatment options.[9] Although many patients gain significant benefit from continuing treatment through several lines of CTX there is minimal high-quality evidence about the relative clinical effectiveness of current treatments[6] and none have demonstrated a survival benefit over any other.[6, 10]

The manufacturer provides an accurate description of current approaches to treatment; however, the ERG notes that whilst overall survival (OS) may be considered to be the most important treatment outcome by clinicians and patients, the length of the likely increase in OS is also of importance to patients; most patients are of the opinion that a 12 month life-extension is worthwhile.[9]

The ERG notes that the manufacturer's statements regarding the lack of evidence as to the relative clinical effectiveness of current treatments and lack of evidence of any survival benefit are consistent with evidence from a recent systematic review[10] and NICE Clinical Guidelines CG81.[6]

Table 1 Current NICE guidance

NICE Guideline/Guidance	Recommendation
CG 81[6] (2009) Advanced breast cancer: diagnosis and treatment	Chemotherapy treatment in the advanced setting commences with an anthracycline-based regimen. If disease progresses following anthracycline treatment or in cases where an anthracycline is unsuitable (if the person has previously received anthracycline-based adjuvant therapy or has a contraindication to anthracyclines), systemic CTX should be offered in the following sequence: First-line: single-agent docetaxel Second-line: single-agent vinorelbine or capecitabine Third-line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment)
CG80[11] (2009) Early and locally advanced breast cancer: diagnosis and treatment	Recommendations for diagnosis and treatment of early and locally advanced breast cancer
NICE Guidance on Cancer Services[12] (2002) Improving outcomes in breast cancer	Recommendations on the provision of services for the treatment, management and care of patients with breast cancer, to ensure that all breast cancer patients across England and Wales receive high-quality healthcare
TA116[13] (2007) Gemcitabine for the treatment of metastatic breast cancer	Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate
TA34[14] (2002) Guidance on the use of trastuzumab for the treatment of advanced breast cancer	Trastuzumab in combination with paclitaxel is recommended as an option for women with tumours expressing HER2 scored at levels of 3+ who have not received CTX for metastatic breast cancer and in whom anthracycline treatment is inappropriate Trastuzumab monotherapy is recommended as an option for women with tumours expressing HER2 scored at levels of 3+ who have received at least 2 CTX regimens for metastatic breast cancer. Prior CTX therapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen receptor positive patients

HER2 =human epidermal growth factor

The manufacturer lists all relevant NICE guidance in relation to LABC/MBC in the MS and notes that in TA116,[13] NICE's recommendation for gemcitabine (combined with paclitaxel) appears to place gemcitabine treatment as a first-line option alongside docetaxel monotherapy and docetaxel plus capecitabine. The manufacturer states that gemcitabine-based therapy is used at second/third-line and thus indicating that more interventions are used at third-line or later than those outlined in NICE CG81.[6] The clinical advisor to the ERG agrees that i) gemcitabine therapy may be used in second/third-line (although as a monotherapy and not combined with paclitaxel) and ii) therapies other than those described in CG81[6] are used in clinical practice in the UK at third line. The ERG is also aware that gemcitabine is not licensed for use as a monotherapy.

Box 4 Eribulin's place in the treatment pathway

The population considered suitable for eribulin treatment within this submission consists of patients with LABC/MBC, whose disease has progressed after at least two prior CTX regimens in the advanced setting. It is therefore anticipated that eribulin will be used as a third-line CTX (as an alternative to capecitabine and vinorelbine). The introduction of eribulin will not change the clinical pathway outlined in the NICE guideline.

The ERG agrees that eribulin would be used as a third-line treatment and emphasises the lack of evidence-based treatment options for patients at this stage of disease.

The ERG is unable to comment on the manufacturer's estimate of the number of patients who might be eligible for treatment with eribulin (Box 5); however, data from the clinical advisor to the ERG support the manufacturer's figure of between 1100 and 1700 patients per year who would be eligible for treatment with eribulin.

Box 5 Estimated number of patients eligible for treatment

There are very limited data in the UK describing the number of patients at different lines of treatment in the metastatic setting. Our best estimates predict there are around 1100-1700 patients. This includes patients who are HER2+. There is no experience of using eribulin in combination with anti-HER2 therapy. According to data from Q3 2010[15] there are 1,100 patients with metastatic breast cancer who have received at least 2 previous CTX treatments in the metastatic setting.
Using a combination of epidemiological data and Synovate[15] data, the following patient numbers can be derived:

- Around 42,600 people were newly diagnosed with breast cancer in England and Wales during 2007[1]
- Approximately 5% (n=2130) of patients initially presenting with breast cancer will be diagnosed with LABC/MBC[6]
- Around 35% (n=14,165) of those with a primary diagnosis of breast cancer at an earlier stage will develop metastases in the future[6] equating to a total of 16,295 patients with LABC/MBC.
- Based on the indication, eribulin monotherapy will be given to patients with LABC or MBC who have progressed after at least two CTX regimens for advanced disease. Assuming that all patients receive active treatment (e.g. CTX, biologic therapy, hormonal therapy), it is estimated that 61.8% (n=10,070) of these will receive first-line CTX for LABC/MABC[15]
- Of those treated with CTX at first-line, around 16.8% will go on to receive CTX at third-line or later[15] equating to 1692 patients who would be eligible for treatment with eribulin

In summary, the ERG considers the manufacturer's account of the underlying health problem and current service provision to be largely accurate.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

In the MS, the manufacturer presents the decision problem issued by NICE,[16] and the manufacturer's rationale for any deviation from this in the MS. Table 2 summarises this.

Table 2 Decision problem as addressed in MS

	NICE Final scope	**Decision problem addressed in MS**	**Rationale if different from the scope**
Population	People with breast cancer who have received two or more CTX regimens for LABC/MBC whose disease has progressed	As defined by scope	As per licensed indication: Treatment of patients with LABC/MBC who have progressed after at least two CTX regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments
Intervention	Eribulin monotherapy	As defined by scope	N/A
Comparator(s)	Vinorelbine Capecitabine Gemcitabine	Treatment of Physicians Choice (TPC) Vinorelbine Capecitabine Gemcitabine	The selection of TPC reflects the real life choices for LABC/MBC patients who have already been treated with an anthracycline and a taxane. There is currently no single pattern of treatment in the UK for patients at this stage of the disease. In line with the final scope, comparisons with specific CTX agents have also been included. The emphasis given to such individual treatment comparisons should be balanced by an understanding of the diversity of options currently employed in clinical practice, as outlined above
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment HRQL	As defined by scope	N/A
Economic analysis	Cost per QALY. Time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	As defined by scope. Time horizon for estimating clinical and cost effectiveness will be patients' lifetime (base case), and as such will be sufficient to capture differences in costs and outcomes between the interventions compared	N/A
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation	The decision problem addressed by this submission reflects the indication for eribulin	N/A

HRQoL= health related quality of life; QALY = quality adjusted life year

3.1 Population

The patients in the key trial (EMBRACE[17]) cited in the MS are those with LABC/MBC (defined in the key trial as locally recurrent or MBC) who have received between two and five prior CTX treatments. In order for a patient to be included in the trial, the following criteria with respect to treatment history had to be met:

i. the prior CTX had to include an anthracycline and a taxane in any combination or order;
ii. one or two of the treatments with anthracycline or a taxane could have been administered as adjuvant and/or neoadjuvant therapy, but at least two had to be given for relapsed or metastatic disease;
iii. disease is refractory to the most recent CTX therapy, documented by progression on or within 6 months of therapy.

Patients with HER2+ tumours could have additionally been treated with trastuzumab and patients could have been treated with hormone therapy. The ERG is confident that the patient population in the key trial cited in the MS matches the population defined in the scope issued by NICE[16] and the eligible UK population.

3.2 Intervention

Eribulin is a first-in-class anti-neoplastic agent belonging to the halichondrin class of drugs. Eribulin exerts its anti-cancer effects via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles, and ultimately, apoptotic cell death following prolonged mitotic blockage. Eribulin monotherapy is administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.[18] It is licensed in Europe[19] for the treatment of patients with LABC/MBC who have progressed after at least two CTX regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

3.3 Comparators

The decision problem issued by NICE in its final scope[16] states that treatment with eribulin should be compared with treatment with either vinorelbine, capecitabine or gemcitabine. The ERG notes from its clinical advisor that, in UK clinical practice, gemcitabine is used as a monotherapy in this setting; however gemcitabine is neither licensed as a monotherapy[20] in this setting nor is it recommended as a monotherapy by NICE.[6, 13]

In the MS, the comparator is treatment of physician's choice (TPC). This is defined in the MS (MS, p.42) as any available single agent CTX, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care (BSC). The TPC treatments given in the key trial are described in the MS (MS, pg 54, Table 10) and are

replicated in Table 7 of this report. In the EMBRACE[17] trial, the majority of patients (93.7%) received treatment with CTX; the remainder were treated with hormone therapy. None of the patients in the trial received BSC alone or radiotherapy. The ERG is aware that there may be a few patients in UK clinical practice that might opt for BSC; however, the ERG notes the difficulties of recruiting patients to the BSC arm of a clinical trial.

The manufacturer discusses in depth the use of TPC as a comparator (MS, pg 33). In justifying TPC as the comparator rather than individual anti-cancer treatments, the manufacturer presents the following lines of argument:

i) Currently there is no single pattern of treatment in the UK for patients at this stage of the disease; in clinical practice, treatment is based on a range of factors, including prior treatment and response to that treatment, tolerability of treatment, patient preference and quality of life. The manufacturer argues that TPC reflects the choices available to patients with LABC/MBC who have been previously treated with an anthracycline or a taxane. The manufacturer also suggests that it would be impractical to conduct large scale trials that compare eribulin with specified therapies

ii) the manufacturer points to NICE's guide to the methods of technology appraisal;[21] this states that comparators put forward in evidence submissions should be selected based on the current standard of care, and that the current standard of care may vary across the NHS. The manufacturer argues that, in this appraisal, a number of comparators are possible, thus the use of TPC is valid

iii) scientific advice from the Committee for Medicinal Products for Human Use (CHMP) at the EMA. The manufacturer states that scientific advice [redacted]

The ERG noted in Section 2 above that a number of treatments additional to those recommended in CG81[6] (i.e. vinorelbine or capecitabine) are used with patients in this setting, and that choice of treatment is dependent on several factors including the patient's response to prior treatment, tolerability, performance status and quality of life (QoL). The final scope issued by NICE[16] includes gemcitabine as a comparator, although CG 81[6]

recommends only vinorelbine or capecitabine in this setting. The ERG is also aware of the potential difficulties in designing a single specific trial comparing eribulin to the possible range of comparators.

The ERG agrees with the manufacturer that the TPC approach is in accord with NICE's guide[21] to the methods of technology appraisal and notes that the European Public Assessment Report[22] (EPAR) for eribulin published by the EMA on 11th April 2011 states that 'the CHMP agreed that a phase-II study and one pivotal phase-III study that included a control arm of Treatment of Physician's Choice could fulfil the requirements for a marketing authorisation application in this setting.' (EPAR, p7). This is in accord with CHMP guideline[7] on the evaluation of anti-cancer medicinal products in man that states that 'if, for a specific target population, there is no regimen with an evidence-based favourable benefit - risk relationship, a regimen used in clinical practice with a well-documented and benign safety profile is acceptable. Alternatively, "investigator's best choice" among a few selected regimens with these characteristics (may include BSC) is acceptable. In these cases, superior efficacy has to be shown versus the pooled results in the reference arm.'

The ERG considers that the use of TPC is pragmatic and reflects patient experience in England and Wales. However, the ERG notes that averaging the effects of a range of diverse treatments (as with TPC) will obscure patient responses to individual treatments.

The manufacturer provides subgroup analyses that compare TPC patient outcomes with the outcomes of the CTX comparators specified in the scope issued by NICE[16] (i.e. vinorelbine, capecitabine and gemcitabine). These subgroup analyses are the basis of the manufacturer's economic case. However, the ERG notes that these subgroups are very small and the trial was not powered to detect differences between individual treatment subgroups; the reliability of the results of any such analyses is questionable.

3.4 Outcomes

The manufacturer has addressed all the outcomes stated in the scope issued by NICE;[16] these include OS, progression-free survival (PFS), objective response rate (ORR), adverse events of treatment (AEs) and health-related quality of life (HRQoL). The primary endpoint of the EMBRACE[17] trial described in the MS is OS; the ERG notes that although OS is considered to be the most robust outcome in trials of anti-cancer treatments, very few trials of treatments for MBC employ OS as the primary endpoint.[17, 23] The ERG also notes that the manufacturer was advised by the CHMP of the EMA that PFS was not an acceptable primary endpoint in the instance of the EMBRACE[17] trial. The manufacturer was advised that OS was the

CHMP's preferred primary endpoint and that the PFS analysis must be consistent with the primary analysis.[22]

In the clinical section of the MS, the manufacturer presents evidence that relates to two populations of the EMBRACE[17] trial; the overall intention to treat (ITT) trial population and a subgroup of the overall trial population described as Region 1. Region 1 patients were those recruited in centres based in North America, Western Europe or Australia.

3.5 Time frame

In the EMBRACE[17] trial, the key source of clinical data, patients were followed up until death or study closure. At the time of the submission of the MS, 589 (77%) of patients had died and the maximum duration of censored OS was 34.66 months (2.89 years). In the eribulin arm, the last observation was a death (uncensored) at 34.66 months. In the TPC arm the last observation was censored (still alive) at 31.80 months; the last death (uncensored) was at 31.05 months. In the manufacturer's economic model, all of the patients in the trial are assumed to have died at the time of the last observation (censored or uncensored).

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

Table 3 provides an outline of the key background/clinical information and its location within the MS. Its purpose is to signpost the reader to the main areas of background/clinical information within the MS.

Table 3 Key clinical information in the MS

Key information	**Section in the MS**
Description of the technology	A
Context	2
Equity and equality	3
Statement of decision problem	4
Literature search	5
Search strategies	9.2
Study selection	5.2
Clinical effectiveness evidence:	
Trial information	5.3
Results: main	5.5
Results: subgroups	5.5
Results: non-RCT evidence	5.8
Results: safety	5.9

4.1.1 Description and appropriateness of manufacturers search strategy

The manufacturer describes the literature searches carried out up to August 2010. The ERG is confident that all major electronic databases were searched including the Cochrane Library (incorporating CENTRAL), Ovid Medline R, Medline In Process and Ovid Embase. Appropriate hand searching was conducted to identify any additional studies, this included clinicaltrials.gov, conference proceedings from the American Society of Clinical Oncology (ASCO) and the manufacturer's own clinical trial database. It is not stated whether the reference lists of previous trials or systematic reviews were also searched.

The MS provides a clear description of the searches carried out to identify primary relevant research. The comprehensive search strategy used drug names and no language restrictions were adopted. The ERG considers the search strategy to be appropriate. The ERG conducted its own searches up to 20th March 2011 (thus updating those presented in the MS) and is confident that no relevant studies have been missed by the manufacturer.

4.1.2 Inclusion/exclusion criteria

The MS provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies. These are described in Table 4.

Table 4 Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Patients with LABC/MBC	Patients with any other disease, including earlier stages of breast cancer
Intervention	Eribulin	Other interventions used for the treatment of LABC/MBC
Outcomes	OS, PFS, ORR, AEs, HRQoL	Pharmokinetic, pharmacodynamic outcomes (bioavailability, dose ranging)
Study design	RCT, Observational studies	Letters, reviews

The ERG is satisfied with the clinical-effectiveness literature review process as described in the MS.

4.1.3 Included and excluded studies

The search conducted by the manufacturer identified one randomised controlled trial (RCT) for inclusion in the review, the EMBRACE[17] trial. The EMBRACE[17] trial is a phase III RCT published in 2011. Two conference abstracts[24, 25] relating to EMBRACE,[17] a published paper[26] describing the methodology of the trial and a clinical study report (CSR)[27] were also identified by the manufacturer.

Three non-RCTs were considered relevant by the manufacturer; all three studies are described as phase II, single arm, open-label and multi-centred. The studies are identified in the MS as Study 201,[28] Study 211[29] and Study 221.[30] Study 201,[28] Study 211[29] are used by the manufacturer to provide information on HRQoL associated with eribulin and all three studies are presented in order to support the results of the EMBRACE[17] trial.

An appropriate PRISMA[31] flow diagram, describing the review process is provided by the manufacturer (MS pg, 40). The manufacturer has helpfully listed the 107 articles that were excluded from the review (MS, pg 216-22).

The ERG is confident that all relevant trials are included in the MS.

4.2 Description of the included RCT

The primary objective of the EMBRACE[17] trial was to evaluate the OS of patients treated with eribulin vs TPC in patients with LABC/MBC who had received two to five prior CTX regimens (MS, pg 43). Secondary objectives were to evaluate PFS, ORR, duration of response and safety. Clinical benefit rate (CBR) is also reported. The definitions of the

clinical effectiveness outcomes are described in Table 5. The key characteristics of the EMBRACE[17] trial are described in Table 6.

Table 5 Clinical outcome definitions

Outcome	Definition and measure	Timing of assessment
OS	The time from the date of randomisation until death from any cause. In the primary analysis, patients lost to follow-up were censored at the last date known to be alive. In the updated analysis, patients alive, or who withdrew consent or were lost to follow-up at data cut-off were censored at that date for OS analyses	Survival was recorded during the study and following treatment discontinuation for any reasons other than consent withdrawal. Follow-up for survival was assessed at three-monthly intervals until death
PFS	The time from randomisation until disease progression or death due to any cause in the absence of disease progression Clinical evaluation or as documented by RECIST[32] criteria Patients alive and progression-free at data cut-off were censored at that date	Baseline tumour assessments were performed within 4 weeks of the start of treatment Follow-up assessment every 8 weeks. Tumour responses confirmed by 2nd assessment ≥ 4 weeks later Patients with CR/PaR or SD who withdrew from treatment before disease progression, continued assessments every 3 months until PD or the start of a new anti-cancer treatment Tumour assessments were made by investigators via imaging data and clinical examinations. Imaging data were independently reviewed (CT, MRI, bone scans, x-rays, and photographs) in a blinded fashion at a central facility
ORR	The number of patients with a confirmed CR or confirmed PaR divided by the number of patients in the analysis population Response rate based on independent review of disease assessment. Unknown or missing data considered as non-responses	
Duration of response	The time from first documented confirmed CR or confirmed PaR (whichever status is recorded first) until disease progression or death from any cause Response derived from independent review of best response For patients in subset of responders who did not progress or die, duration of response was censored	
CBR	The number of patients with a confirmed CR, a confirmed PaR or SD of at least 6 months, divided by the number of patients in the analysis population	

CBR=clinical benefit rate; CT=computed tomography; CR=complete response; HER2=human epidermal growth factor receptor 2; MRI=magnetic resonance imaging; PaR=partial response; PD= progressive disease; SD=stable disease

Table 6 EMBRACE key trial characteristics

Study: Design and patients	**Intervention/comparator**	**Key inclusion criteria**	**Key exclusion criteria**	**Outcomes**
EMBRACE[17] Phase III, open label RCT International, multi-centre 19 countries: 135 centres (10 UK centres, n= 51) Patients with LABC/MBC* who had received between two and five prior CTX regimens (N=762) Pts randomised 2:1 eribulin:TPC <u>Stratification factors</u> *geographic region *prior capecitabine *HER2/neu status	Eribulin administered as an IV infusion of 1.4 mg/m^2 over 2–5 minutes on days 1 and 8 of a 21 day cycle (n=508) TPC: any available single agent CTX, hormonal treatment or biological therapy approved for treatment of cancer, radiotherapy or BSC. All patients received treatment with pharmacotherapy: vinorelbine, gemcitabine, capecitabine, taxanes, anthracyclines, 'others' fulvestrant, letrozole, exemestane, tamoxifen (n=254)	• Female aged ≥ 18 years confirmed carcinoma of the breast. • Patients with LABC/MBC* who had received between two and five prior CTX regimens: ▪ CTX to include an anthracycline and a taxane (any combination or order) ▪ at least two CTX given for relapsed/metastatic disease ▪ documented progression ≤6 months of CTX ▪ HER2+ tumours could have been treated with trastuzumab ▪ Patients could have been treated with hormone therapy ▪ Resolution of all CTX or radiation-related toxicities to Grade 1 severity or lower, (stable sensory neuropathy to ≤ Grade 2 and alopecia) ▪ ECOG 0 to 2 ▪ Life expectancy ≥3 months. ▪ Adequate renal, bone marrow and liver function ▪ Surgically sterile/ adequate contraception measures	• CTX, trastuzumab or hormonal therapy ≤3 weeks, any investigational drug ≤ 4 weeks • Radiation therapy encompassing > 30% of marrow. • Prior treatment with mitomycin C or nitrosourea. • Pulmonary lymphangitic involvement resulting in pulmonary dysfunction requiring active treatment. • Brain or subdural metastases, (unless local therapy complete and use of corticosteroids discontinued ≥ 4 weeks) • Meningeal carcinomatosis • Anti-coagulant therapy other than for line patency • Severe/uncontrolled illness/infection, significant CV impairment or HIV+ • Organ allografts requiring immunosuppression • Neuropathy > Grade 2 • Hypersensitivity to Halichondrin B and/or a chemical derivative. • Prior malignancy (other than previous breast cancer, carcinoma in situ of the cervix, or non-melanoma skin cancer), unless diagnosed and definitively treated ≥ 5 years previously with no evidence of recurrence. • Pregnant/ breast-feeding; no pregnancy test	<u>Primary</u> OS <u>Secondary</u> PFS ORR CBR Duration of response Safety

*LABC defined as locally recurrent; CV= cardiovascular; ECOG= Eastern Co-operative Oncology Group

4.2.1 Description and critique of manufacturers approach to validity assessment

A single phase III RCT (EMBRACE[17]) forms the basis of the majority of the clinical and cost-effectiveness evidence in the MS. Evidence from three phase II single-arm studies (known as 201,[28] 211[29] and 221[30]) is presented to supplement evidence from the EMBRACE[17] trial. The results of the EMBRACE[17] trial have been published previously as have the findings from 201[28] and 211.[29] Study 221[30] has only been published as a conference abstract. This section outlines the strengths and weaknesses of the EMBRACE[17] trial. Data are taken from the MS as well as from data subsequently provided by the manufacturer as part of the STA clarification process.

Trial conduct

The EMBRACE[17] trial is a large, international, multi-centre, open-label RCT. The manufacturer has provided a quality assessment of the trial in the MS; this has been critiqued by the ERG and appears in Appendix 1. The ERG considers the EMBRACE[17] trial to be a well-designed trial.

The EMBRACE[17] trial recruited 762 patients from 135 centres in 19 countries. Randomisation was conducted centrally using an interactive voice recognition system and according to a randomisation schedule. Patients were stratified on three factors: geographical region, HER2 status and prior treatment with capecitabine. There were three designated geographic regions: Region 1 consisted of North America, Western Europe and Australia; Region 2 consisted of Eastern Europe, Russia and Turkey; Region 3 consisted of Latin America and South Africa. Region 1 constitutes the largest number of patients (64%) followed by Region 2 (25%) and Region 3 (11%).

Randomisation to eribulin or TPC was conducted in a 2:1 ratio to receive either eribulin or TPC. In addition, a TPC treatment was identified (via clinician/patient decision) for each patient prior to randomisation; the choice was confirmed by the investigator using the interactive voice response system. The purpose of this was to ensure that each TPC treatment was independently randomised against eribulin to support the conduct and results of subgroup analyses. The ERG considers the method of randomisation used in the EMBRACE[17] trial to be robust. The baseline characteristics of the two arms of the overall EMBRACE[17] trial are presented in the MS (MS, pg 48 to 49). These show that for key characteristics, patients in both arms appear to be well balanced. As part of the clarification process, the ERG requested from the manufacturer a table of baseline characteristics for patients from each Region.

Patients in Regions 1, 2 and 3 appear to have broadly similar characteristics to patients in the overall trial population.

The ERG notes that although the inclusion criteria of the EMBRACE[17] trial state that patients of ECOG performance status 0, 1 or 2 were eligible for enrolment, the majority of patients (63%) appear to have been assessed as being of ECOG performance status 0 or 1. The ERG is aware that in practice, it can be difficult to make a distinction between patients with a performance status of 1 and those with a performance status of 2.

For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. With so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently. The CSR[27] of the EMBRACE[17] trial states that study monitors were responsible for establishing and maintaining regular contact between study centres and the manufacturer. Monitors made regular visits to each study centre (maximum time between visits was 6 weeks) to check adherence to the protocol and inform the manufacturer of any issues arising. The monitor provided written reports to the manufacturer after each contact with the study centre. The ERG is confident that the manufacturer made every effort to ensure that the trial procedures were implemented comprehensively across all study centres.

Any treatment given to patients following disease progression has the potential to impact on OS and, as part of the clarification process, the ERG requested from the manufacturer details of any post-progression treatments given to patients in both arms of the EMBRACE[17] trial. The post-progression treatments given appear to be similar in number and type across both arms of the trial thereby minimising the likelihood of affecting the OS results.

The ERG has concerns regarding the number of patients in EMBRACE[17] trial who were not assessed regularly after baseline. The trial protocol specified that patients were to be followed up every 8 weeks; however, analysis of the clinical data shows that at least 50 patients missed at least one or more scheduled scans. This suggests that the conduct of the trial may not have matched the high standard of the trial design in some aspects.

It is important that the inclusion and exclusion criteria remain unchanged during study recruitment. In response to the ERG's request for clarification, the manufacturer stated that 46 (9.1%) patients in eribulin arm and 32 (13%) patients in the TPC arm violated the EMBRACE[17] trial protocol with regard to the trial eligibility criteria. The most frequently observed violations related to the patient not being refractory to the most recent CTX

(16/3.1% in the eribulin arm and 11/4.3% in the TPC arm), followed by patients having received more than five prior CTX regimens (15/3.0% patients in the eribulin arm and 9/3.5% patients in the TPC arm) and the patient having received only one regimen for locally recurrent or metastatic disease (7/1.4% in the eribulin arm and none in the TPC arm).

Given the large number of protocol violations of major inclusion and exclusion criteria, the ERG considers that the approach to study monitoring was not adequate with respect to ensuring that patients met eligibility criteria. However, the protocol violations were relatively evenly distributed across the two treatment arms. It is therefore unlikely that these protocol violations had any impact on the overall study results, as evidenced by the results of the per protocol (PP) analysis.

The ERG notes that four amendments were made to the original EMBRACE[17] trial protocol. These do not appear to be a cause for concern.

Blinding

In the EMBRACE[17] trial, patients and investigators were not blinded to treatment allocation. From a pragmatic point of view, this is reasonable given that there were a number of different comparator treatments administered in the trial and each comparator has a different dosing regimen and method of administration. Furthermore, the primary outcome of the EMBRACE[17] trial was OS and the assessment of OS is not dependent on subjective assessment. For the trial outcomes dependent on subjective assessment, blinded review was conducted.

The ERG notes that an independent data monitoring committee (DMC) reviewed the safety of eribulin treatment and assessed the interim efficacy data; the trial sponsor remained blinded to OS data until database lock. In addition, the statistician was blinded at the review of sample size.

Applicability to UK clinical practice

Of the 762 patients recruited to the EMBRACE[17] trial, 51 were from UK centres. The ERG is satisfied that enough of the patients in the trial were derived from other European Union countries with similar care pathways to the UK for the findings to be generalisable to UK clinical practice.

The ERG notes that the patients in the overall EMBRACE[17] trial and in the Region 1 subgroup are younger (median of 55 years and 56.5 years respectively) than patients typically seen in UK clinical practice who are likely to have a median age of between 60 and 65 years.

The ERG is aware that patients in clinical trials do tend to be younger than those seen in clinical practice.

The TPC treatments given in the EMBRACE[17] trial reflect those that would be given in UK clinical practice. A breakdown of TPC treatments given in the trial with the percentages of patients who received them are described in Table 7. The majority of patients were treated with CTX (93.7%); the remainder were treated with hormonal therapy.

Table 7 TPC treatments overall trial population

TPC therapy	Number patients receiving TPC (N=254) n (%)
Chemotherapy	238 (93.7%)
Vinorelbine	61 (24.0%)
Gemcitabine	46 (18.1%)
Capecitabine	44 (17.3%)
Taxanes*	38 (15.0%)
Anthracyclines**	24 (9.4%)
Others***	25 (9.8%)
Hormonal therapy	9 (3.5%)
Fulvestrant	4 (1.6%)
Letrozole	3 (1.2%)
Exemestane	1 (0.4%)
Tamoxifen	1 (0.4%)

*Taxanes included paclitaxel (21 patients), docetaxel (10 patients), nab-paclitaxel (five patients) and ixabepilone (three patients) (one patient received paclitaxel in combination with gemcitabine and was included in the gemcitabine group). **Anthracyclines included doxorubicin (19 patients), liposomal doxorubicin (four patients) and mitoxantrone (one patient). *** Other chemotherapeutic agents were cisplatin, carboplatin, cyclophosphamide, etoposide, mitomycin, fluorouracil and methotrexate (one patient received cyclophosphamide and methotrexate)

The manufacturer states that although patients could have been treated with trastuzumab in centres where trastuzumab was available, no patients were thus treated. The ERG is confident that in UK clinical practice, patients at this stage of disease would not be treated with trastuzumab.

4.2.2 Description and critique of manufacturers outcome selection

The primary outcome of the EMBRACE[17] trial was OS, defined as the time from the date of randomisation until death from any cause. The ERG notes that OS is regarded as the most reliable outcome in trials of anti-cancer treatments, but that it is rarely the primary outcome in trials in this area and setting. The ERG further notes that the EMA required that the primary outcome measure for EMBRACE[17] trial should be OS rather than PFS and that any PFS data should support the OS findings. Secondary outcomes were PFS, ORR, duration of response

and clinical benefit rate (CBR); these are all standard outcomes used in trials of anti-cancer treatments and the manufacturer has applied standard definitions to these.

In the MS, the manufacturer presents OS results for a number of different populations. These include the overall trial population, the population of patients from Region 1, the overall trial population by TPC group and the population of patients from Region 1 by TPC group. All secondary outcome data presented in the MS are for the overall EMBRACE[17] trial population.

There was no collection of HRQoL data in the EMBRACE[17] trial; the manufacturer states that any comparison of HRQoL scores would be negated by the use of so many different comparator treatments. The manufacturer has however presented HRQoL data from two single-arm phase II trials in which patients were treated with eribulin.[28, 29] The HRQoL data were collected via FACT-B[33] and the EORTC-QOL C30[34] questionnaires. The ERG notes that patient response to the FACT-B[33] questionnaire was reasonable and that the trial was small (n=104). Patient response to the EORTC-QOL C30[34] questionnaire is described by the manufacturer as 'sparse' and 'difficult to interpret.' (MS p79).[28, 29]

4.2.3 Describe and critique the statistical approach used

The ERG considered the statistical approaches employed in the EMBRACE[17] trial (as presented in the MS, the CSR and following the clarification from the manufacturer) to be generally appropriate. The Statistical Analysis Plan (SAP) for the EMBRACE[17] trial was rightly prepared before database lock and ITT analysis was conducted. However, the ERG notes that changes to the planned analyses were made to incorporate *post-hoc* analyses and subgroups after database lock and thus a number of *post-hoc* and subgroup analyses are also reported. The main change to the analysis plan that may impact on selection bias involved splitting the TPC treatment arm into seven groups (capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines, hormonal therapy and other drugs) without appropriate adjustment for multiple testing, thus increasing the risk of chance findings. The ERG considers that the results from the *post-hoc* analyses of eribulin vs **individual TPC** should be interpreted with caution since these analyses were defined after database lock and the large number of comparisons performed increase the risk of chance findings.

The ERG is also aware that the protocol for censoring patients was changed between the primary and the updated analyses. In the primary analysis, patients lost to follow-up were censored at the last known visit date, whilst in the updated analysis, patients lost to follow-up were censored at the data cut off date. At the updated analysis, a small number of patients (n= 14) were alive, 9 patients were lost to follow-up (8 of these were from the eribulin arm of the trial) and 5 patients had withdrawn consent (1 from the eribulin arm).

The clinical evidence for eribulin presented in the MS is primarily based on data from a single RCT, EMBRACE[17]. This study was the main source for the clinical evaluation as it was the only study directly comparing eribulin and TPC. Therefore, no meta-analysis or indirect comparison was performed by the manufacturer.

4.2.4 Summary statement

The systematic review in the MS, which identified only one RCT comparing eribulin to TPC was complete and reasonable. The search strategy was appropriate and clearly reported. All relevant clinical trials were identified and the validity of the one included trial (EMBRACE[17]) to the decision problem was discussed appropriately by the manufacturer. The trial was well-designed, incorporating a primary endpoint of OS and independent monitoring of investigator assessments of endpoints that measured time to event. The clinical outcomes reported in the single relevant RCT identified cover the relevant outcomes outlined in the final scope issued by NICE[16] (OS, PFS, ORR, duration of response and AEs). Data relating to HRQoL were derived from two single-arm, phase II studies. [27, 28] The ERG noted that the population in the EMBRACE[17] trial is younger than the population of patients likely to be treated in UK clinical practice. The ERG is confident that the manufacturer's statistical approach was appropriate with regard to the main analyses, but advises caution in the interpretation of the results of *post-hoc* subgroup analyses.

4.3 Summary of clinical effectiveness results

In the MS, the manufacturer presents the results of a number of different analyses derived from the EMBRACE[17] trial. These are listed in Table 8. The manufacturer states (MS, pg 58) that the protocol-specified primary analysis was conducted when 422 (55%) patients had died; however, in accordance with requests from regulatory authorities, the manufacturer carried out an updated analysis that took place after 589 (77%) patients had died. The results of both of these analyses are reported in the MS.

In this ERG report, the data for the overall trial population (analyses from both time points) will be discussed first, followed by the results for the subgroup analyses of Region 1 and finally the eribulin vs individual TPCs (overall and Region 1) outcomes.

Table 8 Analyses presented in the MS

Endpoint	Analysis set	Timing of analysis	Analysis type
OS	Overall EMBRACE	Primary – at 55% patient deaths	Pre-specified
OS	Overall EMBRACE	Updated for regulatory authorities – at 77% patient deaths	*Post-hoc*
OS	Region 1 EMBRACE	Primary – at 55% patient deaths	Pre-specified subgroup
OS	Region 1 EMBRACE	Updated for regulatory authorities – at 77% patient deaths	*Post-hoc*
OS	Overall EMBRACE by selected individual TPC	Updated for regulatory authorities – at 77% patient deaths	*Post-hoc* subgroup
OS	Region 1 EMBRACE by selected individual TPC	Updated for regulatory authorities – at 77% patient deaths	*Post-hoc* subgroup
PFS	Overall EMBRACE	Primary – at 55% patient deaths	Pre-specified
ORR	Overall EMBRACE	Primary – at 55% patient deaths	Pre-specified
CBR	Overall EMBRACE	Primary – at 55% patient deaths	Pre-specified
Duration of response	Overall EMBRACE	Primary – at 55% patient deaths	Pre-specified

4.3.1 Overall EMBRACE population

Treatment duration

The MS describes the duration of treatment with eribulin in the safety population (i.e. all patients who were randomised and who received at least a partial dose of study treatment) of the EMBRACE[17] trial. Table 9 shows longer exposure to treatment in the eribulin arm than to TPC. The range of treatment cycles with eribulin was between one and 23; the greatest proportion of patients (36.8%) received more than six cycles of treatment. The manufacturer states that 22.7% (n=114) and 2.4% (n=12) of patients received treatment with eribulin for > 6 months and > 1 year, respectively (MS, pg 57).

Dose delays were required for 49.3% of patients and dose reductions for 28.8% of patients treated with eribulin. The number of cycles completed by patients in the TPC group was not reported by the manufacturer. However, the majority of patients in the TPC arm received CTX (96.4%). For patients receiving CTX, dose delays were required for 41.2% of patients and dose reductions for 26.5% of patients. Dose interruptions were required for 8.8% of patients receiving CTX.

Table 9 Duration of eribulin treatment

	Eribulin (N=503)	TPC-CTX (N=238)	TPC-Hormonal (N=9)
Exposure median days (min- max)	118 (21 to 497)	64.0 (1 to 644)	30.0 (25 to 188)
Number cycles completed on study (n %) 1-2	81 (16.1%)	NA	NA
3-4	127 (25.2%)		
5-6	110 (21.9%)		
>6	185 (36.8%)		
Range	1 - 23 cycles		
Dose intensity, median mg/m^2/week (min-max)	0.85 (0.2 to1.0)	NA	NA
Relative dose intensity, % (min- max)	91% (30 to 110)	NA	NA
Patients with dose interruption, n (%)	28 (5.6%)	21 (8.8%)	2 (22.2%)
Patients with dose delay, n (%)	248 (49.3%)	98 (41.2%)	0 (0.0%)
Patients with dose reduction, n (%)	145 (28.8%)	63 (26.5%)	0 (0.0%)

NA= not applicable

Primary outcome

The OS data for the primary analysis and the updated analysis are described in Table 10. Any relevant Kaplan-Meier figures presented in the MS are replicated in Appendix 2 of this ERG report. As noted by the ERG earlier in this report, the definition for patient censoring differed between the primary and updated analyses. In the updated analysis, those lost to follow-up were censored at data cut-off date, whereas in the primary analysis, there were censored at the last known visit date.

In the primary analysis, treatment with eribulin is associated with a statistically significant improvement in OS compared with treatment based on TPC (HR=0.81; 95% CI 0.66 to 0.99). Median OS in the eribulin arm is 13.1 months/399 days compared to 10.6 months/324 days in the TPC arm (p=0.041); this yields a median OS benefit of eribulin vs TPC of 2.5 months/75 days. The manufacturer reports a sensitivity analysis adjusting for the number of prior CTX treatments and ER status; this demonstrates that results are consistent with the primary analysis (Table 10).

A similar statistically significant OS finding is observed in the updated analysis (HR=0.81; 95% CI 0.67 to 0.96). Median OS in the eribulin arm is 13.2 months/403 days compared to 10.5 months/321 days in the TPC arm. (p=0.014); this yields a median OS benefit of eribulin vs TPC of 2.7 months/82 days.

Table 10 Overall survival EMBRACE ITT population

	Primary analysis (Kaplan-Meier)		**Updated analysis (Kaplan-Meier)**	
	Eribulin (N=508)	TPC (N=254)	Eribulin (N=508)	TPC (N=254)
Number of patients who died n(%)	274 (53.9%)	148 (58.3%)	386 (76.0%)	203 (79.9%)
OS (days)				
Median (95% CI)	399 (360 to 434)	324 (282 to 380)	403 (367 to 438)	321 (281 to 365)
3rd Quartile (95% CI)	650 (573 to NE)	NE (547 to NE)	677 (605 to 752)	636 (533 to 730)
Difference in Medians (95% CI)	75.0 (21.4 to128.6)		82.0 (29.9 to 134.1)	
Stratified log-rank test:	p = 0.041		p = 0.014	
One-year survival rate, proportion (95% CI)	0.54 (0.49 to 0.59)	0.44 (0.37 to 0.50)	0.55 (0.50 to 0.59)	0.43 (0.37 to 0.49)
Two-year survival rate, proportion (95% CI)	0.22 (0.15 to 0.30)	0.27 (0.19 to 0.36)	0.22 (0.18 to 0.26)	0.19 (0.14 to 0.25)
HR, (eribulin/TPC): main analysis* Estimate (95% CI)	0.81 (0.66 to 0.99)		0.81 (0.67 to 0.96)	
HR (eribulin/TPC): sensitivity analysis** Estimate (95% CI)	0.81 (0.66 to 0.99)		0.81 (0.68 to 0.96)	

NE=not estimable due to insufficient events; * HR based on a Cox model including HER2 status, prior capecitabine treatment, and geographical region as strata; ** HR based on a Cox model including HER2 status, prior capecitabine treatment, geographical region as strata, and number of prior chemotherapy regimens, and ER status as covariates

Secondary outcomes

According to the MS (MS, pg 61), investigators assessed disease progression through scans and patient examinations (thus representing clinical practice); whilst the independent reviewers assessed disease progression via imaging data only. The manufacturer states (MS, pg 61) that the independent review was conducted to reduce bias in assessment but that there are limitations associated with this approach, namely:

i. Patients were no longer scanned when the investigator deemed that they had progressive disease (PD), leading to informative censoring. Even if the independent reviewers did not find PD, they could no longer follow the patients' tumour responses since scans were not available to review. A consequence of this is that some progressions in the investigator's review become censored in the independent review.

ii. Progression of patients with non-measureable disease could only be assessed by independent review if non-target lesions progressed or if new lesions appeared.

iii. Patients who progressed clinically without radiologic findings could not be assessed by the independent reviewers.

The manufacturer acknowledges that the limitations noted above could explain any differences in investigator-assessed and independently-assessed results. The manufacturer has appropriately presented the investigator and independent reviewer results in the clinical effectiveness section of the MS and has used the independent reviewer results to populate the economic model. The ERG raised concerns in Section 4.2.1 regarding use of the independent reviewer results due to the numbers of patients with missing follow-up assessments. The ERG considers that, as the independent assessors were only able to verify a reduced number of patient outcomes, the investigator results ought to have been used in the economic evaluation.

Progression free survival

The PFS outcome data (primary analysis) are described in Table 11. Treatment with eribulin is associated with a statistically significant improvement in PFS compared with treatment based on TPC when assessed by the investigator (HR=0.76; 95% CI 0.64 to 0.90) but not when assessed by the independent reviewer (HR=0.87; 95% CI 0.71 to 1.05). In the independent assessment, median PFS is 3.71 months/113 days in the eribulin arm, compared with 2.23 months/68 days in the TPC arm (p=0.137). In the investigator assessment, median PFS in the investigator assessment is 3.61 months/110 days in the eribulin arm, compared with 2.17 months/66 days for the TPC arm (p=0.002). The manufacturer notes that 'this apparent difference arose from the censoring of almost twice as many patients in the independent review than in the investigator review. Study scans stopped once the investigator had declared disease progression, leading to many censored patients in the independent review, who could only be assessed for non-measurable disease for progression if non-target lesions progressed or new lesions appeared'(MS, pg 62). The manufacturer states that for the PP population, the difference was statistically significant for both investigator and independent analyses ($p < 0.05$). In addition, the ERG has noted that a considerable number of patients did not receive scans at all, thus reducing further the quantity of verifiable evidence.

Table 11 Progression-free survival EMBRACE ITT population: primary analysis

	Independent review (Kaplan-Meier)		**Investigator review (Kaplan-Meier)**	
	Eribulin (N=508) n (%)	TPC (N=254) n (%)	Eribulin (N=508) n (%)	TPC (N=254) n (%)
Number of patients who progressed or died n(%)*	357 (70.3%)	164 (64.6%)	429 (84.4%)	206 (81.1%)
PFS (days)				
Median (95% CI)	113 (101 to 118)	68 (63 to 103)	110 (100 to 114)	66 (60 to 79)
p-value	0.137		0.002	
HR (eribulin/TPC)** Estimate (95% CI)	0.87 (0.71 to 1.05)		0.76 (0.64 to 0.90)	
PFS rate proportion (95% CI)				
3 months	0.57 (0.53 to 0.62)	0.45 (0.38 to 0.52)	0.56 (0.51 to 0.60)	0.41 (0.35 to 0.48)
6 months	0.26 (0.22 to 0.31)	0.28 (0.21 to 0.34)	0.27 (0.23 to 0.31)	0.20 (0.15 to 0.25)
9 months	0.12 (0.09 to 0.16)	0.11 (0.05 to 0.17)	0.14 (0.10 to 0.17)	0.10 (0.06 to 0.15)
12 months	0.09 (0.05 to 0.13)	0.07 (0.02 to 0.13)	0.07 (0.04 to 0.10)	0.07 (0.03 to 0.11)

* remaining patients were censored; ** HR based on a Cox model including HER2 status, prior capecitabine treatment and geographical region as strata

Objective response rate and clinical benefit rate

The ORR (patients with complete response or partial response) and CBR (patients with a complete response, partial response or stable disease ≥6 months) for patients with measureable disease at baseline (n=682) are presented in Table 12. The ORR was statistically significantly different in favour of eribulin compared with TPC for both independent-based (12.2% [95% CI 9.4 to 15.5] vs 4.7% [95%CI 2.3 to 8.4] p=0.002) and investigator-based assessments (13.2% [95% CI 10.3 to 16.7] vs 7.5% [95% CI 4.3 to 11.9] p=0.028).

The ERG notes that the ORR in the CSR/MS is not the ORR used in the submitted economic model. The model uses a lower rate as it divides "response" by the whole population whereas the CSR/MS uses "response"/evaluable population. The approach used in the model could be considered to be conservative, but without further information, the ERG is unable to comment.

The CBR for the eribulin arm was greater than in the TPC arm for both independent-based assessment (22.6% [95% CI 18.9 to 26.7] vs. 16.8% [95% CI 12.1 to 22.5]) and investigator-

based assessment (27.8 [95% CI 23.8 to 32.1 vs 20.1% [95% CI 14.9 to 26.1]). The manufacturer notes the overlapping confidence intervals between the treatment arms (indicating a non-statistically significant difference) but argues that this reflects the similar proportions of patients with stable disease in the eribulin and TPC arms. The manufacturer highlights the greater rates of complete and partial responses in the eribulin group and contends that these higher rates suggest a clinically significant benefit of eribulin therapy.

Table 12 Objective response and clinical benefit rates EMBRACE response - evaluable population

	Independent review (Kaplan-Meier)		**Investigator review (Kaplan-Meier)**	
	Eribulin (N=468) n (%)	TPC (N=214) n (%)	Eribulin (N=468) n (%)	TPC (N=214) n (%)
Complete response	3 (0.6%)	0	1 (0.2%)	0
Partial response	54 (11.5%)	10 (4.7%)	61 (13.0%)	16 (7.5%)
Stable disease	208 (44.4%)	96 (44.9%)	219 (46.8%)	96 (44.9%)
Progressive disease	190 (40.6%)	105 (49.1%)	176 (37.6%)	97 (45.3%)
Not evaluable	12 (2.6%)	3 (1.4%)	11 (2.4%)	5 (2.3%)
Unknown	1 (0.2%)	0	0	0
ORR (complete or partial response) 95% CI*	57 (12.2%) 9.4 to 15.5	10 (4.7%) 2.3 to 8.4	62 (13.2%) 10.3 to 16.7	16 (7.5%) 4.3 to 11.9
p-value**	0.002		0.028	
CBR (complete, partial, stable disease ≥6 months) 95% CI*	106 (22.6%) 18.9 to 26.7	36 (16.8%) 12.1 to 22.5	130 (27.8%) 23.8 to 32.1	43 (20.1%) 14.9 to 26.1

* Exact Pearson-Clopper 2-sided CI; ** Fisher's Exact Test

Duration of response

The manufacturer states (MS, pg 65) that in the independent review, the median duration of response amongst patients who responded (n=57) was clinically relevant in the eribulin arm, but not statistically significantly different from that observed in the TPC arm (4.2 months/128 days [95% CI 116 to152] vs 6.7 months/205 days [95% CI 205 to 212] p=0.159).

The manufacturer notes that the numbers of responders in the investigator-assessed TPC arm was very small (n=10) and therefore any comparison between the two groups is highly unreliable.

4.3.2 Subgroup analyses

Region 1 population: Primary outcome

The manufacturer presents OS data for the patients from Region 1; these are described in Table 13. The results are presented for both the primary and updated analyses.

In the primary analysis, treatment with eribulin is associated with a statistically significant improvement in OS compared with treatment based on TPC (HR=0.72; 95% CI 0.57 to 0.92). Median OS in the eribulin arm is 13.1 months/399 days compared to 10.0 months/306 days in the TPC arm (p=0.009); this yields a median OS benefit of eribulin vs TPC of 3.1 months/93 days.

A similar statistically significant result is observed in the updated analysis (HR=0.79; 95% CI 0.64 to 0.98). Median OS in the eribulin arm is 13.2 months/402 days compared to 10.1 months/308 days in the TPC arm (p= 0.031); this yields a median OS benefit of eribulin compared to TPC of 3.1 months/94 days.

The ERG notes that the relative improvement in median OS in the Region 1 population is 3.1 months in both primary and updated analyses, whilst in the overall trial population the relative improvement is 2.5 months (primary analysis) and 2.7 months (updated analysis).

Table 13 Overall survival Region 1 population

	Primary analysis (Kaplan-Meier)		**Updated analysis (Kaplan-Meier)**	
	Eribulin (n=325)	TPC (n=163)	Eribulin (n=325)	TPC (n=163)
Number of patients who died n(%)*	182 (56.0%)	104 (63.8%)	252 (77.5%)	132 (81.0%)
OS (days)				
Median (95% CI)	399 (359 to 452)	306 (255 to 332)	402 (359 to 451)	308 (255 to 332)
Stratified log-rank test	p = 0.009		p = 0.031	
HR, (eribulin/TPC), estimate (95% CI)**	0.72 (0.57 to 0.92)		0.79 (0.64 to 0.98)	

*remaining patients were censored; **HR based on a Cox model including HER2 status, prior capecitabine treatment, and geographical region as strata

Region 1: Secondary outcomes

Secondary outcome data for patients in Region 1 are not presented in the MS. Based on data that were included in the manufacturer's economic model, the ERG was able to calculate PFS (Table 14). The calculations are made using the independent reviewer data from the updated analysis. Median PFS is statistically significantly longer in the eribulin arm than in the TPC arm (3.3 months/100 days vs 2.2 months/66 days p<0.0001). Median PFS for eribulin appears shorter in the Region 1 subgroup than in the overall trial population (3.3 months/100 days vs 3.7 months/113 days); this is despite the longer OS observed by patients in Region 1 compared with the overall population.

Table 14 PFS Region 1 (ERG calculated)

	Eribulin N=325	**TPC N=163**
Median PFS (days/months)	100 days /3.28 months	66 days/2.17 months
95%CI	83.67 to 116.33	61.53 to 70.47
SE median	8.33	2.28
p-value	P<0.0001	
HR (95%CI)	0.80 (0.63 to 1.00) p=0.0104	

Outcome data for ORR for Region 1 are presented in the CSR; however, as noted earlier any comparison is problematic due to the small number of responders in the TPC arm of the trial.

Region 1vs Region 2 and Region 3

The ERG notes that when interpreting the results of a trial, it is conventional to use data from the ITT population of a trial (i.e. the population on which the power calculation is based); subgroup data should only be considered if there is a compelling reason to do so. In the MS, the manufacturer has presented both the results of the overall ITT population of the EMBRACE[17] trial and the results for the subgroup of patients from Region 1only. The manufacturer states (MS, pg54) that geographical region was included as a stratification factor in the EMBRACE[17] trial to take into account of differences in clinical practice and drug availability in different geographical locations.

In order to explore whether or not differences in prognosis exist between patients from Region 1 and the remaining trial population (i.e. patients from Region 2 and Region 3), the ERG has compared the mean OS for Region 1 with the mean OS of Regions 2 and 3 combined (Table 15). There is no significant difference in any of the comparisons described in Table 15; this suggests that patients in Region 1 do not differ (in terms of prognosis) from the patients in the remainder of the trial population. The ERG does not consider the results of

the subgroup analyses of Region 1 only to be more appropriate than those of the overall ITT population. The ERG notes that the European marketing authorisation for eribulin was based on the results of the overall EMBRACE[17] population.

Table 15 Mean OS estimates compared: Region 1 population vs Regions 2 & 3 populations

Regional comparison		Truncation limit (days)	Eribulin			TPC		
			N	Mean OS	SE	N	Mean OS	SE
Region 1 only (not truncated)	Days Months	N/A	325	475.4 15.62	18.7 0.61	163	390.5 12.83	23.4 0.77
Regions 2 and 3 (not truncated)	Days Months	N/A	183	449.7 14.77	21.5 0.71	91	423.9 13.93	31.9 1.05
p (region difference)				0.19	NS		0.21	NS
Region 1 only (truncated)	Days Months	945	325	461.9 15.18	16.8 0.55	163	390.5 12.83	23.4 0.77
Regions 2 and 3 (truncated)	Days Months	802	183	431.4 14.17	18.9 0.62	91	404.4 13.29	27.5 0.90
p (region difference)				0.08	NS		0.58	NS

N/A=not applicable; NS=not significant

Eribulin versus selected individual treatments

The manufacturer carried out an analysis of median OS data by TPC subgroup to compare eribulin with each individual TPC group. Prior to randomisation in the EMBRACE[17] trial, a TPC was identified for each patient. Patients were then stratified and randomised to either eribulin or TPC arm. The subgroup analysis described in Table 16 compares eribulin patients (overall trial population) who would have received that specific TPC had they had been randomised to the TPC arm, against those that did receive that specific TPC agent. The analyses in Table 17 are for patients in Region 1. All results are presented for the updated analysis only.

The analyses presented in the MS have been conducted to address the individual comparator treatments stated in the scope issued by NICE[16] (i.e.vinorelbine, capecitabine, and gemcitabine). The ERG notes that the numbers of patients within each comparison is small and, in individual comparisons, patient numbers do not always seem to reflect the 2:1 randomisation ratio.

Overall survival by TPC group, EMBRACE overall population

The manufacturer states (MS, pg 67) that there is an OS benefit for eribulin vs all comparators. The ERG emphasises that the data described in Table 16 are based on exploratory *post-hoc* analyses and that patient numbers in each treatment group are small.

Table 16 Overall survival by TPC group, overall EMBRACE population

	Treatment group					
	Eribulin (n=[redacted]	Capecitabine (n=[redacted]	Eribulin (n=[redacted]	Vinorelbine (n=[redacted]	Eribulin (n=[redacted]	Gemcitabine (n=[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]						
[redacted]	[redacted]		[redacted]		[redacted]	

[redacted]

Overall survival by TPC group, Region 1 population

The median OS data by TPC group for Region 1 is described in Table 17. [redacted] The cautions noted above are applicable to these analyses.

Table 17 Overall survival by TPC group, Region 1 population

	Treatment group					
	Eribulin (n=[redacted]	Capecitabine (n=[redacted]	Eribulin (n=[redacted]	Vinorelbine (n=[redacted]	Eribulin (n=[redacted]	Gemcitabine (n=[redacted]
[redacted]					[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]						
[redacted]						

[redacted]

4.3.3 Non-RCT evidence

In support of the results of the EMBRACE[17] trial, the manufacturer cites evidence from three phase II trials.[28-30] All three trials, described as multi-centred, single- arm and open-label are summarised in Table 18. The manufacturer has described these studies at length in the MS (MS, pgs 70-82). The findings of the three studies appear to support those of the EMBRACE trial.[17]

Table 18 Summary of non-RCT evidence

Trial	Intervention	Population	Outcomes	Summary of results
Study 201[28] (n=103)	Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1, 8 and 15 of a 28-day cycle (n=70). Because of neutropenia (at Day 15), a further cohort of patients (n=33) was added to explore an alternative regimen of eribulin; 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen)	Patients with advanced/ metastatic breast cancer who had previously received treatment with at least an anthracycline and a taxane. Median age 55 years US/Europe	Primary = ORR Duration of response PFS* OS* CBR HRQoL (FACT-B) Safety	In the PP population (independent review) ORR:11.5% (95% CI 5.7 to 20.1) all responses were PRs Median duration of response: 5.6 months/171 days (range 44 to 363) Median PFS: 2.6 months/79 days (95% CI 54 to 107) Median OS: 9.0 months/275 days (95% CI 216 to 481) CBR: 17.2% (95% CI 10.0 to 26.8) HRQoL: quality of life may be improved in patients who have objective positive tumour response to eribulin treatment
Study 211[29] (n=291)	Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen)	Patients with LABC/MBC, previously treated with an anthracycline, a taxane and capecitabine Median age 56 years US/Europe	Primary = ORR Duration of response PFS* OS* CBR HRQoL (EORTC-QoL) Safety	In the PP population (independent review) ORR: 9.3% (95% CI 6.1to 13.4) all responses were PRs Median duration of response: 4.1 months/126 days (95% CI 89 to 177; range 42 to 258) Median PFS: 2.6 months/79 days (95% CI 64 to 92) Median OS: 10.4 months/315 days (range: 19–604) CBR: 17.1% (95% CI 12.8 to 22.1) HRQoL: results difficult to interpret. Exploratory analysis indicates no symptomatic change among patients with tumour response; symptomatic deterioration experienced by patients with disease progression by the end of treatment cycle two.
Study 221[30] (n=84)	Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen)	Japanese patients with LABC/MBC, previously treated with an anthracycline and a taxane Median age 54 years	Primary = ORR Duration of response PFS** OS** CBR Safety	In the full analysis dataset (independent review) ORR : 21.3% (95% CI 12.9 to 31.8) all responses were PRs Median duration of response: 3.9 months/119 days (95% CI 85 to148) Median PFS: 3.7 months/112 days (95% CI 61to 133) Median OS: 10.9 months/331 days (95% CI 234 to NE)

ORR= objective response rate; PP=per protocol; PR=partial response;
*measured from start of treatment not date of randomisation **measured from date of registration

Health-related quality of life

No HRQoL data were collected during the EMBRACE[17] trial. However, HRQoL data from two of the phase II studies[28, 29] noted in Table 18 are presented in support of the manufacturer's case.

The FACT-B[33] questionnaire was utilised in Study 201.[28] It is a validated, tumour-specific questionnaire containing 36 questions about the patient's emotional, functional, physical and social well-being. The scores from the 36 items are given equal weight and then summed to create a total FACT-B score from 0 to 144, with a higher number correlating to a more favourable QoL. The Trial Outcome Index is the sum of the subscores for the physical well-being, functional well-being and breast cancer subscale domains. None of the participating patients, whose tumours responded to eribulin treatment, reported deterioration in QoL although 11% of the overall study population did report deterioration. Based on the responses to the FACT-B questionnaire,[34] the manufacturer concludes that QoL may be improved in patients whose tumour responds to eribulin treatment. The manufacturer was unable to interpret data for the assessment of tumour-related symptoms due to the level of non-response.

The EORTC-QOL Questionnaire C30 (version 3.0)[34] with the breast cancer specific module BR23 (version 1.0) was utilised in Study 211.[29] This tool comprises a total of 53 questions and 23 functional or symptoms subscales. The latter are transformed via a linear transformation to standardize the raw scores so that scores range from 0 to 100. A higher score represents a better level of functioning or a worse level of symptoms. On this measure, the manufacturer reports that the QoL data results were difficult to interpret (due to the level of non-response) but that exploratory analyses indicated no symptomatic change among patients with tumour response, whereas symptomatic deterioration was experienced by patients who experienced disease progression by the end of treatment cycle two.

The ERG considers the presented HRQoL evidence to be weak since it is based on data from a small number of patients and is derived from trials in which there was no comparator arm.

4.3.4 Adverse events

In the MS (MS, pg 84) the manufacturer notes that any comparison of safety between eribulin and TPC will be subject to the following caveats: i) patients in the TPC group received a wide range of treatments, each of which will have a distinct safety profile and ii) the number of patients receiving each TPC was relatively small. The manufacturer cautions that reliable conclusions cannot easily be drawn from comparing incidences of specific AEs

in the eribuli n and TPC arms of the EMBRACE[17] trial. The AEs reported in the MS are treatment-emergent events, rather than treatment-related (MS, pg 84).

Overall incidence of adverse events

The manufacturer reports (MS, pg 90) that the rates of death at the end of trial cut-off were similar for eribulin and TPC arms 53.9% and 57.9% respectively; the primary cause of death was progressive disease (50.5% vs 54.7%).

The manufacturer (MS, pg 90) notes that the most frequently reported SAEs in the eribulin arm were febrile neutropenia (4.2%) and neutropenia (1.8%); the most frequently reported events in the TPC arm were dyspnoea (3.6%) and asthenia (2.4%).

The overall incidence of AEs is described in Table 28 of the MS. It is noted in the MS (MS, pg 84) that almost all patients in the EMBRACE[17] trial experienced at least one AE; the rate of SAEs was similar for eribulin (25.0%) and TPC (25.9%) arms. There were fewer deaths related to toxicity in the eribulin arm (4.0%) than in the TPC arm (7.3%). Incidences of Grade 3 AEs were lower in the eribulin arm than for TPC patients (61.2% vs 46.2%); however, the converse was true for Grade 4 AEs (29.4% eribulin vs 13.4% TPC).

Fewer patients in the eribulin arm compared to TPC experienced AEs that led to either dose discontinuation or dose interruption (13.3% vs 15.4%). The manufacturer states (MS, pg 91) that the most common AE leading to discontinuation of eribulin treatment was peripheral neuropathy (4.8%); however, 63% of the eribulin patients with Grades 3 or 4 peripheral neuropathy were able to continue treatment.

Most commonly reported adverse events

The most commonly reported AEs (all grades, >10% patients in each arm) in the EMBRACE[17] trial are described in Table 29 of the MS; this is replicated in Table 19 in this report.

The manufacturer notes (MS, pg 86) the most common AEs in each arm of the trial. For eribulin, these were asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy (34.6%) and nausea (34.6%); for TPC, the most common AEs were asthenia/fatigue (39.7%), neutropenia (29.6%), nausea (28.3%), anaemia (22.7%) and constipation (20.6%).

Compared to TPC, more incidences were reported in the eribulin arm of neutropenia (51.7% vs 29.6%), leucopenia (23.1% vs 11.3%), asthenia/fatigue (53.7% vs 39.7%), pyrexia (20.9% vs 12.6%), investigations for weight decrease (21.3% vs 14.2%), anorexia (19.5% vs

13%), arthralgia/myalgia (21.7% vs 11.7%) back pain (15.7% vs 7.3%), headache (19.3% vs 11.7%), peripheral neuropathy (34.6% vs 16.2%), cough (14.3% vs 8.5%) and alopecia (44.5% vs 9.7%).

The manufacturer states (MS, p86) that i) with the exception of neutropenia, the majority of AEs experienced across both groups were Grade 1 or Grade 2; ii) neutropenia, leucopenia, peripheral neuropathy and asthenia/fatigue were the most common AEs reported at Grades 3 and 4 in both treatment arms; iii) in the eribulin arm, Grade 3 and Grade 4 neutropenia were observed in 21.1% and 24.1% of patients respectively and a there was a rate of febrile neutropenia of 4.6%.

The manufacturer asserts that the safety outcomes of the EMBRACE[17] trial 'demonstrate that eribulin is associated with a predictable and well-characterised safety profile and is generally well-tolerated, for a chemotherapeutic agent being used in pre-treated LABC/MBC patients' (MS, pg 83).

Table 19 Most commonly reported adverse events by treatment group EMBRACE

System organ class AEs	Eribulin N=503 n (%)	TPC N=247 n (%)	Vinorelbine N=61 n (%)	Gemcitabine N=46 n (%)	Capecitabine N=44 n (%)
Any AE	497 (98.8 %)	230 (93.1)	57 (93.4%)	44 (95.7%)	41 (93.2%)
Blood and Lymphatic					
Neutropenia	260 (51.7%)	73 (29.6 %)	30 (49.2%)	17 (37.0%)	2 (4.5%)
Anaemia	94 (18.7%)	56 (22.7%)	13 (21.3%)	9 (19.6%)	10 (22.7%)
Leucopoenia	116 (23.1%)	28 (11.3%)	10 (16.4%)	8 (17.4%)	1 (2.3%)
Gastrointestinal					
Nausea	174 (34.6%)	70 (28.3%)	19 (31.1%)	18 (39.1%	9 (20.5%)
Constipation	124 (24.7%)	51 (20.6%)	24 (39.3%)	9 (19.6%)	6 (13.6%)
Diarrhoea	92 (18.3%)	45 (18.2%)	14 (23.0%)	9 (19.6%)	12 (27.3%)
Vomiting	91 (18.1%)	44 (17.8%)	13 (21.3%)	10 (21.7%)	10 (22.7%)
General disorders and administration site					
Asthenia/fatigue	270 (53.7%)	98 (39.7%)	31 (50.8%)	17 (37.0%)	17 (38.6%)
Pyrexia	105 (20.9%)	31 (12.6%)	6 (9.8%)	8 (17.4%)	6 (13.6%)
Mucosal inflammation	43 (8.5%)	25 (10.1%)	3 (4.9%)	3 (6.5%)	7 (15.9%)
Investigations					
Weight decreased	107 (21.3%)	35 (14.2%)	10 (16.4%)	5 (10.9%)	6 (13.6%)
Metabolism and nutrition					
Anorexia	98 (19.5%)	32 (13.0%)	11 (18.0%)	6 (13.0%)	6 (13.6%)
Musculoskeletal and connective tissue					
Arthralgia/ myalgia	109 (21.7%)	29 (11.7%)	7 (11.5%)	3 (6.5%)	8 (18.2%)
Back pain	79 (15.7%)	18 (7.3%)	7 (11.5%)	2 (4.3%)	4 (9.1%)
Bone pain	60 (11.9%)	23 (9.3%)	5 (8.2%)	4 (8.7%)	2 (4.5%)
Pain in extremity	57 (11.3%)	25 (10.1%)	11 (18.0%)	2 (4.3%)	8 (18.2%)
Nervous system					
Headache	97 (19.3%)	29 (11.7%)	9 (14.8%)	6 (13.0%)	8 (18.2%)
Peripheral neuropathy*	174 (34.6%)	40 (16.2%)	12 (19.7%)	2 (4.3%)	5 (11.4%)

System organ class AEs	Eribulin N=503 n (%)	TPC N=247 n (%)	Vinorelbine N=61 n (%)	Gemcitabine N=46 n (%)	Capecitabine N=44 n (%)
Respiratory, thoracic and mediastinal					
Dyspnoea	79 (15.7%)	31 (12.6%)	7 (11.5%)	6 (13.0%)	3 (6.8%)
Cough	72 (14.3%)	21 (8.5%)	4 (6.6%)	7 (15.2%)	3 (6.8%)
Skin and subcutaneous tissue					
Alopecia	224 (44.5%)	24 (9.7%)	2 (3.3%)	3 (6.5%)	3 (6.8%)
Palmar-plantar erythrodysaesthesia syndrome	7 (1.4%)	34 (13.8%)	0	0	19 (43.2%)

CTCAE,=Common Terminology Criteria for Adverse Events;
*Peripheral neuropathy includes peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia.

4.4 Summary of results

4.4.1 Clinical results

- The main source of clinical evidence described in the MS is derived from the EMBRACE[17] trial
- The EMBRACE[17] trial includes 762 patients who had received at least two CTX treatments (including an anthracycline and taxane unless contraindicated) for LABC/MBC
- Median OS (primary analysis) for the overall ITT population of the EMBRACE[17] trial was statistically significantly longer in the eribulin arm compared to the TPC arm (13.1 months vs 10.6 months). Similarly, in the updated analysis, median OS was statistically significantly longer in the eribulin arm compared to the TPC arm (13.2 months vs 10.5 months)
- Median PFS (primary analysis) for the overall ITT population of the EMBRACE[17] trial was greater in the eribulin arm compared to the TPC arm in both independent and investigator assessments. However, only the investigator review results demonstrate a statistically significant difference between the two arms
- ORR and CBR (primary analysis) are available for the overall ITT population of the EMBRACE[17] trial and were higher in the eribulin arm compared to TPC for both independent and investigator assessments
- Median OS (primary analysis) for the Region 1 population of the EMBRACE[17] trial was statistically significantly longer in the eribulin arm compared to the TPC arm (13.1 months vs 10.0 months). Similarly, in the updated analysis, median OS was statistically significantly longer in the eribulin arm compared to the TPC arm (13.2 months vs 10.1 months)
- The most frequently reported SAEs reported in the eribulin arm were febrile neutropenia and neutropenia. The main reason for discontinuation in the eribulin arm of the trial was peripheral neuropathy.

4.4.2 Clinical issues

- Only one RCT compares eribulin with TPC
- The results of the analyses of eribulin vs individual TPCs are unreliable due to small numbers of patients in each comparison
- The HRQoL data on eribulin are available from two Phase II trials with single arms only
- Overall survival gain from Region 1 clinical data is greater than the OS gain shown in the ITT population analyses. Whether or not the results of the subgroup analyses of Region 1 are more appropriate than the OS results from the overall population to decision-makers in England and Wales is uncertain
- The use of PFS data from the investigator review is problematic due to a substantial number of patients not having received routine assessment scans; this raises concerns about the quality of the trial

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the manufacturer of eribulin. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature and (ii) a report of the manufacturer's *de novo* economic evaluation. See Table 20 for a summary of the key information points. The manufacturer also provided an electronic version of the EXCEL- based economic model.

Table 20 Key information in the MS

Key information	Section (MS)
Details of the systematic review of the economic literature	6.1
Model structure	6.2.2 to 6.2.5
Technology	6.2.7
Clinical parameters and variables	6.3.1 to 6.3.8
Measurement and valuation of health effects and adverse events	6.4.1 to 6.4.15
Resource identification, valuation and measurement	6.5.1 to 6.5.8
Sensitivity analysis	6.6.1 to 6.6.3
Results	6.7.1 to 6.7.11
Validation	6.8.1
Subgroup analysis	6.9.1 to 6.9.5
Strengths and weaknesses of economic evaluation	6.10.1 to 6.10.4
Assessment of factors relevant to other parties	7.0

5.2 Overview of manufacturer's cost-effectiveness review

The MS provides a description of the review of published cost-effectiveness evidence undertaken by the manufacturer. The databases searched and the search terms used appear to be reasonable and both inclusion and exclusion criteria are explicitly stated. The search by the manufacturer did not identify any relevant studies for inclusion in the review. Although there is no mention of searching within in-house databases for relevant studies, the ERG is confident that no relevant published studies are available for inclusion in the review.

Although the manufacturer did not identify any papers that had evaluated the cost effectiveness of eribulin as a third-line treatment for MBC, the MS included data extraction tables and quality assessment reviews of nine economic evaluations that were considered

relevant to inform the structure, assumptions and model inputs for the cost-effectiveness analysis of eribulin for the treatment women with LABC/MBC in the UK.

5.3 Overview of manufacturer's economic evaluation

The manufacturer undertook a *de novo* economic evaluation of eribulin for the treatment of patients with LABC/MBC whose disease had progressed after at least two prior CTX regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane in line with the licensed indication for eribulin. This economic evaluation provides the basis for the manufacturer's claim that eribulin is cost effective compared with a range of different treatment options.

5.3.1 Description of manufacturer's economic model

The manufacturer constructed a semi-Markov state transition model in Microsoft Excel to model the lifetime clinical and economic outcomes for a hypothetical cohort of patients with LABC/MBC. The ERG notes that a trial duration time horizon is adopted in the model. This means that at the end of the duration of the trial (2.89 years), all patients that are alive are transitioned into a "terminal" state and no extrapolation of trial outcomes is undertaken. The model assumes an average body surface area (BSA) of 1.74m^2.The structure of the model is presented in Figure 1.

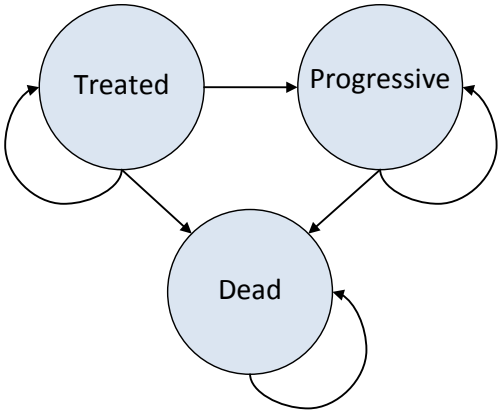

Figure 1 Structure of the model

The model consists of three main health states: treated, progressive and dead. All patients in the model were initially assigned to the "treated" health state which comprises both stable and responsive patients. These patients matched those recruited into the EMBRACE[17] trial and were therefore eligible for treatment with eribulin or the treatment options within TPC. The "treated" state captures the costs of drug acquisition and administration as well as Grade 3/4

AEs. Patients in the model remain in the assigned treatment drug until disease progression or death, as would be the case in clinical practice. The “progressive” state captures the clinical outcomes and resource use for patients whose disease progresses following previous treatments. Cycles continue until all patients are in the “dead” state – for the purposes of resource use and QoL estimations, patients are assumed to enter a “terminal” state for one cycle prior to entering the “dead” state.

5.3.2 Parameters and values

The base case model parameters and values used in the submitted economic model and described in the MS are presented in Table 21. Eribulin has recently been approved by the Department of Health and the lower Patient Access Scheme (PAS) price is used in the economic model. More detailed information is presented in the MS (MS, Appendix 14).

Table 21 Parameters and values used by the manufacturer in the economic model

Model variable	**Costs per vial**	**Costs per cycle**		
Drug costs	**Unit costs (£)**	**Drug acquisition (£)**	**Administration (£)**	**Total (£)**
Eribulin (PAS price)	220 (1mg / 2mL)	1320	420	1738
TPC*	N/A	930	296	1335
Vinorelbine	61.25 (30mg X1)	919	681	1599
Gemcitabine	162.57 (1000mg)	974	454	1428
Capecitabine	265.55 (500mg X120)	531	210	740
Progression free survival (Region 1, K-M); value (95% CI) [distribution]				**Source**
Eribulin vs TPC HR	0.8930 (0.6960 to 1.1450) [normal]			Independent review
Eribulin vs capecitabine HR	0.6195 (0.2962 to 1.2957) [normal]			Independent review
Eribulin vs gemcitabine HR	0.8141 (0.4245 to 1.5613) [normal]			Independent review
Eribulin vs vinorelbine HR	0.6906 (0.4353 to 1.0956) [normal]			Independent review
Overall survival (Region 1, K-M); value (95% CI) [distribution]				**Source**
Eribulin vs TPC HR	0.7910 (0.6390 to 0.9810) [normal]			Independent review
Eribulin vs capecitabine HR	0.3539 (0.1543 to 0.8078) [normal]			Independent review
Eribulin vs gemcitabine HR	0.6790 (0.3605 to 1.2787) [normal]			Independent review
Eribulin vs vinorelbine HR	0.5805 (0.3651 to 0.9229) [normal]			Independent review
Utility values; value (range)				**Source**
Treated/stable	0.715 (0.620 to 0.810)			QoL searches
Treated/responsive	0.790 (0.790 to 0.840)			QoL searches
Progressive	0.443 (0.33 to 0.650)			QoL searches
Terminal	0.160 (0.130 to 0.250)			QoL searches
Anaemia, anorexia, dyspnoea, oedema, heart failure, hyperbilirubinaemia, hypertension, hypokalemia, neuropathy, neutropenia, pain, peripheral neuropathy, pulmonary embolism, thrombocytopenia, urinary tract infection	-0.124 (-0.16 to -0.09)			QoL searches – mean of 5 utilities reported by Lloyd et al
Diarrhoea, vomiting	-0.103 (-0.13 to -0.08)			QoL searches
Fatigue	-0.115 (-0.14 to -0.09)			QoL searches
Febrile neutropenia	-0.150 (-0.19 to -0.11)			QoL searches
Stomatitis	-0.151 (-0.19 to -0.11)			QoL searches

*An additional £4 for pre-medications is required for TPC

5.3.3 Treatment effectiveness within the MS

Clinical data from the EMBRACE[17] trial (Region 1 only) were utilised to populate the submitted economic model.

Progression free survival and overall survival in the EMBRACE study

The economic evaluation is based on the analyses of the latest clinical dataset (after 77% of the patients in the EMBRACE[17] trial had died). Progression-free survival and OS functions are estimated independently for the eribulin and comparator arms using Kaplan-Meier estimates. The data used to inform progression are from the independent review of progression; the manufacturer considers this approach to be conservative.

The model allows the use of either the Kaplan-Meier curves of the eribulin and of the comparator arm or the application of the relevant HR to the Kaplan-Meier curve of the comparator.

In the model, direct use of the Kaplan-Meier curves leads to an underestimate of the OS gain due to censoring of the study data. To overcome this, the HR generated by the clinical analysis is applied to the Kaplan-Meier curve of the comparator arm. The manufacturer notes that this approach increases the size of the OS difference between the two arms and reduces the size of the ICER.

Extrapolation of data

Data are not extrapolated beyond the trial period. This means that the difference in total life years attributable to eribulin does not reflect the greater number of patients alive at the end of the study in the eribulin arm of the trial.

5.3.4 Population

The economic evaluation is based on the clinical-effectiveness results of the EMBRACE[17] trial (Region 1). Patients in Region 1 make up 65% of the patients in the EMBRACE[17] trial. Table 22 shows that the number of patients in each of the CTX comparisons is small; this is most apparent in the eribulin vs capecitabine comparison.

Table 22 Number of patients in the EMBRACE trial in Region 1 only

	Eribulin	Comparator
Eribulin vs TPC	325	163
Eribulin vs gemcitabine	51	27
Eribulin vs vinorelbine	94	45
Eribulin vs capecitabine	31	22

TPC=treatment of physician's choice

5.3.5 Comparator technology

The comparator technology to eribulin in the economic evaluation is TPC. In addition, the manufacturer presents incremental cost-effectiveness ratios (ICERs) for the following comparisons:

- eribulin vs gemcitabine
- eribulin vs vinorelbine
- eribulin vs capecitabine

5.3.6 Health related quality of life

In the EMBRACE[17] trial, EQ-5D questionnaires were not administered to patients. However, HRQoL data related to eribulin have been collected by the manufacturer using the EORTC-QLQ-C30[34] and FACT-B[33] questionnaires from two relevant phase II trials.[28, 29] The manufacturer reports that the HRQoL of patients does not deteriorate and in many cases improves in patients who have objective positive tumour response to eribulin treatment whereas patients who progress may suffer deterioration in their HRQoL (Section 5.8). A systematic review was conducted by the manufacturer in order to identify HRQoL studies relevant to the decision problem with utility data appropriate for the economic model. The manufacturer identified five studies of interest and focussed on the study by Lloyd et al;[35] this study assessed UK-based societal preferences for different stages of MBC and toxicities. In addition, the manufacturer also considered utility values identified via the cost-effectiveness literature review discussed in Section 5.2; data from nine sources were summarised in the MS (MS, Table 36).

In the MS the manufacturer uses the following utility values from the Lloyd et al[35] study for the treated health state (0.715/stable disease and 0.790/responsive) and the progressive health state (0.443); the value used for the terminal health state (0.160) comes from the paper by Hutton et al.[36]

In the model, only Grade 3 and Grade 4 AEs affecting 10% or more patients are considered to be of interest. Where available, the manufacturer uses utility decrements for individual AEs from the study published by Lloyd et al;[35] where unavailable, the manufacturer uses the mean of the disutilities reported in Lloyd et al[35] for individual AEs (

Table 21).

5.3.7 Resources and costs

In the economic evaluation, the manufacturer identifies three major types of costs: intervention and comparator costs, health state costs and AE costs. The manufacturer provides tables in the MS which summarise the unit costs associated with all of the drugs used in the economic model (MS, Tables 39-43); the health states and associated costs used in the economic model (MS, Tables 44-46); and the main AEs and the costs of treating these AEs as used in the economic model (MS, Table 47).

Intervention and comparators' costs: unit drug costs, pre-medication drugs and administration

Unit drugs costs (including co-medications) were based on the prices listed in the British National Formulary 60.[37] In the base case, the median listed price for the largest available package size was used. For solutions and powders, it was assumed that any drug leftover from a treatment was wasted. Since ixabepilone is not available in the UK, no cost was applied in the model for this treatment.

The manufacturer recognises that vinorelbine can be prescribed as an i.v. infusion or as a capsule. The manufacturer focuses on the use of capsules in the base case and considers i.v. infusion as part of the sensitivity analysis. Only docetaxel and paclitaxel are associated with (inexpensive) pre-medication costs.

The average cost of the treatment in the TPC arm is calculated from a weighted average of the cost of drugs according to the usage of drugs in the EMBRACE[17] trial.

Drug administration costs were based on NHS Reference Costs 2008/09.[38] As a simplifying assumption all CTX was considered by the manufacturer as part of ongoing therapy, eliminating the need for separate initial and subsequent HRG codes. All CTX was assumed to be delivered in the out-patient setting. Drug administration costs for injectable CTXs were incurred at each treatment; for oral CTX, the cost was assigned once per model cycle.

Health state costs: treated, progressive and terminal

Resource use and associated costs were dependent on the health state occupied by the patient and were assigned per model cycle. Resources consumed in all three health states included CTX support medication, special interventions, scans and laboratory tests, hospitalisations and outpatient visits; otherwise known as "active treatment". In the stable health state, additional resources were also included when considered as "follow up" care and included CTX support medication, special interventions and scans and laboratory tests. Categories and components of resource use were defined for each of the three states based on a literature review and clinical opinion solicited by the manufacturer. To elicit clinical opinion the manufacturer conducted an advisory board meeting with five leading oncologists in the field of BC; in addition, seven oncologists were interviewed face to face using a pre-specified proforma to capture resource during each state.

Unit costs for each resource were typically based on NHS Reference Cost data (2008/09).[38]

Adverse event costs

Treatment-related AEs reported in the EMBRACE[17] trial were mapped to a representative subset of AEs (n=20) according to clinical opinion (MS, Table 32). In the base case, Grade 3 and Grade 4 AEs affecting 10% or more patients are included; this means that only 14 AEs are included, six of which are simply costed as: "Consultant led: Follow-up attendance non-admitted face-to-face, medical oncology."

All costs were based on day-case appointment NHS Reference Cost data (2008/09).[38]

5.3.8 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS and PSS in England and Wales. The time horizon set was 2.89 years. Both costs and benefits were discounted at 3.5% per annum.

5.3.9 Model validation

The methodological approach to economic modelling adopted by the manufacturer was validated by a Professor of Health Economics based at a UK university. Validation of data inputs was carried out in consultation with UK clinicians and commissioners of oncology treatment services.

The manufacturer provided details of the model validation checklist used (MS, Section 6.8.1). The economic model was checked for functionality, clarity, accuracy, consistency, validity and platform along the project lifecycle.

5.3.10 Results included in manufacturer's submission

Using data from Region 1 only, base-case results for the incremental cost per QALY gained are available for the following comparisons: eribulin vs TPC; eribulin vs gemcitabine; eribulin vs vinorelbine and eribulin vs capecitabine. All of the results presented in this section are based on the PAS approved price of eribulin of [redacted] per vial.

Table 23 Base-case cost-effectiveness results *with* patient access scheme (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental cost per QALY gained
TPC	£30,449	0.5674			
Eribulin	£36,035	0.6887	£5,586	0.1213	£46,050
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.6885	£5,177	0.1904	£27,183
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.6291	£4,041	0.1136	£35,602
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.7853	£12,779	0.2683	£47,631

TPC= treatment of physician's choice; QALY=quality adjusted life year; ICER= incremental cost-effectiveness ratio

The MS presents a series of tables (MS, Tables 52-59) showing detailed disaggregated costs and benefits for the four key comparisons (eribulin vs TPC, vs gemcitabine, vs vinorelbine and vs capecitabine.

Table 24 and Table 25 show the summary of costs by health state and cost category and the summary of QALY gain by health state for the eribulin vs TPC comparison

Table 24 Summary of costs by health state and cost category for eribulin vs TPC

Costs	Cost intervention (Eribulin)	Cost comparator (TPC)	Increment	Absolute increment	% absolute increment
Infusion	£3,174	£2,250	£924	£924	15.63%
Drug	[redacted]	[redacted]	£3,984	£3,984	67.40%
Stable	£1,141	£916	£224	£224	3.80%
Progressive	£3,596	£3,015	£581	£581	9.83%
Terminal	£18,819	£18,970	-£151	£151	2.55%
Grade 3	£18	£30	-£12	£12	0.20%
Grade 4	£54	£18	£36	£36	0.60%
Total	£36,035	£30,449	£5,586	£5,911	1.000

Table 25: Summary of QALY gain by health state for eribulin vs TPC

Health state	QALY intervention (Eribulin)	QALY comparator (capecitabine)	Increment	Absolute increment	% absolute increment
Stable	0.287	0.229	0.058	0.058	47.69%
Progressive	0.393	0.329	0.063	0.063	52.25%
Terminal	0.009	0.009	0.000	0.000	0.06%
Total	0.689	0.567	0.121	0.121	100.00%

The scatter plots and cost effectiveness acceptability curves for each of the four comparisons generated by the manufacturer are presented in the MS (MS, Section 6.6.7). For the eribulin vs TPC comparison, the cost effectiveness acceptability curve shows that, at a willingness to pay of £20,000 to £30,000 per QALY gained, the probability of eribulin being cost effective compared to TPC is 0%.

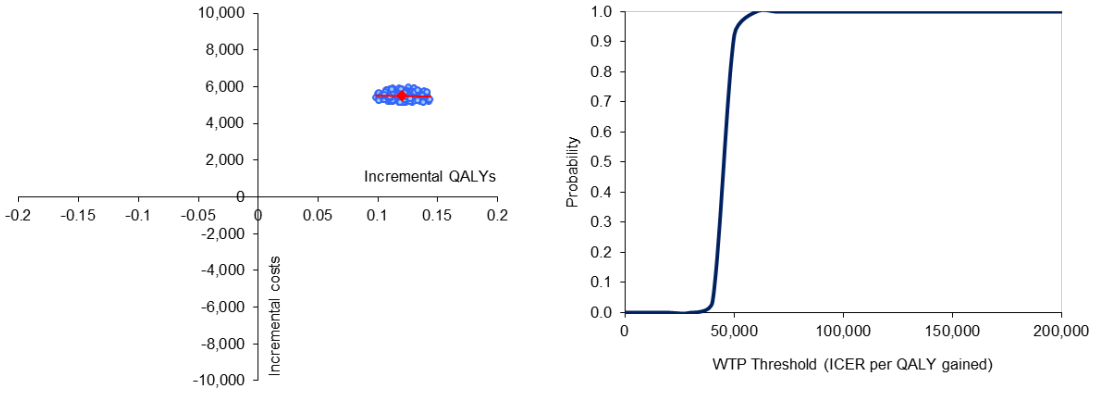

Figure 2 Scatter plot and cost effectiveness acceptability curve (eribulin vs TPC)

Sensitivity analyses

Extensive sensitivity analyses and probabilistic sensitivity analyses have been carried out by the manufacturer. The results of these analyses are provided in Section 6.7.7 to Section 6.7.10 (32 pages) of the MS. Three different sets of analyses have been carried out:

- One way deterministic sensitivity analysis on all model parameters except OS and PFS and the ten most influential parameters were reported

- Scenario analyses (1-4)
    - Application of NICE's 'End of Life' guidance
    - Price of eribulin calculated per mg rather than per vial (assumes no wastage)
    - Price of vinorelbine calculated using the IV formula price instead of oral tablets
    - Data from all regions included

- Structural sensitivity analyses using HRs calculated from the clinical trial to estimate the survival of patients in each of the treatment arms instead of using Kaplan-Meier curves.

The results of the analyses undertaken are presented for the following comparisons:

- eribulin vs TPC
- eribulin vs gemcitabine
- eribulin vs vinorelbine
- eribulin vs capecitabine

In Section 6.6.7 of the MS, the manufacturer reports the top ten parameters of influence as tornado diagrams for each of the base case analyses. For the comparison of eribulin vs TPC, the top ten parameters are: eribulin cost, eribulin dose, mean BSA, utility (progressive state), utility (stable state), utility (responsive state), vinorelbine dose, vinorelbine cost, paclitaxel dose, gemcitabine cost.

In Section 6.7.10 of the MS, the manufacturer summarises the main findings from the sensitivity analyses.

- Base case results show that eribulin versus TPC results in a cost per QALY of £46,050. For the comparators outlined in the NICE scope, the cost per QALY ranges from £27,183 to £47,631. Probabilistic sensitivity analyses demonstrate a low level of uncertainty around the base case results.

- A scenario analysis was conducted on the assumption that eribulin qualifies for consideration under NICE's 'End of 'Life' guidance (see Section 5.5.6 and Section 7 for full discussion of NICE's 'End of Life' criteria and how the manufacturer makes the case for eribulin).The application of NICE 'End of Life' guidance reduces the ICER substantially to £26,589 compared with TPC and ranges from £15,019 to £27,356 when compared with individual components of TPC as outlined in the NICE scope.

- Applying the cost per milligram for eribulin in the model which assumes no drug wastage (representing the practices of the most efficient centres) also reduces the ICER to £42,672 compared with TPC and to £26,330-£45,085 when compared with individual comparators.

- Using vinorelbine in its i.v. formulation at a higher cost than the oral formulation, the cost per QALY would increase from that demonstrated in the base case to £52,407 compared with TPC and to £54,817 compared with vinorelbine.

5.4 Assessment of the manufacturer's economic model

Table 26 shows how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis as set out in the NICE reference case checklist. In general the manufacturer's analysis matches the requirements set by NICE.[39] The manufacturer's decision problem matches the question posed in the final scope issued by NICE.[16] However, given the small number of patients in each of the individual (TPC) subgroup analyses, the clinical data in support of eribulin are unconvincing.

Table 27 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond10-point checklist.[40] The ERG's main criticism of the submitted economic evaluation is related to the identification, measurement and valuation of costs and consequences. In particular, the ERG notes that the manufacturer fails to accurately estimate the costs of the comparators to eribulin and that the manufacturer's approach to utility estimation is flawed.

Table 26 NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes. Third-line treatment of patients with BC is uncertain. The manufacturer appears to have covered, excluding BSC, all of the realistic alternatives.
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. Manufacturer does not extrapolate data but adopts a "worst case scenario" and assumes that all patients at the end of the trial die.
Synthesis of evidence on outcomes	Systematic review	N/a – the manufacturer only uses data from the EMBRACE trial. This is appropriate.
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Partial. In the main, the manufacturer uses values from published literature that have been used in previous STAs. However, the ERG argues that a modification to the published values is required.
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Partial. A minor error was identified and corrected by the ERG.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

Table 27 Critical appraisal checklist

Item	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Partial	The question was well-defined but cannot be answered with confidence given the limited clinical data available for eribulin vs gemcitabine/vinorelbine/capecitabine (the patient numbers in each comparison are very small, especially in Region 1).
Was a comprehensive description of the competing alternatives given?	Yes	Yes. Third-line treatment of patients with BC is uncertain. The manufacturer appears to have covered, excluding BSC, all of the realistic alternatives.
Was the effectiveness of the programme or services established?	Partial	Data from EMBRACE (key trial) are appropriate for decision making – however, subgroup comparisons using data from EMBRACE may not be meaningful due to small patient numbers.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Not always	No, several errors (e.g. CTX costs, terminal care costs, OS gain) were identified by the ERG (see Section 5.6).
Were the cost and consequences valued credibly?	Not always	No, several errors were identified by the ERG (see Section 5.6). Use of NHS Ref Costs 08/09 is out of date as NHS Ref Costs 09/10 were available at the time of writing.
Were costs and consequences adjusted for differential timing?	Partial	ERG corrected a minor error in method of discounting used.
Was an incremental analysis of costs and consequences of alternatives performed?	Partial	An incremental analysis could not be performed as per the usual approach as the cost and benefit data in the eribulin arm is different for each comparison. Incremental analysis was conducted for each individual comparison.
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Yes; deterministic and probabilistic sensitivity analyses were undertaken.
Did the presentation and discussion of study results include all issues of concern to users?	Yes	Yes; all issues of concern to users were discussed.

5.5 Detailed critique of manufacturer's economic model

The manufacturer's economic model is constructed as a Microsoft EXCEL workbook, with Visual Basic routines used to implement specific features, most notably sensitivity analyses. The model is generally well-constructed, with appropriate annotation and identification of data sources and methods of calculation. The only criticism that the ERG would make of the model design is that the structure adopted for handling parameter values appears to be overly complex, with multiple references across intermediate worksheets between the initial data entry and the point at which the value is used in the main model calculations. This makes the tracking of data values through the model unduly circuitous and time-consuming.

5.5.1 Cost of chemotherapy drugs

All of the CTX treatments currently recommended for treatment of MBC are dosed on the basis of the BSA of the individual patient. The submitted model does not take account of BSA differences between patients,[41] but uses a fixed average value for all patients ($1.74m^2$) sourced from a UK survey of CTX patients. The costs of CTX drugs per cycle in nine regimens have been re-estimated by the ERG using BSA values from the Sacco et al[41] study in the population of patients receiving palliative CTX, and are shown in Table 28. For all regimens but one (Nab-paclitaxel), the ERG estimated cost (including wastage) is lower than that used in the manufacturer's model, in several cases very substantially.

Table 28 Chemotherapy costs per cycle (excluding administration costs)

Treatment	Submitted cost per cycle	Re-estimated cost per cycle	Change in cost per cycle
Eribulin (without PAS)	£1,878.00	£1,859.11	- £18.89
Eribulin (PAS discounted)	[redacted]	[redacted]	- £13.28
Vinorelbine (IV)	NR	£408.02	NA
Vinorelbine (oral)	£989.70 (all cycles)	£715.72 (cycle 1) £944.51 (cycle 2+)	- £273.98 - £45.19
Gemcitabine	£975.42	£676.20	- £299.22
Capecitabine	£531.10	£306.83	- £224.05
Docetaxel	£1,604.25	£1,265.74	- £338.51
Paclitaxel	£1,644.49	£648.28	- £996.21
Nab-Paclitaxel	£1,230.00	£1,234.85	+ £4.85
Doxorubicin*	£275.00	£235.62	- £39.38
Lipid doxorubicin*	£1,393.50	£1,333.76	- £59.74

NR =not reported; NA =not applicable
* limited to maximum of seven cycles to avoid cumulative cardio-toxicity (as per SPC)

5.5.2 Cost of chemotherapy administration

Three aspects of the method used by the manufacturer to cost the administration of CTX were found to require correction by the ERG (Table 29):

- unit costs of administration relate to the 2008/2009 NHS Reference Costs,[38] rather than the most recent figures (2009/2010);[42]

- all CTX administration is allocated costs appropriate to an out-patient department, but our clinical advice is that such therapy will normally be administered in a designated CTX day-case unit;

- the manufacturer has ignored the different healthcare resource group (HRG) costs appropriate to the first administration of a course of therapy (using the 'subsequent cycles' costs instead).

Table 29 Chemotherapy administration costs per cycle

Treatment arm / Cycle	Submitted cost per cycle	ERG re-estimated cost per cycle	Change in cost per cycle
Eribulin			
Cycle 1	£454	£491	+ £37
Cycle 2+	£454	£569	+ £115
TPC			
Cycle 1	£400	£418	+ £18
Cycle 2-7	£400	£480	+ £80
Cycle 8+ *	£400	£396	- £4

* doxorubicin limited to maximum of seven cycles to avoid cumulative cardio-toxicity (as per SPC)

5.5.3 Costs of supportive care

In progression-free survival (PFS) state

The manufacturer's model assumes that patients will receive one computed tomography (CT) scan and one out-patient consultation with an oncologist per quarter as recommended in the NICE clinical guidelines.[6] In addition, a quarterly bone scan is also included, together with a set of pathology tests twice per treatment cycle. Regular bone scans for monitoring patient condition are specifically not recommended in the NICE guidelines, and for costing purposes the ERG consider that routine pre-infusion pathology testing is included within the HRG costs for CTX delivery. However, the manufacturer's model includes no provision for the cost of primary and community based services received prior to disease progression.

Using NHS Reference costs for 2009/10 [42] and PSSRU Unit Costs of Health & Social Care 2010,[43] the ERG considers the annual cost of monitoring and supportive care in the PFS state to be £2,915.34. The corresponding figure used in the submitted base case is £2,836.24.

In post-progression survival (PPS) state

For PPS, the ERG considers that the most appropriate and consistent basis for cost estimation is that used in the NICE guideline,[6] based on a package of care from community nurses (including nurse specialist), therapist and GP home visits. Using the latest PSSRU unit costs,[43] this package involves an annual cost of £5,720.79 per patient. By contrast, the manufacturer's model appears to be based on a more hospital-centric pattern of care with out-patient visits to a specialist oncologist every 3 weeks, and to an oncology nurse every 6 weeks. A battery of pathology tests is included every 3 weeks, and regular bone scans and CT scans continue. In addition, approximately 10% of patients receive radiotherapy in each 3-week model period. The total estimated annual cost per patient in the submitted model is £4,059.82.

Terminal care

The terminal care state is defined as the last 14 days of life. The cost per patient in the manufacturer's model is very large (£19,711.85) and is dominated by hospice care. In the absence of available cost information for hospice services, the model authors have employed hospital critical care daily costs as a proxy. The ERG considers that a more appropriate approach to estimating the cost of terminal care in the UK setting is to use the method described in the NICE guidance,[6] based on a Marie Curie report (which assumes 40% of patients die in hospital, 10% in a hospice and 50% at home), updating the cost estimates to current prices. This yields an estimate of £4,003.05 per patient.

5.5.4 Health state and adverse event utility values

Calculation of utility values for EMBRACE population from model by Lloyd et al

The manufacturer has chosen to employ the Lloyd et al[35] mixed model analysis results to generate utility values for their economic model. However, no account has been taken of the non-linear nature of the analysis which involves a logistic transformation of the raw study data. This means that none of the model parameters function as simple additive factors in generating the final state utility estimate.

It is also important to recognise that the age parameter in the published paper refers to the age of 100 participants in the valuation exercise, and not to the age of patients. For consistency with the standard UK EQ-5D tariff scores, the mean age should be set to 47 – the mean age of the original York study.[44] Recalculating the expected utility values for patients in the stable, responder and progression states (without AEs) on this basis produces revised utility estimates consistently higher than those in the submitted model (0.756 instead of 0.715 for stable; 0.823 instead of 0.790 for responder; 0.496 instead of 0.443 for progression).

Disutility due to adverse events

The utility model by Lloyd et al[35] includes only six specific AEs, and therefore has limited scope for reflecting the full range of AEs encountered in a clinical trial. To overcome this limitation, the manufacturer's model has extended the range of AEs which may be included in the analysis, by calculating an average disutility for four of the six AEs estimated by Lloyd et al[35] and then applying this average value to all other AEs. This method is prone to serious distortion as some of the AEs featuring in the EMBRACE[17] trial have been found in other studies to have larger disutility values than the average used here (-0.124).

Limited coverage of AEs

The base case submitted model limits consideration to only those AEs which feature in 10% or more of patients. There is an option to use a 5% threshold instead. These arbitrary restrictions risk excluding small events of great importance in terms of disutility and cost because they have too few events recorded (even though the difference between trial arms may be significant). A clear example in this trial is the incidence of Grade 3/4 febrile neutropenia, which occurred in 4.6% of eribulin patients but only 1.6% of TPC patients and was therefore excluded from the model, despite being one of the most serious and potentially life-threatening consequences of CTX.

Methods for calculating total costs and loss of utility from AEs

The methods used to calculate costs and loss of patient utility from AEs are flawed in several respects and are likely to lead to both over- and under-estimation of the impact of AE-related incremental differences in the submitted model:

i) The data used to indicate the magnitude of AEs experienced in the clinical trial relate only to the proportion of patients who experienced a treatment-related Grade 3 or Grade 4 event at some time during the trial. This does not reflect the number of such events experienced per patient, or the total duration of such events. However these data are employed without modification to the total time spent by patients prior to disease progression. This implies that Grade 3 and 4 Grade event(s) continue for the whole duration of treatment (over-estimation), and that, where the same patient experiences both a Grade 3 and a Grade 4 event of the same type, then both occur concurrently for the whole period (over-estimation and logically inconsistent), but that each patient experiences only one event of each type and grade (under-estimation).

ii) This method also does not recognise that frequently a serious clinical event may involve several important AEs occurring simultaneously, so that cost and disutility effects should be subsumed within accounting for a single event, rather than multiple events (over-estimation).

iii) The costs attributed to AEs are based on typical episode descriptions from clinical opinion. However, all the AEs treatment costs used appear to be very low estimates involving minimal intervention. The most obvious example relates to febrile neutropenia where the same cost (£478) is applied to both Grade 3 and Grade 4 events. This may be compared to the detailed estimate prepared by NICE's Decision Support Unit[45] relating to another appraisal where patients affected by CTX related febrile neutropenia were estimated to suffer 1.4 episodes per patient at a mean cost at 2007 prices of £2,286 (including a mix of in-patient and out-patient treatments). Updating this figure for inflation suggests a figure of £2,415 per patient affected may be more appropriate. The submitted model excludes the effects of febrile neutropenia altogether as it does not achieve at least 5% incidence in either trial arm. However, this is not warranted since both the costs and disutility associated with febrile neutropenia are considerable. The incidence of Grade 3 and Grade 4 febrile neutropenia was 4.6% in the eribulin arm and 1.6% in the TPC arm, and the ERG has entered these values as a model correction together with the adjusted cost per patient, and a recalculated disutility value.

Another AE of particular interest is peripheral neuropathy; clinical advice suggests that it is of importance to patients even at Grade 2. In the EMBRACE[17] trial, the incidence of Grade 2+ peripheral neuropathy was 18.5% for eribulin patients compared to only 8.5% among TPC patients. Despite this important difference, the ERG cannot currently trace any appropriate sources for either the cost of treating this condition, or the disutility value associated with it, and so is unable to assess its impact on the cost effectiveness of eribulin.

Eliminating all of these problems is impossible without full access to detailed patient data, and would involve a very resource-intensive analysis. In some cases this would require reference back to the investigating physicians of the EMBRACE[17] trial. The ERG has attempted to estimate the effect of corrections to the manufacturer's submitted model to address some of these problems, but most remain unresolved.

5.5.5 Options for timing of disease progression

The data set of patient records from the EMBRACE[17] trial include two separate estimates of the date of confirmed disease progression - that assessed by the clinical investigator, and that assigned by an independent assessor from evidence available from sequential scans. The investigator records are essentially complete for all patients, whereas those from the independent assessor are only available where sufficient scan results were available for the patient. The manufacturer has chosen to employ the independently determined values in their model (supplemented as necessary by investigator data to supply missing values), on the basis that this should be considered more objective. However, they note that in fact investigators were able to draw on a wider range of clinical evidence in their determinations, and that this more accurately reflects decision-making in normal clinical practice. The ERG concurs with the latter argument in terms of the generalisability of the investigator data, and also since it represents a consistent source, rather than a non-systematic hybrid.

5.5.6 'End of Life' ICER adjustment

The manufacturer includes a facility in the submitted model to apply an amendment to the estimated ICER which aims to adjust the utility value of additional life-years attributable to use of eribulin to match that of the general UK population, rather than patients with advanced or MBC. Some minor transcription errors were identified in the use of the UK population norms[44] which have a small effect of the adjusted ICERs.

It is important to recognise that this method of adjusting the ICER if an appraisal appears to meet the NICE 'End of Life' criteria is not the most commonly used approved procedure, although it has been proposed as a possible alternative to applying a higher threshold of acceptability. In particular, the results of such an analysis should only be considered as relevant to the normal NICE range of acceptability (£20,000 - £30,000 per QALY gained), rather than the normal practice used in most appraisals of applying a higher threshold value. Using both together would amount to double-counting.

5.5.7 Minor corrections and amendments

Six minor errors were detected in the manufacturer's model, and corrections were implemented by the ERG. These covered the method of discounting costs and outcomes, three problems with the calculations relating to the terminal period, the correct use of a mid-cycle correction, and a transcription error in using source data for the 'End of Life' default utility. Taken together, these changes lead to only a small increase in the size of the base case ICER.

5.5.8 Survival estimation

The manufacturer's model does not employ projective modelling of patient survival experience, but uses the EMBRACE[17] patient data directly to drive all aspects of the model logic. Kaplan-Meier product-limit estimates of PFS and OS are calculated from the patient records for the selected population and comparators up to the time of death or censoring. Instead of projecting expected life-time experience of those individuals still alive at the time of data cut-off, the modellers have assumed that all such patients are deemed to die at the time of censoring. This is considered to be a conservative assumption, since it precludes the accumulation of any additional net survival gains for eribulin. However, there are two aspects of this approach to modelling which warrant careful consideration:

- although the method of dealing with censored individual records seems straightforward, there is potential for bias to be introduced, which can significantly impact on the incremental survival (survival gain);

- the NICE Reference Case [21] requires decision analysis to take account of costs and outcomes which are likely to be affected by the choice of treatment at any subsequent time, and in the case of advanced or metastatic cancers this is generally interpreted as the whole of the remaining lifetime of patients.

Censoring and truncation

The Kaplan-Meier algorithm accumulates survival experience over time by calculating the proportionate reduction in estimated survival from one event-time to the next. This method is generally stable and unbiased when used with moderate or large samples, and as long as a sufficiently large proportion of patients (say 20-30%) remain at risk of further events. However, it is widely accepted that the behaviour of a Kaplan-Meier plot can become unstable and erratic when only small numbers of cases remain alive and uncensored, since a single event can give rise to very large changes in the survival estimate towards the tail of the distribution. Of particular concern is the influence this problem can have on estimates of mean survival, which is equivalent to the total area under the Kaplan-Meier plotted curve (AUC), especially when one or two patients continue alive and uncensored for long periods after all other patients have left the trial. This long tail can contribute disproportionately to the estimated mean survival, and since it may occur in either arm of a trial it can, in some cases, completely reverse a small but consistent treatment benefit seen in the bulk of the trial population. There are a number of different analytical rules which can be applied to mitigate this weakness, but none is clearly superior and not subject to some residual risks of uncorrected bias.

The manufacturer's model does not make any adjustments to ameliorate this risk, and therefore it is likely that in some model scenarios, OS may be either over- or under-estimated by using the Kaplan-Meier analyses without amendment. To test the potential size and importance of this problem, the ERG has undertaken a revised survival analysis to compare with unadjusted survival estimates. This involves truncating the accumulation of survival time (AUC) at a common time in both trial arms, to eliminate the effect of residual 'tails' of different sizes and durations. To preserve as much of the original data as possible, this time was set by comparing the times at which the last recorded trial event (i.e. death in the case of OS) occurred in the two trial arms, and truncating the analysis at the earlier of these values. This has the effect of eliminating the most vulnerable extended 'tails' on the Kaplan-Meier curves, whilst preserving the large bulk of patient experience over a common time interval.

The size of effect this truncation can have is shown in the upper section of Table 30 and Table 31. In both populations, the estimated mean gain in OS from use of eribulin is reduced by 10-14 days (14-15%) which alone may increase the size of the estimated ICER by approximately 18-19%.

Treatment by physician choice (TPC) subgroups

It may also be observed in Table 30 and Table 31 (and Figure 3) that subgroup analyses of OS gain are subject to substantial uncertainty, due to the small number of patients available for analysis in the TPC arm resulting from the use of a 2:1 randomisation trial design. Significant differences were only observed for the three most common TPC regimens (vinorelbine, gemcitabine and capecitabine).

Table 30 Re-estimation of mean overall survival for the ITT population of the EMBRACE trial, truncating extreme distribution tails

ITT population			TPC			Eribulin			OS gain			
Treatment of Physician Choice (TPC)		Truncation limit (days)	N	Mean	SE	N	Mean	SE	Mean	SE	p (difference of means)	p (log-rank test)
All regimens (not truncated)	Days	N/A	254	402.8	*18.9*	508	473.5	*15.3*	70.7	*16.6*	0.00001	0.017
	Months			13.23	*0.62*		15.56	*0.50*	**2.32**	***0.55***		
All regimens (truncated)	Days	968	254	402.8	*18.9*	508	462.7	*13.8*	59.9	*15.7*	0.0001	0.018
	Months			13.23	*0.62*		15.20	*0.45*	**1.97**	***0.52***		
Vinorelbine (truncated)	Days	790	65	357.3	*32.8*	121	412.8	*22.4*	55.5	*26.5*	0.036	0.235
	Months			11.74	*1.08*		13.56	*0.74*	**1.82**	***0.87***		
Gemcitabine (truncated)	Days	761	46	343.6	*34.2*	102	439.8	*22.7*	96.2	*26.8*	0.0003	0.021
	Months			11.29	*1.12*		14.45	*0.75*	**3.16**	***0.88***		
Capecitabine (truncated)	Days	741	45	401.6	*39.3*	77	472.2	*29.3*	70.6	*33.4*	0.034	0.107
	Months			13.19	*1.29*		15.51	*0.96*	**2.32**	***1.10***		
Taxanes (truncated)	Days	885	41	458.4	*48.8*	70	424.2	*33.5*	-34.1	*39.8*	0.39	0.596
	Months			15.06	*1.60*		13.94	*1.10*	**-1.12**	***1.31***		
Anthracyclines (truncated)	Days	735	24	427.6	*48.5*	73	428.4	*28.1*	0.8	*34.3*	0.98	0.563
	Months			14.05	*1.59*		14.07	*0.92*	**0.03**	***1.13***		
Hormonal, etc. (truncated)	Days	896	33	375.6	*54.0*	65	420.6	*36.1*	45.0	*43.0*	0.29	0.521
	Months			12.34	*1.78*		13.82	*1.19*	**1.48**	***1.41***		

Table 31 Re-estimation of mean overall survival for the Region 1 population of the EMBRACE trial, truncating extreme distribution tails

Region 1 only			**TPC**			**Eribulin**			**OS gain**			
Treatment of Physician Choice (TPC)		Truncation limit (days)	N	Mean	SE	N	Mean	SE	Mean	SE	p (difference of means)	p (log-rank test)
All regimens (not truncated)	Days	N/A	163	390.5	23.4	325	475.4	18.7	84.9	*20.4*	0.00003	0.015
	Months			12.83	0.77		15.62	0.61	**2.79**	***0.67***		
All regimens (truncated)	Days	945	163	390.5	*23.4*	325	461.9	*16.8*	71.4	*19.2*	0.0002	0.016
	Months			12.83	*0.77*		15.18	*0.55*	**2.35**	***0.63***		
Vinorelbine (truncated)	Days	790	45	348.9	*37.7*	94	427.3	*26.0*	78.4	*30.3*	0.010	0.103
	Months			11.46	*1.24*		14.04	*0.85*	**2.57**	***1.00***		
Gemcitabine (truncated)	Days	761	27	328.7	*48.3*	51	443.4	*33.4*	114.7	*39.2*	0.003	0.067
	Months			10.80	*1.59*		14.57	*1.10*	**3.77**	***1.29***		
Capecitabine (truncated)	Days	547	22	285.9	*40.8*	31	408.4	*30.0*	122.6	*34.9*	0.0004	0.037
	Months			9.39	*1.34*		13.42	*0.99*	**4.03**	***1.15***		
Taxanes (truncated)	Days	885	33	479.6	*57.0*	53	425.9	*38.0*	-53.7	*46.3*	0.25	0.452
	Months			15.76	*1.87*		13.99	*1.25*	**-1.76**	***1.52***		
Anthracyclines (truncated)	Days	735	20	439.6	*52.7*	60	433.1	*31.8*	-6.6	*38.1*	0.86	0.664
	Months			14.44	*1.73*		14.23	*1.05*	**-0.22**	***1.25***		
Hormonal, etc. (truncated)	Days	896	16	338.1	*76.6*	36	406.4	*47.3*	68.37	*57.90*	0.24	0.422
	Months			11.11	*2.52*		13.35	*1.55*	**2.25**	***1.90***		

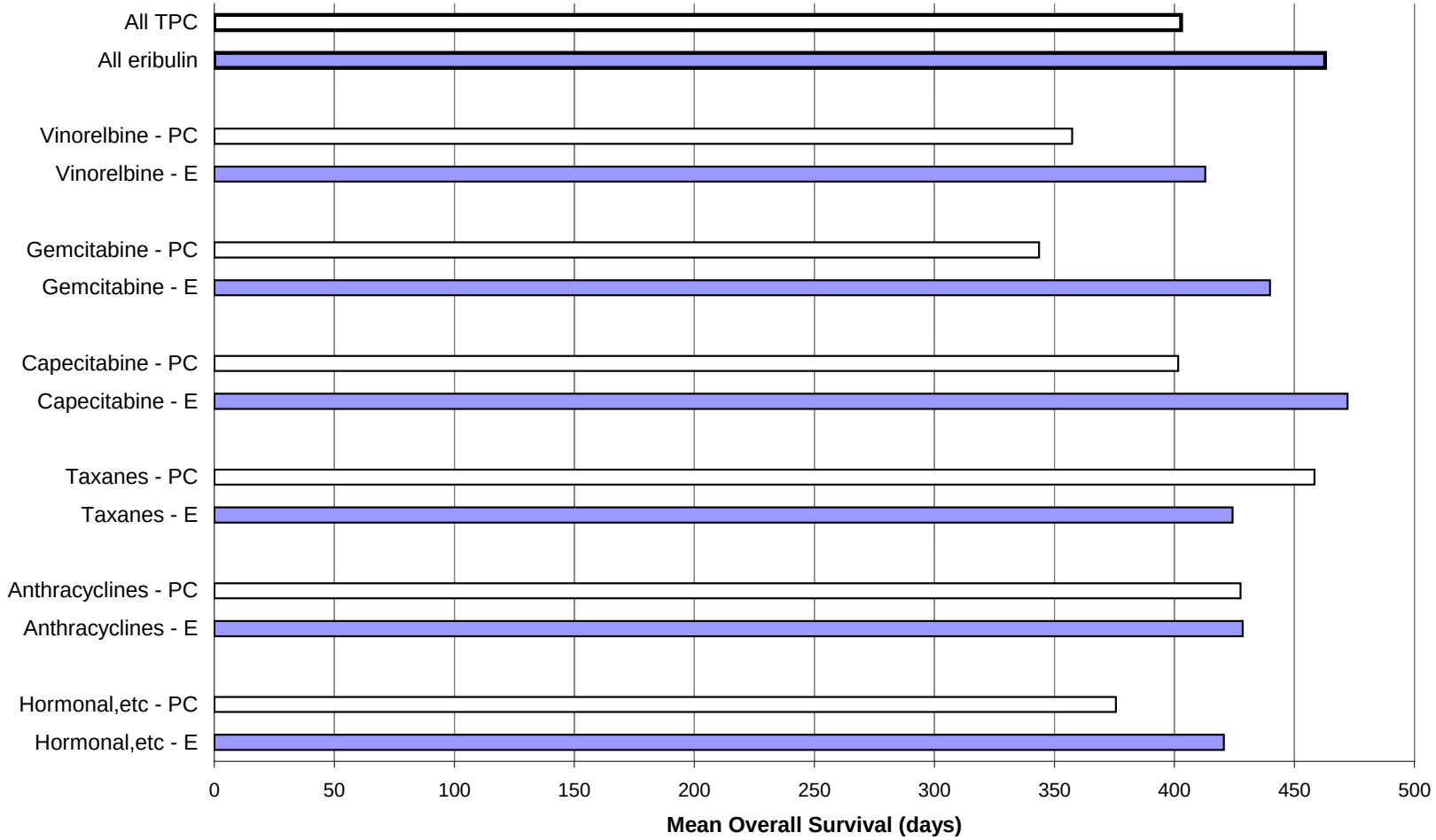

Figure 3 Mean overall survival truncated Kaplan-Meier estimates (ITT population) by TPC subgroup

Projected survival

In order to explore the potential impact on cost-effectiveness results of projecting survival trends to the end of life, the ERG examined the cumulative mortality hazard plots for the EMBRACE[17] trial arms. These reveal consistent long-term linear trends for both eribulin and TPC beyond the first 3 to 4 months of the trial, indicating that exponential survival functions would be appropriate for projecting OS beyond the available data. Maximum likelihood exponential parameter values were estimated from the post-100 days trial evidence. The lifetime estimated OS was then obtained as the sum of the observed survival time (AUC) up to 750 days from randomisation, and the exponential projected survival time from 750 days until the death of all patients. It was not possible for the ERG to amend the submitted model directly to incorporate the effects of using projected OS estimates. However, a good approximation was achieved by increasing the aggregated post-progression survival, and adjusting post-progression costs and post-progression utility values in parallel.

Table 32 summarises all of the estimates of OS including the ERG projected values. The gain in OS estimated from use of eribulin only exceeds 3 months when projective modelling is applied to the Region 1 subset of the EMBRACE[17] trial population.

Table 32 Estimates of overall survival summarised

		Eribulin	TPC	OS gain
ITT population				
Manufacturer's model	days (months)	473 (15.53)	402 (13.20)	71 (2.33)
K-M no truncation / no projection	days (months)	474 (15.56)	403 (13.23)	71 (2.32)
K-M with truncation / no projection	days (months)	463 (15.20)	403 (13.23)	60 (1.97)
K-M to 750 days / projection >750 days	days (months)	523 (17.19)	441 (14.50)	82 (2.69)
Region 1 population				
Manufacturer's model	days (months)	474 (15.58)	389 (12.78)	85 (2.80)
K-M no truncation / no projection	days (months)	475 (15.62)	391 (12.83)	85 (2.79)
K-M with truncation / no projection	days (months)	462 (15.18)	391 (12.83)	71 (2.35)
K-M to 750 days / projection >750 days	days (months)	528 (17.37)	430 (14.12)	99 (3.25)

6 ADDITIONAL WORK UNDERTAKEN BY ERG

Detailed results obtained by the ERG from making modifications to the manufacturer's model are shown in Table 33 (for the Region 1 population) and Table 34 (for the ITT population).

The original submission did not include the effects of the patient access scheme (PAS) proposed pricing arrangement, details of which were received later by the ERG. Incorporating these alterations resulted in an amended manufacturer's base-case analysis, shown as the second line of results in the tables.

The following eight rows of the tables indicate the sensitivity of this revised base-case scenario to the application of the various ERG amendments detailed above, one at a time. The combined effect of all of these amendments and corrections is then shown as the ERG revised estimate of cost effectiveness. Finally, two further sensitivity analyses are shown based on the ERG revised estimate relating to:

-the impact of using i.v. vinorelbine rather than vinorelbine in tablet form (as assumed in the manufacturer's model)

- the impact of employing projected (rather than truncated) estimates of OS.

It is evident from the detailed results that the single dominant contribution to the large change in ICERs in the ERG revised estimates is from the revised costs of TPC drug acquisition and administration. The other changes are minimal or, taken together, are mildly beneficial to the case for eribulin. The large differences between TPC acquisition costs arise from the use of proprietary product prices, using a single vial size for all patients, and calculating doses on the basis of an average patient rather than being individualised to patient characteristics (body weight or BSA).

In summary, the ERG concludes that if the whole population of the EMBRACE[17] trial is considered sufficiently representative of UK patients and clinical practice, then the best estimated ICER for eribulin exceeds £76,000 per QALY gained but may fall to about £68,000 if projected lifetime estimates of OS are preferred to truncated estimates. If only Region 1 patients are deemed representative of the UK NHS context, then the ERG estimated ICER exceeds £61,000 per QALY gained, but reduces to almost £56,000 if survival projections are preferred.

Table 33 ERG revisions to cost-effectiveness model results for Region 1 population

	Eribulin costs					TPC costs					Utility (QALYs)		Incremental		
	Tx	AE	Supp care	EoL	Total	Tx	AE	Supp care	EoL	Total	Eribulin	TPC	Costs	QALYs	ICER
Submitted model *	£16,311	£72	£4,737	£18,819	£39,939	£7,615	£48	£3,931	£18,970	£30,564	0.6887	0.5674	£9,375	0.1213	£77,285
Model revised for PAS	**£12,408**	**£72**	**£4,737**	**£18,819**	**£36,035**	**£7,615**	**£48**	**£3,931**	**£18,970**	**£30,564**	**0.6887**	**0.5674**	**£5,472**	**0.1213**	**£45,106**
+Discounting logic	£12,526	£72	£4,811	£19,173	£36,582	£7,677	£48	£3,990	£19,308	£31,023	0.6986	0.5751	£5,559	0.1235	£45,009
+Terminal period logic	£12,408	£72	£4,737	£18,857	£36,073	£7,615	£48	£3,931	£19,008	£30,601	0.6644	0.5428	£5,471	0.1215	£45,031
+Mid-cycle correction	£12,116	£68	£4,660	£18,819	£35,663	£7,440	£45	£3,853	£18,970	£30,308	0.6644	0.5431	£5,354	0.1214	£44,123
+Amend drug & admin costs	£13,044	£72	£4,737	£18,819	£36,671	£5,482	£48	£3,931	£18,970	£28,431	0.6887	0.5674	£8,240	0.1213	£67,928
+Amend state based costs	£12,408	£72	£6,240	£3,822	£22,541	£7,615	£48	£5,190	£3,852	£16,705	0.6887	0.5674	£5,836	0.1213	£48,108
+Amend utility values	£12,408	£72	£4,737	£18,819	£36,035	£7,615	£48	£3,931	£18,970	£30,564	0.7524	0.6204	£5,472	0.1320	£41,452
+Investigator PFS data	£11,906	£73	£4,756	£18,819	£35,555	£6,994	£45	£3,963	£18,970	£29,973	0.6841	0.5603	£5,583	0.1237	£45,115
+Febrile neutropenia	£12,408	£137	£4,737	£18,819	£36,101	£7,615	£72	£3,931	£18,970	£30,588	0.6886	0.5674	£5,513	0.1212	£45,486
ERG revised estimate	**£12,320**	**£133**	**£6,307**	**£3,899**	**£22,658**	**£4,952**	**£63**	**£5,264**	**£3,926**	**£14,205**	**0.7189**	**0.5821**	**£8,454**	**0.1368**	**£61,804**
Additional sensitivity analyses based on ERG revised estimate															
+ IV vinorelbine	£12,320	£133	£6,307	£3,899	£22,658	£4,868	£63	£5,264	£3,926	£14,121	0.7189	0.5821	£8,538	0.1368	£62,418
+ projected OS estimation	£12,320	£133	£7,103	£3,899	£23,455	£4,952	£63	£5,861	£3,926	£14,802	0.7849	0.6301	£8,454	0.1548	£55,905

* after removal of erroneous sensitivity value for cost per vial of vinorelbine (in cell 'Drug Costs'!F53)

Table 34 ERG revisions to cost-effectiveness model results for ITT population

	Eribulin costs					TPC costs					Utility (QALYs)		Incremental		
	Tx	AE	Supp care	EoL	Total	Tx	AE	Supp care	EoL	Total	Eribulin	TPC	Costs	QALYs	ICER
Submitted model *	£17,196	£72	£4,695	£18,822	£40,786	£9,261	£43	£3,983	£18,947	£32,234	0.6932	0.6018	£8,551	0.0914	£93,565
Model revised for PAS	**£13,081**	**£72**	**£4,695**	**£18,822**	**£36,670**	**£9,261**	**£43**	**£3,983**	**£18,947**	**£32,234**	**0.6932**	**0.6018**	**£4,436**	**0.0914**	**£48,536**
+Discounting logic	£13,210	£73	£4,769	£19,181	£37,233	£9,352	£43	£4,044	£19,270	£32,708	0.7032	0.6102	£4,524	0.0930	£48,645
+Terminal period logic	£13,081	£72	£4,695	£18,859	£36,707	£9,261	£43	£3,983	£18,985	£32,272	0.6689	0.5773	£4,436	0.0916	£48,447
+Mid-cycle correction	£12,790	£68	£4,618	£18,822	£36,298	£9,087	£40	£3,906	£18,947	£31,979	0.6689	0.5775	£4,318	0.0914	£47,251
+Amend drug & admin costs	£13,756	£72	£4,695	£18,822	£37,345	£6,573	£43	£3,983	£18,947	£29,547	0.6932	0.6018	£7,798	0.0914	£85,323
+Amend state based costs	£13,081	£72	£6,157	£3,822	£23,133	£9,261	£43	£5,188	£3,848	£18,340	0.6932	0.6018	£4,793	0.0914	£52,446
+Amend utility values	£13,081	£72	£4,695	£18,822	£36,670	£9,261	£43	£3,983	£18,947	£32,234	0.7565	0.6558	£4,436	0.1006	£44,076
+Investigator PFS data	£12,766	£73	£4,708	£18,822	£36,368	£8,456	£42	£4,025	£18,947	£31,470	0.6904	0.5925	£4,898	0.0978	£50,074
+Febrile neutropenia	£13,081	£138	£4,695	£18,822	£36,736	£9,261	£65	£3,983	£18,947	£32,256	0.6931	0.6018	£4,480	0.0913	£49,081
ERG revised estimate	**£13,245**	**£132**	**£6,206**	**£3,900**	**£23,482**	**£5,950**	**£58**	**£5,285**	**£3,920**	**£15,214**	**0.7248**	**0.6161**	**£8,269**	**0.1086**	**£76,110**
Additional sensitivity analyses based on ERG revised estimate															
+ IV vinorelbine	£13,245	£132	£6,206	£3,900	£23,482	£5,857	£58	£5,285	£3,920	£15,120	0.7248	0.6161	£8,362	0.1086	£76,970
+ projected OS estimation	£13,245	£132	£6,944	£3,900	£24,220	£5,950	£58	£5,866	£3,920	£15,794	0.7860	0.6631	£8,269	0.1229	£68,590

* after removal of erroneous sensitivity value for cost per vial of vinorelbine (in cell 'Drug Costs'!F53)

7 END OF LIFE CRITERIA

7.1 Introduction

This section provides an overview and critique of the manufacturer's case for eribulin as an 'End of Life' treatment for patients with LABC/MBC. The NICE 'End of Life' treatment criteria[46] has three key points: (i) treatment is indicated for patients with a short life expectancy, normally less than 24 months and (ii) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with NHS treatment and (iii) the treatment is licensed or otherwise indicated for small patient populations.

7.2 Application of end of life treatment criteria

The NICE end of life treatment criteria are discussed below for the case of eribulin as a CTX treatment for patients with LABC/MBC.

The manufacturer follows the supplementary advice from NICE[46] to assess the impact of "giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age;" this method is one of two currently available options. The manufacturer conducts additional analyses assigning the healthy UK female utility (weighted by the age distribution of the EMBRACE[17] trial) of 0.83 to the extended survival period of eribulin, i.e. patients in the eribulin arm surviving longer than the cumulative survival of the comparator arm. The results of adopting this approach should only be considered as relevant to the normal NICE range of acceptability (£20,000 - £30,000 per QALY gained), rather than the normal practice of using a higher threshold value. A summary of the manufacturer's 'End of Life' incremental costs and QALY values are presented in Table 35; the PAS price of eribulin is used in these analyses.

Table 35: Summary of end-of-life scenario analyses in the MS

Scenario	Incremental Costs	Incremental QALYs	ICER
Eribulin vs TPC: end of life	£5586	0.21	£26,589
Eribulin vs gemcitabine: end of life	£5177	0.34	£15,019
Eribulin vs vinorelbine: end of life	£4042	0.19	£20,875
Eribulin vs capecitabine: end of life	£12,779	0.47	£27,359

7.2.1 Patient life expectancy of less than 24 months

The manufacturer makes the case that the OS of untreated patients with LABC/MBC is 12 months and the life expectancy of patients with LABC/MBC treated with CTX is between 18 and 24 months (MS, pg 36). The ERG agrees with the manufacturer that the life expectancy of patients with LA/MBC is likely to be less than 24 months.

7.2.2 Life extension of at least 3 months

In the MS, the manufacturer reports a median life extension of 3.1 months OS gain for eribulin vs TPC for the Region 1 population; this is equivalent to a mean OS gain of 2.8 months (this estimate is derived directly from the manufacturer's submitted model). The ERG has projected a mean OS gain of 3.25 months for the Region 1 population.

The manufacturer reports a median extension of 2.7 months OS gain for eribulin vs TPC for the overall (ITT) population; this is equivalent to a mean OS gain of 2.33 months (this estimate is derived directly from the manufacturer's submitted model). The ERG has projected a mean OS gain of 2.69 months for the overall (ITT) population.

7.2.3 Licensed for a small population

It is noted in the MS that there are very limited data in the UK describing the number of patients at different lines of treatment in the metastatic setting. The manufacturer estimates that the size of the eligible patient population for eribulin is somewhere in the region of 1100 to 1700 patients (MS, pg 36). The ERG agrees with the manufacturer and is of the opinion that eribulin is licensed for what might be considered by NICE to be a small patient population.

7.2.4 Conclusion

For the comparison of eribulin vs TPC, the three key elements of the NICE 'End of Life' criteria appear to be met when the clinical data from Region 1 are used to estimate mean OS gain. When mean OS data from the overall (ITT) population are used, the ERG estimates that the OS gain is likely to be less than 3 months.

8 DISCUSSION

The manufacturer presents the case for the use of eribulin compared to TPC for patients with LABC/MBC who have previously been treated with an anthracycline and a taxane. The EMBRACE[17] trial is considered by the ERG to be a well-designed RCT; the design of the trial reflects UK clinical practice and utilises a robust primary endpoint. However, the ERG is concerned that the conduct of the EMBRACE[17] trial is not of the same high standard as the trial design. In particular, analysis of the clinical data reveals that a substantial proportion of patients did not receive their routine assessment scans as specified in the trial protocol.

The EMBRACE[17] trial is a pragmatic trial and uses TPC (a mix of treatment comparators) instead of a single intervention. The ERG agrees that the design of the trial is valid and appropriate as there is no standard treatment available for this group of patients. Unfortunately, the use of TPC also has an important disadvantage: the number of patients in each of the comparator subgroups (eribulin vs gemcitabine, vs capecitabine, vs vinorelbine) is small. In the EMBRACE[17] trial, clinical practice in Region 1 (North America, Western Europe and Australia) is considered to be most similar to UK clinical practice; however, by excluding data from Region 2 and Region 3, the number of patients in the comparator subgroups is further reduced.

The EMBRACE[17] trial is large and the outcomes of the trial demonstrate a statistically significant OS benefit of eribulin compared to TPC in patients who had received a number of prior treatments for LABC/MBC. No unexpected safety findings were noted. In the EMBRACE[17] trial, eribulin patients in Region 1 appear to benefit from a greater OS gain compared to patients in the TPC arm than was reported for the overall population. The results of the eribulin vs TPC comparison in the EMBRACE[17] trial are applicable to the UK, with the caveat common to RCTs, that the patients in the trial are younger than those seen in UK clinical practice.

The ERG is of the opinion that the *post-hoc* subgroup analyses of eribulin compared to vinorelbine, capecitabine and gemcitabine are not credible due to the small patient numbers in each subgroup. The manufacturer included these subgroup analyses in response to the final scope issued by NICE.

The PAS price of eribulin has been approved recently by the Department of Health and the ERG's considerations are based on the economic model which uses the lower price of eribulin. The ERG offers a detailed critique of the manufacturer's model and has identified several weaknesses and limitations. Addressing these individual weaknesses has the effect of both increasing and decreasing the size of the manufacturer's base-case ICER; taken together,

the ERG's ICERs are always greater than the manufacturers' base-case ICERs. In all scenarios, the size of the ICER is greater in the ITT population compared to the ICER estimated using Region 1 data only.

Two key amendments made by the ERG significantly affect the size of the ICER and so merit discussion; the other modifications made to the submitted economic model are less important as they have a limited influence on the size of the ICER.

Firstly, the ERG considers that the manufacturer failed to estimate accurately the costs of the comparator treatments described in the economic evaluation. Using Region 1 data, correction of the drug costing errors/inconsistencies has the greatest effect and increases the size of the ICER (ICER increases from £45,106 per QALY gained to £61,804 per QALY gained). Secondly, the ERG considers that it is appropriate to estimate projected values for OS gain. After all of the other amendments have been made, using projected OS values reduces the size of the ICER from £62,418 per QALY gained to £55,905 per QALY gained. These two changes have similar magnitudes of effect on the ICERs related to the ITT population.

It is important to consider whether or not it is appropriate to exclude data from Region 2 and Region 3 and use only data from Region 1. The MS states that this was a pre-planned subgroup of patients and is of direct relevance to the population of England and Wales; geographical region was one of three stratification factors used in the trial and this subgroup analysis was described as exploratory in the published paper from the trial.[17] The manufacturer provided two sets of clinical results; the first was performed when 55% of patients had died. A further updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up. Using updated clinical data from Region 1 only, the ERG's revised base case ICER (including projection) for the comparison of eribulin vs TPC is £55,905 per QALY gained. Using updated clinical data from the ITT population, the ERG's revised base case ICER (including projection) for the comparison of eribulin vs TPC is £68,590 per QALY gained. The ERG is of the opinion that NICE's 'End of Life' criteria are met when data from Region 1 only are used.

8.1 Implications for research

This ERG report has highlighted that there is currently no standard of care for patients who have already received a number of prior treatments for LABC/MBC. It is also noted that only limited evidence is available to support the clinical effectiveness of those treatments currently used in clinical practice. The EMBRACE[17] trial is a large, well-designed RCT that showed an OS gain for eribulin compared to TPC and also, despite small patient numbers, appeared to show an OS gain when compared to a range of CTX treatments. There is now a need for a programme of studies to provide evidence of the clinical benefit of eribulin compared to the specific treatments used in every day clinical practice. Such trials may also provide much needed QoL and safety data in respect of eribulin compared with other treatments.

This ERG report has also highlighted the need for more accurate data collection in England and Wales on the number of people with LA/MBC. Specific data that describe the number of patients at different lines of treatment in the metastatic setting are required.

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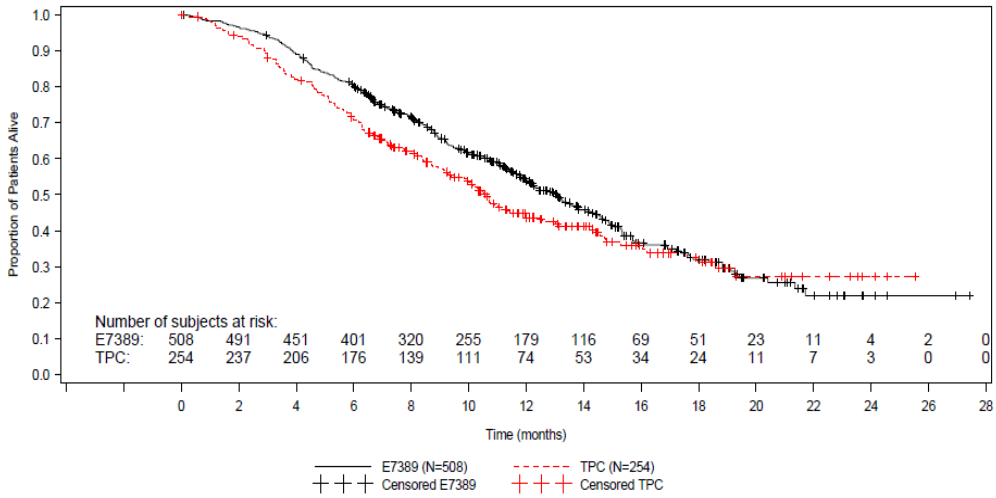
10 APPENDICES

Appendix 1 Key trial quality assessment

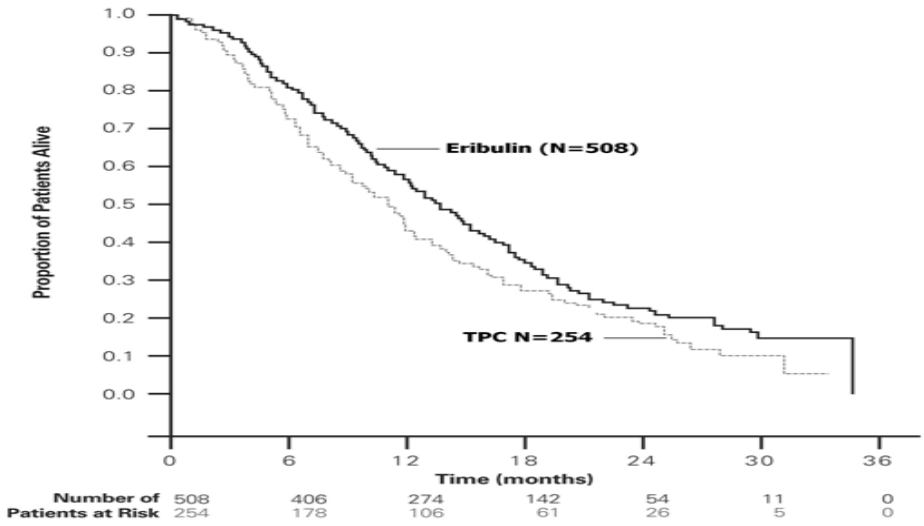
Study question	How is the question addressed in the study?	Grade *	ERG comment
Was randomisation carried out appropriately?	For all patients, the agent chosen for the arm receiving TPC was first defined and confirmed by the investigator using an interactive voice response system. Patients were pre-stratified according to geographical region, HER2 status, and prior treatment with capecitabine, and then randomised in a 2:1 ratio to receive either eribulin or TPC according to a randomisation schedule.	Yes	Agree
Was the concealment of treatment allocation adequate?	Investigators and patients were not blinded to study treatment as this was an open-label study.	NA	Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The two treatment groups were well matched in terms of demographic characteristics, prior CTX regimens, and baseline disease and tumour characteristics (e.g. HER2 status, ER/PR status, and site of disease), with the exception of cancer staging at diagnosis.	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Investigators and patients were not blinded to study treatment as this was an open-label study. However, the Eisai study team was blinded to data for the primary outcome (OS) until database lock to avoid potential bias. Independent statisticians conducted an interim analysis – after 50% of the planned deaths had been observed – and assisted with queries surrounding all death events. The primary outcome of OS is precise, being documented by the date of death and would therefore not be subject to assessment bias by unblinded investigators. An independent, blinded review of tumour scanning data was performed for outcomes of tumour response (e.g. PFS, ORR), in addition to the investigator review.	NA	Agree It is noted that the independent review results are used in the efficacy analyses
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexplained differences.	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes measured were presented in the CSRs.	No	Agree
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary analysis of the primary outcome (OS) was compared between the eribulin and TPC groups in the ITT population, with patients for whom a date of death was not recorded being censored at the time of last contact. Secondary outcomes were also measured in the ITT population, with secondary analyses being performed in the PP population.	Yes	Agree

CSR= Clinical study report; ER = oestrogen receptor; HER2=Human Epidermal Growth factor Receptor 2; ITT= intent-to-treat; PR=Progesterone Receptor; PP= per protocol; Grade*= yes/no/not applicable (NA)

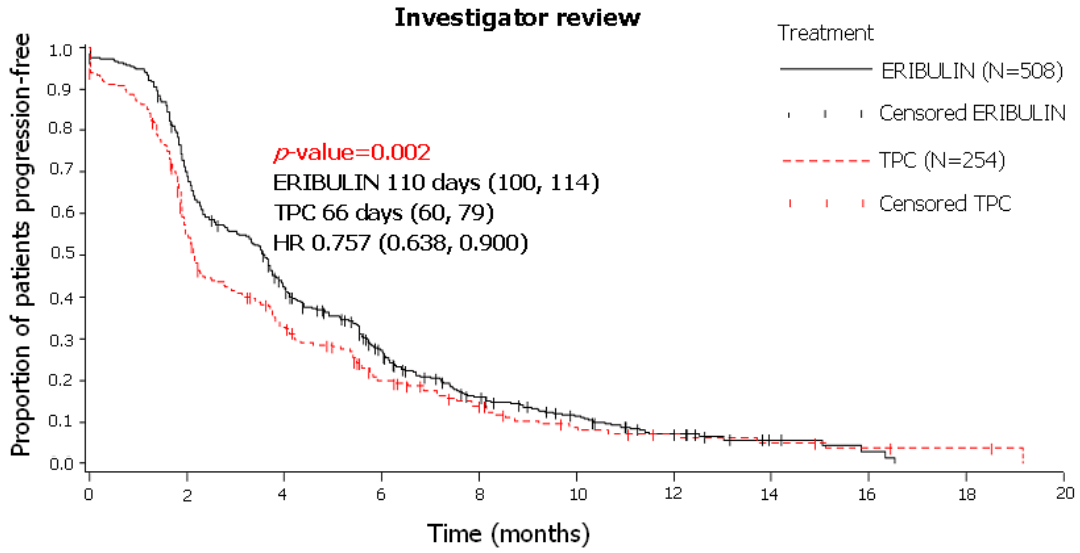
Appendix 2 Kaplan-Meier figures – clinical effectiveness (taken from the MS)

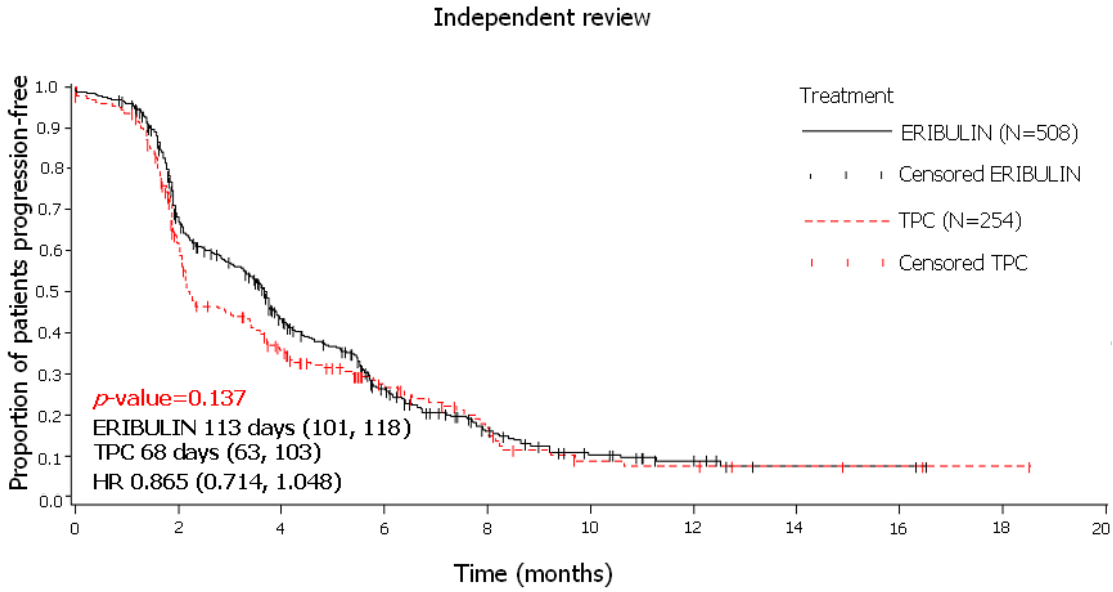


Kaplan-Meier analysis of overall survival (primary analysis): EMBRACE study



Kaplan-Meier analysis of overall survival (updated analysis): EMBRACE study





Kaplan-Meier analysis of progression-free survival: EMBRACE study

ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Eribulin for the treatment of locally advanced or metastatic breast cancer: derivation of ERG chemotherapy acquisition and administration costs

This report was commissioned by the NIHR HTA Programme as project number 10/19

Completed July 1st 2011

DOES NOT CONTAIN IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

This document provides additional detail relating to the derivation of the ERG estimated cost estimates for chemotherapy (CTX) drugs (Section 5.5.1 and Table 28) and for CTX administration (Section 5.5.2 and Table 29) in the ERG report.

2 CHEMOTHERAPY DRUG ACQUISITION COSTS

All of the CTX treatments currently recommended for treatment of LABC/MBC are dosed on the basis of the BSA of the individual patient. The submitted model does not take account of BSA differences between patients, but uses a fixed average value for all patients ($1.74m^2$) sourced from a UK survey of CTX patients.[1]

The costs of CTX drugs per cycle in nine regimens were re-estimated by the ERG using BSA values from the Sacco et al study[1] in the population of patients receiving palliative CTX. The raw BSA data from UK survey were obtained from the corresponding author, and the late stage female breast cancer patients selected for analysis. Using the Dubois and Dubois[2] formula estimates, the distribution of BSA was found to be distributed normally with mean 1.7386 and standard deviation 0.1800.

For each possible combination of vial sizes available to treat an individual patient, the maximum BSA which could receive the specified dose was calculated as the upper limit of a dosing band. Then the cumulative normal distribution of BSA was used to estimate the proportion of patients in the population who could be treated up to and including that BSA limit. Finally, the difference between cumulative proportions for successive upper band limits provided the estimated portion of the patients requiring that particular vial combination to receive the correct dose of drug. These proportions were used to compute a weighted average number of vials of each size, and thence a weighted average cost per treatment dose. If more than one dose is required per cycle, then the cost per cycle is obtained as the appropriate multiple of the cost per dose.

The method of calculation is the same for all other CTX regimens, but is more complex where more than one vial size is available, especially if the cost per unit of active agent differs between vial sizes. The situation may arise where a particular combination of vials is always more expensive than other combinations covering the same range of BSA (i.e. it is dominated); such combinations are removed from the table prior to estimating the proportions of patients in each BSA band.

1.4 Acquisition cost of eribulin

Table 1 shows the calculation for treatment with eribulin where only one vial size is available, dosing at 1.4 mg per m^2 with two doses per cycle.

Table 1 ERG calculation: acquisition cost of eribulin per cycle of treatment

Number of 1mg vials	Maximum BSA for 1.4mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
1	0.7143	0.00000	0.00000
2	1.4286	0.04253	0.04253
3	2.1429	0.98765	0.94512
4	2.8571	1.00000	0.01235
5	3.5714	1.00000	0.00000
		Mean vials per dose	2.9698
		Mean vials per cycle	5.9396
Mean eribulin cost per cycle		(without PAS)	**£1,859.11**
		(with PAS)	[redacted]

1.5 Acquisition cost of intravenous vinorelbine

Table 2 shows the calculation for treatment with IV vinorelbine where two vial sizes are available, dosing at 25 mg per m^2 with three doses per cycle. The BNF[3] list price of 10mg vial of non-proprietary vinorelbine is £29.00, and of a 50mg vial is £139.

Table 2 ERG calculation: acquisition cost of intravenous vinorelbine per cycle of treatment

Number of 10mg vials	Number of 50mg vials	Maximum BSA for 25mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
2	0	0.8	0.00000	0.00000
3	0	1.2	0.00139	0.00139
4	0	1.6	0.22074	0.21935
0	1	2.0	0.92681	0.70607
1	1	2.4	1.00000	0.07319
0.9548	0.7793	Mean vials per dose		
2.8643	2.3378	Mean vials per cycle		
			Mean vinorelbine cost per cycle	**£408.02**

1.6 Acquisition cost of oral vinorelbine

Table 3 and

Table 4 show the calculations for treatment with oral vinorelbine where three capsule sizes are available, dosing at 80 mg per m^2 (60 mg in cycle 1) with three doses per cycle. There is a maximum allowable dose of 160 mg per week. The BNF[3] list prices are: 20mg capsule for £43.98, 30mg capsule for £65.98 and 80mg capsule for £175.92.

Table 3 ERG calculation: acquisition cost of oral vinorelbine for the first cycle

Number of 20mg capsules	Number of 30mg capsules	Number of 80mg capsules	Maximum BSA for 60mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
0	2	0	1.00	0.00002	0.00002
2	1	0	1.17	0.00074	0.00072
0	0	1	1.33	0.01219	0.01144
0	3	0	1.50	0.09255	0.08036
1	0	1	1.67	0.34482	0.25227
0	1	1	1.83	0.70075	0.35593
2	0	1	2.00	1.00000	0.29925
0.8522	0.5978	0.9189	Mean capsules per dose		
2.5567	1.7933	2.7567	Mean capsules per cycle		
				Mean vinorelbine cost per cycle	**£715.72**

Table 4 ERG calculation: acquisition cost of oral vinorelbine for the subsequent cycles

Number of 20mg capsules	Number of 30mg capsules	Number of 80mg capsules	Maximum BSA for 80mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
0	0	1	1.000	0.00002	0.00002
0	3	0	1.125	0.00033	0.00031
1	0	1	1.250	0.00332	0.00300
0	1	1	1.375	0.02171	0.01839
2	0	1	1.500	0.09255	0.07084
1	1	1	1.625	0.26408	0.17153
0	2	1	1.750	0.52536	0.26128
2	1	1	1.875	0.77578	0.25042
0	0	2*	2.000	1.00000	0.22422
0.8171	0.9638	1.2239	Mean capsules per dose		
2.4512	2.8915	3.6717	Mean capsules per cycle		

Mean vinorelbine cost per cycle	**£944.51**

* 160mg maximum allowable dose

1.7 Acquisition cost of gemcitabine

Table 5 shows the calculation for treatment with gemcitabine where four vial sizes are available, dosing at 1250 mg per m^2 with two doses per cycle. The BNF[3] list prices for non-proprietary gemcitabine are: 200mg vial for £32.00, 1000mg vial for £162.00, 1500mg vial for £213.93 and 2000mg vial for £324.00.

Table 5 ERG calculation: acquisition cost of gemcitabine per cycle of treatment

No. of 200mg vials	No. of 1000mg vials	No. of 1500mg vials	No. of 2000mg vials	Maximum BSA for 1250mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
1	1	0	0	0.96	0.00001	0.00001
0	0	1	0	1.20	0.00139	0.00138
1	0	1	0	1.36	0.01773	0.01635
2	0	1	0	1.52	0.11235	0.09462
3	0	1	0	1.68	0.37249	0.26014
4	0	1	0	1.84	0.71348	0.34100
0	1	1	0	2.00	0.92681	0.21333
1	1	1	0	2.16	0.99039	0.06358
0	0	2	0	2.40	0.99988	0.00949
1	0	2	0	2.56	1.00000	0.00012
2.4137	0.2769	1.0096	0.0000	Mean vials per dose		
4.8274	0.5538	2.0192	0.0000	Mean vials per cycle		
					Mean gemcitabine cost per cycle	**£676.20**

1.8 Acquisition cost of capecitabine

Table 6 shows the calculation for treatment with capecitabine where two pack sizes are available, dosing at 1.25 mg per m^2 twice daily for 14 days per cycle. The BNF[3] list prices for capecitabine are: 60 tablets for £40.02, and 120 tablets for £265.55. It is assumed that on average when treatment discontinues half a pack of any packs dispensed will be wasted. This wastage is averaged over 5.82 cycles of treatment.

Table 6 ERG calculation: acquisition cost of capecitabine per cycle of treatment

Number of 60 tab packs	**Number of 120 tab packs**	**Maximum BSA for 1.25mg/m2 dose**	**Cumulative normal distribution**	**Proportion of patients in BSA band**
0	3	1.20	0.00139	0.00139
1	3	1.32	0.01003	0.00864
2	3	1.44	0.04860	0.03857
0	4	1.60	0.22074	0.17214
1	4	1.72	0.45896	0.23822
2	4	1.84	0.71348	0.25452
0	5	2.00	0.92681	0.21333
1	5	2.12	0.98296	0.05615
2	5	2.24	0.99733	0.01437
3	5	2.36	0.99972	0.00239
0	6	2.40	1.00000	0.00028
0.9251	4.2382	Mean tablets per dose		
0.4317	0.9889	Mean packs per cycle		
£3.44	£22.82	Mean cost of unused packs per cycle#		
			Mean capecitabine cost per cycle	**£306.15***

wastage alters slightly when ERG mid-cycle correction is applied and investigator assessments are used
* N.B. a transcription error wrongly showed the total cost per cycle as £306.83 in the ERG report

1.9 Acquisition cost of docetaxel

Table 7 shows the calculation for treatment with docetaxel where three vial sizes are available, dosing at 100 mg per m^2 with one dose per cycle. The BNF[3] list prices for non-proprietary gemcitabine are: 200mg vial for £32.00, 1000mg vial for £162.00, 1500mg vial for £213.93 and 2000mg vial for £324.00.

Table 7 ERG calculation: acquisition cost of docetaxel per cycle of treatment

Number of 20mg vials	Number of 80mg vials	Number of 160mg vials	Maximum BSA for 100mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
1	1	0	1.0	0.00002	0.00002
2	1	0	1.2	0.00139	0.00137
3	1	0	1.4	0.03000	0.02861
0	2	0	1.6	0.22074	0.19074
1	2	0	1.8	0.63359	0.41285
2	2	0	2.0	0.92681	0.29322
3	2	0	2.2	0.99482	0.06801
0	3	0	2.4	0.99988	0.00506
1	3	0	2.6	1.00000	0.00012
1.2919	1.9596	0.0000	Mean vials per dose		
1.2919	1.9596	0.0000	Mean vials per cycle		
				Mean docetaxel cost per cycle	£1,258.18
				Mean dexamethasone cost per cycle	£7.98
				Mean overall cost per cycle of docetaxel	**£1,266.15***

* N.B. a transcription error wrongly showed the total cost per cycle as £1,265.74 in the ERG report

1.10 Acquisition cost of paclitaxel

Table 8 shows the calculation for treatment with paclitaxel where four vial sizes are available, dosing at 175 mg per m^2 with one dose per cycle. The BNF[3] list prices for non-proprietary gemcitabine are: 30mg vial for £66.85, 100mg vial for £200.35, 150mg vial for £300.52 and 300mg vial for £601.03.

Table 8 ERG calculation: acquisition cost of docetaxel per cycle of treatment

Number of 30mg vials	Number of 100mg vials	Number of 150mg vials	Number of 300mg vials	Maximum BSA for 175mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
1	0	1	0	1.029	0.00004	0.00004
0	2	0	0	1.143	0.00047	0.00043
2	0	1	0	1.200	0.00139	0.00092
1	2	0	0	1.314	0.00921	0.00783
0	1	1	0	1.429	0.04253	0.03332
2	2	0	0	1.486	0.08007	0.03754
1	1	1	0	1.600	0.22074	0.14067
0	0	0	1	1.714	0.44639	0.22565
2	1	1	0	1.771	0.57246	0.12608
0	2	1	0	2.000	0.92681	0.35435
2	0	0	1	2.057	0.96163	0.03482
1	2	1	0	2.171	0.99191	0.03028
3	0	0	1	2.229	0.99676	0.00485
0	1	0	1	2.286	0.99882	0.00206
1	1	0	1	2.457	0.99997	0.00115
0	0	1	1	2.571	1.00000	0.00003
0.5932	1.1641	0.6857	0.2686	Mean vials per dose		
0.5932	1.1641	0.6857	0.2686	Mean vials per cycle		
					Mean docetaxel cost per cycle	£640.36
					Mean dexamethasone and cimetidine cost per cycle	£8.33
					Mean overall cost per cycle of docetaxel	**£648.69***

* N.B. a transcription error wrongly showed the total cost per cycle as £648.28 in the ERG report

1.11 Acquisition cost of nab-paclitaxel

Table 9 shows the calculation for treatment with paclitaxel where one vial size is available, dosing at 260 mg per m^2 with one dose per cycle. The BNF[3] list price for nab-paclitaxel is £246.00 for a 100mg vial.

Table 9 ERG calculation: acquisition cost of nab-paclitaxel per cycle of treatment

Number of 100mg vials	Maximum BSA for 260mg/m^2 dose	Cumulative normal distribution	Proportion of patients in BSA band
3	1.1538	0.00058	0.00058
4	1.5385	0.13316	0.13258
5	1.9231	0.84735	0.71418
6	2.3077	0.99922	0.15187
7	2.6923	1.00000	0.00078
		Mean vials per dose	5.0197
		Mean vials per cycle	5.0197
		Mean eribulin cost per cycle	**£1,234.85**

1.12 Acquisition cost of doxorubicin

Table 10 shows the calculation for treatment with doxorubicin where three vial sizes are available, dosing at 67.5 mg per m^2 with one dose per cycle. The BNF[3] list prices for non-proprietary doxorubicin are £18.72 for a 10mg vial, £96.86 for a 50mg vial and £275.00 for a 200mg vial.

Table 10 ERG calculation: acquisition cost of doxorubicin per cycle of treatment

Number of 10mg vials	Number of 50mg vials	Number of 200mg vials	Maximum BSA for 67.5mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
2	1	0	1.0370	0.00005	0.00005
3	1	0	1.1852	0.00106	0.00101
4	1	0	1.3333	0.01219	0.01113
0	2	0	1.4815	0.07663	0.06444
1	2	0	1.6296	0.27256	0.19593
2	2	0	1.7778	0.58626	0.31370
3	2	0	1.9259	0.85105	0.26479
4	2	0	2.0741	0.96884	0.11779
0	3	0	2.2222	0.99639	0.02756
1	3	0	2.3704	1.00000	0.00361
2.1401	2.0190	0.0000	Mean vials per dose		
2.1401	2.0190	0.0000	Mean vials per cycle		
				Mean doxorubicin cost per cycle	**£235.62**

1.13 Acquisition cost of lipid doxorubicin

Table 11 shows the calculation for treatment with lipid doxorubicin where one vial size is available, dosing at 67.5 mg per m^2 with one dose per cycle. The BNF[3] list price for lipid doxorubicin (cephalon) is £455.68 for a 50mg vial.

Table 11 ERG calculation: acquisition cost of lipid doxorubicin per cycle of treatment

Number of 50mg vials	Maximum BSA for 67.5mg/m2 dose	Cumulative normal distribution	Proportion of patients in BSA band
2	1.4815	0.07663	0.07663
3	2.2222	0.99639	0.91977
4	2.9630	1.00000	0.00361
		Mean vials per dose	2.9270
		Mean vials per cycle	2.9270
		Mean eribulin cost per cycle	**£1,333.76**

3 CHEMOTHERAPY DRUG ADMINISTRATION COSTS

The cost of administration was estimated by the ERG by assigning NHS Reference Cost HRG codes to each day case attendance, and using the average cost per visit from the published 2009/10 cost analysis.[4] Four HRG codes were used defined as follows:

SB11Z Deliver exclusively oral CTX

SB12Z Deliver simple parenteral CTX at first attendance

SB13Z Deliver more complex parenteral CTX at first attendance

SB15Z Deliver subsequent elements of a CTX cycle

Table 12 details the calculations involved in estimating the administration cost for each treatment cycle. All non-oral regimens have a separate cost for the first visit, and a different cost for all subsequent visits. The exception is for doxorubicin, which should not be given for more than 7 cycles due to cumulative cardio-toxicity. The manufacturer's model requires a weighted average of TPC costs to be calculated; this is should in three bands – first visit, all visits up to the end of cycle seven, and all subsequent visits without doxorubicin patients.

Table 12 ERG calculation: administration cost of chemotherapy per cycle of treatment

HRG code & cost per attendance		**SB11Z £151.95**	**SB12Z £206.74**	**SB13Z £207.62**	**SB15Z £284.45**	
Treatment	**Cycle**	**Attendances per cycle**				**Cycle cost**
Eribulin	1	0	1	0	1	£491.20
	2+	0	0	0	2	£568.91
Gemcitabine	1	0	1	0	1	£491.20
	2+	0	0	0	2	£568.91
Capecitabine	All	1	0	0	0	£151.95
Docetaxel	1	0	1	0	0	£207.62
	2+	0	0	0	1	£284.45
Paclitaxel & nab-paclitaxel	1	0	0	1	0	£207.62
	2+	0	0	0	1	£284.45
Doxorubicin & lipid doxorubicin	1	0	1	0	0	£206.74
	2-7	0	0	0	1	£284.45
TPC (weighted average)	1					£417.93
	2-7					£479.61
	8+					£376.14*

* N.B. a transcription error wrongly showed the weighted cost per cycle as £396 in the ERG report

4 REFERENCES

1. Sacco JJ, MacBeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: A multicentre retrospective study PLoS ONE. 2010; 5(1).
2. Dubois D, Dubois FF. A formula to estimate the approximate surface area if height and weight be known. Archives of Internal medicine. 1916; 17:863-71.
3. British National Formulary. BNF 60. 2010; Available from: http://www.bnf.org/bnf/ (Accessed: 01/05/2011).
4. Department of Health. NHS Reference Costs (2009-2010). 2011: Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591

National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Eribulin for the treatment of locally advanced or metastatic breast cancer

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from Liverpool Reviews and Implementation Group to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm, 2 June 2011** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 –"In the MS, the comparator is treatment of physician's choice (TPC)".	This is incorrect. The manufacture submitted as comparators TPC, vinorelbine, gemcitabine and capecitabine as specified in the scope	This was discussed at length at the scoping meeting and direction was given that the mentioned comparators will be required for evaluation of eribulin. This was specified in the final scope.	The ERG will add a statement to the effect that the manufacturer also identifies vinorelbine, gemcitabine and capecitabine as comparators.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 24 that at least 50 patients missed at least one or more scheduled scans. This suggests that the conduct of the trial may not have matched the high standard of the trial design in some aspects.	We are not sure where this figure comes from and if this relates to a misunderstanding on how censoring was performed. Our principle statistician conducted an analysis on the entire trial population using a definition of missed scan as 18 week on-treatment window without tumour assessment, as assessed by the investigator, and we only identified 15 patients (11 eribulin and 4 TPC) in keeping with 2:1 randomisation who had a missed scan. This analysis is available if NICE wish to see it. Patients who had clinical progression as deemed by the investigator did not receive any further scanning. Of the 762 patients included in the study, 682 had measurable disease at baseline, this does not correlate to missed scans. It is worth noting that inspections of the trial by Regulatory Agencies had no major findings and considered the conduct of the trial appropriate for registration. Inspections of Sponsor, CRO and selected investigator sites were performed by the FDA and by the PMDA (Japan), the latter accompanied by an inspector from the MHRA.	This is not factually correct and should be amended. Three major regulatory agencies have evaluated and scrutinised the trial data and did not come to any conclusion that high standards had not been maintained	In the course of the appraisal process, the ERG identified a substantial number of cases where patients appeared to have continued treatment beyond the time that they were documented as having progressive disease. The ERG requested clarification of these cases from the manufacturer. The manufacturer's response detailed the FDA-agreed requirements for censoring rules that were applied throughout the EMBRACE trial. The ERG considers that in the light of these complex censoring rules and by implication, the censored nature of the data included in the independent review, the investigator's assessment data are likely to be a more useful reflection of the time to progression outcomes of the trial. The ERG will remove both the reference to 50 scans and the statement that the conduct of the trial may not have matched the high standard of trial design.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36 "There is no significant difference in any of the comparisons described in Table 15; this suggests that patients in Region 1 do not differ (in terms of prognosis) from the patients in the remainder of the trial population"	This is incorrect. Randomisation was pre-stratified by geographical region and hence the analyses are stratified by geographical regions. Region 2 which consists of an Eastern Europe patient population entered the trial much later and subsequently the data is less mature in terms of outcomes (only 48% of events had occurred). Also there is a difference in the prior use of capecitabine. Importantly hormonal medications were predominantly prescribed in Eastern Europe (71% of total Hormonal anti-cancer use for the study) and a much and lower use of vinorelbine and gemcitabine. This would not be consistent with practice in England and Wales. Region 3 contains a small population form Latin America and South Africa .There is over 1 month's difference in the survival in regions in the estimated table (table 15) which is significant at this stage of the disease. Region 1 (North America, western Europe and Australia) accounts for 2/3 of the trial population and was a specified stratification factor. The region 1 population in terms of how they were treated and the therapies they received best represents how patients with advanced breast cancer are managed in the UK and therefore the most relevant population for this STA.	As this was global, there can be variations in how patients are managed, particularly at this stage of the disease. Region 1 best represents how patients with breast cancer are managed in the UK in terms of treatments they would be expected to receive.	The ERG considers that in the updated analyses, there is very little difference in the maturity of the survival data between regions: Region 1 at 79%, Region 2 at 73% and Region 3 at 80%. The percentage of patients pre-treated with capecitabine in the overall trial population was 68%.There is not much difference in prior capecitabine use between regions: Region 1 patients = 80%; Region 2 patients= 61%; Region 3 patients = 65%. The manufacturer has provided additional information as part of the factual error check. The ERG has only considered the data made available in the MS and as part of the clarification process.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 56 table 25 The 3rd column has incorrectly being labelled 'capecitabine'.	This should be labeled TPC	Factual correction required in the table heading	ERG to amend the table heading.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63 table 28 It is not quite clear how some of the drug cost have been calculated. The Sacco paper clearly states that the mean BSA is 1.74m^2 for breast cancer with 95%CI 1.72- 1.76m^2. The small difference in BSA doesn't significantly change drug costs. Also the preparations in TPC come in branded and generic forms and in different strengths and sizes. The market share of generics versus branded medicines in 3rd line MBC is not available. A mean of the two prices was used. ERG appears to have not rounded vials used per administration up to the nearest vial	An explanation is required exactly how body surface area data were used to calculate drug cost Calculated drug costs should be rounded up to the nearest vial	It is important to understand for transparency how the drugs cost we evaluated and calculated	The drugs were costed according to body surface area as outlined in the Sacco paper cited in the ERG report. Costs are estimated by the ERG for individual patients across the full range of BSA variation (using standard deviation of the sampled population), using the optimal vial size in each case to minimise costs; the ERG considers this approach to drug costing to be the norm rather than the exception., since it most closely matches clinical practice.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64 table 29 It is not clear how ERG have calculated administration costs	Eribulin is a simple 2-5 minute infusion and there is no reason why it can't be given in an outpatient setting. Using the NHS reference costs 2009-2010 and codes SB12Z for first administration and SB15Z for subsequent administrations results in a cost of £460 for cycle 1 and for Cycle 2+ a cost of £424. Outpatient costs were used in the NICE advanced breast cancer guidelines. This is also a very simplistic approach as the drugs used in the TPC can vary in their administration ranging from a 3 hour infusion, 30 minutes infusion and weekly administration and individual comparisons with TPC specific drugs should be made Also there is no reason to explain why eribulin would cost more than TPC to administer	It appears that ERG have not taken accounts of the fact that eribulin is a simple 2-5 minute infusion without the requirement for reconstitute and offers an alternative to more complex regimens in terms of administration	HRG costs are top-down, crude estimates of NHS costs. HRG costs take into consideration whether the resource use is related to a simple/complex intervention; 1st attendance/subsequent attendance; inpatient/outpatient/day case. The simple HRG cost reflects a time period of 5-60 minutes as any activity within this time interval does not significantly affect throughput of patients, The ERG used 2009-10 HRG costs, the manufacturer used 2008-9 costs

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 – Projected survival - There is very limited information provided to interpret what has been done to project survival as this is based on questionable assumption about baselines survival function and thus the reliability. The benefits appear to be at the bottom of the range of credible estimates according to our internal model.	The estimates of gains in overall survival are at the low end of possible estimates. A parametric model (Weibull curve and hazard ratios) that provides a better fit to the trial results generated results significantly in excess of those generated by the ERG. These analyses were offered to the ERG and can be provided to NICE. It also contains results for the three comparators	Professional advice given to us from experts in modelling, recommended that the most appropriate methodology to project survival beyond the trial period would be to use a parametric model as described.	The analyses were not presented to the ERG in the MS or offered during the clarification phase. The analyses were submitted too late in the STA process for consideration by the ERG. Survival estimation is always based on the modeller's subjective interpretation of the data. The ERG considers that the survival method described in the ERG report was the most appropriate based on the data available at the time of writing the ERG report.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 33. ERG have produced a table with amended values for the cost effectiveness against TPC but no such tables has been produced for gemcitabine, vinorelbine and capecitabine as specified in the scope.	The model use by Eisai assumes a very conservative approach- all patients die at the trial end, utilising independent rather than investigator PFS and lower rates of ORR As ERG have conducted a modification of the TPC results the same should be applied to the three comparators as required by the scope	ERG have modified the results for TPC including survival projection and the same should be done for the 3 specified comparators as per the scope	No change required. The ERG considers that the number of patients involved in these calculations is very small and any results based on such numbers would be unreliable/meaningless.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65 – ERG states that the post progression state cost should be based on a package of care from community.	It should be noted that there is very limited provision for such a service in the UK. Patient are usually treated in the hospital setting and community based treatment is given in the last few weeks of life	The costs given in the post progression state by the manufacturer are based on clinical experts who manage breast cancer on a daily basis. ERG approach is based on a service delivery that is seldom available from primary care for this state	No change required. The ERG has acted in accordance with NICE guidance and with previous appraisals.

ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Eribulin for the treatment of locally advanced or metastatic breast cancer

This report was commissioned by the NIHR HTA Programme as project number 10/19

Completed June 14th 2010

DOES CONTAIN IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains erratum in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change.

Page No.	Change
8	Section 1.4.2 removal of text relating to scans
15	Section 3.3 addition of individual comparators
24	Paragraph 4 removal of text relating to scans
46	Section 4.4.2 removal of text relating to scans
55	CiC added to PAS price of eribulin
56	Table 25 3rd column label changed to TPC
62	Table 28 CiC added to costs of eribulin
80/81	1st paragraph p81 removal of text relating to scans

(ICER) for eribulin vs TPC (Region1) is £46,050 per QALY gained. The manufacturer also presents the following ICERs: eribulin vs gemcitabine (£27,183 per QALY gained); eribulin vs vinorelbine (£35,602 per QALY gained) and eribulin vs capecitabine (£47,631 per QALY gained). The manufacturer showed the ICERs to be robust when subjected to extensive deterministic and probabilistic sensitivity analysis (PSA). The manufacturer also claims that eribulin (vs any comparator using data from ITT population or Region 1 data) meets NICE's 'End of Life' criteria.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The manufacturer cites evidence from a well-designed trial (EMBRACE) of the clinical benefit of eribulin vs TPC as a treatment for LABC/MBC following treatment failure with an anthracycline and a taxane. The trial is large, multi-centred and international with a robust primary outcome of OS.

1.4.2 Weaknesses

There is only a single RCT (EMBRACE) which compares eribulin to TPC described in the MS. Analyses of eribulin vs individual TPCs are presented, but due to the small number of patients in each group and the *post-hoc* nature of these analyses, the reliability of these results is questionable.

No HRQoL data were collected during the EMBRACE trial. In the clinical section of the MS the manufacturer relies on HRQoL data collected from two single arm phase II studies.

The main weakness in the economic evaluation is related to the manufacturer's inaccurate costing of comparators to eribulin. The submitted model does not take account of BSA differences between patients and instead uses a fixed average value for all patients. The administration costs of CTX drugs are also flawed – out of date NHS Reference Costs are used, all CTX drugs are assumed to be administered in an out-patient setting and differential healthcare resource group (HRG) costs are ignored.

1.4.3 Areas of uncertainty

The key area of uncertainty is whether or not the clinical effectiveness data from Region 1 patients only are preferred to data from the ITT population. In the EMBRACE trial, Region 1 patients are from North America, Western Europe and Australia and the manufacturer asserts that this patient population is of direct relevance to patients in the NHS in England and Wales. In the eribulin vs TPC comparison, the incremental OS gain is higher in Region 1 patients compared with the incremental

3.1 Population

The patients in the key trial (EMBRACE[17]) cited in the MS are those with LABC/MBC (defined in the key trial as locally recurrent or MBC) who have received between two and five prior CTX treatments. In order for a patient to be included in the trial, the following criteria with respect to treatment history had to be met:

i. the prior CTX had to include an anthracycline and a taxane in any combination or order;
ii. one or two of the treatments with anthracycline or a taxane could have been administered as adjuvant and/or neoadjuvant therapy, but at least two had to be given for relapsed or metastatic disease;
iii. disease is refractory to the most recent CTX therapy, documented by progression on or within 6 months of therapy.

Patients with HER2+ tumours could have additionally been treated with trastuzumab and patients could have been treated with hormone therapy. The ERG is confident that the patient population in the key trial cited in the MS matches the population defined in the scope issued by NICE[16] and the eligible UK population.

3.2 Intervention

Eribulin is a first-in-class anti-neoplastic agent belonging to the halichondrin class of drugs. Eribulin exerts its anti-cancer effects via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles, and ultimately, apoptotic cell death following prolonged mitotic blockage. Eribulin monotherapy is administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.[18] It is licensed in Europe[19] for the treatment of patients with LABC/MBC who have progressed after at least two CTX regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

3.3 Comparators

The decision problem issued by NICE in its final scope[16] states that treatment with eribulin should be compared with treatment with either vinorelbine, capecitabine or gemcitabine. The ERG notes from its clinical advisor that, in UK clinical practice, gemcitabine is used as a monotherapy in this setting; however gemcitabine is neither licensed as a monotherapy[20] in this setting nor is it recommended as a monotherapy by NICE.[6, 13]

In the MS, the comparator is treatment of physician's choice (TPC). The manufacturer also identifies vinorelbine, gemcitabine and capecitabine as comparators. In the MS (MS, p.42) TPC is defined as any available single agent CTX, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care (BSC). The TPC treatments given in the key trial are described in the MS (MS, pg 54, Table 10) and are

Patients in Regions 1, 2 and 3 appear to have broadly similar characteristics to patients in the overall trial population.

The ERG notes that although the inclusion criteria of the EMBRACE[17] trial state that patients of ECOG performance status 0, 1 or 2 were eligible for enrolment, the majority of patients (63%) appear to have been assessed as being of ECOG performance status 0 or 1. The ERG is aware that in practice, it can be difficult to make a distinction between patients with a performance status of 1 and those with a performance status of 2.

For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. With so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently. The CSR[27] of the EMBRACE[17] trial states that study monitors were responsible for establishing and maintaining regular contact between study centres and the manufacturer. Monitors made regular visits to each study centre (maximum time between visits was 6 weeks) to check adherence to the protocol and inform the manufacturer of any issues arising. The monitor provided written reports to the manufacturer after each contact with the study centre. The ERG is confident that the manufacturer made every effort to ensure that the trial procedures were implemented comprehensively across all study centres.

Any treatment given to patients following disease progression has the potential to impact on OS and, as part of the clarification process, the ERG requested from the manufacturer details of any post-progression treatments given to patients in both arms of the EMBRACE[17] trial. The post-progression treatments given appear to be similar in number and type across both arms of the trial thereby minimising the likelihood of affecting the OS results.

The ERG has concerns regarding the number of patients in EMBRACE[17] trial who were not assessed regularly after baseline. The trial protocol specified that patients were to be followed up every 8 weeks; however, analysis of the clinical data shows that there were patients who missed at least one or more scheduled scans.

It is important that the inclusion and exclusion criteria remain unchanged during study recruitment. In response to the ERG's request for clarification, the manufacturer stated that 46 (9.1%) patients in eribulin arm and 32 (13%) patients in the TPC arm violated the EMBRACE[17] trial protocol with regard to the trial eligibility criteria. The most frequently observed violations related to the patient not being refractory to the most recent CTX

4.4 Summary of results

4.4.1 Clinical results

- The main source of clinical evidence described in the MS is derived from the EMBRACE[17] trial
- The EMBRACE[17] trial includes 762 patients who had received at least two CTX treatments (including an anthracycline and taxane unless contraindicated) for LABC/MBC
- Median OS (primary analysis) for the overall ITT population of the EMBRACE[17] trial was statistically significantly longer in the eribulin arm compared to the TPC arm (13.1 months vs 10.6 months). Similarly, in the updated analysis, median OS was statistically significantly longer in the eribulin arm compared to the TPC arm (13.2 months vs 10.5 months)
- Median PFS (primary analysis) for the overall ITT population of the EMBRACE[17] trial was greater in the eribulin arm compared to the TPC arm in both independent and investigator assessments. However, only the investigator review results demonstrate a statistically significant difference between the two arms
- ORR and CBR (primary analysis) are available for the overall ITT population of the EMBRACE[17] trial and were higher in the eribulin arm compared to TPC for both independent and investigator assessments
- Median OS (primary analysis) for the Region 1 population of the EMBRACE[17] trial was statistically significantly longer in the eribulin arm compared to the TPC arm (13.1 months vs 10.0 months). Similarly, in the updated analysis, median OS was statistically significantly longer in the eribulin arm compared to the TPC arm (13.2 months vs 10.1 months)
- The most frequently reported SAEs reported in the eribulin arm were febrile neutropenia and neutropenia. The main reason for discontinuation in the eribulin arm of the trial was peripheral neuropathy.

4.4.2 Clinical issues

- Only one RCT compares eribulin with TPC
- The results of the analyses of eribulin vs individual TPCs are unreliable due to small numbers of patients in each comparison
- The HRQoL data on eribulin are available from two Phase II trials with single arms only
- Overall survival gain from Region 1 clinical data is greater than the OS gain shown in the ITT population analyses. Whether or not the results of the subgroup analyses of Region 1 are more appropriate than the OS results from the overall population to decision-makers in England and Wales is uncertain

5.3.10 Results included in manufacturer's submission

Using data from Region 1 only, base-case results for the incremental cost per QALY gained are available for the following comparisons: eribulin vs TPC; eribulin vs gemcitabine; eribulin vs vinorelbine and eribulin vs capecitabine. All of the results presented in this section are based on the PAS approved price of eribulin of [redacted] per vial.

Table 1 Base-case cost-effectiveness results *with* patient access scheme (Region 1)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental cost per QALY gained
TPC	£30,449	0.5674			
Eribulin	£36,035	0.6887	£5,586	0.1213	£46,050
Gemcitabine	£30,152	0.4980			
Eribulin	£35,329	0.6885	£5,177	0.1904	£27,183
Vinorelbine	£29,983	0.5155			
Eribulin	£34,024	0.6291	£4,041	0.1136	£35,602
Capecitabine	£26,766	0.5170			
Eribulin	£39,545	0.7853	£12,779	0.2683	£47,631

TPC= treatment of physician's choice; QALY=quality adjusted life year; ICER= incremental cost-effectiveness ratio

The MS presents a series of tables (MS, Tables 52-59) showing detailed disaggregated costs and benefits for the four key comparisons (eribulin vs TPC, vs gemcitabine, vs vinorelbine and vs capecitabine). **Error! Reference source not found.** and

Table 3 show the summary of costs by health state and cost category and the summary of QALY gain by health state for the eribulin vs TPC comparison.

Table 2 Summary of costs by health state and cost category for eribulin vs TPC

Costs	Cost intervention (Eribulin)	Cost comparator (TPC)	Increment	Absolute increment	% absolute increment
Infusion	£3,174	£2,250	£924	£924	15.63%
Drug	[redacted]	[redacted]	£3,984	£3,984	67.40%
Stable	£1,141	£916	£224	£224	3.80%
Progressive	£3,596	£3,015	£581	£581	9.83%
Terminal	£18,819	£18,970	-£151	£151	2.55%
Grade 3	£18	£30	-£12	£12	0.20%
Grade 4	£54	£18	£36	£36	0.60%
Total	£36,035	£30,449	£5,586	£5,911	1.000

Table 3: Summary of QALY gain by health state for eribulin vs TPC

Health state	QALY intervention (Eribulin)	QALY comparator (TPC)	Increment	Absolute increment	% absolute increment
Stable	0.287	0.229	0.058	0.058	47.69%
Progressive	0.393	0.329	0.063	0.063	52.25%
Terminal	0.009	0.009	0.000	0.000	0.06%
Total	0.689	0.567	0.121	0.121	100.00%

The scatter plots and cost effectiveness acceptability curves for each of the four comparisons generated by the manufacturer are presented in the MS (MS, Section 6.6.7). For the eribulin vs TPC comparison, the cost effectiveness acceptability curve shows that, at a willingness to pay of £20,000 to £30,000 per QALY gained, the probability of eribulin being cost effective compared to TPC is 0%.

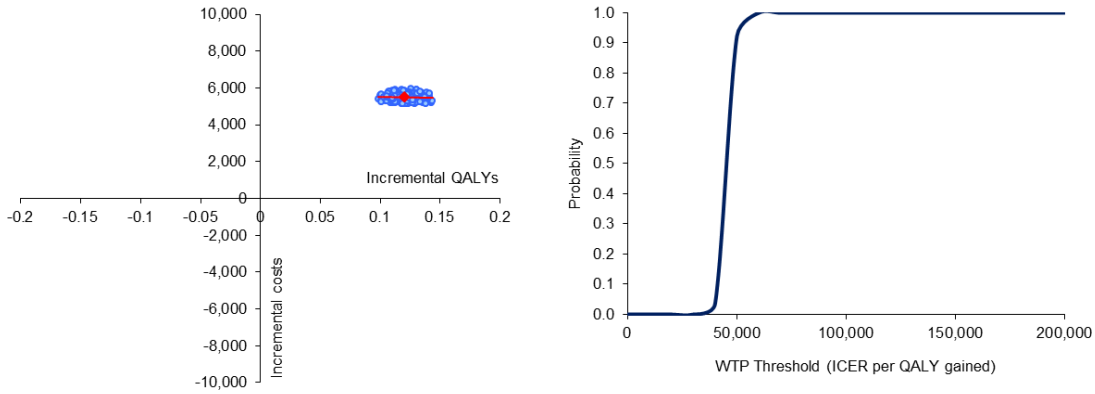


Figure 1 Scatter plot and cost effectiveness acceptability curve (eribulin vs TPC)

5.5 Detailed critique of manufacturer's economic model

The manufacturer's economic model is constructed as a Microsoft EXCEL workbook, with Visual Basic routines used to implement specific features, most notably sensitivity analyses. The model is generally well-constructed, with appropriate annotation and identification of data sources and methods of calculation. The only criticism that the ERG would make of the model design is that the structure adopted for handling parameter values appears to be overly complex, with multiple references across intermediate worksheets between the initial data entry and the point at which the value is used in the main model calculations. This makes the tracking of data values through the model unduly circuitous and time-consuming.

5.5.1 Cost of chemotherapy drugs

All of the CTX treatments currently recommended for treatment of MBC are dosed on the basis of the BSA of the individual patient. The submitted model does not take account of BSA differences between patients,[41] but uses a fixed average value for all patients ($1.74m^2$) sourced from a UK survey of CTX patients. The costs of CTX drugs per cycle in nine regimens have been re-estimated by the ERG using BSA values from the Sacco et al[41] study in the population of patients receiving palliative CTX, and are shown in Table 4. For all regimens but one (Nab-paclitaxel), the ERG estimated cost (including wastage) is lower than that used in the manufacturer's model, in several cases very substantially.

Table 4 Chemotherapy costs per cycle (excluding administration costs)

Treatment	Submitted cost per cycle	Re-estimated cost per cycle	Change in cost per cycle
Eribulin (without PAS)	£1,878.00	£1,859.11	- £18.89
Eribulin (PAS discounted)	[redacted]	[redacted]	- £13.28
Vinorelbine (IV)	NR	£408.02	NA
Vinorelbine (oral)	£989.70 (all cycles)	£715.72 (cycle 1) £944.51 (cycle 2+)	- £273.98 - £45.19
Gemcitabine	£975.42	£676.20	- £299.22
Capecitabine	£531.10	£306.83	- £224.05
Docetaxel	£1,604.25	£1,265.74	- £338.51
Paclitaxel	£1,644.49	£648.28	- £996.21
Nab-Paclitaxel	£1,230.00	£1,234.85	+ £4.85
Doxorubicin*	£275.00	£235.62	- £39.38
Lipid doxorubicin*	£1,393.50	£1,333.76	- £59.74

NR =not reported; NA =not applicable

* limited to maximum of seven cycles to avoid cumulative cardio-toxicity (as per SPC)

8 DISCUSSION

The manufacturer presents the case for the use of eribulin compared to TPC for patients with LABC/MBC who have previously been treated with an anthracycline and a taxane. The EMBRACE17 trial is considered by the ERG to be a well-designed RCT; the design of the trial reflects UK clinical practice and utilises a robust primary endpoint.

The EMBRACE17 trial is a pragmatic trial and uses TPC (a mix of treatment comparators) instead of a single intervention. The ERG agrees that the design of the trial is valid and appropriate as there is no standard treatment available for this group of patients. Unfortunately, the use of TPC also has an important disadvantage: the number of patients in each of the comparator subgroups (eribulin vs gemcitabine, vs capecitabine, vs vinorelbine) is small. In the EMBRACE17 trial, clinical practice in Region 1 (North America, Western Europe and Australia) is considered to be most similar to UK clinical practice; however, by excluding data from Region 2 and Region 3, the number of patients in the comparator subgroups is further reduced.

The EMBRACE17 trial is large and the outcomes of the trial demonstrate a statistically significant OS benefit of eribulin compared to TPC in patients who had received a number of prior treatments for LABC/MBC. No unexpected safety findings were noted. In the EMBRACE17 trial, eribulin patients in Region 1 appear to benefit from a greater OS gain compared to patients in the TPC arm than was reported for the overall population. The results of the eribulin vs TPC comparison in the EMBRACE17 trial are applicable to the UK, with the caveat common to RCTs, that the patients in the trial are younger than those seen in UK clinical practice.

The ERG is of the opinion that the post-hoc subgroup analyses of eribulin compared to vinorelbine, capecitabine and gemcitabine are not credible due to the small patient numbers in each subgroup. The manufacturer included these subgroup analyses in response to the final scope issued by NICE.

The PAS price of eribulin has been approved recently by the Department of Health and the ERG's considerations are based on the economic model which uses the lower price of eribulin. The ERG offers a detailed critique of the manufacturer's model and has identified several weaknesses and limitations. Addressing these individual weaknesses has the effect of both increasing and decreasing the size of the manufacturer's base-case ICER; taken together, the ERG's ICERs are always greater than the manufacturers' base-case ICERs. In all scenarios, the size of the ICER is greater in the ITT population compared to the ICER estimated using Region 1 data only.

Two key amendments made by the ERG significantly affect the size of the ICER and so merit discussion; the other modifications made to the submitted economic model are less important as they have a limited influence on the size of the ICER.

Firstly, the ERG considers that the manufacturer failed to estimate accurately the costs of the comparator treatments described in the economic evaluation. Using Region 1 data, correction of the drug costing errors/inconsistencies has the greatest effect and increases the size of the ICER (ICER increases from £45,106 per QALY gained to £61,804 per QALY gained). Secondly, the ERG considers that it is appropriate to estimate projected values for OS gain. After all of the other amendments have been made, using projected OS values reduces the size of the ICER from £62,418 per QALY gained to £55,905 per QALY gained. These two changes have similar magnitudes of effect on the ICERs related to the ITT population.

It is important to consider whether or not it is appropriate to exclude data from Region 2 and Region 3 and use only data from Region 1. The MS states that this was a pre-planned subgroup of patients and is of direct relevance to the population of England and Wales; geographical region was one of three stratification factors used in the trial and this subgroup analysis was described as exploratory in the published paper from the trial.17 The manufacturer provided two sets of clinical results; the first was performed when 55% of patients had died. A further updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up. Using updated clinical data from Region 1 only, the ERG's revised base case ICER (including projection) for the comparison of eribulin vs TPC is £55,905 per QALY gained. Using updated clinical data from the ITT population, the ERG's revised base case ICER (including projection) for the comparison of eribulin vs TPC is £68,590 per QALY gained. The ERG is of the opinion that NICE's 'End of Life' criteria are met when data from Region 1 only are used.