STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072]

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072]

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All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

AEs	Adverse events
BSA	Body surface area
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMBRACE	Eisai metastatic breast cancer study assessing physician's choice versus e7389
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol-5 dimension
ER	Oestrogen receptor
ERG	Evidence Review Group
FAD	Final appraisal determination
GHS	Global Health Status
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan-Meier
LABC/MBC	Locally advanced or metastatic breast cancer
LYG	Life year gained
MBC	Metastatic breast cancer
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression-free survival
PH	Proportional hazard(s)
PPS	Post-progression survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QLG-BR23	Quality of Life Questionnaire BR23
QLG-C30	Treatment of Cancer Quality of Life Questionnaire C30
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
STA	Single technology appraisal
TPC	Treatment of physician’s choice
TSAP	Trial statistical analysis plan
TTD	Time to treatment discontinuation

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 Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE by Eisai in support of the use of eribulin (Halaven®).

Eribulin was appraised previously by NICE in 2012. At that time, eribulin was licensed by the European Medicines Agency (EMA) for the treatment of adult patients with locally advanced or metastatic breast cancer (LABC/MBC) who had progressed after **at least two** chemotherapy regimens for advanced disease. Prior chemotherapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments. Eribulin was not recommended by NICE as a treatment option for the licensed population (TA250).

In 2014, the EMA licence for treatment with eribulin was broadened to include less heavily treated patients. The broader EMA licence is for the treatment of adult patients with LABC/MBC who have progressed after **at least one** chemotherapy regimen for advanced disease. Again, prior chemotherapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments.

In June 2016, the company submitted evidence to NICE (STA ID964) that focussed on two different subgroups of the licensed population:

1. Subgroup 1: patients with human epidermal growth factor receptor 2 (HER2)-negative LABC/MBC whose disease has progressed after **one** prior chemotherapy regimen in the advanced setting and
2. Subgroup 2: patients with LABC/MBC whose disease has progressed after **at least two** prior chemotherapy regimens for advanced disease, which includes capecitabine (if indicated).

Following discussions between the company, NICE and the ERG, the scope of the 2016 appraisal was amended so that its immediate focus was a review of the 2012 NICE guidance (TA250), i.e. the Subgroup 2 population. As a result, updated NICE guidance was published in December 2016 (TA423). The updated NICE guidance recommends eribulin as an option for LABC/MBC when the disease has progressed after **at least two** chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine) and if the company provides eribulin with the discount agreed in the Patient Access Scheme (PAS).

In August 2016, NICE issued an updated scope for the appraisal of eribulin for treating LABC/MBC after **one** chemotherapy regimen (interpreted by the company and ERG as

meaning after **only one** prior chemotherapy regimen). In August 2017, NICE requested that the ERG examine the evidence for the population identified in the new scope. No new submission was provided by the company; hence, the population considered by the company in the current appraisal is the Subgroup 1 population. However, the company did respond to the clarification questions that it received from the ERG in September 2017.

1.2 Critique of the decision problem in the company's submission

The updated scope issued by NICE in August 2016 specifies the patient population to be adults with LABC/MBC that has progressed after one prior chemotherapy regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable). However, the focus of the population in the company submission (CS) is narrower, Subgroup 1: patients with HER2-negative LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting. In its description of the decision problem, the company states that the patients who are most likely to benefit from treatment with eribulin after one prior chemotherapy regimen in the advanced setting are those with HER2-negative disease. In the clarification response, the company stated its main rationale for focussing only on patients with HER2-negative disease at this stage in the treatment pathway "is due to current clinical practice [patients with HER2-negative LABC/MBC are considered a particularly difficult group to manage effectively] and the unmet clinical need in this patient population" (company response to ERG clarification question, A2a). The Subgroup 1 population therefore represents only a subgroup of the population specified in the updated scope issued by NICE in August 2016. The population in the updated scope issued by NICE is in itself a subgroup of the total population for whom eribulin is indicated since the indication set out in the 2014 EMA licence specifies that patients must have LABC/MBC that has progressed after one or more chemotherapy regimens for advanced disease.

The ERG considers capecitabine or vinorelbine to be the most appropriate comparators to eribulin for patients previously treated with only one prior chemotherapy regimen for LABC/MBC. Both of these chemotherapy drugs are currently recommended as second-line treatment options by NICE for patients with LABC/MBC. For the Subgroup 1 population, direct evidence of the relative clinical effectiveness of eribulin is only available in comparison with capecitabine. Capecitabine is also the comparator in the company's base case cost effectiveness analysis. As specified in the updated scope issued by NICE in August 2016, the company expresses the cost effectiveness of treatments in terms of the incremental cost per quality adjusted life year (QALY) gained. In the base case analysis, outcomes are assessed over a 5-year time horizon; 10- and 20-year time horizons are considered in scenario analyses. Costs are considered from an NHS perspective. A simple PAS offering a discount to the list

price of eribulin was formally agreed between the company and the Department of Health on 14 January 2016. This cost is used in the company's cost effectiveness analysis.

The updated scope issued by NICE in August 2016 specifies that if the evidence allows, consideration should be given to subgroups according to HER2 status and oestrogen receptor (ER) status. The CS does not include clinical or cost effectiveness evidence by ER status.

1.3 Summary of clinical effectiveness evidence submitted by the company

Clinical effectiveness evidence is derived from Study 301, a multi-centre, phase III, open-label, randomised controlled trial (RCT) comparing eribulin with capecitabine as first-, second-, or third-line therapy for the treatment of LABC/MBC. Only data for patients who have received one prior chemotherapy regimen for LABC/MBC (i.e. second-line therapy) are directly relevant to this appraisal.

A total of 1102 participants were randomised in Study 301; 554 to the eribulin treatment arm and 548 to the capecitabine treatment arm. A total of 392 (35.6%) participants randomised in Study 301 were included in the Subgroup 1 population; 186 in the eribulin treatment arm and 206 in the capecitabine treatment arm. Patient characteristics were well balanced across treatment arms.

In the overall trial population of Study 301, the difference in median overall survival (OS) for patients treated with eribulin or capecitabine was not statistically significant (15.9 months versus 14.5 months; hazard ratio [HR]=0.879, 95% confidence interval [CI]:]: 0.77 to 01.00). [redacted]

No statistically significant differences were observed for median progression-free survival (PFS) in the overall trial population. This was true of eribulin versus capecitabine whether independently assessed PFS (4.1 months versus 4.2 months, HR=1.08, 95% CI: 0.93 to 1.25) or investigator assessed PFS (4.2 months versus 4.1 months, HR=0.98, 95% CI: 0.86 to 1.11). Only investigator assessed median PFS was reported for the Subgroup 1 population. [redacted]

The data from the overall trial population of Study 301 show that most patients in both arms experienced an adverse event (AE) (94.1% with eribulin, 90.5% with capecitabine). Most AEs were considered treatment-related in both arms (84.6% with eribulin, 77.1% with capecitabine). There were few differences between arms in terms of AEs that led to dose delays (31.8% with eribulin, 35.7% with capecitabine) or dose reductions (32.0% with eribulin,

31.9% with capecitabine). Fatal AEs were reported by 4.8% of patients treated with eribulin and 6.6% of patients treated with capecitabine.

In the Subgroup 1 population, compared with capecitabine, neutropenia (53.3% versus 14.6%), leucopenia (31.0% versus 9.3%), pyrexia (14.1% versus 4.9%), peripheral sensory neuropathy (16.3% versus 4.9%) and alopecia (34.8% versus 2.9%) were all much more common with eribulin. In contrast, the incidences of diarrhoea (14.1% versus 24.9%) and palmar-plantar erythrodysaesthesia syndrome were much lower (0.5% versus 48.3%) with eribulin than capecitabine. Other AEs reported by ≥20% of patients in either arm included asthenia/fatigue (31.5% versus 25.4%), anaemia (21.2% versus 19.5%) and nausea (20.7% versus 21.0%). The frequencies of the AEs cited for either arm in the Subgroup 1 population were similar to the frequencies reported for the overall trial population.

Results from health-related quality of life (HRQoL) analyses are available for all patients in Study 301 (n=1062 at baseline) and for all patients with HER2-negative disease (n=718 at baseline) in Study 301; HRQoL results are not available for patients in Subgroup 1 only. HRQoL was assessed using the following questionnaires: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0) (EORTC QLQ-C30) and breast module Quality of Life Questionnaire BR23 (version 1.0) (QLQ-BR23). The principal pre-specified outcome was overall quality of life (QoL), expressed as change from baseline in Global Health Status (GHS)/QoL measured on a 0 (worst) to 100 (best) scale on the EORTC QLQ-C30 questionnaire.

Overall, the median GHS/QoL scores in the overall trial population were similar in the eribulin and capecitabine arms. The majority of patients (≥74%) in both treatment arms maintained or improved their GHS/QoL scores versus their baseline scores at 6 weeks, 3 months and 6 months. A similar pattern was observed in patients with HER2-negative disease. The results of the other HRQoL analyses reported in the CS are based on post-hoc analyses of Study 301 data. These findings suggested diminished HRQoL for patients treated with eribulin for systemic therapy side-effects (dry mouth, food and drink taste, painful eyes, hair loss, feeling ill/unwell, hot flushes, headaches) and for patients treated with capecitabine for gastrointestinal side-effects (nausea, vomiting and diarrhoea). Patients receiving eribulin had comparatively worse scores than patients receiving capecitabine for body image and sexual functioning as measured by the QLQ-BR23. On the other hand, a higher proportion of patients receiving capecitabine reported a meaningful worsening on the ‘future perspective’ scale than those receiving eribulin.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Overall, the ERG is satisfied with the clinical effectiveness systematic review process as described in the CS. However, since the CS was submitted to NICE in 2016, the results of the searches are now out of date. The ERG's updated literature searches identified subgroup analyses of data from Study 301 that were published by Twelves et al in 2016.

The ERG considers that Study 301 was generally well designed and well conducted and concurs with the company's view that the trial has a low risk of bias. The ERG considers that the findings from Study 301 suggest that the Subgroup 1 population [redacted] The ERG notes that the population in Subgroup 1 was defined retrospectively and that the study was not powered to find a difference in OS within this specific population.

From the additional subgroup analyses of data from Study 301 published by Twelves et al in 2016, the ERG considers:

- [redacted] a statistically significant gain in OS for eribulin compared to capecitabine is observed for all patients with HER2-negative status who were enrolled into the trial (median 15.9 months versus 13.5 months; HR=0.84, 95% CI: 0.71 to 0.98)
- There is a trend towards an OS gain for patients in the licensed population (≥1 prior chemotherapy for LABC/MBC), although this result does not reach statistical significance at the 5% level of significance (median 16.0 months versus 14.5 months; HR=0.87, 95% CI: 0.75 to 1.01).
- The OS results for the population specified in the final scope issued by NICE (i.e. LABC/MBC patients whose disease has progressed after **only one** prior chemotherapy regimen in the advanced setting), suggest that these patients may experience a beneficial treatment effect from eribulin in comparison to capecitabine regardless of HER2 status, although this result does not quite reach statistical significance at the 5% significance level ([redacted]; HR=0.83, 95% CI: 0.69 to 1.00)
- There is a trend towards an OS gain for the subgroup of patients with HER2-negative status who have also had ≥1 prior chemotherapy for LABC/MBC, although this does not quite reach statistical significance at the 5% level of significance (median 15.9 months versus 13.4 months; HR=0.84, 95% CI: 0.70 to 1.00)
- Analyses show that there is no statistically significant difference between arms for patients with HER2-positive disease, whether considering all the patients with HER2-positive disease in Study 301 (median 18.2 months with eribulin, 16.8 months with capecitabine; HR=0.89, 95% CI: 0.69 to 1.35), or only those in the licensed population (median 15.8 months and 16.4 months respectively; HR=0.88, 95% CI: 0.60 to 1.29).

Regarding PFS, results consistently show there is no statistically significant difference and little numerical difference between the eribulin and capecitabine arms in either the overall trial population, [redacted] or across other relevant subgroups.

Analyses of trial data from Study 301 do not suggest that there are any safety concerns with either drug. Due to diminishing sample sizes over time, the ERG considers that the HRQoL data from Study 301 should be treated with caution.

1.5 Summary of submitted cost effectiveness evidence

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with eribulin versus capecitabine. The model comprised three mutually exclusive health states: pre-progression or stable disease, post-progression or progressive disease, and dead. All patients enter the model in the stable health state and remain in this state until disease progression. The model time horizon is set at 5 years in the base case with monthly cycles. The model perspective is that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE. Survival was estimated based on data from Study 301. Utility values were mapped to EuroQol-5 dimension (EQ-5D) values from the responses of patients in Study 301 completing the EORTC QLQ-C30 questionnaire. Resource use and costs were estimated based on information from Study 301, published sources and clinical experts.

In the base case, eribulin generates more benefits than capecitabine [redacted] life years gained [LYG] and +[redacted] QALYs) at an increased cost of [redacted]. The company base case incremental cost effectiveness ratio (ICER) for eribulin versus capecitabine is £36,244 per QALY gained. The company carried out a range of deterministic sensitivity analyses. The resultant ICERs range from £32,095 to £47,148 per QALY gained, i.e. ranging from £4,149 less than the base case to £10,904 greater than the base case.

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters. There is a 20% probability of treatment with eribulin being cost effective at a threshold of £30,000 per QALY gained and a 69% probability of it being cost effective at a threshold of £50,000 per QALY gained.

The company carried out six scenario analyses. Using a time horizon of 20 years had the largest impact and lowered the ICER to £29,743 per QALY gained (an 18% reduction in the base case result).

1.6 Summary of the ERG's critique of cost effectiveness evidence

The company used Kaplan-Meier (K-M) data directly to model OS in the base case analysis. The company appended projective functions to the K-M data from 5 years onwards to model OS in the scenario analyses where the time horizons were varied. The ERG's analysis shows that the method by which the company appends projections to the K-M data yields an underestimate of OS gain for treatment with eribulin. This underestimation has a small effect on the 5-year base case results, but is more pronounced in results of the time horizon scenario analyses.

The ERG identified, and subsequently corrected, a number of issues relating to the way in which the company has costed drugs. Two logic errors were identified, one relating to the cost of vinorelbine (used post-progression) and the other to the cost of administering eribulin. The ERG also identified issues with the body surface area (BSA) values used to calculate the acquisition cost of chemotherapy, a dose intensity multiplier that only had an effect when the company's alternative approach to calculating drug costs (i.e. without wastage) was applied, and an arbitrary dose capping measure. In addition, the company provided two approaches to estimating the cost of further lines of chemotherapy, both of which lead to anomalous results. The ERG has, therefore, provided results using a different approach to costing further lines of chemotherapy.

The ERG questions the appropriateness of the algorithm applied by the company to convert EORTC QLQ-C30 values to EQ-5D utility values. In addition, the ERG notes that the value used in the company model to represent the HRQoL of patients with stable disease (but not responding to treatment) is very similar to the value for progressed disease (0.70 versus 0.68) and considers this level of similarity to be implausible. The ERG has, therefore, generated cost effectiveness results using their preferred utility estimates.

Three further issues have been identified by the ERG. First, within the company model, costs and benefits are discounted on a continuous basis rather than annually in line with NHS budgeting and accounting years. Second, the method employed by the company to carry out PSA does not take into account uncertainty related to correlated values; furthermore, drug costs are only varied in a deterministic manner. Third, the ERG does not consider that the company has explored parameter uncertainty sufficiently.

1.7 Summary of company's case for end of life criteria being met

The company makes the following case for eribulin to be considered under NICE's end of life criteria:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months. In Study 301, median OS in the eribulin arm was 15.9 months versus 14.5 months in the capecitabine arm
2. There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, **normally** of a mean value of at least an additional 3 months, compared with current NHS treatment. The results of the company's cost effectiveness analysis for patients in the Subgroup 1 population show a mean OS benefit for eribulin of 4.61 months (CS, Table 36).

1.8 ERG commentary on end of life criteria

The ERG considers:

1. The mean OS of patients receiving capecitabine is probably less than 18 months based on the ERG's OS estimate for patients in the capecitabine arm of the Subgroup 1 population
2. The mean OS gain attributable to treatment with eribulin is subject to uncertainty, since the direct measure of OS in the Subgroup 1 population indicates a gain of 5.94 months but indirect estimation in the context of post-progression survival suggests less than 3 months (although possibly subject to bias).

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical effectiveness evidence

- Study 301 compared the efficacy and safety of eribulin with capecitabine, a commonly used treatment used at this stage of the treatment pathway
- Almost fully mature clinical effectiveness data are available (82.1% of all Study 301 patients and [redacted] of all the Subgroup 1 population had died at the time of the data cut-off)
- Study 301 is the only currently available source of good-quality clinical effectiveness evidence describing treatment with eribulin in patients who have received only one prior chemotherapy regimen for LABC/MBC.

Cost effectiveness evidence

- The availability of almost fully mature survival data allows a reliable assessment of the relative effectiveness of treatment with eribulin versus capecitabine to be carried out for the Subgroup 1 population.

1.9.2 Weaknesses and areas of uncertainty

Clinical effectiveness evidence

- [redacted] the difference between arms for all patients who have received one prior chemotherapy regimen for LABC/MBC, regardless of HER2 status (i.e. the population specified in the updated NICE scope) does not quite reach statistical significance
- Using data from Study 301, findings from analyses of the overall trial population of Study 301 and from a subgroup population (licensed population) suggest there is no OS benefit for patients with HER2-positive disease treated with eribulin compared to those treated with capecitabine. It is unclear if this is because eribulin is less efficacious when used to treat patients at this stage in the treatment pathway or whether the size of the subgroups of patients with HER2-positive disease means that they are underpowered to detect a statistically significant difference
- As eribulin is considered to be a viable treatment option for patients with HER2-positive disease later in the treatment pathway (i.e. after at least two prior chemotherapy regimens for LABC/MBC), the main area of clinical uncertainty, therefore, relates to whether patients with HER2-positive disease could also benefit from treatment with eribulin after only one prior chemotherapy regimen for LABC/MBC

Cost effectiveness evidence

- The ERG has identified several issues relating to the methods employed by the company to estimate drug acquisition and administration costs
- Within the company model, costs and benefits have been discounted continuously rather than annually
- The company has used an implausibly high post-progression utility value
- The exploration of parameter uncertainty undertaken by the company is insufficient.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

For the cost effectiveness comparison of treatment with eribulin versus capecitabine using data from the Subgroup 1 population, the ERG suggested ten individual corrections/modifications to the company's economic model. When these ten changes are implemented individually they both increase and decrease the size of the company's base case ICER. The three most influential ERG changes are the use of PFS K-M results from Study 301 (+£14,621), the choice of utility value for the progressive disease health state (+£10,904), and the method used to cost subsequent lines of treatment (+£11,109). Using a PAS price for eribulin, the combined effect of all of the ERG changes yields an ICER of £82,743 per QALY gained which is substantially higher than the company's submitted base case ICER of £36,244 per QALY gained.

In conclusion, the ERG considers that the company's base case ICER substantially underestimates the size of the most probable ICER per QALY gained (by £46,499) for the comparison of eribulin versus capecitabine in patients with LABC/MBC for the Subgroup 1 population, i.e. patients with HER2-negative LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

2 CONTEXT

2.1 Introduction

2.1.1 Original NICE guidance TA250 (2012)

In April 2012, the National Institute for Health and Care Excellence (NICE) published guidance on the use of eribulin for the treatment of locally advanced or metastatic breast cancer (LABC/MBC).[1] Eribulin was not recommended by NICE as a treatment option for the licensed population. At that time, eribulin was licensed by the European Medicines Agency (EMA) for the treatment of adult patients with LABC/MBC who had progressed after **at least two** chemotherapy regimens for advanced disease. A year earlier, in April 2011, eribulin was first made available to some NHS patients in England via regional panels of the Cancer Drugs Fund (CDF).

2.1.2 Updated EMA licence for eribulin (2014)

In July 2014, the EMA granted an extension to the 2012 indication for eribulin. This updated licence enabled eribulin to be used earlier in the treatment pathway. The current indication for eribulin is for the treatment of adult patients with LABC/MBC who have progressed after **one or more** chemotherapy regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless these treatments were not suitable.

2.1.3 New NICE guidance TA423 (ID964, 2016)

In April 2016, NICE issued a scope (ID964) for the appraisal of eribulin within its (updated, 2014) indication for the treatment of adults with breast cancer who have received **one or more** chemotherapy regimens for locally advanced or metastatic disease.[2] In the company submission (CS)[3] for the 2016 appraisal, the company interpreted the new remit to consist of two elements (CS, p10):

- LABC/MBC – following one prior chemotherapy (appraisal of new indication)
- LABC/MBC – following two prior chemotherapies (review of TA250).

The company matched these two elements to two distinct populations and each population was supported by evidence from different trials:

- Subgroup 1:
    - **Population**: patients with human epidermal growth factor receptor 2 (HER2)-negative LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting
    - **Main evidence source**: Study 301,[4] a phase III randomised controlled trial (RCT) in which treatment with eribulin is compared with treatment with capecitabine
- Subgroup 2:
    - **Population**: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease, which includes capecitabine (if indicated)
    - **Main evidence source**: Study 305 (EMBRACE),[5] a phase III RCT in which treatment with eribulin is compared with 'treatment of physician's choice' (TPC).

The company provided only one economic model and, within that model, the Subgroup 1 population and Subgroup 2 were considered separately, with a distinct 'model' being run for each subgroup and cost effectiveness results being presented separately.

After considering evidence submitted by the company (and critiqued by the ERG) for Subgroup 2, updated NICE guidance was published in December 2016 (TA423).[2] The updated guidance recommended eribulin as an option for LABC/MBC when the disease has progressed after **at least two** chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine) and if the company provides eribulin at the discounted price set out in the Patient Access Scheme (PAS).

2.1.4 Current single technology appraisal (2017)

In August 2016, NICE issued an updated scope for eribulin for treating LABC/MBC after **one** chemotherapy regimen[6] (interpreted by the company and ERG as meaning after **only one** prior chemotherapy regimen). In August 2017, NICE requested that the ERG examine the evidence for the population identified in the new scope. No new submission was provided by the company (hence the population considered by the company for the current appraisal is the Subgroup 1 population). However, the company did respond to the clarification questions that it received from the ERG in September 2017.

The remainder of this report is concerned only with the evidence submitted by the company for the Subgroup 1 population. Evidence is derived from the original 2016 CS and from the company's response to ERG questions during the clarification process (September 2017). It is important to note that NICE guidance resulting from this appraisal is intended to supplement, rather than replace, the guidance issued in 2016 (TA423).[2]

2.2 Critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Sections 1.3 and 3 of the CS. The ERG considers that the company's description presents an accurate summary of the underlying health problem and highlights a few key points that it considers to be of particular relevance to the current appraisal in Box 1.

Box 1 Key points from the company's description of underlying health problem

Incidence, survival and HER2 status

- Breast cancer is the most common malignancy in the UK; it accounts for 15% of all new cases and the lifetime risk of developing breast cancer for a woman is 1 in 8.[7] … The risk of developing breast cancer is strongly correlated with age; 80% of cases in the UK occur in women aged 50 years and over.[7] [The ERG notes that Cancer Research UK has stated: …almost half (48%) of breast cancer cases in the UK each year are diagnosed in people aged 65 and over (2012-2014)[8]]
- As many as 35% of women diagnosed with early breast cancer will eventually progress to or relapse with locally advanced breast cancer or metastatic breast cancer (LABC/MBC).
- The subgroup of patients with HER2-positive MBC has been associated in the past with more aggressive disease and poorer patient outcomes; however, with the recent development of human epidermal growth factor receptor 2 (HER2)-positive targeted therapies, the prognosis of HER2-positive MBC has reversed.[9] In a … study of 798 patients with metastatic breast cancer, the hormone-receptor (HR)-positive/HER2-negative subtype was associated with a significantly worse survival, as compared to the HR-positive/HER2-positive group (median 34.4 vs 24.8 months).[10]
- Approximately 85% of patients with LABC/MBC are diagnosed with HER2-negative disease.

LABC/MBC and health-related quality of life

- 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.[11]
- Overall, quality of life is poor in patients with MBC.[12]

Source: CS, Sections 1.3 and 3

2.3 Critique of company's overview of current service provision

The company's overview of current service provision is presented in Sections 1.3, 2.4 and 3 of the CS. The ERG considers that the company's overview presents an accurate summary of current service provision and highlights a few key points that it considers to be of particular relevance to the current appraisal in Box 2.

In addition to vinorelbine or capecitabine, the ERG notes that treatment with gemcitabine may also be a valid option, either as a monotherapy or in combination with another agent. However, as acknowledged by the company (CS, p120), recommendations from NICE for the use of gemcitabine are based on its use in combination with paclitaxel only.[13] The company (and the ERG) are unaware of any data for the comparative effectiveness of gemcitabine monotherapy.

In some instances, patients may also be re-challenged with a taxane at this stage of the treatment pathway (or later). However, clinical advice to the ERG is that this is only likely to be an option when a number of years have passed since the patient last received treatment with a taxane (in the adjuvant setting).

Box 2 Key points from the company's overview of current service provision

Treatment aim

- As recognised in recent NICE guidelines,[11] 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. However, none of the available NICE-approved treatment options have demonstrated a survival benefit over any other.[10,11]

Current treatment options

- Based on the NICE clinical guideline for advanced breast cancer (Clinical Guideline 81)[11] … following anthracycline treatment … systemic chemotherapy should be offered in the following sequence:
  - First-line: single-agent docetaxel [i.e. a taxane]
  - Second-line: single-agent vinorelbine or capecitabine
  - Third-line: single agent vinorelbine or capecitabine (whichever was not used as second-line treatment).
- The tolerability of current locally advanced or metastatic breast cancer (LABC/MBC) treatment varies; chemotherapy agents can be particularly toxic and are recognised to be the most burdensome aspect of cancer management for patients.[14]
- Side effects of chemotherapy … can adversely affect a patients' quality of life,[14] be costly to manage[15] and lead to early discontinuation of a particular therapy[16] in a significant number of patients, thereby impacting on overall treatment outcomes.

Human epidermal growth factor receptor (HER) status

- Pre-treated HER2-negative patients (e.g. patients who are not eligible for targeted agents and who have already received initial 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.

Eribulin

- Eribulin is the first and only single chemotherapy agent to demonstrate a statistically significant overall survival benefit in patients with late stage LABC/MBC and patients with HER2-negative tumours.
- In addition, eribulin is administered as a quick and convenient 2 to 5 minute intravenous infusion with no special handling or tubing required, thereby reducing the inconvenience and burden to the patient associated with longer infusion times.

Source: CS, Sections 1.3, 2.4 and 3

2.4 Number of patients potentially eligible for eribulin

As previously noted (Section 2.1.2), eribulin is indicated for the treatment of adult patients with LABC/MBC who have progressed after one or more chemotherapy regimens for advanced disease. The company has estimated that the total number of all patients (regardless of HER2-status) in England and Wales who are potentially eligible to receive treatment with eribulin following one prior chemotherapy regimen for advanced disease is 3883 (Table 1). The company's estimates are based on prevalence data. The ERG notes that alternative estimates can be calculated using incidence data (Table 2). The resultant alternative estimate (4083) is reasonably similar.

Table 1 Company estimate of the number of patients potentially eligible for treatment with eribulin following one prior chemotherapy regimen for advanced disease

Population	Number	%	Source
Population of England and Wales	57,408,700		ONS mid-year estimate, 2014[17]
Prevalence of breast cancer	80,372	0.14	Cancer Mpact database[18]
Prevalence of metastatic breast cancer	5940	7.39	Cancer Mpact database[18]
Patients receiving first-line chemotherapy	5940	100.00	Company assumption
Patients receiving second-line chemotherapy	3883	65.37	Cancer Mpact database[18]
Patients with HER2-negative disease	2660	68.50	Study 301

HER2= human epidermal growth factor receptor 2; ONS=Office for National Statistics
Source: CS, Table 85

Table 2 ERG estimate of the number of patients potentially eligible for treatment with eribulin following one prior chemotherapy regimen for advanced disease

Population	Number	%	Source
Breast cancer incidence in England and Wales	44,683		Cancer Research UK[19]
Incidence with known stage of disease	40,101	84.10	Cancer Research UK[20]
Incidence of patients with Stage III to IV disease	6246	13.10	Cancer Research UK[20]
Patients receiving first-line chemotherapy	6246	100.00	Company assumption
Patients receiving second-line chemotherapy	4083	65.37	Cancer Mpact database[21]
Patients with HER2-negative disease	2797	68.50	Study 301

HER2= human epidermal growth factor receptor 2

The ERG considers the company's assumption, that 100% of patients receive first-line chemotherapy, to be an overestimate. In the original STA for eribulin (TA250), the ERG notes that the company estimated the proportion to be 61.8% based on market share data for the third quarter of 2010.[22] Clinical opinion received by the ERG, in this current appraisal, is that a more reasonable estimate of the proportion of patients receiving first-line chemotherapy may be approximately 75%. Assuming the proportion of patients receiving first-line chemotherapy to be 75% changes the estimated potentially eligible patient numbers and the new estimates range from 1995 (company) and 2098 (ERG) for the Subgroup 1 population, i.e. patients with HER2-negative disease.

The proportion of patients with HER2-negative disease, on the other hand, may be underestimated in Table 1 and Table 2. The estimated proportion used (68.5%) is the proportion of patients with HER2-negative disease from Study 301, the trial from which evidence for the Subgroup 1 population is derived. However, if the patients who were not tested for HER2-status in Study 301 are excluded, the proportion of patients with HER2-negative disease is 81.7%. Furthermore, elsewhere in the CS, and in the clarification response, the company cites the proportion of patients with HER2-negative disease to be 85% (see also Box 1 of this ERG report). Clinical advice to the ERG is that the proportion of patients with HER2-negative disease may be 80% or more. If a proportion of 80% is assumed, final estimates of the potential size of the Subgroup 1 population should be multiplied by 1.2.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem described by the company in the CS in relation to the updated scope issued by NICE is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.6).

Table 3 Updated NICE scope (August 2016) and company's decision problem

Parameter	Specification in the final scope issued by NICE	Summary of a comparison between the decision problem stated in the NICE scope and addressed in the company submission
Population	Adults with locally advanced or metastatic breast cancer that has progressed after one prior chemotherapy regimen for advanced disease (including both an anthracycline and a taxane, unless these treatments were not suitable)	Subgroup 1: patients with locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has progressed after one prior chemotherapy regimen for advanced disease (including both an anthracycline and a taxane, unless these treatments were not suitable)
Intervention	Eribulin	Eribulin
Comparator (s)	Vinorelbine, capecitabine, gemcitabine	Clinical effectiveness analysis: capecitabine Cost effectiveness analysis: capecitabine Cost effectiveness scenario analysis: vinorelbine (50%) and capecitabine (50%)
Outcomes	Overall survival, progression-free survival, response rates, adverse effects of treatment, health-related quality of life	Subgroup 1: overall survival and progression-free survival; adverse event data presented during the clarification process
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 The availability of any Patient Access Schemes for the intervention or comparator technologies will be taken into account	The results from the cost effectiveness analysis are expressed in terms of incremental cost per quality adjusted life year The base case time horizon was set at 5 years. In addition, 10- and 20-year time horizons are provided as additional sensitivity analysis scenarios with the latter considered by the company to approximate the lifetime horizon The company has agreed a Patient Access Scheme with the Department of Health for eribulin. Results from all cost effectiveness analyses are based on the price for eribulin agreed in the Patient Access Scheme and from the NHS perspective
Other considerations	If the evidence allows, consideration will be given to subgroups according to HER2 status and oestrogen receptor status Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	The company has not presented any evidence according to oestrogen receptor status

Source: Updated scope issued by NICE in August 2016 and CS, adapted from Table 1

3.1 Population

The focus of the company's submission is patients with HER2-negative LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting (described as Subgroup 1). This represents a subgroup of the population specified in the updated NICE scope issued in August 2016 which states that patients should have LABC/MBC which has progressed after one prior chemotherapy regimen in the advanced setting. The ERG notes that there is no stipulation about the HER2 status of patients in the population specified in the updated NICE scope and that the company has not presented evidence for patients with HER2-positive disease.

The population in the updated NICE scope is in itself a subgroup of the population for whom eribulin is indicated since the EMA licence (2014) specifies that patients must have LABC/MBC that has progressed after **one or more** chemotherapy regimens for advanced disease. A summary of the different populations is presented in Table 4.

Table 4 Summary of different patient populations addressed in the current single technology appraisal

Licensed population	Population in NICE scope	Subgroup 1
Patients with LABC/MBC whose disease has progressed after **at least one prior chemotherapy regimen** in the advanced setting	Patients with LABC/MBC whose disease has progressed after **one prior chemotherapy regimen** in the advanced setting	Patients with **HER2-negative** LABC/MBC whose disease has progressed after **one prior chemotherapy regimen** in the advanced setting

LABC/MBC=locally advanced or metastatic breast cancer

The company's rationale for focussing on the Subgroup 1 population in the CS (Table 1) is that this is where treatment with eribulin yields the greatest clinical benefit. However, elsewhere in the CS, it is stated that patients with HER2-negative LABC/MBC are considered a particularly difficult group to manage effectively: "…It is therefore proposed that in this HER2-negative patient population, eribulin be used as a second-line chemotherapy" (CS, p34). This suggests there were two different reasons for focusing on the Subgroup 1 population and so the ERG sought further clarification from the company. In its response, the company clarified (company response to ERG clarification question, A2a): "The main rationale for focussing only on patients with HER2-negative disease is due to current clinical practice and the unmet clinical need in this difficult to treat patient population." The company reiterated that while historically, HER2-positive disease was associated with more aggressive disease and poorer patient outcomes than those with HER2-negative disease, the opposite was now the case, citing evidence from Lobbezoo et al 2013[10] (see also Box 1 of this ERG report).

The ERG agrees with the company that, compared with HER2-positive patients, patients with HER2-negative LABC/MBC are a particularly difficult group to manage effectively; this is, in part, due to targeted agents, such as trastuzumab or ado-trastuzumab emtansine, not being

available to HER2-negative patients early in the treatment pathway. Hence, patients with HER2-negative disease now tend to have poorer patient outcomes than those with HER2-positive disease. Clinical advice to the ERG is that it is unlikely that clinicians would want to limit treatment with eribulin to patients with HER2-negative disease. On the other hand, the ERG notes that most patients (≥80%) seen in clinical practice would have HER2-negative disease (see Section 2.4 of this ERG report). It is further noted by the ERG that treatment with eribulin is an option for patients with any HER2-status (positive or negative) later in the treatment pathway.

Clinical effectiveness evidence for the Subgroup 1 population is derived from a post-hoc subgroup, of the phase III RCT known as Study 301. Patients in the Subgroup 1 population constitute 35.6% of the overall trial population. Alongside the evidence presented for the Subgroup 1 population, the company presents evidence for the overall trial population but it does not present evidence for the population specified in the NICE scope. The overall trial population represents a broader population than the licensed population as it also includes patients receiving first-line treatments for LABC/MBC (20.0% of the overall trial population). Study 301 also includes a broader population than that specified in the updated NICE scope (in addition to patients treated first-line, 28.0% of the overall trial population had received ≥2 prior chemotherapy regimens for LABC/MBC).

In the CS, cost effectiveness evidence is only presented for patients in the Subgroup 1 population.

3.2 Intervention

Eribulin is a first-in-class anti-neoplastic agent belonging to the halichondrin class of drugs. Anti-cancer effects are exerted 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.[23,24] Eribulin monotherapy is administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle. The company notes that pre-medication (antihistamine or steroids) to prevent hypersensitivity reactions is not routinely required prior to injection with eribulin, which sets treatment with eribulin apart from many intravenous (IV) chemotherapy agents. The company also states that, for patients treated with eribulin, the location of care, level of staff usage, cost of administration, frequency and type of monitoring and tests are all of a similar magnitude to other IV chemotherapy agents currently used in clinical practice.

3.3 Comparators

The ERG considers capecitabine or vinorelbine to be the most appropriate comparators to eribulin for patients with LABC/MBC that has been previously treated with one prior chemotherapy regimen. Both of these chemotherapy drugs are currently recommended as second-line treatment options for LABC/MBC by NICE.[11] As previously highlighted (Box 2 of this ERG report), none of the available NICE-approved treatment options have demonstrated a survival benefit over any other.[10,11] Alongside capecitabine and vinorelbine, gemcitabine is included as a comparator in the NICE scope. Clinical advice to the ERG is that, while gemcitabine may be used to treat patients at this stage, it is far more commonly reserved as a treatment option for more heavily pre-treated patients.

Clinical advice to the ERG is that the choice between capecitabine or vinorelbine depends on the patient's previous treatment, i.e. if capecitabine has already been used, then vinorelbine will be the preferred option, and vice versa. If neither capecitabine nor vinorelbine has been previously used, the choice varies based on a multitude of factors including the preferences of clinicians and patients. However, the ERG also notes that, in the previous appraisal for eribulin (TA423),[2] the clinical expert present at the Appraisal Committee meeting stated that most patients in the NHS receive capecitabine as a second-line treatment for LABC/MBC. Capecitabine is arguably, therefore, the most appropriate comparator for patients who have received only one prior chemotherapy regimen for LABC/MBC.

For patients in Subgroup 1, evidence describing the relative clinical effectiveness of eribulin is only available versus capecitabine. Capecitabine is also the comparator in the company's cost effectiveness base case analysis. Treating 50% of patients with capecitabine and 50% of patients with vinorelbine (a 50/50 mix of both oral and IV formulation) is compared with treating 100% of patients with eribulin in one of the company's scenario analyses. However, this analysis does not use efficacy data from vinorelbine studies since efficacy data for vinorelbine is not available. Instead, the analysis simply includes cost data for vinorelbine alongside that of capecitabine, and the efficacy of the mixed comparator is assumed to be equivalent to that of capecitabine.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs) and health-related quality of life (HRQoL); these are standard outcomes used in oncology clinical trials and are the most important outcome measures for this appraisal. All these outcomes were measured in Study 301 and reported in the CS. For patients in Subgroup 1, however, only OS and PFS data are presented in the CS. During the clarification process, the company provided some AE data for the Subgroup 1 population.

3.5 Economic analysis

Cost effectiveness evidence is only presented for patients in the Subgroup 1 population. As specified in the final scope issued by NICE, the company expresses the cost effectiveness of treatments in terms of the incremental cost per quality adjusted life year (QALY) gained. In the base case, outcomes are assessed over a 5-year time horizon and 10- and 20-year time horizons are considered in the company's scenario analyses. Costs are considered from an NHS perspective. A simple PAS offering a discount to the list price of eribulin was formally agreed between the company and the Department of Health on 14 January 2016. The PAS price is used in the company's cost effectiveness analyses.

3.6 Other considerations

The company has not presented any evidence according to ER status or, as noted in Section 3.1, for patients with HER2-positive disease. Clinical advice to the ERG is that like patients with HER2-negative LABC/MBC, patients with ER-positive disease may also be considered a difficult to treat population. This is because at this stage of the disease pathway, they will normally have exhausted endocrine therapy options and are therefore likely to have more advanced and treatment resistant disease.

4 CLINICAL EFFECTIVENESS

The company originally conducted two systematic reviews, one to find evidence for the Subgroup 1 population and the other to find evidence for the Subgroup 2 population. Only the former review is relevant to this appraisal (see Section 2 of this ERG report), and it is, therefore, only information related to the Subgroup 1 population that has been summarised and critiqued in this Section.

4.1 Critique of the review methods

While some specific detail relating to the methods was lacking (see Sections 4.1.1 to 4.1.4 of this ERG report), overall the ERG considers that the clinical effectiveness systematic review process as described in the CS is satisfactory. However, the ERG notes that since the CS was submitted to NICE in 2016, the results of the searches are now out of date.

4.1.1 Literature search methods

The CS adequately describes the search strategies used to identify relevant studies. The company conducted a systematic search for RCT evidence. Separate searches were conducted for the retrieval of cost effectiveness studies (see Section 5.2 of this ERG report).

Searches for evidence indexed in electronic databases

Full details of the search terms used to locate clinical evidence are reported in the CS (Section 4.1 and Appendix 2). The company searched the following databases: MEDLINE (via PubMed), Embase (via Scopus) and The Cochrane Library. Searches covered the period from 1 January 2009 to 30 November 2015 and were restricted to English language. One clinical trial registry (clinicaltrials.gov) was searched (12 February 2016) and the company's own clinical trial database was also searched (date not reported).

Overall, the ERG considers that the strategies used to search the electronic databases are appropriate and adequately described in the CS. Indeed, the ERG was able to run updated searches on 29 August 2017 by replicating the same search terms and databases to look for any additional relevant studies published since the company last ran its searches. These searches were run covering the following time span: 1 November 2015 to 29 August 2017.

Searches for evidence presented at conferences

In addition to searches of bibliographic databases, the company also conducted hand searches of four conference sites on 23 December 2015: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Association for Cancer Research (AACR) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). For completeness, the ERG also hand searched the

conference websites previously searched by the company (from 2015 onwards) on 11 September 2017.

4.1.2 Eligibility criteria

In the CS, a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies is presented. These criteria are described in Table 5 of the CS. The ERG considers that the eligibility criteria are appropriate to the decision problem set out in the final scope issued by NICE.

As described in Appendix 2 to the CS, two reviewers independently undertook study selection in three steps:

1. Review of abstracts (initial review)
2. Review of abstracts (excluded publications)
3. Review of full text papers.

All publications that met inclusion criteria were included and summarised in a Microsoft Excel document (Step 1). Publications not meeting the stated inclusion criteria were excluded and the reason for exclusion was listed (Step 2). Full text publications were retrieved from those abstracts meeting inclusion criteria in Step1 and those meeting the inclusion criteria were data extracted. Publications not meeting the stated inclusion criteria were excluded and the reason for exclusion was listed. It is not stated how disagreements about whether to include or exclude a paper were resolved.

4.1.3 Data extraction

After applying the eligibility criteria to the full-text papers, all the papers meeting the inclusion criteria were retained for data extraction. Data were extracted by two reviewers independently. In case of disagreement, the full paper was examined and reviewed by both reviewers until they reached an agreement.

4.1.4 Quality assessment methods

The company carried out a risk of bias assessment for all of the RCTs included in their systematic review of clinical effectiveness using the approach recommended by NICE.[25] It is, however, unclear to the ERG whether this assessment was completed by one reviewer, or independently by two reviewers.

4.2 Identified studies in the systematic review

The searches conducted by the company identified eight relevant citations for possible inclusion in the systematic review, as follows:[4,26-32]

- Three of the citations reported on Study 301,[4,26,32] a multi-centre, phase III, open-label, RCT comparing eribulin with capecitabine as first-, second-, or third-line therapy for the treatment of LABC/MBC, and include the clinical study report (CSR),[26] data on file[32] and the full published paper from 2015[4]
- Four of the citations report on pooled analyses of Study 301 and Study 305 (EMBRACE) including two conference presentations[27,29] subsequently reported in a published paper[28] and an associated erratum;[30] as per Study 301, Study 305 (EMBRACE) was a multi-centre, phase III, open-label, RCT
- The final citation is a published paper of a phase II RCT designed primarily to assess safety (peripheral neuropathy) in patients with LABC/MBC treated with eribulin mesylate or ixabepilone.[33]

Only 'Study 301 data on file' is directly relevant to patients in Subgroup 1. These data are reported in the CS. The CSR for Study 301 includes subgroup analyses relevant to the licensed population and the population specified in the final scope issued by NICE.

The updated searches conducted by the ERG identified two further citations, relevant to the licensed population but not relevant to patients in Subgroup 1:

- Subgroup analyses of Study 301 published by Twelves et al 2016[34]
- Pooled analyses of patients who had received one or more prior chemotherapy regimens for LABC/MBC (licensed population) in Study 301 and Study 305 (EMBRACE) by Pivot et al 2016.[35]

The ERG has summarised some results from the subgroup analyses of Study 301 in Section 4.7 of this ERG report since this publication includes results which could be considered to be supporting evidence for the efficacy of eribulin by HER2 status and for patients who have received only one or one or more prior chemotherapy regimens for LABC/MBC. The ERG concluded that the results from the pooled analyses were of limited additional value to the current appraisal for the following reasons:

- Only 588 (31.5%) patients included in the pooled analysis had received one prior chemotherapy regimen for LABC/MBC; all these patients were from Study 301
- The comparator arm in the pooled analysis was a combination of capecitabine and TPC; all 548 patients in the comparator arm of Study 301 but only some (n=44) of the patients in Study 305 (EMBRACE) received capecitabine; 592 (31.8%) in total
- 775 (41.6%) of the patients included in the pooled analysis had already received treatment with capecitabine (in addition to an anthracycline and a taxane).

4.3 Risk of bias assessment for Study 301

The company assessed the risk of bias in Study 301 using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[36] The company's risk of bias assessment, and ERG comments, are presented in Table 5.

Overall, the ERG considers that Study 301 was generally well designed and well conducted and the ERG agrees with the company's conclusion that the trial has a low risk of bias for most domains. However, the open-label design provides the opportunity for investigator-assessed outcomes to be biased.

Table 5 Assessment of risk of bias for Study 301

Study question	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	n/a	Disagree that this question is n/a Participants were randomised via IVRS and therefore treatment allocation was concealed
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	n/a	Disagree that this question is n/a The open-label nature of the trials provides an opportunity for subjective results and investigator-assessed outcomes to be biased
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree, all outcomes measured according to the protocol were reported in the CSR for Study 301
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree, the ITT population was the primary analysis population for all efficacy data and appropriate populations were defined for safety and HRQoL data

CSR=clinical study report; HRQoL=health-related quality of life; ITT=intention-to-treat; n/a=not applicable; IVRS=interactive voice response system; n/a=not applicable
Source: CS, adapted from Table 22 and Appendix 3

4.4 Summary of trial characteristics and methodology for Study 301

A summary of the characteristics of Study 301 is provided in Table 6. Of note, Study 301 did not include any centres from the UK.

Table 6 Summary of Study 301 characteristics

Parameter	Study 301
Intervention and comparator	Eribulin (N=554, randomised) Eribulin administered as an IV infusion of 1.23mg/m^2 (equivalent to 1.4mg/m^2 eribulin mesilate) over 2 to 5 minutes on days 1 and 8 of a 21 day cycle Capecitabine (N=548, randomised) Capecitabine 1250mg/m^2 administered orally twice daily in two equal doses on days 1 to 14, every 21 days
Eligibility criteria for participants	• Patients previously treated with up to 3 chemotherapy regimens, including a taxane and an anthracycline; no more than two regimens had to have been given for LABC/MBC • Resolution of all chemotherapy or radiation-related adverse events to Grade 1 severity or lower, except for stable sensory neuropathy to Grade ≤2 and alopecia • ECOG PS 0 to 2 • Life expectancy of ≥3 months • Adequate renal, bone marrow and liver function, as determined by laboratory tests, based on pre-specified values • Prior treatment with capecitabine was not permitted
Location	210 secondary care centres in 24 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Poland, Romania, Russia, Singapore, South Africa, Spain, Taiwan, Ukraine and the United States)
Permitted and disallowed concomitant medications	Medications included: any medication considered necessary for patient's welfare not expected to interfere with evaluation of study 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 included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone therapy, radiation therapy, gene therapy, biologics, or immunotherapy
Primary outcomes	Overall survival and progression-free survival
Secondary outcomes	Objective response rate, safety and health-related quality of life

ECOG=Eastern Cooperative Oncology Group; G-CSF=granulocyte-colony stimulating factor; IV=intravenous; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; PS=performance status; IV=intravenous
Source: CS, adapted from Table 12

4.4.1 Statistical approach adopted for the conduct and analysis of Study 301

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during Study 301 that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the CSR,[26] the trial protocol,[37] the trial statistical analysis plan (TSAP)[37] and the CS. Only the CS included a post-hoc subgroup analysis of the Subgroup 1 population.

Outcomes analysed in Study 301

OS and PFS were the co-primary outcomes of Study 301. The definitions, assessment measures and statistical analysis methodology used for OS and PFS in Study 301 are summarised in the Appendices to this ERG report, Table 26. The ERG considers that the definitions, assessment measures and statistical analysis methodology used for OS and PFS were appropriate and were pre-defined in the TSAP.[37] The ERG notes that the assumption of proportional hazards (PH) is required for the interpretation of hazard ratios (HRs) estimated using Cox PH methodology. From examining the Kaplan-Meier (K-M) data provided to the ERG, the ERG is satisfied that the PH assumption is not violated for OS or PFS in either the overall trial population or within the Subgroup 1 population.

Objective response rate (ORR) and HRQoL were secondary outcomes of Study 301. The definitions and measures used to assess these secondary outcomes are provided in Table 9 of the CS. ORR data were not reported for the Subgroup 1 population whereas HRQoL data were presented for the overall trial population of Study 301 and all patients with HER2-negative disease in Study 301. Safety data for all patients in Study 301 were presented as summaries of all AEs, serious AEs (SAEs), deaths, treatment-related AEs and treatment discontinuation due to AEs.

During the clarification process (company response to ERG clarification question, A1), the company confirmed that the data for Study 301 reported in the CS are from the most recent (final) data-cut (March 2012). The data are almost fully mature with there being 905 (82.1%) deaths in the overall population and [redacted] deaths in the Subgroup 1 population.

ERG critique of statistical approach

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from Study 301 is provided in Table 7. Having carried out these checks, the ERG considers that the pre-planned statistical approach employed by the company is adequate.

The ERG emphasises that the results presented in the CS, which are directly relevant to this appraisal, are those reported for the Subgroup 1 population. The patient population in Subgroup 1 was defined retrospectively following the completion of Study 301. The ERG notes the inherent limitation of reduced statistical power when conducting subgroup analyses, particularly those defined post-hoc.

Table 7 ERG assessment of statistical approach used to analyse data from Study 301

Component	Statistical approach with ERG comments
Analysis populations	• Four analysis populations were defined in the CS (Table 13); the ITT population, PP population, HRQoL population and safety population. • Analyses of efficacy endpoints were performed on the ITT and PP populations. Safety analyses were performed only on the safety population and HRQoL analyses were performed only on the HRQoL population. • The ERG is satisfied that the analysis populations were provided in the TSAP (p11) and that results for each outcome for the relevant populations were provided in the CSR. • The ERG notes that the focus of the CS is the Subgroup 1 population, defined as HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting. This subgroup was defined post-hoc.
Sample size calculation	The sample size calculation is presented in Table 13 of the CS. The sample size calculation was based on a superiority test for comparing OS between the two groups treated with eribulin or capecitabine. When the total number of events (deaths) observed was 905, an overall 0.04 level two-sided log rank test had approximately 90% power to detect a difference between the two survival curves if the alternative hypothesis HR was 0.80 (a 3-month increase in median survival over the 12-month median survival of capecitabine). To account for censoring in the study, a total of 1100 randomised subjects was planned. The ERG is satisfied that this sample size calculation was provided in the TSAP (p11)
Protocol amendments	• Protocol amendments and the rationale for amendments were listed in the CSR (pp73-75). • The ERG is satisfied with the rationale for the amendments and that all amendments were made before the data cut off (12 March 2012, CSR, p3) so amendments were unlikely to have been driven by the results of the trial. • Ad-hoc analyses were also performed to investigate the apparent discordance between the primary endpoints of OS and PFS, to summarise subsequent anticancer therapies received after discontinuation of study drug and to evaluate their potential impact on OS. The additional analyses were performed according to an ad-hoc SAP, dated 14 Jan 2013 (after initial data cut off 12 March 2012). The ad-hoc SAP was detailed in an Appendix to the CSR not made available to the ERG, therefore the ERG cannot comment on whether the additional analysis methodology was appropriate. • The ERG acknowledges the rationale for the additional ad-hoc analyses and is satisfied that results of all ad-hoc analyses are provided in the CSR (pp113-130).
Pre-planned subgroup analyses	• Pre-planned subgroup analyses of efficacy endpoints in the Study 301 are available in the TSAP (pp15-16). • For efficacy and HRQoL outcomes, participants were pre-stratified according to geographical region and HER2 status. Subgroup analyses were performed for efficacy outcomes according to hormone receptor status, disease status and demographics. Results of subgroup analyses are presented in the CSR (pp102-110). • The ERG notes that the focus of the CS is the Subgroup 1 population, defined as HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting. This subgroup was defined post-hoc so this subgroup analysis was not included in the Study 301 protocol, TSAP or CSR.
Pre-planned sensitivity analyses	• Pre-planned sensitivity analyses of efficacy endpoints in the Study 301 are available in the TSAP (pp20-23, 30). No sensitivity analyses are presented within the CS. • The ERG notes that the only results of sensitivity analyses presented within the CSR are sensitivity analyses conducted as part of the ad-hoc analysis described in 'Protocol Amendments' above. The results of other pre-specified sensitivity analyses have not been made available to the ERG.

Component	Statistical approach with ERG comments
Analysis of AEs	• In accordance with the plan for analysis of AEs outlined in the TSAP (p30), many different summaries of AEs are provided as summary tables and as narrative descriptions in the CSR (pp144-173). • All AEs, SAEs, deaths, TEAEs and treatment discontinuation or treatment dose reduction due to AE are summarised by treatment arm, by system organ class and according to preferred term and by CTCAE grade. AEs of interest are also presented separately.
Analysis of PROs	• HRQoL was assessed using the using EORTC QLQ-C30 (version 3.0) and the breast module QLQ-BR23 (version 1.0) questionnaires at baseline, 6 weeks and 3, 6, 12, 18 and 24 months (or disease progression/treatment change), and at unscheduled visits. Further details of these questionnaires are provided in Table 10 of the CS. • Detailed statistical methodology of HRQoL is presented in Table 13 of the CS. • The ERG is satisfied that the methodology used to analyse HRQoL was appropriate, that the methodology is presented in the TSAP (pp28-29) and that all results are reported in the CSR (pp111-112), however some numerical tables of HRQoL results have not been made available to the ERG.

AEs=adverse events; CS=company submission; CSR=clinical study report; CTCAE=common toxicity criteria for adverse events; EORTC=European Organisation for Research on the Treatment of Cancer; ERG=Evidence Review Group; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; HRQoL=health-related quality of life; ITT=intention-to-treat; OS=overall survival; PFS=progression-free survival; PP=per protocol; PROs=patient reported outcomes; QLQ-BR23=EORTC breast cancer-specific quality of life questionnaire; QLQ-C30=Quality of Life Questionnaire-Core 30; SAE=serious adverse events; SAP=statistical analysis plan; TEAE=treatment emergent adverse events; TSAP=trial statistical analysis plan
Source: CS, adapted from Table 10 and Table 13, Study 301 CSR, Study 301 protocol, Study 301 TSAP and ERG comment

4.5 Characteristics of patients enrolled in Study 301

4.5.1 Patient disposition

Details of patient flow in Study 301, including reasons for discontinuation from study treatment in the overall trial population, are summarised in the Appendices to this ERG report, Table 27. Briefly, a total of 1102 participants were randomised in Study 301; 554 to the eribulin treatment arm and 548 to the capecitabine treatment arm. A total of 392 (35.6%) participants randomised in Study 301 were included in the Subgroup 1 population; 186 in the eribulin treatment arm and 206 in the capecitabine treatment arm. The vast majority of patients (99.1%) in each arm of Study 301 had discontinued study treatment at the time of the final data cut-off. For patients in the Subgroup 1 population, the proportions who discontinued study treatment were similar; 98.9% in the eribulin arm and 99.0% in the capecitabine arm. The reasons for discontinuation were broadly similar in each arm and in both populations (i.e., in the overall trial population and in the Subgroup 1 population only). The most common reason for discontinuing treatment was disease progression.

4.5.2 Exposure to treatment

Overall exposure to study treatment was similar in the eribulin arm compared with the capecitabine arm; 125 days versus 119 days respectively in the overall trial population and 126 days versus 119 days respectively in the Subgroup 1 population (See the Appendices to this ERG report, Table 28). In the overall trial population, the mean dose intensity for patients treated with eribulin and capecitabine was relatively high, 0.87 and 0.86, respectively. Mean dose intensity was not reported for the Subgroup 1 population. The relative dose intensity with both drugs was also high: 92% for eribulin and 90% for capecitabine in the overall trial population and 94% and 91%, respectively, in the Subgroup 1 population. Relative dose intensity was calculated by dividing the actual dose intensity (mg/m^2/week) by the planned dose intensity. The planned dose intensity was calculated as follows:

- eribulin = 1.4*2/3 = 0.933 (mg/m^2/week)
- capecitabine = 2500*14/3 = 11667 (mg/m^2/week).

4.5.3 Baseline characteristics

Demographic data, baseline disease, and tumour characteristics are provided in the CS for each treatment arm of Study 301 for the overall trial population (CS, Table 19 to 21) and for the Subgroup 1 population (Table 30), with additional data provided to the ERG during the clarification process (company response to ERG clarification question, A6). The ERG considers that the presented data suggest that patient characteristics are well balanced across treatment arms, with the exception for age in Subgroup 1. In summary:

- the median age of patients was 54 years in the overall trial, 53 years in the Subgroup 1 population; however the median age in the Subgroup 1 population was 55 years in the eribulin arm and 52 years in the capecitabine arm, reflecting the fact that there were proportionately fewer patients aged ≤40 years in the eribulin arm (8.6% versus 17.5%) and proportionately more patients aged ≥65 years (18.8% versus 9.7%)
- most patients were white, 89.9% in the overall trial and 90.3% in the Subgroup 1 population
- most patients were from Eastern Europe (55.5% in the overall trial, 53.8% in the Subgroup 1 population) and around a quarter of patients were from North America, Western Europe and Asia (24.4% in the overall trial, 25.5% in the Subgroup 1 population); all other patients were from Latin America and South Africa 20.1% in the overall trial, 20.2% in the Subgroup 1 population)
- the median time since diagnosis was between 2.6 years and 3.0 years in the capecitabine and eribulin arms of the overall trial, and between 2.7 years and 3.4 years in the Subgroup 1 population
- most patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 (43.6% in the overall trial, 44.9% in the Subgroup 1 population) or ECOG PS 1 (53.9% in the overall trial, 53.3% in the Subgroup 1 population)
- the most common sites for metastases in the overall trial and the Subgroup 1 population were, respectively, bone (55.1% and 58.2%), lung (50.7% and 52.0%), lymph nodes (49.2% and 49.5%) and liver (47.0% and 48.0%)
- most patients had visceral disease, 86.2% in the overall trial and 87.0% in the Subgroup 1 population
- approximately half of all patients had disease progression within 60 days of last dose of taxane (46.3% in the overall trial, 50.8% in the Subgroup 1 population).

Regarding differences in age in the Subgroup 1 population, clinical advice to the ERG is that younger patients (aged ≤40 years) may have a worse prognosis than older patients as they have biologically more aggressive disease. On the other hand, older patients may have a worse prognosis because they are at greater risk of death and may have deteriorating performance statuses due to various chronic conditions and co-morbidities. Therefore, the differences in age are not considered by the ERG to bias the results in favour of either arm of the trial.

Other than the differences in age between arms being less pronounced in the ITT population than the Subgroup 1 population, the main differences between the overall trial population and the Subgroup 1 population are related to HER2 and ER status. 100% of patients in the Subgroup 1 population had HER2-negative disease compared to 68.5% of patients in the overall trial. ER status was not determined for all patients: 10.5% of patients in the overall trial were not tested for ER status compared to 1.0% of patients in the Subgroup 1 population. Therefore, it appeared that there were imbalances in the proportions of patients with ER-positive disease (overall population: 48.7%; Subgroup 1: 56.1%). However, when patients who were not tested for ER status are excluded from a comparison of the overall population with the Subgroup 1 population, the proportion in the overall population (54.5%) is similar to that in the Subgroup 1 population (56.6%). As with ER status, not all patients were tested for HER2 status. If the patients with unknown HER2-status are excluded from a comparison of the overall trial population with that of the Subgroup 1 population, the proportion of patients with HER2-negative disease in Study 301 is 81.7%.

As is common with most clinical trials, patients included in Study 301 tended to be younger than those who would most typically be seen in clinical practice. It is also notable that only a minority of patients in Study 301 were treated in Western Europe, with no patients treated in the UK. However, while the patient population may therefore differ in some ways to patients seen in clinical practice in England, based on other trial and baseline characteristics presented, the ERG nonetheless considers the results of the trial are likely to be generalisable to clinical practice in England.

4.6 Results from Study 301

4.6.1 Co-primary efficacy outcome: overall survival and progression-free survival

In the overall trial population of Study 301, neither the differences in OS or PFS between arms were statistically significant.

[redacted]

(Table 8).

Table 8 Efficacy findings for the overall population and the Subgroup 1 population of Study 301

Parameter	ITT population		Subgroup 1	
	Eribulin (N = 554)	Capecitabine (N = 548)	Eribulin (N = 186)	Capecitabine (N = 206)
Overall survival (OS)				
Number of patients who died, n (%)	446 (80.5)	459 (83.8)	[redacted]	
Median OS, months (95% CI)	15.9 (15.2 to 17.6)	14.5 (13.1 to 16.0)	[redacted]	
Hazard ratio (95% CI) ¥	0.88 (0.77 to 1.00)		[redacted]	
p-value	0.056		[redacted]	
Progression-free survival (PFS) - independent review				
Number of patients who progressed or died, n (%) †	385 (69.0)	360 (66.0)	NR	NR
Median PFS, months (95% CI)	4.1 (3.5 to 4.3)	4.2 (3.9 to 4.8)	NR NR	NR NR
Hazard ratio (95% CI) §	1.079 (0.93 to 1.25)		NR	
p-value	0.304		NR	
Progression-free survival (PFS) - investigator review				
Number of patients who progressed or died, n (%) †	470 (84.8)	468 (85.4)	[redacted]	
Median PFS, months (95% CI)	4.2 (3.9 to 4.3)	4.1 (3.7 to 4.5)	[redacted]	
Hazard ratio (95% CI) §	0.98 (0.86 to 1.11)		[redacted]	
p-value §	0.736		[redacted]	

CI=confidence interval; NR=not reported
* Primary analysis for study 301 was carried out when 82% of total study patients had died
† The remaining patients were censored
¥ HR and p-value based on a Cox model including HER2 status and geographical region as strata for the ITT population [redacted]
§ HR and p-value based on a Cox model including HER2 status and geographical region as strata for the ITT population [redacted]
Source: CS, adapted from Tables 24 and 26, Figure 12 and Appendix 4

Of note, patients in both arms could receive subsequent treatment following disease progression. As reported by the company (company response to ERG clarification question, A7, Table 4), proportionately more patients received subsequent treatment in the eribulin arm (overall trial population: 70.4%; Subgroup 1: 75.3%) than the capecitabine arm (overall trial population: 62.0%; Subgroup 1: 64.1%). Except for capecitabine, the types of treatment and the proportion of patients receiving these subsequent treatments were similar in both arms. Capecitabine, on the other hand, was more commonly received by patients in the eribulin arm (overall trial population: 49.6%; Subgroup 1: 57.5%) than the capecitabine arm (overall trial population: 15.7%; Subgroup 1: 14.6%). The receipt of subsequent eribulin was rare in either arm (<1%).

The increased use of capecitabine for patients in the eribulin arm is not unexpected because, as mentioned in Section 2.3 of this ERG report (Box 2), it is commonly used as a second or third-line therapy. Therefore, since patients in the eribulin arm had not received prior capecitabine (as patients who had received capecitabine previously were not permitted to enter Study 301), it remained a third-line option for most patients in this arm of the trial. The ERG notes that the company conducted exploratory ad-hoc analyses to examine the effect of post-progression treatment on OS in the overall trial population and reported the results in the CSR (pp115-118).

[redacted]

4.6.2 Safety data

Safety data in the CS are reported for all patients in Study 301. During the clarification process, the company provided data for the most commonly reported AEs by treatment arm for the Subgroup 1 population only (company response to ERG clarification question, A3).

Adverse events reported by all patients in Study 301

The data from Study 301 (CS, Table 33) show that most patients in both arms experienced an AE (94.1% with eribulin, 90.5% with capecitabine). Most AEs were considered treatment-related in both arms although the proportion of treatment-related AEs was higher with eribulin (84.6%) than with capecitabine (77.1%). The proportion of Grade 3 AEs was marginally higher in the eribulin arm (37.1%) than in the capecitabine arm (33.5%) but the incidence of Grade 4 AEs was much higher (23.5% versus 5.9%). The incidence of SAEs was marginally lower with eribulin than with capecitabine (17.5% versus 21.1%), whether reported to be fatal (4.8% versus 6.6%) or not. There was little difference between arms in terms of AEs that led to dose delays (31.8% versus 35.7%) or dose reductions (32.0% versus 31.9%). AEs that led to dose interruptions were infrequent (1.8% versus 0.2%). None of these AE data were available for the Subgroup 1 population.

Most common adverse events reported by patients in Subgroup 1 in Study 301

In the Subgroup 1 population, compared with capecitabine, neutropenia (53.3% versus 14.6%), leucopenia (31.0% versus 9.3%), pyrexia (14.1% versus 4.9%), peripheral sensory neuropathy (16.3% versus 4.9%) and alopecia (34.8% versus 2.9%) were all much more common with eribulin. In contrast, the incidences of diarrhoea (14.1% versus 24.9%) and palmar-plantar erythrodysaesthesia syndrome were much lower (0.5% versus 48.3%) with eribulin than capecitabine. Other AEs reported by ≥20% of patients in either arm included asthenia/fatigue (31.5% versus 25.4%), anaemia (21.2% versus 19.5%) and nausea (20.7% versus 21.0%). The frequencies of the AEs cited for either arm in the Subgroup 1 population were similar to the frequencies reported for the overall trial population.

Comparison of adverse event data from Study 301 with data from Study 305 (EMBRACE)

The CS also included AE data from Study 305 (EMBRACE) for patients who had received at least two prior chemotherapy regimens for LABC/MBC, i.e. patients who were further along the treatment pathway (CS, Tables 33 and 34). It is noticeable that, in the eribulin arms, the proportion of patients reporting any AE, any Grade 3 or Grade 4 AEs, SAEs, AEs that led to treatment discontinuation, dose delay or dose interruption were all lower for patients treated with eribulin in Study 301 than for patients treated with eribulin in Study 305 (EMBRACE). The difference was particularly marked for Grade 3 AEs (37.1% in Study 301 compared with 61.2% in Study 305 [EMBRACE trial]). On the other hand, AEs that led to dose reduction were higher in Study 301. The incidence of fatal SAEs was similar in the eribulin arms of both trials. Generally, the most common types (>10% occurring in either arm) of AEs were also less frequently reported for patients treated with eribulin in Study 301 compared with Study 305 (EMBRACE). This difference was most marked for asthenia/fatigue (32.0% versus 53.7%) and peripheral neuropathy (13.4% versus 34.6%). It should be noted that peripheral neuropathy was defined differently in the two trials and so cross-trial comparisons are difficult for this AE. The most notable case of a difference in the incidence between trials where this was higher in Study 301 than in Study 305 (EMBRACE) was for leucopenia (31.4% versus 23.1%).

Regarding AEs associated with capecitabine in the two trials, as with eribulin, these were generally reported at similar or lower frequencies in Study 301 than in Study 305 (EMBRACE). The most notable exceptions were the incidences of AEs that led to dose delays (22.7% versus 35.7%), AEs that led to dose reduction (18.2% versus 31.9%), neutropenia (4.5% versus 15.9%) and leucopenia (2.3% versus 10.4%). Of note, the incidence of AEs that led to dose interruptions of capecitabine was 0.2% in Study 301 compared with 22.7% in Study 305 (EMBRACE).

It is important to note that the number of patients taking capecitabine in Study 305 (EMBRACE) was small (n=44). Therefore any comparisons regarding the incidence of AEs reported from treatment with capecitabine between trials should be interpreted with caution.

4.6.3 Health-related quality of life data

HRQoL was assessed using the following questionnaires: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0) (EORTC QLG-C30) and breast module Quality of Life Questionnaire BR23 (version 1.0) (QLG-BR23). The principal pre-specified outcome was overall quality of life (QoL), expressed as change from baseline in Global Health Status (GHS)/QoL measured on a 0 (worst) to 100 (best) scale on the QLG-C30 questionnaire.

Questionnaires were administered to patients at baseline, at 6 weeks, and at 3, 6, 12, 18, and 24 months or until disease progression or initiation of other antitumor treatment. Patients were asked to complete questionnaires at each clinic visit, even if they had declined to do this previously.

Results for HRQoL were available for all patients in Study 301 and for all patients with HER2-negative disease in Study 301; HRQoL data were not available for the patients in Subgroup 1. It is stated in the CS that, of the 1102 patients randomised in Study 301, 1062 (96.4%) completed the EORTC questionnaire at baseline and thus formed the HRQoL population. The proportion who responded at baseline in the HER2-negative group was 95.1% (718 out of a possible 755, see company response to ERG clarification question, A8).

The company cautions that, due to the smaller sample sizes, the results of HRQoL analyses that were carried out after 6 months should be interpreted with caution. While response rates at 6 months were high (>87.0% in either treatment arm, as calculated by the number of patients who responded divided by the number of patients eligible to respond), the number of patients responding with a GHS/QoL score, as a proportion of all patients who entered the trial, was relatively low (333 [30.2%]). This is because only patients who remained free from progressive disease were asked to complete the questionnaires.

Overall, the median GHS/QoL scores in the overall trial population were similar in the eribulin and capecitabine arms. The majority of patients (≥74%) in both treatment arms maintained or improved their GHS/QoL versus their baseline scores at 6 weeks, 3 months and 6 months (CS, Figure 15). A similar pattern was observed in patients with HER2-negative disease although by 6 months, the proportion was 74% in the eribulin arm and 69% in the capecitabine arm (CS, Figure 16 and company response to ERG clarification question, A8). The difference is not described as being statistically significant or clinically meaningful. However, again, it should be noted that the proportion of patients who responded (as a proportion of all patients at baseline) was relatively low (207 out of a possible 755 [27.4%], see company response to ERG clarification question, A8).

The results of the other HRQoL analyses reported in the CS are based on post-hoc analyses of Study 301 data. Patients treated with eribulin had statistically significant and clinically meaningfully worse scores, and more rapid time to symptom worsening, for systemic therapy side-effects (dry mouth, food and drink taste, painful eyes, hair loss, feeling ill/unwell, hot flushes, headaches) than patients treated with capecitabine. Patients treated with capecitabine had statistically significant and clinically meaningfully worse scores, and more rapid time to symptom worsening, for gastrointestinal side-effects (nausea, vomiting and diarrhoea) than patients treated with eribulin. While there were no differences between the two treatment arms in terms of impact on patients' functioning over time, as measured by the EORTC QLQ-C30, patients receiving eribulin had comparatively worse scores than those receiving capecitabine regarding the body image and sexual functioning scales measured by QLQ-BR23. On the other hand, a higher proportion of patients receiving capecitabine reported a meaningful worsening on the 'future perspective' scale than those receiving eribulin.

It is stated in the CS that "…the results in the HER2-negative subgroup of Study 301 were similar to those in the overall population in all analyses" (CS, p101). However, only the following outcomes are reported for patients with HER2-negative disease:

- Proportion of patients with improved/stable GHS/QoL (as reported above)
- Eribulin symptom burden versus capecitabine (CS, Figure 17).

Regarding the latter, the company states "…Patient burden of gastrointestinal adverse events was even more significantly lower for eribulin patients and is consistent with its known adverse event profile." (CS, page 101)

4.7 Additional work on clinical effectiveness undertaken by ERG

This section includes information from a publication that is linked to Study 301 that was published by Twelves et al 2016[34] after the company ran its searches for evidence. The evidence is derived from a set of subgroup analyses that were undertaken according to HER2 status and/or number of prior chemotherapies. The main subgroup analysis focusses on patients with HER2-negative disease in Study 301 treated with ≥1 prior chemotherapies for LABC/MBC (i.e. a subgroup of the licensed population). This study[34] also includes efficacy data that the company provided to the ERG during the clarification process (company response to ERG clarification question, A2). Table 9 presents the results of the subgroup analyses. Comparing the results of these additional subgroup analyses to the results presented in the CS for patients in Subgroup 1 (see Table 8 of this ERG report), the ERG considers the OS and PFS results to be generally consistent across all subgroups of patients with HER2-negative disease and/or ≥1 prior chemotherapy for LABC/MBC.

[redacted] a statistically significant gain in OS for eribulin compared to capecitabine is observed for the subgroup of patients with HER2-negative status. There is a trend towards an OS gain for the subgroup of patients with HER2-negative status who have also had ≥1 prior chemotherapy for LABC/MBC, although this does not quite reach statistical significance at the 5% level of significance. When considering prior chemotherapies alone (1 or ≥1 prior chemotherapy for LABC/MBC), a trend towards an OS gain for eribulin compared to capecitabine is also observed. However, this gain does not reach statistical significance at the 5% level of significance.

In addition to data summarised by the ERG in Table 9, the CSR for Study 301 and Twelves et al 2016 and both include data for patients with HER2-positive disease. The analyses show that there is no statistically significant difference between arms for patients with HER2-positive disease, whether considering all the patients with HER2-positive disease in Study 301 (median 18.2 months with eribulin, 16.8 months with capecitabine; HR=0.89, CI: 0.69 to 1.35), or only those in the licensed population (median 15.8 months and 16.4 months respectively; HR=0.88, 95% CI: 0.60 to 1.29).

It is important to note that, as subgroup analyses are not powered to detect differences, a lack of statistical significance may only indicate that patient numbers were too small to detect a statistically significant treatment effect. Certainly, it is evident that the numbers of patients in the HER2-positive subgroups (overall trial population, n=169, licensed population, n=131) are much smaller than the numbers of patients in the HER2-negative subgroups, as would be expected in clinical practice.

Table 9 Additional efficacy subgroup analyses of Study 301

Parameter[a]	HER2-negative*		≥1 prior chemotherapy for LABC/MBC		1 prior chemotherapy for LABC/MBC*		HER2-negative and ≥1 prior chemotherapy for LABC/MBC	
	Eribulin (N=375)	Capecitabine (N=380)	Eribulin (N=438)	Capecitabine (N=444)	Eribulin (N=280)	Capecitabine (N=293)	Eribulin (N=290)	Capecitabine (N=305)
OS								
Number of patients who died, n (%) [a]	296 (78.9)	316 (83.2)	359 (82.0)	379 (85.4)	[redacted]	[redacted]	NR	NR
Median OS, months	15.9	13.5	16.0	14.5	[redacted]	[redacted]	15.9	13.4
HR (95% CI)[b]	0.84 (0.71 to 0.98)		0.87 (0.75 to 1.01)		0.83 (0.69 to 1.00)		0.84 (0.70 to 1.00)	
p-value[b]	0.030		0.059		0.050		0.048	
PFS - investigator review								
Number of patients who progressed or died, n (%)[c]	267 (71.2)	258 (67.9)	311	292	NR	NR	NR	NR
Median PFS, months	4.0	4.0	4.1	4.2	NR	NR	4.1	3.9
HR (95% CI)[b]	1.04 (0.87 to 1.23)		1.07 (0.91 to 1.26)		1.03 (0.84 to 1.26)		0.93 (0.78 to 1.12)	
p-value[b]	0.689		0.394		NR		0.461	

CI=confidence interval; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; NR=not reported; OS=overall survival; PFS=progression-free survival

* Pre-specified subgroup analysis, includes patients who were treated first-line for LABC/MBC

[a] Subgroup analyses were conducted using the same approach as the primary analysis, see Table 8 of this ERG report and Appendices to this ERG report, Table 26. All subgroup analyses except * were conducted post-hoc

[b] P-value and HR are estimated from a Cox model including HER2 status and geographical region as strata

[c] The remaining patients were censored

Source: Twelves 2016,[34] Figure 2, Figure 3 and Figure 4; Study 301 CSR, Figure 14.2.8.3.1; company response to ERG clarification question, A2

Overall, therefore, the findings from the Twelves et al 2016 paper suggest that patients with HER2-negative disease treated with eribulin do have improved OS when compared with patients treated with capecitabine. There is also a trend to improved OS for all patients, regardless of HER2 status, whether they have received only one prior chemotherapy regime or at least one prior chemotherapy regime.

Results for PFS consistently show no statistically significant difference and little numerical difference in PFS between the eribulin and capecitabine arms across all relevant subgroups. The ERG notes that median PFS results for participants with one prior chemotherapy are not available. However, based on the observed HRs, these results are likely to be in line with results for Subgroup 1 population and for participants with ≥1 prior chemotherapy for LABC/MBC presented in Table 8 and Table 9 respectively of this ERG report.

4.8 Conclusions of the clinical effectiveness section

The updated NICE scope specifies the population relevant to this appraisal is adults with LABC/MBC that has progressed after one prior chemotherapy regimen for advanced disease. The data presented by the company are for a subgroup of this population identified post-hoc, the Subgroup 1 population, adults with HER2-negative LABC/MBC that has progressed after one prior chemotherapy regimen for advanced disease. Results of efficacy analyses for the Subgroup 1 population show that [redacted].

[redacted]

Pre-specified and post-hoc analyses of Study 301 that have considered efficacy according to HER2 status in the overall trial population and in the licensed population have shown statistically significant improvements in OS for eribulin versus capecitabine for patients with HER2-negative disease. Results also show that, when considering prior chemotherapies (1 or ≥1 prior chemotherapy for LABC/MBC), a trend towards improved OS for patients treated with eribulin compared to patients treated with capecitabine is observed, regardless of HER2 status. It is unclear if the apparent lack of benefit for patients with HER2-positive disease in the population of Study 301 arises because eribulin is less efficacious when used to treat patients at this stage in the treatment pathway or whether the size of the subgroups of patients with HER2-positive disease means that they are underpowered to detect a statistically significant difference.

For patients in the Subgroup 1 population, the incidences of neutropenia, leucopenia, pyrexia, peripheral sensory neuropathy and alopecia were all higher with eribulin than with capecitabine, whereas incidences of diarrhoea and palmar-plantar erythrodysaesthesia syndrome were lower. Data from the overall trial population in Study 301 and from patients in Study 305 (EMBRACE) appear to suggest that the AEs reported for patients in the Subgroup 1 population are broadly similar to those experienced by all patients treated with eribulin. Dose-intensity was high for both eribulin and capecitabine in Study 301, suggesting that both drugs appear to have manageable safety profiles.

In Study 301, there were no statistically significant or clinically meaningful differences between treatment arms in the pre-specified measure of HRQoL, i.e. GHS/QoL. Differences in AEs between the treatment arms do appear to translate into differences in HRQoL related to AEs (systemic therapy side-effects with eribulin and gastrointestinal side-effects with capecitabine).

The patient population in Study 301 appears to be younger than patients seen in clinical practice in England. In addition, only a minority of patients were from Western Europe with no patients recruited from the UK. Nonetheless, based on other trial and baseline characteristics presented, the ERG considers the results of the trial are likely to be generalisable to clinical practice in England.

5 COST EFFECTIVENESS

5.1 Introduction

A summary of the evidence provided by the company in support of the use of eribulin for the treatment of HER2-negative patients with LABC/MBC whose disease has progressed following one prior chemotherapy regimen for advanced disease (including both an anthracycline and a taxane, unless these treatments were not suitable), i.e., the group of patients labelled as the Subgroup 1 population by the company. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation, which included the development of a model using Microsoft Excel.

5.2 ERG critique of the company's review of cost effectiveness evidence

5.2.1 Objective of the company's systematic review

The company conducted a systematic review of published cost effectiveness studies relevant to the decision problem for the Subgroup 1 population on 23rd December 2015. Embase (via the Scopus platform), MEDLINE and MEDLINE In-Process (via the PubMed platform) and the Cochrane Library were searched from 1 January 2009 to 30 November 2015; retrieved studies were restricted to those published in the English language. This search was supplemented by additional searching of the clinicaltrials.gov website on 12th February 2016 and by hand searching proceedings from the ASCO, ESMO, AACR and International Society for ISPOR conferences on 23rd December 2016. Details of the search strategies employed by the company are provided in Appendix 2 to the CS.

5.2.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used by the company to facilitate study selection are described in Table 37 of the CS. The ERG considers that the eligibility criteria were appropriate to the objective of the company's review of cost effectiveness evidence.

5.2.3 Included and excluded studies

The company did not identify any cost effectiveness studies conducted from a UK perspective that were relevant to the Subgroup 1 population. Three economic evaluations were initially identified.[38-40] However, none of these studies[38-40] was considered by the company to address the final scope issued by NICE. One study[38] was conducted outside of the UK, and two studies[39,40] discussed the direct and indirect costs associated with treatment of LABC/MBC

with eribulin or its comparators from the perspective of the US healthcare system and did not provide relevant data for the UK setting.

5.2.4 Findings from the cost effectiveness review

The company did not identify any cost effectiveness studies to support the use of eribulin for the treatment of LABC/MBC in patients whose disease has progressed following at one prior chemotherapy regimen for advanced disease.

5.2.5 ERG critique of the company's cost effectiveness review

The ERG is satisfied with the company's search strategy and considers that the databases searched and search terms used appear to be reasonable. The ERG notes that the searches were carried out in December 2015 and therefore some relevant studies may have been missed. The ERG updated the company searches for the period between December 2015 and 29th August 2017 and is satisfied that no relevant economic studies have been missed by the company.

5.3 Summary and critique of the company's submitted economic evaluation by the ERG

5.3.1 ERG summary of the company's submitted economic evaluation

The company has developed a de novo economic model to compare the cost effectiveness of two treatment regimens (i.e., eribulin versus capecitabine) for patients in the Subgroup 1 population.

5.3.2 NICE reference case checklist

Table 10 NICE reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. Population consists of patients with HER2-negative LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting (Subgroup 1)
Comparator(s)	As listed in the scope developed by NICE	Partial. Capecitabine; Scenario analysis - vinorelbine (50%) and capecitabine (50%)
Perspective costs	NHS and Personal Social Services	Partial. NHS costs only
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
Synthesis of evidence on outcomes	Systematic review	Yes. The company uses data from Study 301, the only trial identified by the company's systematic review. This is appropriate
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	No. Disease-specific quality of life trial data from Study 301 were used and were converted by a generic mapping algorithm to approximate EQ-5D values
Benefit valuation	Time-trade off or standard gamble	Partial. Mapped onto time-trade off scale
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Partial. Disease-specific quality of life trial data from Study 301 were used and were converted by a generic mapping algorithm to approximate EQ-5D values
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
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	Partial. PSA lacks the facility to include correlated parameter values

EQ-5D=EuroQol-5 dimension; HER2=human epidermal growth factor receptor 2; HRQoL=health related quality of life; LABC/MBC=locally advanced or metastatic breast cancer; QALY=quality adjusted life year; PSA=probabilistic sensitivity analysis

5.3.3 Model structure

The cost effectiveness model presented by the company is based on a partitioned survival model comprising three mutually exclusive health states: pre-progression or stable disease, post-progression or progressive disease, and dead. All patients enter the model in the stable health state and remain in this state until disease progression. At the beginning of each time period patients can either remain in the same health state or move to a worse health state. For example, patients in the stable health state can move to the progressive health state or to the dead health state, whilst patients in the progressive health state can only move to the dead health state. The dead health state is the terminal state. A schematic of the company model is presented in the CS and reproduced in Figure 1.

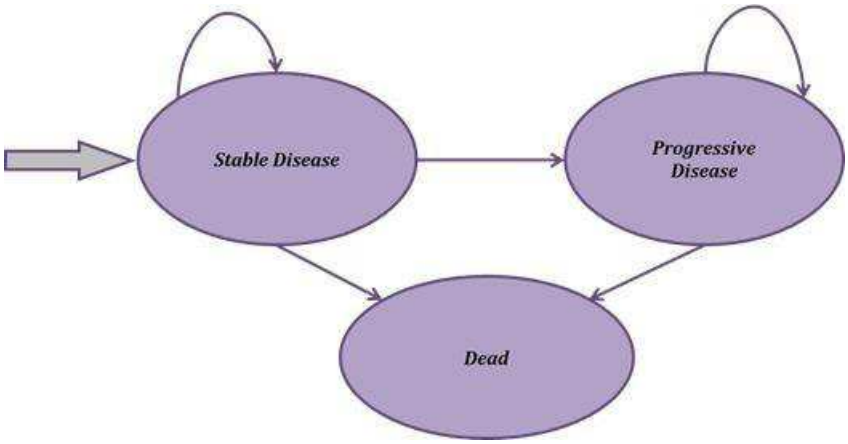


Figure 1 Company model structure

Source: CS, Figure 26

Estimates of OS and PFS are based on K-M data from Study 301. The model uses a cycle length of one month (30.42 days).

Treatment with the intervention or comparator begins when the patient enters the model in the stable health state and is assumed, in the base case, to continue until the patient has received the appropriate number of cycles of treatment (which varies depending on therapy) or until disease progression, whichever comes first.

5.3.4 Population

The population reflected in the company model is HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting, i.e. the Subgroup 1 population.

5.3.5 Interventions and comparators

Primary treatments

Eribulin is implemented in the model in line with the licensed dose, i.e. 1.23mg/m^2 administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle.

The base case comparator in the cost effectiveness analysis is capecitabine. Capecitabine was selected as the base case comparator to reflect the design of Study 301; patient level data from this study are used in the model to estimate clinical and cost effectiveness outcomes.

In a scenario analysis, the company also considered a comparator arm in which patients were treated with a combination of capecitabine (50%) and oral vinorelbine (50%). Capecitabine and oral vinorelbine were assumed to have the same efficacy and safety as there is no clinical effectiveness evidence to support treating this specific patient group with vinorelbine.

Secondary treatments

Patients transitioning from the stable to progressive health states are assumed to receive secondary chemotherapy treatments in the proportions shown in Table 11. The ERG notes that information for the secondary treatments used in the model are based on Study 305 (EMBRACE) for Subgroup 2 (TA423). Secondary treatments derived from Study 301 are presented in Table 12. The ERG notes that patients in Subgroup 2 are assumed to have received prior treatment with capecitabine; therefore, TPC for Subgroup 2 patients excludes capecitabine. In Study 301, half (overall trial population) or more (Subgroup 1 population) of patients that received eribulin were treated with capecitabine following disease progression.

Table 11 Subsequent treatment received on disease progression in company model

Treatment on disease progression	Proportion of patients
Vinorelbine	36.8%
Gemcitabine	27.7%
Taxanes	
Paclitaxel	15.7%
Docetaxel	6.0%
Anthracycline (doxorubicin)	13.9%
Total	100.0%

Source: CS, adapted from Table 43

Table 12 Subsequent treatment received on disease progression in Study 301

Treatment on disease progression	ITT population		Subgroup 1	
	Eribulin (N=554)	Capecitabine (N=548)	Eribulin (N=186)	Capecitabine (N=206)
Any, n (%)	390 (70.4)	340 (62.0)	140 (75.3)	132 (64.1)
Eribulin, n (%)	3 (0.5)	2 (0.4)	1 (0.5)	1 (0.5)
Capecitabine, n (%)	275 (49.6)	86 (15.7)	107 (57.5)	30 (14.6)
Taxanes, n (%)	85 (15.3)	118 (21.5)	31 (16.7)	44 (21.4)
Cisplatin	0	1 (0.2)	0	0
Docetaxel	36 (6.5)	49 (8.9)	15 (8.1)	15 (7.3)
Ixabepilone	10 (1.8)	19 (3.5)	3 (1.6)	6 (2.9)
Paclitaxel	46 (8.3)	63 (11.5)	16 (8.6)	27 (13.1)
Other	1 (0.2)	3 (0.5)	0	1 (0.5)
Anthracycline, n (%)	54 (9.7)	67 (12.2)	12 (6.5)	32 (15.5)
Anti-HER2 therapy, n (%)	22 (4.0)	34 (6.2)	2 (1.1)	4 (1.9)
Biologics, n (%)	27 (4.9)	23 (4.2)	11 (5.9)	7 (3.4)
Combination, n (%)	1 (0.2)	4 (0.7)	0	3 (1.5)
Gemcitabine, n (%)	81 (14.6)	99 (18.1)	28 (15.1)	39 (18.9)
Hormonal therapy, n (%)	114 (20.6)	97 (17.7)	41 (22.0)	45 (21.8)
Platinum therapy, n (%)	73 (13.2)	98 (17.9)	22 (11.8)	40 (19.4)
TKI therapy, n (%)	6 (1.1)	6 (1.1)	3 (1.6)	4 (1.9)
Vinorelbine, n (%)	136 (24.5)	132 (24.1)	50 (26.9)	53 (25.7)
Other, n (%)	75 (13.5)	80 (14.6)	23 (12.4)	33 (16.0)

HER2=human epidermal growth factor receptor 2; TKI=tyrosine kinase inhibitors; ITT=intention-to-treat
Source: Company response to ERG clarification question, A4 (Table 4)

Treatment duration

In the base case, the maximum treatment duration in the model for patients in the Subgroup 1 population is set at 8 months. This includes all treatments received in both the stable and progressive health states (primary plus secondary treatments). The duration of any secondary treatment received in the progressive health state following treatment with eribulin or capecitabine is therefore linked to the duration of the primary treatment in the stable health state. An alternative scenario is also presented by the company in which patients receive initial treatment until disease progression and then do not receive any further treatments. Further details on the company's analysis of treatment duration are provided in Table 44 of the CS.

Dose intensity

Dose reductions and treatment delays due to AEs are included in the model using a dose intensity modifier. Dose intensity for patients treated with eribulin is 0.87, based on the mean dose intensity observed for patients treated with eribulin in the ITT population of Study 301. Dose intensity for patients treated with capecitabine is 0.86, based on the mean dose intensity observed for patients treated with capecitabine in the ITT population of Study 301.

Wastage

Doses are calculated for each of the intervention and comparator drugs using a normal distribution of body surface area (BSA) and the licensed dose per m^2 of BSA. An estimate of $1.74m^2$ for women with breast cancer in the UK (Sacco et al 2010)[6] is used. The cost of any drugs wasted is included in the base case analysis.

The company also performed a scenario analysis in which drug wastage was minimised. A rounding rule was employed to adjust the calculated dose for any given BSA. This dose adjustment was based on 10% of the smallest pack size available for each drug. For example, the smallest pack size available for eribulin is 0.88mg and so the dose adjustment limit for eribulin is 0.08mg. A patient receiving treatment with eribulin who requires a dose of 1.85mg will receive a dose of 1.76mg (two 0.88mg packs) with no wastage. A patient whose required eribulin dose is 1.86mg will receive their full dose from three 0.88mg packs and 0.78mg is wasted.

5.3.6 Perspective, time horizon and discounting

The company states that the cost effectiveness analysis is undertaken from the perspective of the NHS in England and Wales. The analysis excludes patients' out-of-pocket expenses, carers' costs, lost productivity derived costs and PPS costs. Medical costs are included in stable disease and following disease progression. The time horizon in the base case is 5 years, with 10- and 20-year time horizons included as scenario analyses. Costs and benefits are discounted at a rate of 3.5% per annum.

5.3.7 Treatment effectiveness and extrapolation

The primary data source for the economic model is patient-level data from Study 301 which included patients with HER2-negative LABC/MBC whose disease has progressed after one chemotherapy regimen only. The data from this trial were almost fully mature, with only 13.8% of the Subgroup 1 population in either arm still alive at the time of the OS data-cut for the ITT population (March 2012). Given the maturity of the available survival data, the company was able to use the K-M data from Study 301 directly to model OS for both eribulin and capecitabine in the base case analysis using a 5-year time horizon.

For the 10- and 20-year time horizon scenario analyses, the company projected OS beyond the available K-M data from Study 301 by appending an exponential curve to the K-M data at 5 years. The company also investigated using a Weibull curve to project beyond 5 years, but concluded (as a result of visual inspection) that an exponential extrapolation was more appropriate.

5.3.8 Health-related quality of life

HRQoL data were collected as part of Study 301 and are discussed in Section 0 of this ERG report. The ERG notes that the HRQoL data is reported for the overall trial population of patients in Study 301, including those receiving eribulin as a first-line therapy and third-line therapy and not specifically for the Subgroup 1 population. HRQoL was assessed in Study 301 using the EORTC QLQ-C30 questionnaire and mapped to EuroQol-5 dimension (EQ-5D) derived utility scores using a published regression algorithm.[41] The EQ-5D utilities were constructed using the original UK tariff.[42]

The mapped utility values from patients treated with eribulin and treated with capecitabine in Study 301 are used to represent the equivalent health states in this analysis. The 'baseline' and 'tumour response' values for eribulin and capecitabine groups were adjusted in order to take into account differing rates of tumour response and AEs (see Table 13).

Table 13 Health state utility values

Health state	Eribulin	Capecitabine
Baseline	0.704	0.691
Tumour response	0.780	0.783
Incremental utility of response	0.076	0.092
Tumour response rate	11.0%	11.5%
Disutility of AEs	-0.0071	-0.0042
Stable disease	0.705	0.697
Progressive disease	0.679	0.679

AEs=adverse events
Source: CS, Table 56

A linear mixed-effects model was used to predict the impact of specific AEs on utility scores from the EORTC QLQ-C30 data collected during Study 301 (see Table 14). Only serious AEs (≥ Grade 3 with a prevalence ≥2%) are included within the model.

The estimated disutility value of each AE is then multiplied by the prevalence of each AE over the entire treatment duration and is used to estimate a monthly AE rate for each arm of the trial. This value is then used to calculate an overall disutility for eribulin and capecitabine (see Table 13). Alopecia, peripheral neuropathy and hand foot syndrome are not part of the EORTC QLQ-C30 questionnaire and therefore these utility values should be interpreted with caution.

Table 14 Adverse event disutility values

Health state	Disutility
Anaemia	-0.010
Nausea	-0.021
Neutropenia	-0.007
Febrile neutropenia	-0.012
Alopecia (all-Grade)	0.000
Leukopenia	-0.003
Diarrhoea	-0.006
Asthenia/fatigue	-0.029
Peripheral neuropathy	-0.014
Dyspnoea	-0.027
Palmar-Plantar Erythro-Dysaesthesia Syndrome	0.000

Source: CS, Table 55

The rates of AEs used by the company to calculate costs and effects differ. For utilities, Grade ≥3 AEs with prevalence greater than 2% are included, with the addition of alopecia, in line with feedback to the company from the ERG during TA250. For costs, an additional criterion of 'AEs that require treatment or hospitalisation' is also applied.

5.3.9 Adverse events

The company assumes there is only one episode of any single AE for each affected patient; this could lead to a large underestimation of the true AE costs. No further information on the duration or the severity of the AEs included in the model is included in the CS. The costs of AEs are detailed in Table 15.

Table 15 Adverse event costs

	Cost per episode (£)	HRG code	Description
Anaemia	516.55	SA04K	Iron deficiency anaemia with CC Score 2 to 5 (non-elective short stay)
Nausea	399.42	JA12L	Malignant breast disorders without Interventions, with CC Score 0 to1 (non-elective short stay)
Neutropenia	127.70	XD25Z	Neutropenia drugs band 1
Febrile neutropenia†	6,060.00	PA45Z (2012-2013)	Febrile neutropenia with malignancy
Alopecia (all-Grade)	0.00		Assumption - no cost
Leucopenia	127.70	XD25Z	Neutropenia drugs band 1
Diarrhoea	399.42	JA12L	Malignant breast disorders without Interventions, with CC Score 0 to1 (non-elective short stay)
Asthenia/fatigue	38.00	N/A	1hour community nurse visit per day for duration of adverse event
Peripheral neuropathy†	146.33	AB05Z (2013-2014)	Procedures in outpatient Intermediate pain procedures
Dyspnoea	490.00	DZ20E	Pulmonary oedema without Interventions, with CC Score 6+
Palmar-Plantar Erythro-Dysaesthesia Syndrome	429.65	JD07J	Skin Disorders without Intervention, with CC Score 2 to 5 (non-elective inpatient short stay)

CC=with complications; HRG=Healthcare Resource Group
†Inflated to 2014-2015 using PSSRU 2015,[43] The hospital & community health services (HCHS) index for 2014, Table 16.3 (Pay + prices)
Source: CS, Table 66

5.3.10 Resources and costs

Drug costs

The price of eribulin used in the model is the approved PAS price. The costs used for the secondary chemotherapy treatments are based on the proportions of each of the individual treatment options used during Study 305 (Table 11). Drug acquisition costs are presented in Table 16.

Table 16 Drug acquisition costs per pack/vial

Drug	Tablet dose/ vial concentration	Pack size/ vial volume	Cost per vial/pack	Source
Eribulin	Solution vial	2ml (0.88mg)	[redacted]	CS
		3ml (1.32mg)	[redacted]	
Vinorelbine (oral)	Soft capsules	10 capsules x 20mg	£439.80	MIMS[44]
		10 capsules x 30mg	£659.80	
		10 capsules x 80mg	£1,759.20	
Vinorelbine (IV)	Solution vial	10mg	£5.04	eMIT[45]
		50mg	£18.24	
Capecitabine	Tablets	60 tablets x 150mg	£7.73	eMIT[45]
		120 tablets x 500mg	£29.59	
Gemcitabine	Powder vial	200mg	£3.99	eMIT[45]
		1000mg	£30.89	
		2000mg	£21.39	
Docetaxel	Solution vial	20mg	£4.92	eMIT[45]
		80mg	£12.47	
		160mg	£34.83	
Paclitaxel	Solution vial	30mg	£3.41	eMIT[45]
		100mg	£8.50	
		150mg	£11.50	
		300mg	£21.48	
Doxorubicin	Solution vial	10mg	£1.53	eMIT[45]
		50mg	£4.04	
		200mg	£20.30	

IV=intravenous; eMIT=electronic Medicines Information Tool; CS=company submission
Source: CS, Table 69

Administration costs

Administration costs for eribulin and each of the treatment options are shown in Table 17. Paclitaxel is considered to be a complex chemotherapy due to the long infusion time associated with this treatment.

All chemotherapy is considered part of ongoing therapy, eliminating the need for separate initial and subsequent Healthcare Resource Group (HRG) codes.

Table 17 Cost of administration

Treatment	Type of administration	Currency code	Cost per administration	Source
Capecitabine & oral vinorelbine	Deliver exclusively oral chemotherapy	SB11Z	£171.10	NHS Reference Costs 2014/15[46]
Eribulin, gemcitabine, docetaxel & doxorubicin	Deliver simple parenteral chemotherapy at first attendance	SB12Z	£239.12	NHS Reference Costs 2014/15[46]
Paclitaxel	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	SB14Z	£389.41	NHS Reference Costs 2014/15[46]

Source: CS, adapted from Table 63

Direct medical costs

The costs of monitoring patients receiving eribulin and chemotherapy and the cost of care at the end of life are provided in Table 18. Supportive palliative care costs are assumed to be necessary in the final 6 months of life. End of life costs are resource intensive and attributable to the 2-week period prior to death. The total cost is weighted according to the proportion of people likely to spend this 2-week period in a hospital (40%), a hospice (10%) or at home (50%).

Computed tomography scans and community nurse home visits are not assumed to be necessary for all patients.

Table 18 Direct medical costs

Type of cost	Health state	Cost	Usage	Source
Stable and progressive disease costs				
Medical oncologist – follow-up	Stable and progressive disease	£158.54		NHS Reference Costs 2014/15[46]
GP contact		£44.00		PSSRU 2015[43]
CT scan		£92.03	33% usage assumed	NHS Reference Costs 2014/15[46]
Supportive palliative care costs				
Medical oncologist – follow-up	Progressive disease (6 markov cycles prior to transitioning to "Dead" health state)	£158.54		NHS Reference Costs 2014/15[46]
GP home visit		£44.00		PSSRU 2015[43]
Clinical nurse specialist		£88.00		
Community nurse home visit		£58.00	67% usage assumed	
End of life costs				
Hospital/medical institution	Progressive disease (0.5 markov cycles prior to transitioning to "Dead" health state)	£5135.25*	Assumed to apply to 40% of patients	NICE Breast Cancer Guidance (2009), Marie Curie report on End of Life Costs[a]
Hospice		£6402.15*	Assumed to apply to 10% of patients	
At home (with community support)		£2649.47*	Assumed to apply to 50% of patients	

Source: CS, adapted from Table 64
*Inflated to 2014-2015 using PSSRU 2015,[43] The Hospital & Community Health Services (HCHS) Index for 2014, Table 16.3 (Pay + prices); [a] Actual source not stated in CS

5.3.11 Cost effectiveness results

Total costs, life years gained (LYG), QALYs and incremental costs per QALY gained for the cost effectiveness comparison of treatment with eribulin versus capecitabine are shown in Table 19. In the base case, eribulin generates more benefits than capecitabine [redacted] LYG and +[redacted] QALYs) at an increased cost of [redacted]. The company base case incremental cost effectiveness ratio (ICER) for eribulin versus capecitabine is £36,244 per QALY gained.

Table 19 Base case cost effectiveness results

	Total			Incremental			ICER per QALY gained
Technologies	**Costs**	**LYG**	**QALYs**	**Costs**	**LYG**	**QALYs**	
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,244
Capecitabine	£11,586	[redacted]	[redacted]				

LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, Table 71

A summary of the predicted drug, drug administration and direct medical costs is presented in Table 20. Approximately three-quarters of the difference in costs between the intervention and comparator technologies is due to differences in the cost of the primary therapy (eribulin or capecitabine).

Table 20 Summary of predicted resource use by category of cost

Item	Therapy		Increment	Absolute increment (£)	Absolute increment (%)
	Eribulin	**Capecitabine**			
Drug and administration costs					
Primary therapy	[redacted]	£137	[redacted]	[redacted]	70.51
Secondary therapy (TPC)	[redacted]	£157	[redacted]	[redacted]	0.06
Administration	[redacted]	£2,873	[redacted]	[redacted]	18.84
Direct medical costs					
Medical	[redacted]	£2,701	[redacted]	[redacted]	11.25
Palliative care	[redacted]	£1,581	[redacted]	[redacted]	0.07
End of life	[redacted]	£3,587	[redacted]	[redacted]	2.59
Adverse events	[redacted]	£550	[redacted]	[redacted]	2.01
Total costs	[redacted]	**£11,586**	[redacted]	[redacted]	**100.00**

TPC=treatment of physician's choice
Source: CS, Table 77

5.3.12 Sensitivity analyses

Deterministic sensitivity analyses

Cost effectiveness results from nine different scenarios are presented in the CS and summarised in Table 21. These results are also displayed in a Tornado diagram (see Figure 2). The resultant ICERs range from £32,095 to £47,148 per QALY gained, i.e. ranging from £4,149 less than the base case to £10,904 greater than the base case.

Table 21 Results of deterministic sensitivity analysis

Scenario	Parameter	ICER per QALY gained	
		Lower value	Upper value
Base case			£36,244
1	Benefits discount rate (0% and 6%)	£33,499	£38,232
2	Costs discount rate (0% and 6%)	£35,583	£37,255
3	Costs and benefits discount rate (0% and 6%)	£34,433	£37,535
4	Eribulin price (±20%)	£32,095	£40,394
5	Comparator price (±20%)	£36,132	£36,356
6	Administration costs (±20%)	£34,879	£37,610
7	Direct healthcare costs (±20%)	£35,622	£36,866
8	Prevalence of AEs (±20%)	£36,098	£36,390
9	Progressive disease utility (HRG costs of AEs [±20%])	£35,091	£47,148

AE=adverse event; HRG=Healthcare Resource Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, p191 and Table 81

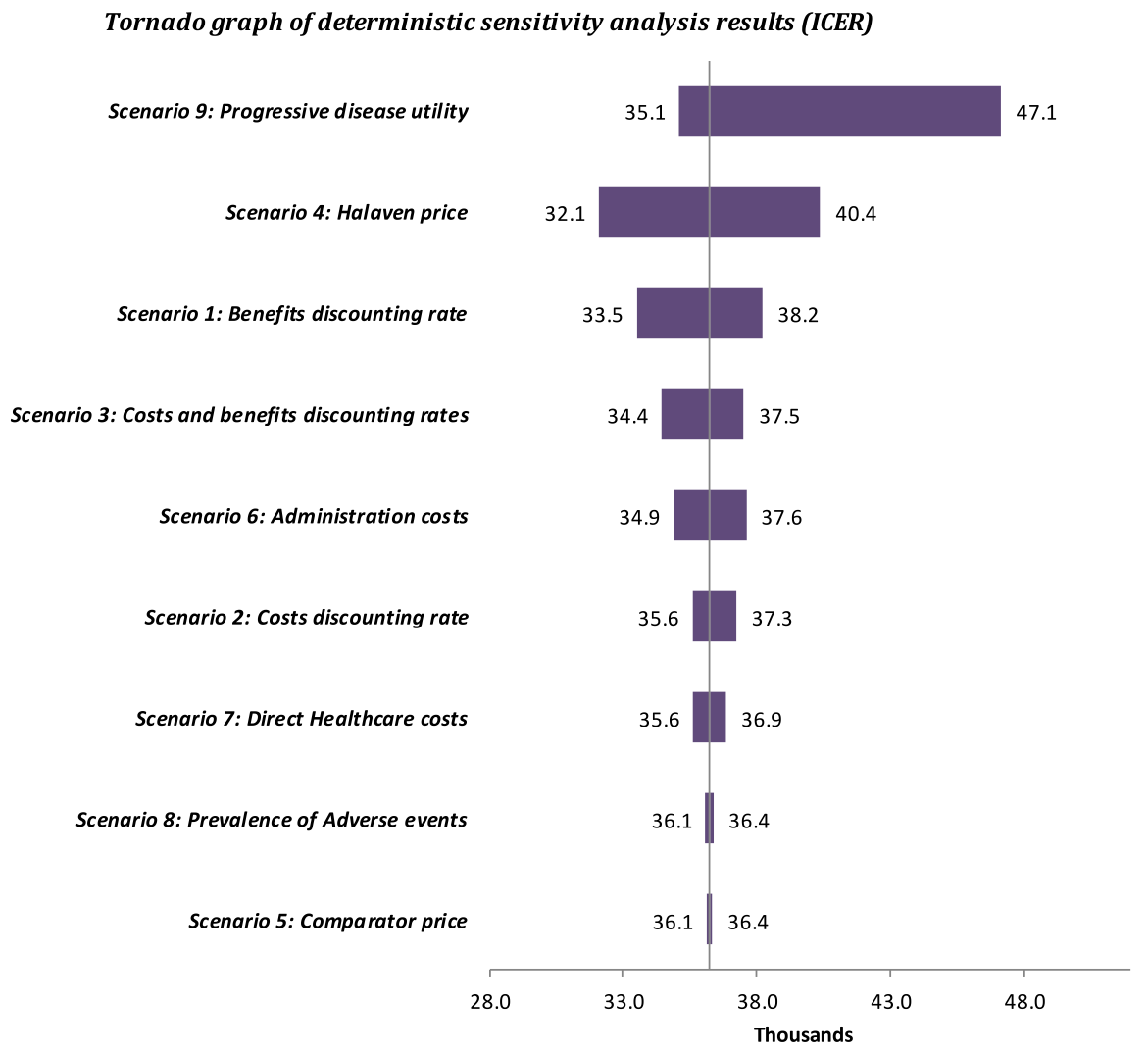


Figure 2 Deterministic sensitivity analysis results displayed in a tornado diagram

Source: CS, Figure 47

Probabilistic sensitivity analyses

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters (utility [baseline, tumour response and disease progression]), primary and secondary therapy drug costs, and survival [stable disease, progressive disease and end of life]). The cost effectiveness plane and the cost effectiveness acceptability curves for the company's base case for the Subgroup 1 population is shown in Figure 3 and Figure 4 respectively. Results from the company's PSA show that, for the Subgroup 1 population, for the comparison of eribulin versus capecitabine, the ICERs per QALY gained range from £15,681 to £531,000. Results also show that, for this treatment comparison, there is a 20% probability of treatment with eribulin being cost effective at a threshold of £30,000 per QALY gained and a 69% probability of eribulin being cost effective at a threshold of £50,000 per QALY gained.

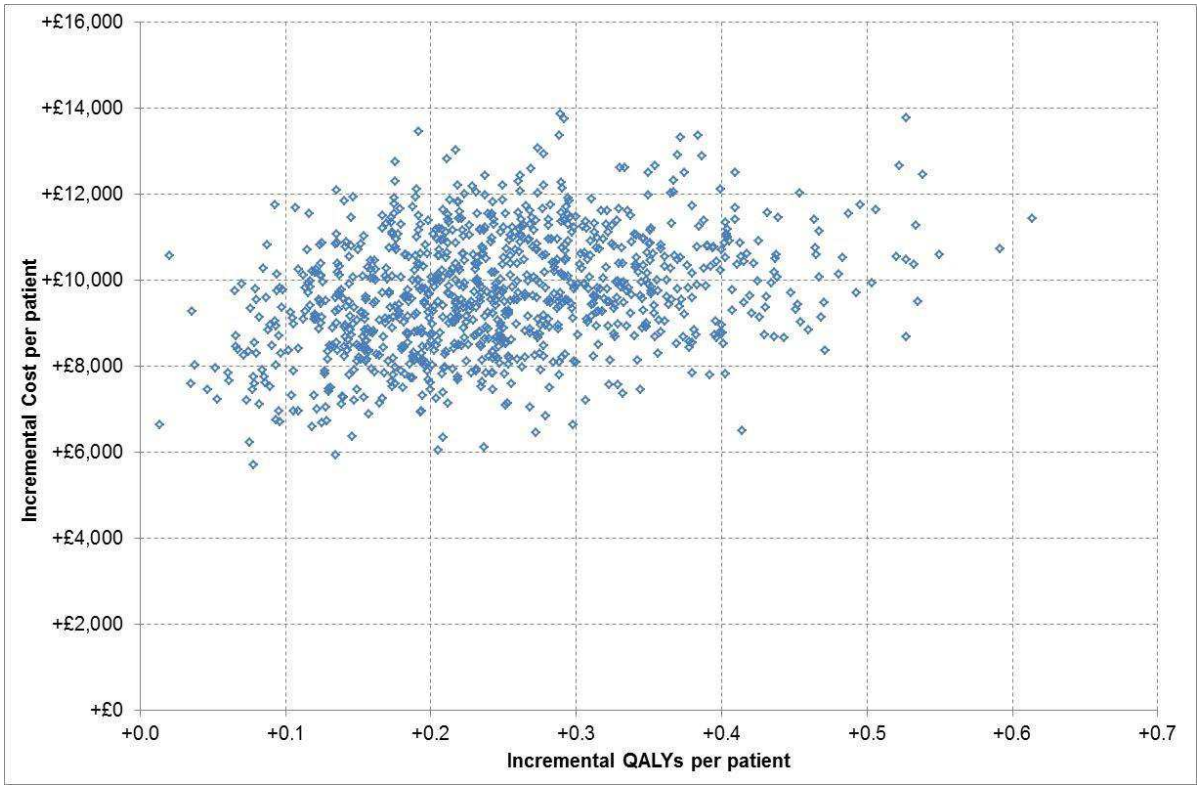


Figure 3 Cost effectiveness plane (Subgroup1)

Source: Company model

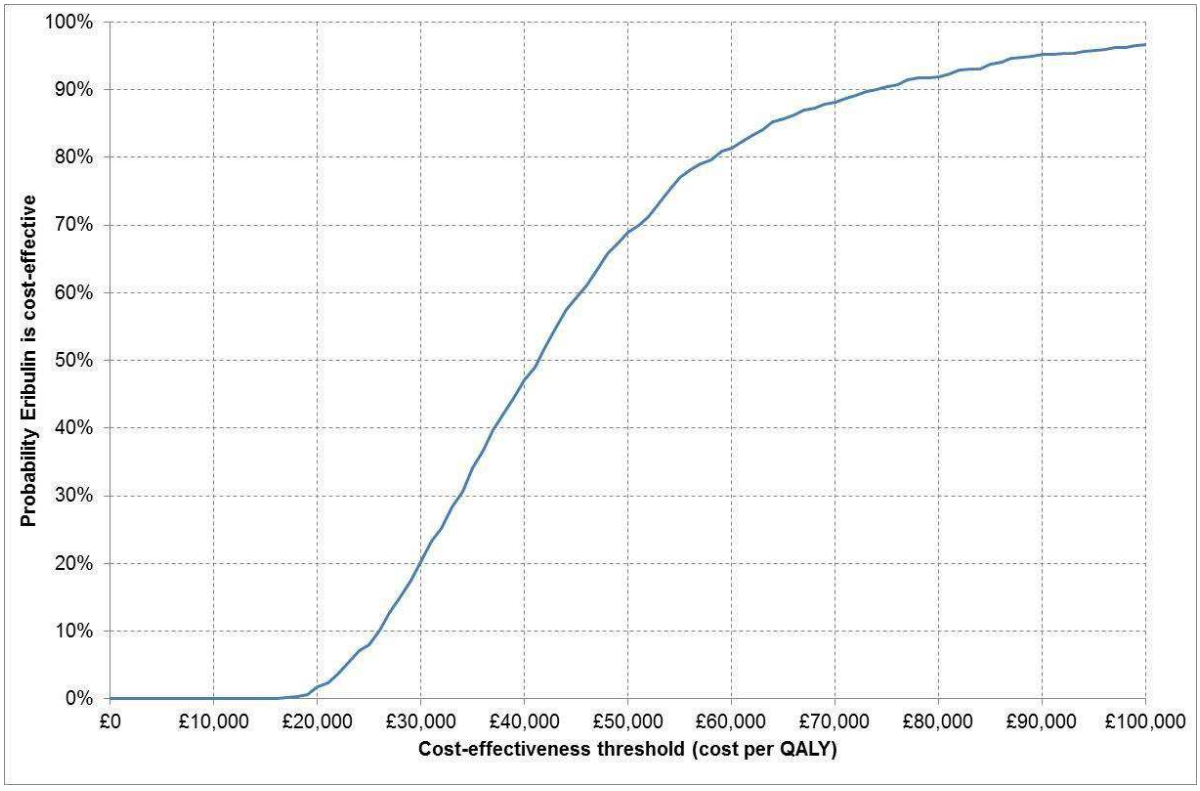


Figure 4 Cost effectiveness acceptability curve (Subgroup 1)

Source: Company model

5.3.13 Scenario analyses

The company carried out six scenario analyses. Results from these analyses are presented in Table 22. Only extending the treatment duration to 12 months resulted in an increase in the ICER per QALY gained (a 5% increase in the base case result). All of the other scenarios lowered the size of the base case ICER per QALY gained, with the biggest effect occurring when considering a time horizon of 20 years (an 18% reduction in the size of the ICER per QALY gained).

Table 22 Scenario analysis results

Scenario	Incremental			ICER per QALY gained
	LYG	QALY	Cost	
Base case	0.36	0.24	£8,875	£36,244
Maximum treatment duration threshold of 12 months	0.36	0.24	£9,348	£38,175
Excluding wastage	0.36	0.24	£8,081	£33,000
Mix of capecitabine and vinorelbine as comparator	0.36	0.24	£8,241	£33,654
Prevalence of AEs Grade ≥3	0.36	0.24	£8,869	£36,221
Time horizon 10 years	0.45	0.31	£9,346	£30,217
Time horizon 20 years	0.46	0.32	£9,399	£29,743

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life year
Source: CS, Table 84

5.3.14 Model validation and face validity check

The company took a number of steps to try to ensure the validity of the extrapolations and parameter values employed in their model:

- Trial survival data were used directly in the base case (5-year time horizon) analysis. To generate results for the 10-year and 20-year time horizon scenarios, the company employed the Tremblay et al[38] decision making criteria (which are based on the NICE Decision Support Unit document on survival extrapolations[47]) to select approaches to extrapolate the available trial survival data
- Costs were primarily based on the NICE Advanced Breast Cancer guidelines[11] and NHS Reference Costs (2014 to 2015)[46]
- Utility and disutility values used in the model were kept as conservative as possible
- AE costs were based on a HRG/Diagnosis-related group (DRG) approach
- Grade ≥3 AEs with a prevalence of greater than 2% were included in the analyses to ensure the inclusion of all important AEs and to facilitate consistency with the approach taken by the company to estimate disutilities.

The company's internal health economics and outcome research experts, as well as an external health economist, carried out quality control. An expert from the University of Glasgow validated the company's survival extrapolations.

Table 23 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	[redacted]
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Not always	Several errors were identified (see Section 5.4)
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?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	Deterministic sensitivity analysis was reported, but the PSA lacked the facility to include correlated parameters
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

ERG=Evidence Review Group

5.4 Detailed critique of the company's economic model

5.4.1 Design structure and implementation of the company model

The decision model submitted by the company is designed as a partitioned survival model (though some features are occasionally described as though it were a Markov model). The model is implemented as a Microsoft Excel workbook. It has been structured in an inconsistent manner, which increases the complexity of the logic and provides scope for error. The model features individual monthly cycles at the end of which patient status, resource use and costs are updated. However, all of the treatments included in the model are prescribed on either a weekly or 3-weekly basis. For accuracy, instead of monthly cycles, it would have been preferable for the model to employ weekly cycles although 3-weekly cycles would also have been a reasonable alternative. In addition, in some parts of the model, time conversions are based on 365 days per year, but elsewhere 365.25 days is used (including leap years). This difference is small but the effects can accumulate over a lifetime horizon.

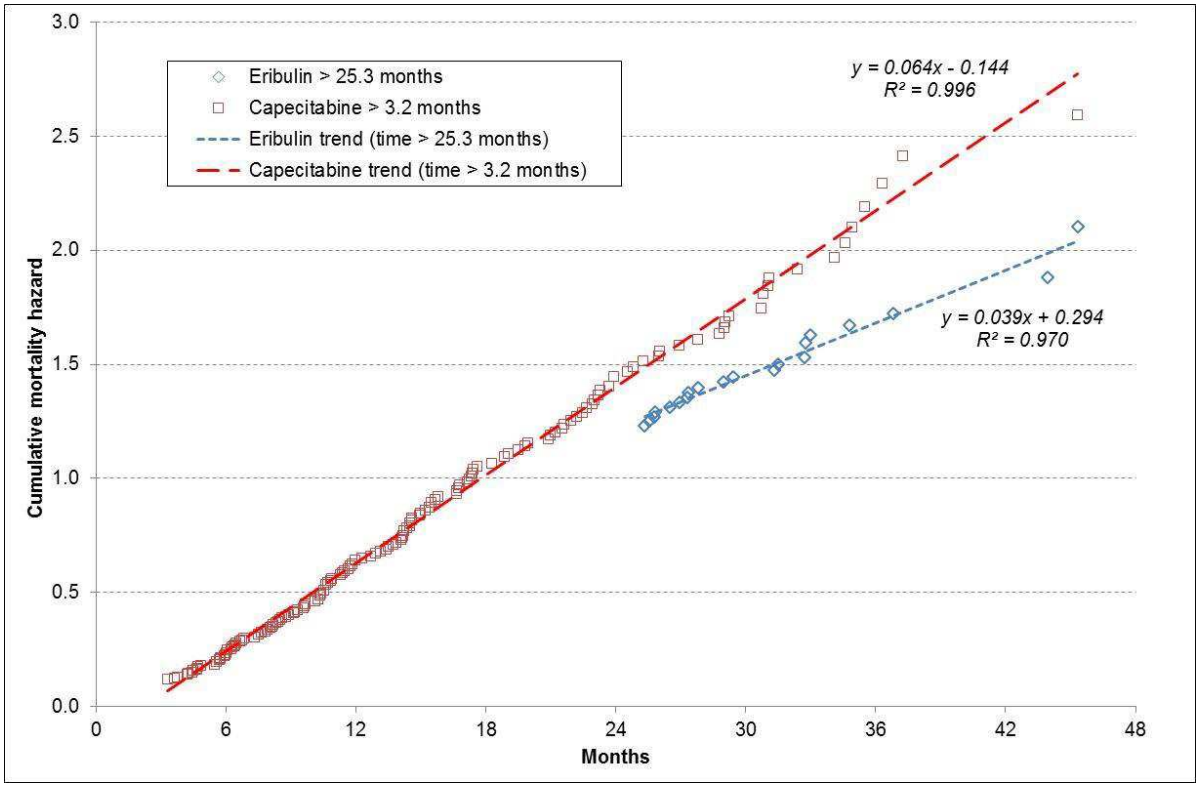
5.4.2 Patient survival and disease progression

The ERG submitted a clarification request for detailed K-M analysis results for OS, PFS, post-progression survival (PPS) and time to treatment discontinuation (TTD) for patients in the Subgroup 1 population of Study 301, and the company provided these data.

Overall survival

The OS K-M data from the Subgroup 1 population indicate that, for patients in both the eribulin and capecitabine arms, the trial data extend to about 4 years and are almost fully mature.

To create time horizon scenarios, the company calibrated exponential projective functions to the entire OS data sets from each trial arm and applied the results to both arms from month 60 onwards. The ERG has adopted a different approach to projecting OS, namely examining the trends in cumulative hazard plots of the trial data and identifying the time point in each trial arm where a long-term exponential trend becomes established (i.e. where a straight line trend is evident). This occurs after 25.3 months in the eribulin arm and after 3.2 months in the capecitabine arm (Figure 5). The ERG then applied the calibrated trend lines in place of the trial K-M data at the time at which the trend line most closely replicated the trial data (month 30 for eribulin and month 35 for capecitabine) to extrapolate OS to 20 years. This indicates a mean estimated OS of 23.72 months for patients treated with eribulin, and 17.78 months for patients receiving capecitabine therapy, a net gain of 5.94 months per patient attributable to eribulin.



NB: One data point in the eribulin arm which occurred more than 12 months later was excluded from trend fitting due to a wide confidence interval and potential bias from multiple prior censoring

Figure 5 Cumulative mortality hazard long-term trends in the Subgroup 1 population data from Study 301

Progression-free survival

Examination of PFS trial data (Figure 6) suggests a close correspondence between the timing of progressive disease developing regardless of the treatment used. To test this hypothesis, the ERG re-ran the K-M analysis. This showed that there is no statistically significant difference between the risks of suffering disease progression in the two trial arms (Log-Rank test p=0.131, Breslow test p=0.071, Tarone-Ware test p=0.106). Therefore, the ERG carried out a pooled analysis of PFS data from both trial arms (Figure 7). This identified a long-term constant hazard trend allowing PFS to be extrapolated to a 20-year horizon, with an estimated common mean PFS per patient of 7.65 months, contrasting with the advantage claimed by the company model of 0.57 months in favour of eribulin.

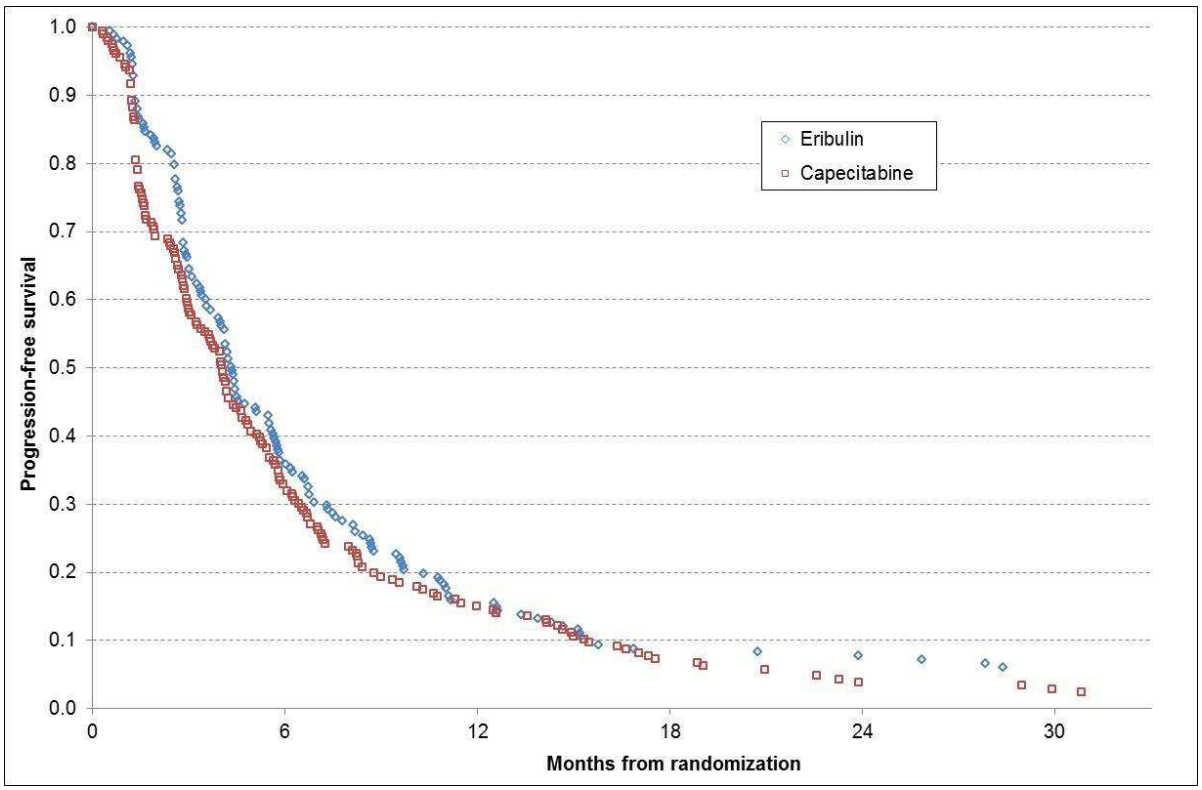
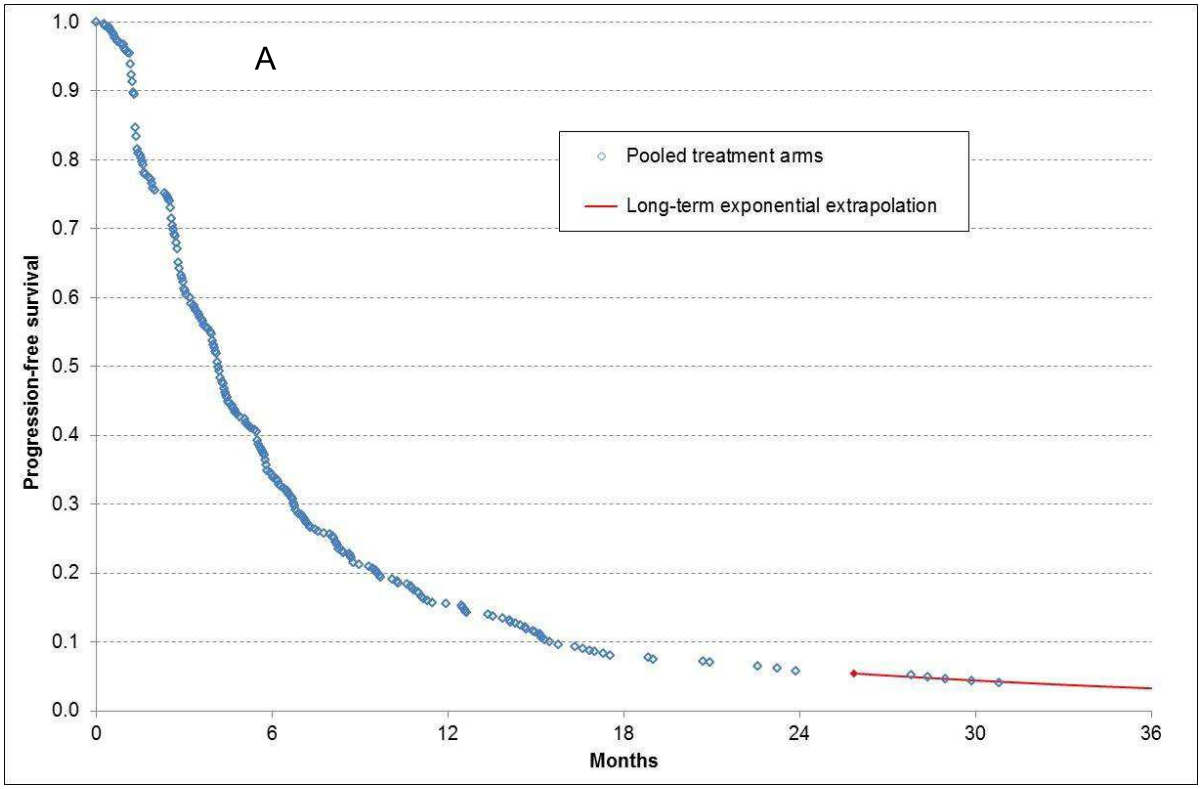


Figure 6 Progression-free survival Kaplan-Meier data from Subgroup 1 of Study 301



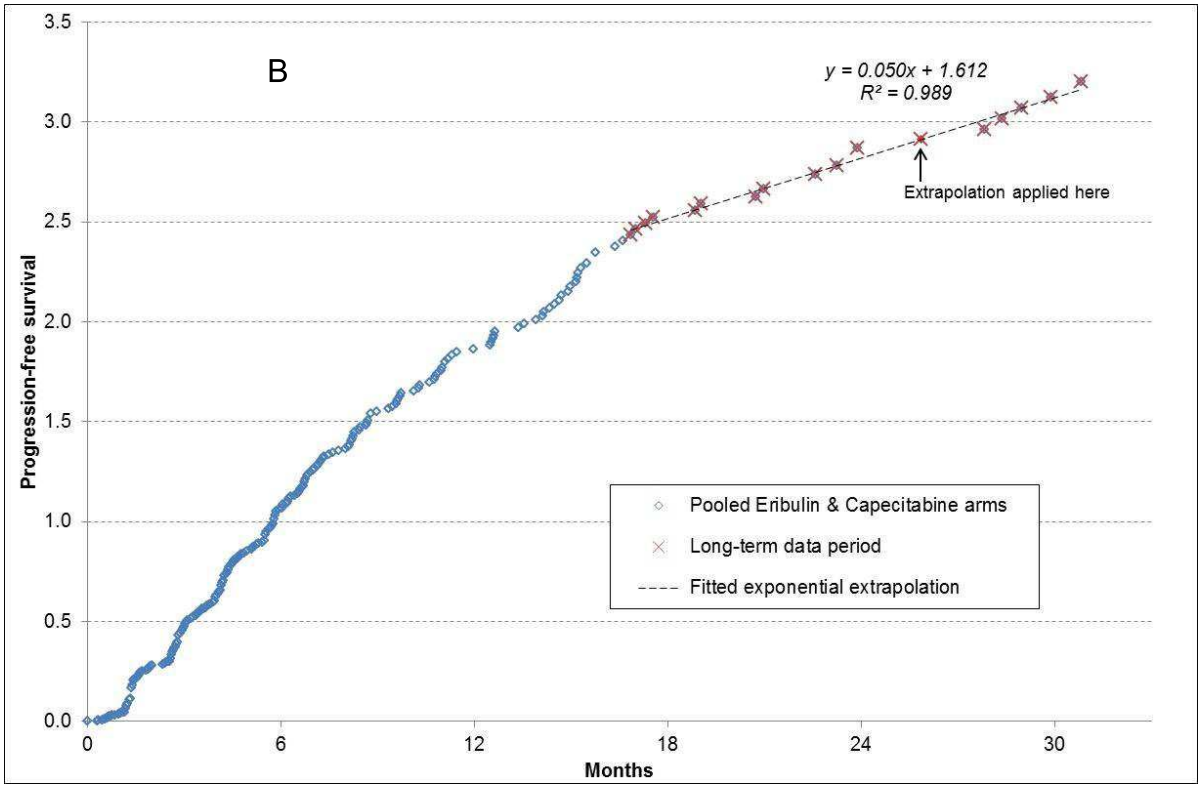


Figure 7 Pooled PFS Kaplan-Meier data from the Subgroup 1 population of Study 301, showing linear long-term hazard trend (B), and exponential extrapolation (A)

Post-progression survival

Analysis of PPS trial data (Figure 8) allowed parametric models to be fitted to both treatment arms. When these trends were extrapolated to the maximum 20 year horizon (from 26 months for eribulin and from 28 months for capecitabine), a small advantage of 1.92 months in favour of eribulin was estimated (14.44 versus 12.52 months). However, these estimates apply only to the proportion of randomised patients who experience a non-fatal progression episode, which differs between the treatment arms (81.3% versus 76.1%). When the greater proportion of patients surviving to enter the post-progression state is taken into account, the estimated PPS gain for patients treated with eribulin increases to 2.21 months.

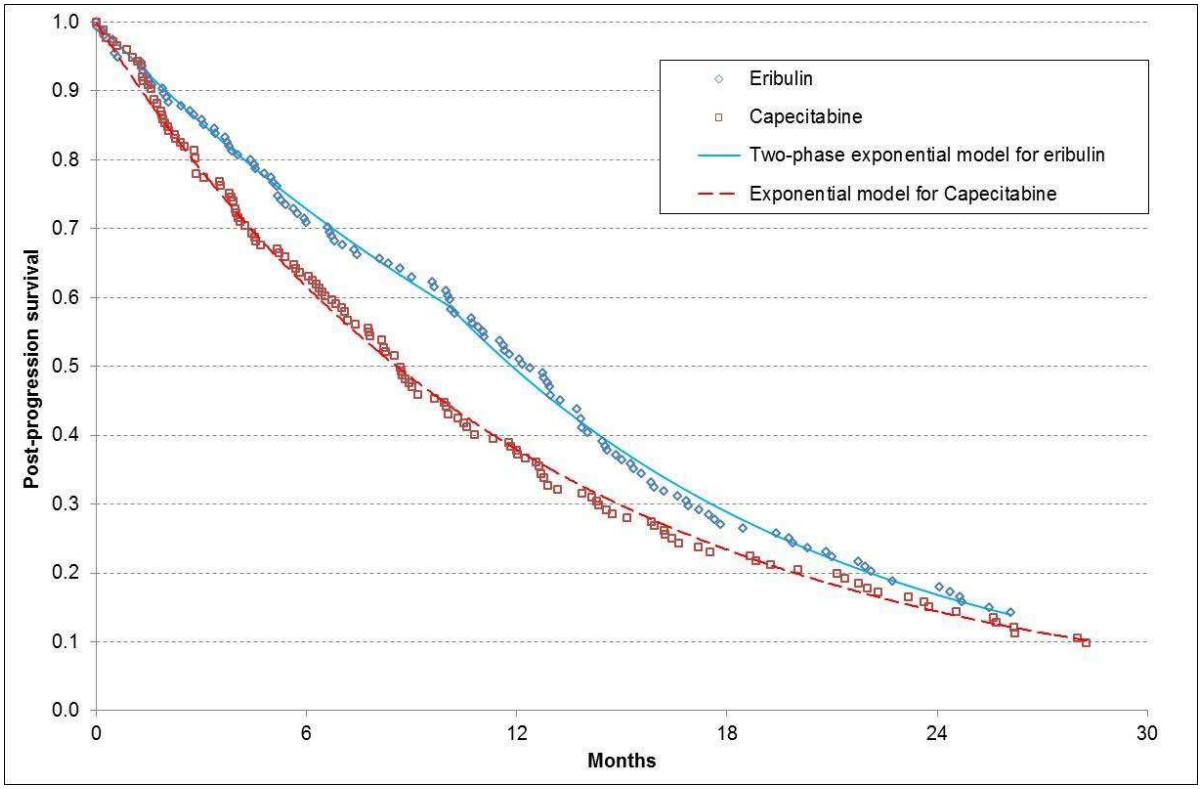


Figure 8 PPS Kaplan-Meier data from the Subgroup 1 population of Study 301, showing fitted trend lines: a simple exponential model for capecitabine and a 2-phase exponential model for eribulin

The ERG recognises that there is potential for bias in this analysis, where the characteristics of patients surviving a disease progression event are not well-balanced, or the pattern of right-censoring differs between treatment arms. It is not possible to assess the extent of these effects without access to patient-level data. However, the comparison between the estimated survival gain obtained as the difference between the estimates of mean OS and PFS, and that shown above is suggestive of the degree of uncertainty in estimates of additional survival benefit after disease progression.

Time to treatment discontinuation

In the decision model submitted by the company, treatment costs are estimated for all patients remaining in the pre-progression health state at the beginning of each monthly cycle. This is consistent with the trial protocol which specified treatment continues until disease progression. However, in any clinical trial there are some patients whose treatment is terminated early due to a variety of reasons, including treatment-related AEs. It is very likely that using estimated PFS as a measure of the average number of cycles of treatment will tend to overstate the cost of both treatments over time.

Figure 9 compares the proportions of randomised patients remaining on trial treatments over time with the corresponding pooled PFS estimates. Over the first 4 months of the trial period, all three data sets are very similar. Thereafter, a clear separation appears indicating a steady differential between PFS and the two on-treatment trends, indicating that using PFS as a proxy for estimating treatment costs introduces a systematic error, overstating costs in both trial arms. This can be mostly corrected by applying an adjustment multiplier to PFS for each treatment, estimated by the ERG to be 0.8708 for eribulin and 0.8471 for capecitabine.

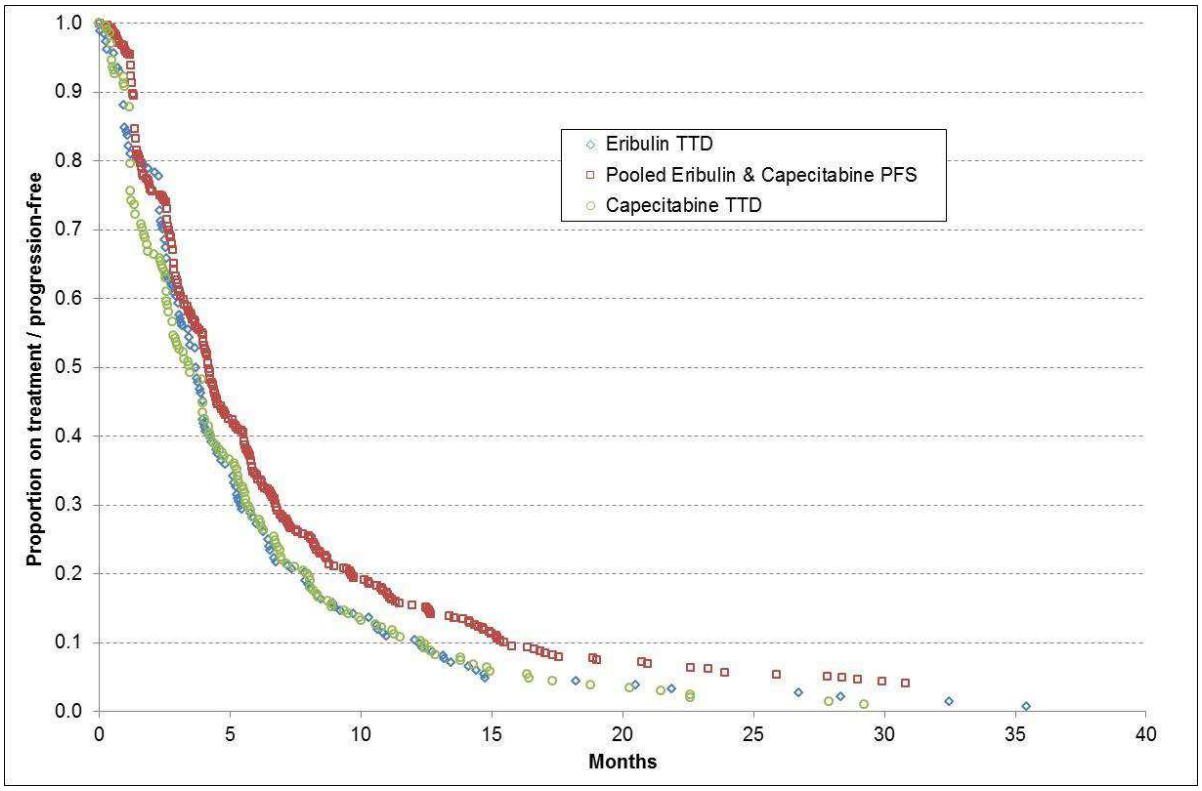


Figure 9 Comparison of PFS and TTD for estimating treatment costs

5.4.3 Logic error

An important logic error has been identified in the company model. This relates to the calculation of the cost of treatment with oral vinorelbine. This results in a very low estimate for the cost of this drug being applied to the comparator arm of the model and, consequently, an excessive incremental cost being used to estimate the ICER per QALY gained for eribulin versus capecitabine. Correcting this error has only a limited effect on the size of the estimated ICER, as only a small number of patients will receive oral vinorelbine as a post-progression treatment.

5.4.4 Acquisition cost of chemotherapy

The company has estimated the cost of chemotherapy drugs (capecitabine and others used in the post-progression period) dosed in terms of BSA using UK BSA estimates from published survey data.[48] However, the company modellers have confused standard error and standard deviation when calculating the costs of chemotherapy doses according to BSA. The standard error is a measure of the uncertainty in the estimated mean (average) BSA across the whole population, and does not represent the much larger variation in BSA across all individual patients. When dosing calculations are carried out using the distribution of BSA in individual patients (using the standard deviation) the range of required doses and costs is much greater, resulting in greater scope for drug wastage and consequently higher overall volumes and costs of drugs used.

In addition, no account has been taken of the therapeutic intent of the treatments included in the published survey data.[48] This information is included in the full data set, available as a download from the journal web-site of the published paper.[49] The ERG has selected only survey breast cancer patients whose treatment intent is not listed as adjuvant, neo-adjuvant or palliative, as the closest survey subset to the patients treated in Study 301. This yields a slightly higher mean BSA (1.7448) and a standard deviation of 0.1785 (standard error 0.00924) than is used by the company. All relevant chemotherapy treatment costs have been re-estimated by the ERG using updated NHS prices and compared with those used in the company model (Table 24). The unit cost per dose of chemotherapy has been substantially underestimated for eribulin, oral vinorelbine and capecitabine, with smaller differences for all other agents. Unfortunately, it has not been possible for the ERG to resolve the model error for oral vinorelbine within the time available, and figures for this treatment are not included in Table 24. However, this treatment is only relevant to costing subsequent treatments in the post-progression period, and represents only 18% of such treatments.

Table 24 Unit costs of chemotherapy drug acquisition, comparing ERG estimates to company model parameter values (including wastage)

Treatment	Unit	Company model	ERG estimate	Difference (ERG vs company model)
Eribulin	Per dose	[redacted]	[redacted]	+£82.91 (+16.8%)
Vinorelbine (IV)	Per dose	£18.24	£17.85	-£0.39 (-2.1%)
Gemcitabine	Per dose	£21.39	£20.39	-£1.00 (-4.7%)
Docetaxel	Per dose	£34.83	£23.43	-£11.40 (-27.7%)
Paclitaxel	Per dose	£21.48	£30.16	+£8.68 (+40.4%)
Doxorubicin	Per dose	£11.14	£12.02	+£0.88 (+7.9%)
Capecitabine	Per cycle	£48.94	£35.00	+£13.94 (+39.8%)

ERG=Evidence Review Group; IV=intravenous

5.4.5 Dose intensity and time on treatment

The company model features a parameter to represent dose intensity as measured in the trial. It should be noted that this feature is not the same as the TTD adjustment described above to correct for using PFS as a proxy for the number of patients on treatment. It does not have any effect on the estimated cost of treatments, nor on the company base case ICER per QALY gained. The ERG has amended the company model to replace PFS by TTD estimates for patients continuing on treatment. This is a separate and additional correction to the dose intensity adjustment used in the company model. It is assumed that treatment with both eribulin and capecitabine ceases at 39 months.

5.4.6 Probabilistic sensitivity analysis

The company model includes a facility to carry out PSA. However, the model does not generate a probabilistic estimated ICER per QALY gained that can be compared with the deterministic ICER per QALY gained. The PSA in the company model cannot be considered to be a true PSA since it lacks any facility to incorporate uncertainty related to correlated parameter values, such as are present in the utility values estimated from Study 301 data, and the pre- and post-progression estimates based on regression coefficients. Moreover, drug cost estimates are only varied by a crude +/- 10% variation, an approach that is more akin to deterministic sensitivity analysis than PSA. As a result, the ERG does not consider that the PSA routines included in the company model provide any useful or reliable evidence as to the impact of parameter uncertainty.

5.4.7 Discounting

In the company model discounting of costs and outcomes is applied on a continuous basis, rather than annually in line with NHS budgeting and accounting years. This has the effect of increasing the incremental QALYs more than the incremental costs. Correcting this error has the effect of reducing the company base case deterministic ICER per QALY gained by approximately £133.

5.4.8 Health-related utility values

The company has applied a mapping algorithm, published by Crott and Briggs in 2010,[41] to estimate EQ-5D values from the EORTC-QLQ-C30 quality of life questionnaire administered to patients in Study 301. The algorithm was based on data made available from a historical clinical trial, which recruited patients from 1993-1996 (median follow-up 5.5 years) and compared two chemotherapy regimens. The published trial results[50] indicate that only untreated patients with locally advanced (but not metastatic) breast cancer and good performance status were recruited, and only neo-adjuvant treatments were administered. The contrast between Study 301 and the trial[50] upon which Crott and Briggs[41] based their utility mapping exercise must raise serious questions about the appropriateness of applying this reported algorithm to generate utility values for patients receiving chemotherapy after prior disease progression.

The alternative, previously considered by the ERG during TA250, is a utility value set published by Lloyd et al 2006[51] specifically for breast cancer patients receiving chemotherapy using the Standard Gamble methodology. The utility values estimated by this method for stable disease and patients responding to treatment are quite similar to the values used in the company model. However, a very large discrepancy is observed for patients in the progressive disease health state; 0.68 in the company model compared to 0.496 from the Lloyd et al[51] analysis. It is noted that the value used in the company model for patients with stable disease (but not responding to treatment) is very similar to the value used for patients with progressed disease (0.70 versus 0.68); the ERG considers this approach to be implausible.

The ERG has tested the effect of substituting the progressive disease utility value from the Lloyd et al publication[51] in place of the company's preferred estimate, and can confirm a resulting increase in the size of the estimated ICER of nearly £11,000 per QALY gained.

5.4.9 Subsequent lines of chemotherapy

The company model offers two options for the estimation of the cost of further lines of chemotherapy beyond treatment with eribulin or capecitabine, as third-line therapy for LABC/MBC:

- Limiting the number of cycles of therapy overall (in the base case to no more than eight cycles)
- "Treat to progression", which means that nobody who progresses alive whilst on eribulin or capecitabine incurs the costs associated with any subsequent chemotherapy (fourth, fifth, etc.,. lines of treatment).

Each of these approaches leads to anomalous results. The first option completely ignores an important component of differential costs – that patients who achieve a good response to third-line treatment will, on average, continue third-line therapy for a longer period than those with poor response, and may subsequently have a better performance status leading to a greater probability of proceeding to further lines of treatment. The second option effectively caps the cost of all subsequent treatments, which results in a bias in favour of eribulin since the ERG's analysis of PPS data shows that eribulin treatment is associated with additional PPS time and therefore leads to more use of additional lines of treatment with their associated costs. It should be noted that these options relate only to the estimated cost of subsequent treatments, and have no effect on estimated survival gain or additional QALYs.

The ERG has developed a modification of the company model to provide a third option. This involves two changes:

1) The company cap on the maximum number of cycles (months) of further treatment is effectively removed by resetting the model cycle limit from eight to 600.
2) The company references a study by Kantar Health[18] which shows the proportion of breast cancer patients progressing between lines of therapy from first to fifth lines. The ERG has calculated the proportion of patients suffering a non-fatal progression event that go on to receive an extra course of treatment; this ranges from 54% to 66%. The ERG has, therefore, amended the company model to estimate the costs of such care for 60% of the patients still alive in the progressed health state each month.

Applying this modification results in an increase in the incremental cost per patient of £2,720 and an increase in the size of the deterministic ICER of about £11,000 per QALY gained.

Of note, the company model uses the same usage data for subsequent lines of therapy as that used for TA423, i.e. based on Study 305 (EMBRACE) for Subgroup 2. The estimated cost per patient of subsequent treatments is very small (£162 eribulin versus £157 capecitabine for the Subgroup 1 population), contributing less than 0.1% to the incremental cost per patient. The ERG considered that any differences in the mix of different types of subsequent treatments (e.g. applying the mix reported for Study 301) could not have any meaningful influence on the estimated ICER, and did not warrant further consideration.

5.4.10 Logic error in calculation of eribulin administration costs

The ERG has identified a logical anomaly that can result in doses of eribulin being given to patients after month 6 but with no corresponding administration cost being calculated. When this error is corrected, the incremental cost of treatment with eribulin versus capecitabine increases by £722, and the company's base case ICER increases by nearly £3,000 per QALY gained.

5.5 Impact on the ICER of additional ERG analyses

To address the points raised in Section 5, the ERG has made the following ten changes to the submitted company model (Table 25):

- use of ERG preferred PFS estimates (R1)
- use of ERG preferred OS estimates (R2)
- use of annual rather than continuous discounting (R3)
- use of TTD for costing treatments (R4)
- use of ERG revised unit cost of eribulin (R5)
- use of ERG revised unit costs of other drugs (R6)
- use of ERG alternative utility value for progressed disease (R7)
- use of ERG method for estimating subsequent therapy costs (R8)
- correction of logic error in calculating eribulin administration costs (R9)
- correction of error in calculating cost of oral vinorelbine (R10)

The three most influential ERG changes to the company model are: use of PFS K-M results (R1), the choice of utility value for the progressive disease health state (R7), and the method used to cost capecitabine and subsequent lines of treatment (R8).

Table 25 Cost effectiveness (eribulin versus capecitabine): ERG revisions to company base case

Model scenario ERG revision	Eribulin			Capecitabine			Incremental			ICER per QALY gained	ICER Change
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years		
A. Company base case	[redacted]	[redacted]	[redacted]	***£11,586***	***0.933***	***1.365***	[redacted]	[redacted]	[redacted]	***£36,244***	**-**
R1) ERG analysis of K-M PFS data	[redacted]	[redacted]	[redacted]	**£11,288**	**0.937**	1.365	[redacted]	[redacted]	[redacted]	**£50,866**	**+£14,621**
R2) ERG analysis of K-M OS data	[redacted]	[redacted]	[redacted]	**£11,724**	**0.923**	**1.350**	[redacted]	[redacted]	[redacted]	**£37,646**	**+£1,402**
R3) Annual discounting applied	[redacted]	[redacted]	[redacted]	**£11,758**	**0.947**	**1.386**	[redacted]	[redacted]	[redacted]	**£36,111**	**-£133**
R4) Replace PFS with TTD for drug costing	[redacted]	[redacted]	[redacted]	**£11,731**	0.933	1.365	[redacted]	[redacted]	[redacted]	**£39,286**	**+£3,041**
R5) ERG eribulin estimated unit costs	[redacted]	[redacted]	[redacted]	£11,586	0.933	1.365	[redacted]	[redacted]	[redacted]	**£40,630**	**+£4,386**
R6) ERG other drug estimated unit costs	[redacted]	[redacted]	[redacted]	**£11,640**	0.933	1.365	[redacted]	[redacted]	[redacted]	**£36,021**	**-£224**
R7) ERG preferred progression utility value	[redacted]	[redacted]	[redacted]	£11,586	**0.743**	1.365	[redacted]	[redacted]	[redacted]	**£47,148**	**+£10,904**
R8) ERG alternative method of costing capecitabine and subsequent lines of therapy	[redacted]	[redacted]	[redacted]	**£17,151**	0.933	1.365	[redacted]	[redacted]	[redacted]	**£47,354**	**+£11,109**
R9) Correct logic error on eribulin administration costs	[redacted]	[redacted]	[redacted]	£11,586	0.933	1.365	[redacted]	[redacted]	[redacted]	**£39,192**	**+£2,947**
R10) Correct error estimating oral vinorelbine costs	[redacted]	[redacted]	[redacted]	**£12,335**	0.933	1.365	[redacted]	[redacted]	[redacted]	**£36,341**	**+£97**
B. ERG revised base case A+ (R1 to R10)	[redacted]	[redacted]	[redacted]	**£17,393**	**0.794**	**1.370**	[redacted]	[redacted]	[redacted]	***£82,743***	***+£46,499***

Costs and QALYs discounted; life years undiscounted
ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation
Note: **Figures in bold** represent costs, QALYs and/or life years that change from the values in the base case as a result of the implemented revision

5.6 Conclusions of the cost effectiveness section

The ERG has considered carefully the design and implementation of the company's decision model and identified ten aspects requiring modification. Seven of these lead to important changes in the estimated cost effectiveness of eribulin versus capecitabine and are directly linked to the estimated relative effectiveness of eribulin in terms of survival outcomes (OS, PFS and PPS), the costs of the various treatments (including subsequent therapies following disease progression), and the appropriateness of the estimated health-related patient utility value in the post-progression health state.

The combined impact of the modifications implemented by the ERG is to increase substantially the estimated deterministic ICER to more than £83,000 per QALY gained. It is notable that applying the ERG's clinical effectiveness modifications together, or the ERG's drug costing changes together, each generate an estimated ICER greater than £50,000 per QALY gained, whilst the ERG's preferred post-progression utility value results in an ICER exceeding £47,000 per QALY gained. Thus, adopting ERG modification to any one of these key aspects of the submitted model is sufficient to lead to the estimation of high deterministic ICER per QALY gained values.

Unfortunately, the company's approach to programming a PSA facility within their model does not allow for the important effects of correlated model variables, and therefore cannot be relied upon to generate meaningful results.

6 END OF LIFE

For eribulin to be considered eligible for assessment as a NICE End of Life treatment, it is necessary that eligible patients should have a life expectancy of less than 2 years, and that the treatment is expected to provide additional survival of at least 3 months compared to the comparator.

The K-M analysis of the Subgroup 1 population of the Study 301 individual patient data allows both these criteria to be considered. The ERG's view is that:

- the mean OS of patients receiving capecitabine is probably less than 18 months based on the ERG estimate for patients in the capecitabine arm of the Subgroup 1 population

- the mean OS gain attributable to treatment with eribulin is subject to uncertainty, since the direct measure of OS in the Subgroup 1 population indicates a gain of 5.94 months but indirect estimation in the context of post-progression survival suggests less than 3 months (although possibly subject to bias).

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness

The population in the updated NICE scope (patients with LABC/MBC whose disease has progressed after only one prior chemotherapy regimen in the advanced setting) is a subgroup of the population for whom eribulin is indicated (patients with LABC/MBC whose disease has progressed after at least one prior chemotherapy regimen in the advanced setting. The company has only presented evidence for a subgroup of the NICE scope, Subgroup 1 defined as patients with HER2-negative LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Almost fully mature efficacy data from Study 301 (a good quality multi-centre, phase III, open-label, randomised parallel two-arm trial of 1102 patients) do not show any statistically significant differences in OS or PFS between eribulin and capecitabine when the overall trial population with LABC/MBC is treated. Similar results are observed for 573 patients who have received only one prior chemotherapy regimen for LABC/MBC. [redacted]

Evidence for patients with HER2-positive disease in the overall trial population (n=169) and the licensed population (n=131) does not suggest a statistically significant difference between patients treated with eribulin or capecitabine. It is unclear if this is because eribulin is less efficacious for patients at this stage of the treatment pathway or whether the subgroups of patients with HER2-positive disease are underpowered to detect a difference. Given eribulin is considered to be a viable treatment option for patients with HER2-positive disease later in the treatment pathway, the main area of uncertainty, therefore, relates to whether patients with HER2-positive disease could also benefit from treatment with eribulin after only one prior chemotherapy regimen for LABC/MBC.

The safety profile associated with eribulin differs to that of capecitabine: in Study 301, the incidences of neutropenia, leucopenia, pyrexia, peripheral sensory neuropathy and alopecia were all higher with eribulin than with capecitabine, whereas incidences of diarrhoea and palmar-plantar erythrodysaesthesia syndrome were lower. Dose-intensity was high for both eribulin and capecitabine, suggesting that both drugs appear to have manageable safety profiles.

No statistically significant or clinically meaningful difference in the pre-specified measure of HRQoL, GHS/QoL, was reported for the overall trial population of Study 301 or for the subgroup of patients with HER2-negative disease.

The patient population in Study 301 appears to be younger than patients seen in clinical practice in England. In addition, only a minority of patients were from Western Europe with no patients recruited from the UK. Nonetheless, based on other trial and baseline characteristics presented, the ERG considers the results of the trial are likely to be generalisable to clinical practice in England.

7.2 Cost effectiveness

In terms of cost effectiveness, the ERG considers that the company substantially underestimates the size of the most probable base case deterministic ICER per QALY gained for eribulin versus capecitabine in the Subgroup 1 population. Using the PAS price for eribulin, the company's base case ICER is £36,244 per QALY gained, which is £46,499 less than the ICER estimated by the ERG (£82,743 per QALY gained).

7.3 Implications for research

The analysis of the time-to-event data from Study 301 shows that eribulin provides no additional benefit compared to capecitabine prior to disease progression. However, there is evidence to suggest that there is a modest improvement in survival following disease progression that can be attributed to treatment with eribulin. Further research may be warranted to explore differences in the mode of action of the two treatments which could explain this unusual effect in this subgroup of patients suffering from LABC/MBC.

It is unclear if the apparent lack of benefit for patients with HER2-positive disease arises because eribulin is less efficacious for patients at this stage in the treatment pathway or whether the subgroups of patients with HER2-positive disease are underpowered to detect a difference. Further investigation of the efficacy of eribulin in patients with HER2-positive disease who have received one prior chemotherapy regimen and one or more chemotherapy regimens for LABC/MBC may therefore be warranted.

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9 APPENDICES

9.1 Additional tables for Study 301

Table 26 Assessment measures and statistical analysis methodology of Study 301 co-primary outcomes

Outcome and definition	Assessment Measures	Statistical analysis methodology
OS Defined as the time from the date of randomisation until date of death from any cause or the last date the subject was known to be alive	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	• OS was compared between the randomised treatment arms in the ITT population, using a two-sided log-rank test (stratified by HER2 status and geographical region) at a significance level of 0.04. • K-M survival curves were used to summarise OS, using 95% limits at selected time points. • K-M estimates of the median survival time, and first and third quartiles were presented with 95% CIs. • HR was computed together with the two-sided 95% CI using Cox regression model and was stratified according to the type of treatment received, HER2 status and geographical region. • An additional Cox regression model was fitted in which the HR was also adjusted for the number of prior chemotherapies for advanced or metastatic disease and time to progression after the last chemotherapy. • For participants 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
PFS Defined as the time from the date of randomisation to the date of recorded progression of the disease or the death of the subject from any cause, whichever occurred first	Tumour assessment was performed according to the RECIST methodology. Baseline tumour assessments were performed within 28 days 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 participants every second cycle (starting Cycle 2) between Days 15 and 21, or sooner if there was evidence 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. If subjects remained on study for more than 12 cycles after starting treatment, the assessments described above were performed every three cycles until disease progression. Bone scans were repeated every sixth cycle (starting Cycle 6) between Day 15 of the sixth cycle and Day 7 of the following cycle.	• 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 • K-M plots and the K-M estimates of the medians, and first and third quartiles were presented with the 95% CI for PFS • PFS was compared between the treatment arms using a two-sided 0.01 level stratified log-rank test • HR was computed together with the two-sided 95% CI using Cox regression model and was stratified according to the type of treatment received, HER2 status and geographical region • Participants who had not progressed on the data cut-off date or who were lost to follow-up, were censored at that date

Outcome and definition	Assessment Measures	Statistical analysis methodology
	Tumour responses were confirmed by a second assessment ≥ 4 weeks later. Participants with CR/PaR or SD* 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. Analyses were conducted based on the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data	

*Further details of tumour response assessment categories are provided in Table 10 and Table 11 of the CS
CI=confidence interval; CR=complete response; CT=computed tomography; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; ITT=intention=to-treat; K-M=Kaplan-Meier; MRI=magnetic resonance imaging; OS=overall survival; PaR=partial response; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumours; SD=stable disease
Source: CS, adapted from Table 9 and Table 13

Table 27 Patient disposition in Study 301

Reason for treatment discontinuation	Overall trial population				Subgroup 1			
	Eribulin		Capecitabine		Eribulin		Capecitabine	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised (ITT population)	554	(100.0)	548	(100.0)	186	(100.0)	206	(100.0)
Patients who did not meet entry criteria	4	(0.7)	1	(0.2)	1	(0.5)	1	(0.5)
Patients who withdrew – subject's decision	2	(0.4)	0	(0)	1	(0.5)	0	(0)
Patients who withdrew – withdrew consent	3	(0.5)	1	(0.2)	0	(0)	0	(0)
Patients who withdrew – other	1	(0.2)	0	(0)	0	(0)	0	(0)
Patient who received at least some study treatment (Safety population)	544	(98.2)	546	(99.6)	184	(98.9)	205	(99.5)
Progressive disease, n (%)	409	(73.8)	405	(73.9)	145	(78.0)	155	(75.2)
Clinical progression, n (%)	27	(4.9)	24	(4.4)	7	(3.8)	13	(6.3)
Adverse event, n (%)	45	(8.1)	59	(10.8)	15	(8.1)	19	(9.2)
Physician decision, n (%)	15	(2.7)	14	(2.6)	1	(0.5)	3	(1.5)
Withdrew consent	8	(1.4)	5	(0.9)	3	(1.6)	0	(0)
Death, n (%)	1	(0.2)	0	(0)	1	(0.5)	0	(0)
Other, n (%)	5	(0.9)	9	(1.6)	1	(0.5)	3	(1.5)
On treatment, n (%)	5	(0.9)	5	(0.9)	2	(1.1)	2	(1.0)

ITT=intention-to-treat
Source: CS, adapted from Table 17 and company response to ERG clarification question, A4

Table 28 Exposure to eribulin in Study 301 (Safety population)

	ITT Population		Subgroup 1	
	Eribulin (N=544)	**Capecitabine (N=546)**	**Eribulin (N=184)**	**Capecitabine (N=205)**
Duration of exposure, median days (min, max)[a]	125 (21 to 1372)	119 (21 to 1442)	126 (21 to 1183)	119 (21 to 994)
Number of cycles, n (%)				
1 to 2	118 (21.7%)	151 (27.7%)	37 (20.1%)	58 (28.3%)
3 to 4	120 (22.1%)	107 (19.6%)	37 (20.1%)	39 (19.0%)
5 to 6	107 (19.7%)	73 (13.4%)	38 (20.7%)	28 (13.7%)
>6	199 (36.6%)	215 (39.4%)	72 (39.1%)	80 (39.0%)
Range	1 to 65 cycles	1 to 61 cycles	1 to 53 cycles	1 to 42 cycles
Dose intensity, median mg/m^2/week (min, max)[b]	0.86 (0.4 to 1.0)	10524 (1694 to 12456)	0.88 (0.4 to 1.0)	10662 (5048 to 12161)
Relative dose intensity, % (min, max)[c]	92 (40 to 100)	90 (10 to 100)	94 (40 to 100)	91 (40 to 100)
Patients with dose interruption, n (%)	7 (1.3%)	NA	1 (0.5%)	NA

ITT=intention-to-treat; NA=Not available.
[a] For eribulin, duration of treatment = last cycle Day 1 – date of first dose + 21, if day 1 was last dose of last cycle. For capecitabine, duration of treatment = last cycle Day 1 – date of first dose + 21.
b Actual dose intensity (mg/m2/week) = total dose received during study / (duration of treatment in days/7).
c Relative dose intensity = actual dose intensity (mg/m^2/week) / Planned dose intensity. Planned dose intensity for eribulin = 1.4*2/3 = 0.933 (mg/m2/week). Planned dose intensity for capecitabine = 2500*14/3 = 11667 (mg/m2/week).
Source: adapted from company response to ERG clarification question, A5

9.2 ERG Revisions to company's model

All revisions are activated by a logic switch with 0 = unchanged, 1 (or any non-zero number) = apply ERG modification.

Logic switches are indicated by range variables Mod_*n* where n = 1 – 10

A menu of revisions/Mod numbers appears on the 'Results' worksheet together with summary results as used to transfer to the ERG report

.

ERG Results Table Row Title	Associated detail	Implementation instructions
R1. ERG PFS estimates (Binary switch Mod_1)	ERG survival estimates for PFS are included as a new columns H and J in worksheet 'ERG_survival'	In Sheet 'Appendix Partition' **Replace** formula in cell E8 by =IF(Mod_1=1,ERG_survival!H4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(E$5&E$7&$P$9&$P$8&$W$9,EXT_Key,0))) **Copy** formula in cell E8 to range E9:E248 **Replace** formula in cell F8 by =IF(Mod_1=1,ERG_survival!J4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(F$5&F$7&$P$9&$P$8&$W$9,EXT_Key,0))) **Copy** formula in cell F8 to range F9:F248
R2. ERG OS estimates (Binary switch Mod_2)	ERG survival estimates for OS are included as a new columns I and K in worksheet 'ERG_survival'	In Sheet 'Appendix Partition', **Replace** formula in cell G8 by =IF(Mod_2=1,ERG_survival!I4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(G$5&G$7&$P$9&$P$8&$W$7,EXT_Key,0))) **Copy** formula in cell G8 to range G9:G248 **Replace** formula in cell H8 by =IF(Mod_2=1,ERG_survival!K4,INDEX(EXT_data, MATCH($B8,EXT_Cycle,0), MATCH(H$5&H$7&$P$9&$P$8&$W$7,EXT_Key,0))) **Copy** formula in cell H8 to range H9:H248
R3. Discounting method (Binary switch Mod_3)	None	In Sheet 'Appendix PSA', **Replace** formula in cell C63 by =1/((1+$I$19)^IF(Mod_3=0,B63,INT(B63/12))) **Replace** formula in cell D63 by =1/((1+$I$18)^IF(Mod_3=0,B63,INT(B63/12))) **Copy** range C63:D63 **Paste** to range C64:D123

ERG Results Table Row Title	Associated detail	Implementation instructions
		In Sheet 'Appendix Transition', **Replace** formula in cell K19 by =IF(Mod_3=1,1/((1+Discounting_cost)^(12*INT(D19))), 1/((1+Discounting_cost)^(B19))) **Replace** formula in cell L19 by =IF(Mod_3=1,1/((1+Discounting_ben)^(12*INT(D19))), 1/((1+Discounting_ben)^(B19))) **Replace** formula in cell M19 by =IF(Mod_3=1,1/((1+Discounting_ben)^(12*INT(D19))), 1/((1+Discounting_ben)^(B19))) **Copy** range K19:M19 **Paste** to range K20:M259 and to range K272:M512
R10. Correct logic error in oral vinorelbine costing (Binary switch Mod_7)	None	In Sheet 'Appendix dose and BSA', **Replace** formula in cell S76 by =IF(Mod_7=1,S75*$J$53, S75*$F$53) **Replace** formula in cell S77 by =IF(Mod_7=1, S76*$J$54, S76*$F$54) **Replace** formula in cell S78 by =IF(Mod_7=1,P78*$H$60+R78*$J$60+$I$60*Q78, P78*$K$60+R78*$M$60+$L$60*Q78) **Copy** cell S78 **Paste** to range S79:S138
R5. ERG estimated eribulin unit costs (Binary switch Mod_5)	1072 eribulin 2 ReworkedDrugCosts (ERG).xlsx	In Sheet 'Appendix dose and BSA', **Replace** formula in cell H75 by =SUMPRODUCT(($D$78:$D$138)*(H$78:H$138))*IF(Mod_5=1.167927,1) **Replace** formula in cell I75 by =SUMPRODUCT(($D$78:$D$138)*(I$78:I$138))*IF(Mod_5=1.167927,1)
R4. (Binary switch Mod_4)	ERG_TTD/PFS data for drug use and admin costs are included as new columns L and M in worksheet 'ERG_survival'	In Sheet 'Appendix – transition' **Replace** formula in cell AB19 by =IF(Mod_4=1,ERG_survival!L4,$F19)*'Model parameters'!$P$77 **Copy** cell AB19 **Paste** to range AB20:AB259 **Replace** formula in cell AB272 by =IF(Mod_4=1,ERG_survival!M4,$F272)*'Model parameters'!$P$90 **Copy** cell AB272

ERG Results Table Row Title	Associated detail	Implementation instructions
		Paste to range ABAB273:AB512 **Replace** formula in cell AD272 by =IF('Model parameters'!$Q$13="Progression", (IF(Mod_4=1,ERG_survival!M4,$F272)*'Model parameters'!$R$90),IF($B272<='Model parameters'!$R$17,(IF(Mod_4=1,ERG_survival!M4, $F272)*'Model parameters'!$R$90),0)) **Copy** cell AB272 **Paste** to range AB273:AB512
R4 and R9. (Binary switches Mod_4 and Mod_10)	ERG_TTD/PFS data for drug use and admin costs Plus correcting erroro in Eribulin admin costs	In Sheet 'Appendix – transition' **Replace** formula in cell AD19 by =IF(Mod_10=1,IF(AB19>0,IF(Mod_4=1,ERG_survival! L4,$F19)*'Model parameters'!$R$77,0), IF('Model parameters'!$Q$13="Progression",(IF(Mod_4=1,ERG_ survival!L4,$F19)*'Model parameters'!$R$77),IF($B19<='Model parameters'!$R$17,(IF(Mod_4=1,ERG_survival!L4,$F1 9)*'Model parameters'!$R$77),0))) **Copy** cell AD19 **Paste** to range AD20:AD259

ERG Results Table Row Title	Associated detail	Implementation instructions
R6. ERG estimated comparator costs (Binary switch Mod_6)	ReworkedDrugCosts (ERG).xlsx	In Sheet 'Appendix dose and BSA', **Replace** formula in cell M75 by =SUMPRODUCT(($D$78:$D$138)*(M$78:M$138)) *IF(Mod_6=1, 0.978668,1) **Replace** formula in cell N75 by =SUMPRODUCT(($D$78:$D$138)*(N$78:N$138)) *IF(Mod_6=1, 0.978668,1) **Replace** formula in cell S75 by =SUMPRODUCT(($D$78:$D$138)*(S$78:S$138)) *IF(Mod_6=1,1.272909,1) **Replace** formula in cell T75 by =SUMPRODUCT(($D$78:$D$138)*(T$78:T$138)) *IF(Mod_6=1,1.272909,1) **Replace** formula in cell Y75 by =SUMPRODUCT(($D$78:$D$138)*(Y$78:Y$138)) *IF(Mod_6=1, 1.398345,1) **Replace** formula in cell Z75 by =SUMPRODUCT(($D$78:$D$138)*(Z$78:Z$138)) *IF(Mod_6=1, 1.398345,1) **Replace** formula in cell AF75 by =SUMPRODUCT(($D$78:$D$138)*(AF$78:AF$138)) *IF(Mod_6=1, 0.895303,1) **Replace** formula in cell AG75 by =SUMPRODUCT(($D$78:$D$138)*(AG$78:AG$138)) *IF(Mod_6=1, 0.895303,1) **Replace** formula in cell AM75 by =SUMPRODUCT(($D$78:$D$138)*(AM$78:AM$138)) *IF(Mod_6=1, 0.722909,1) **Replace** formula in cell AN75 by =SUMPRODUCT(($D$78:$D$138)*(AN$78:AN$138)) *IF(Mod_6=1, 0.722909,1) **Replace** formula in cell AT75 by =SUMPRODUCT(($D$78:$D$138)*(AT$78:AT$138)) *IF(Mod_6=1, 1.403897,1) **Replace** formula in cell AU75 by =SUMPRODUCT(($D$78:$D$138)*(AU$78:AU$138)) *IF(Mod_6=1, 1.403897,1) **Replace** formula in cell AZ75 by =SUMPRODUCT(($D$78:$D$138)*(AZ$78:AZ$138)) *IF(Mod_6=1, 1.079265,1) **Replace** formula in cell BA75 by =SUMPRODUCT(($D$78:$D$138)*(BA$78:BA$138)) *IF(Mod_6=1, 1.079265,1)

ERG Results Table Row Title	Associated detail	Implementation instructions
R7. ERG preferred progression utility value (Binary switch Mod_8)	None	In Sheet 'Utility', **Replace** formula in cell F29 by =IF(Mod_8=1,0.496,F11) **Replace** formula in cell H29 by =IF(Mod_8=1,0.496,H11)
R8. ERG alternative option for costing subsequent treatments (Binary switch Mod_9)	'Model parameters':Q13 must be set to "Maximum number of cycles"	In Sheet 'Model parameters', **Replace** formula in cell R17 by =IF(Mod_9=1,600,8) **Enter** in cell N92 the text *Proportion of Tx post progression* **Replace** formula in cell P91 by =SUMPRODUCT((J79:J89)*(P79:P89))*P93 **Replace** formula in P93 by =IF(Mod_9=1, 60%,100%)
Additional logic adjustment to prevent 'divide by zero' errors	None	In Sheet 'Appendix – Transition', **Replace** formula in cell V90 by =IF(F90+G90<0.0001,100%,(H96-H90)/SUM(F90:G90)) **Copy** cell V90 **Paste** formula only to range V91:V259